Clinical Guideline

Metastatic malignant disease of unknown primary origin

Evidence Review

Metastatic malignant disease of unknown primary origin: evidence review

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Cancer of Unknown Primary clinical guideline

1. Early specialist oncology input for people with metastatic cancer and undiagnosed primary

Last updated: 26/ 6/ 2009.

Short summary

There was no direct evidence about the early referral of people with metastatic cancer of unidentified primary to specialist oncologists.

However there is a body of evidence that supports specialist cancer care in general. It is reasonable to assume that early referral to a specialist would mean earlier initiation of therapy and the avoidance of inappropriate tests or treatment.

Recent NHS initiatives emphasise the importance of early specialist oncologist input for people who present as an emergency due to undiagnosed cancer or chemotherapy treatment.

Rationale

Patients with cancer present in many different ways. Their presentation can be regarded as a continuum, ranging from circumstances where a diagnosis is immediately apparent, to a situation in which metastatic cancer is evident but no primary site is found despite extensive investigation. The aim for all patients with cancer is to clarify the nature and extent of the disease as rapidly and effectively as possible, but for those with metastatic disease whose primary site defies initial elucidation, current management practices, which do not benefit from specialised oncology expertise, often fail to achieve this aim.

In other branches of acute medicine traditional approaches to diagnosis have recently been revised, through the development of rapid diagnosis units. In this setting, newly presenting patients are investigated in a timely fashion, with early assessment by senior clinicians to streamline the diagnostic process. This has advantages both to patients, and hospitals (in terms of more efficient resource use).

Some problems encountered in managing patients with metastatic malignancy without an identified primary site may be resolved if a similar approach was employed early in the diagnostic process, bringing to bear the expertise of senior oncology clinicians. Expert assessment including application of relevant investigations in a rational order, use of special tests at an appropriate stage, and decision making about the extent of testing based on likely treatment plans could all contribute to an improved outcome.

A formal analysis of the evidence for the benefits of early oncology intervention following diagnosis of metastatic cancer will determine whether a service development comprising “acute oncologist assessment” can be recommended. Evidence to be examined includes all studies of “acute medical assessment” in which cancer patients are included, and any studies which have specifically addressed the question of acute assessment in the oncology setting.

Methods

Study types

There was no restriction on study design.

Participants

People with metastatic cancer without an identified primary in the period immediately after diagnosis.

Interventions

Assessment and investigation by a team with oncology expertise or dedicated MDT in the period immediately after diagnosis of metastatic cancer, prior to traditional oncology referral on tumour site-specific grounds.

Outcomes

Number and appropriateness of investigations, overall duration of pathway from initial presentation to treatment and treatment outcomes (including psychological morbidity).

Study selection

The literature search identified ten potentially relevant studies. All were ordered for appraisal but only one (Seve et al, 2006) was included as evidence. A high level search of Medline for systematic reviews of process of care in people with cancer identified several systematic reviews, two of which were included

Search results

DESCRIPTION OF INCLUDED STUDIES

There was no direct evidence about the effect of early specialist oncologist in people presenting with metastases and an undiagnosed primary tumour. One Canadian cancer registry study (Seve et al, 2006) reported patterns of referral to cancer centres in patients with CUP. One systematic review (Grilli et al, 1998) examined the effect of specialisation on the care received by cancer patients. Another review (Gruen et al, 2009) summarised the evidence for link between hospital or physician case volume and mortality in patients with cancer.

Evidence summary

Seve et al (2006) reported patterns of referral to cancer centres in Canadian patients with cancer of unknown primary. Not all patients were evaluated at cancer centres. Those referred for evaluation (and possible treatment) at cancer centres tended to have better prognosis than those were not referred. Both univariate and multivariate analysis showed that age older than 75 years, comorbidity, peritoneal involvement, and poor performance status (PS 2 or more) were correlated with not being evaluated at a cancer centre.

The median survival was 151 days for patients referred to cancer centres, this compares with 21 days for patients not evaluated at cancer centres. The Seve study illustrates the difficulties of this type of research: patients referred to specialists tend to be a selected group and investigators need to adjust for this bias in their analyses.

Grilli et al (1998) reviewed the evidence for specialist cancer care. In eleven studies specialist care was defined variously as: the presence of an oncology department, oncologist, or cancer centre. Results were generally in favour of specialist care: patients treated by specialist oncologists were more likely to receive appropriate diagnostic or staging investigations. There was some evidence that patients received more appropriate treatment in centres with oncology departments, but this was limited to five studies in patients with breast or ovarian cancer.

Indirect evidence of the benefit of specialist treatment comes from studies of the relationship between hospital or physician case volume and patient outcome. The assumption is that specialist physicians or hospitals treat more patients. Gruen et al (2009) published a systematic review of the link between case volume and patient outcome in surgical oncology. In general patients treated in higher case volume had lower risk of perioperative mortality.

A report published in 2008 by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD, 2008), examined the process of care of patients who died within 30 days of receiving systemic anti-cancer therapy in June or July 2006. The report highlighted deficiencies in the initial assessment of patients, treatment decisions and in the management of complications and oncological emergencies. The report's advisors recommended the establishment of an acute oncology service (with access to specialist oncologist advice) in all hospitals with emergency departments.

NHS Institute for Innovation and Improvement published a report about (NHSIII, 2009) about improving the care pathway for people diagnosed cancer after emergency admission to hospital. The report's authors examined hospital episode data from 20 acute trusts. They also studied care pathways for this patient group in three cancer centres and three cancer units. They observed that *"[in cases where cancer is possible] it is vital that the cancer team is notified early on. This can prevent often unnecessary admission, speed up the diagnosis and improve the patients overall experience."*

The characteristics of the optimised care pathway for this patient group were: early identification of potential cancer in sick patients, prevention of unnecessary emergency admissions, alert/tracking systems to drive responsive care, rapid access to assessment and diagnostics for sick patients with possible cancer (ideally within 6 – 12 hours), getting patients on the right pathway at the earliest opportunity (ideally within 12 – 24 hours) and supporting organisational factors

References

Grilli R, Minozzi S, Tinazzi A, Labianca R, Sheldon TA and Liberati A. *Do specialists do it better? The impact of specialization on the process and outcomes of care for cancer patients*. Annals of Oncology 1998; 9:365-374

Gruen RL, Pitt V, Green S, Parkhill A, Campbell D, Jolley D. *The effect of provider case volume on cancer mortality*. CA: A Cancer Journal for Clinicians 2009; 59:192-211

National Confidential Enquiry into Patient Outcome and Death. *Systemic Anti-Cancer Therapy: For better, for worse?*. 2008;

NHS Institute for Innovation and Improvement. *Focus on: Cancer*. 1 June, 2009;

Seve P, Sawyer M, Hanson J, Broussolle C, Dumontet C, Mackey JR. *The influence of comorbidities, age, and performance status on the prognosis and treatment of patients with metastatic carcinomas of unknown primary site: a population-based study*. Cancer 2006; 106: (9) 2058-66

Cancer of Unknown Primary clinical guideline

1. Early specialist oncology input for people with metastatic cancer and undiagnosed primary

Last updated: 26 / 6 / 2009.

Characteristics of included studies

Grilli-1998

Methods	Systematic review.
Participants and Country	RCTs and prospective and retrospective cohort studies that compared specialist with non-specialist clinicians or centres. 32 studies were included
Interventions	Specialist cancer care. Specialisation was defined in the following ways: specialization of individual clinicians or institutions (hospitals, centres); and proxy indicators of specialization including hospital teaching status and hospital size (assuming larger centres to be more specialized
Outcomes	**Outcomes included:** Mortality at 3 and 5 years; proportion of patients treated according to optimal care criteria, proportion lost to follow up or proportion having defined investigative procedures; proportion with incomplete information on staging, histology; use of breast conserving surgery or specified cancer care management including pain management; and number of surgical interventions received. **Results** Quality of studies varied: 12 out of 24 (50%) provided information on process of care. 17 of 32 studies (53%) provided information on outcomes and adjusted the comparison for more than one variable. Only 1 randomised trial was identified. **Specialization and process of care** 11 observational studies provided information on the impact of specialization for various cancer sites. 5 defined specialisation at the clinician level and 6 at the level of centres. Overall results favoured specialized clinical centres or clinicians. Only 5 studies adequately adjusted for the case mix between comparison groups. Studies were mostly low-quality and tended to show cancer centres performed specific diagnostic staging procedures more often in breast cancer, childhood cancers and ovarian cancers. Breast conserving surgery (3 studies) was more frequently offered in centres with oncology departments or wards. Mixed results were reported for losses to follow-up. **Proxy definitions of specialization and process of care** 17 studies compared hospital patterns of care according to teaching status (11 studies) and hospital size (5 studies). 13 studies were on breast cancer, 2 on ovarian cancer or included multiple sites. Studies scoring 2 or more on case mix adjustment criteria showed greater reporting of clinical and pathological staging in the notes and greater use of two-stage surgery in larger or teaching centres. Conservative surgical procedures were more commonly used in larger or teaching centres. No difference between non-specialized vs specialized was noted in the use of adjuvant chemotherapy for breast cancer. **Specialization (however defined) and mortality** Generally patients had a lower risk of long-term mortality when treated by specialised centres/clinicians though results from two studies differed. **Specialization (however defined) and mortality for breast cancer (5 studies):** all had an adjustment score of 2 or more. Lower 5 year mortality reported when treated in specialist centres or by specialized clinicians OR = 0.82 (95%CI: 0.77, 0.88). Heterogeneity chi-squared = 0.08, P = 0.99. Specialization (however defined) and mortality for haematological cancer (4 studies one of which dealt with 3 types of tumour, giving 6 treatment arms): 5 of the 6 treatment arms showed lower mortality when treated in specialized situations. Specialization (however defined) and mortality

	for ovarian cancer (7 studies): 6 of 7 studies showed lower mortality when treated in specialized situations. Quality of studies and definition of specialization differed. Heterogeneity chi-squared = 4.5, P = 0.60. **Specialization and mortality for other solid tumours (5 studies):** two studies reported statistically significantly lower mortality for colorectal cancer and prostate cancer in teaching vs non-teaching hospitals. Lung cancer (1 study, 2 histological types) results differed according to histology. Testicular cancer (1 study): showed an advantage only for the availability of on-staff urologists and not for oncologist. Few studies focused on types of neurological tumours, sarcomas, or childhood cancers. There was only a limited number of poor quality studies in these fields. Impact of specialization on outcomes other than long-term mortality. Quality of life in breast cancer (1 RCT): no difference between groups. Studies reporting post-operative/in- hospital mortality in gastrointestinal (1 study), lung (1 study) and ovarian (1 study) showed contradictory results.
Notes	

Gruen-2009

Methods	Systematic review of observational studies.
Participants and Country	137 studies, including more than 1 million patients with oesophageal, gastric, hepatic, pancreatic, colon or rectal cancer.The majority of studies were retrospective analyses of data collected from hospital databases, cancer registries and a range of other specialist databases.
Interventions	Surgery for cancer
Outcomes	**Perioperative mortality - unadjusted analysis (105 studies)** There was a consistent relationship between perioperative mortality rate and hospital case volume for all cancer type, except rectal cancer. The odds ratios of perioperative mortality for each doubling of provider volume ranged from 0.77 for liver cancer surgery to 0.90 to colon cancer surgery. **Overall survival - analyses adjusted for counfounders (11 studies)** All studies reported at least one statistically significant association between case volume and mortality
Notes	The authors calculated that between 10 and 50 patients per year (depending on cancer type) would need to be moved from low to high case volume hospitals to prevent one additional perioperative death. Almost one third of the studies did not find a significant case volume effect on mortality. The authors suggest that using hospital case volume as a proxy for quality of healthcare is questionable and more direct measures of quality are needed.

NCEPOD-2008

Methods	A 2008 report by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD), examined the process of care of patients who died within 30 days of receiving systemic anti-cancer therapy (SACT) in June or July 2006.
Participants and Country	Patients who died within 30 days of receiving systemic anti-cancer therapy (SACT) in June or July 2006. Patients were identified via questionnaires sent to individual National Health Service hospitals in England, Wales and Northern Ireland, as well as hospitals in the independent sector and public hospitals in the Isle of Man, Guernsey and Jersey.
Interventions	Systemic anti cancer therapy.
Outcomes	**Quality of Care** The NCEPOD advisors judged that 35% of patients who died within 30 days of SACT received good care. In 49% of the patients patients the advisors identified room for improvement in care. **Discussion of treatment plan by MDT**

	The clinical management plan was discussed at an MDT meeting in only 58% (335/578) of patients who died within 30 days of SACT. The cohort included 23 patients with CUP (4.8% of the total number). 10 of these patients had their treatment plan agreed by an MDT, 10 did not and there was no information about the remaining 3 patients. **Recommendations of the report's advisors** All hospitals with A&E departments should establish an acute oncology service with access to specialist oncological advice. Decisions to initiate chemotherapy should be taken at the consultant level. Constultants should use standardised consent forms including details of both common and serious toxicities, which have been discussed with the patient Recommendations were also made about the prescribing, dispensing and delivery of chemotherapy, patient information, recording of toxicity, end of treatment record, models of service delivery, leadership, clinical governance, peer review, data collection and training.
Notes	

NHSIII-2009

Methods	Qualitative and quantiative study
Participants and Country	Patients admitted as an emergency and subsequently diagnosed with cancer. The study used HES data from 20 trusts as well as qualitative information from hospital visits to three cancer centres and three cancer units.
Interventions	The study compared different care pathways using observation and semi-structured interviews with the staff involved.
Outcomes	Length of stay and number of admissions for patients admitted as an emergency and diagnosed with a new cancer. The report investigators worked with the hospitals involved to formulate an optimised pathway for the care of sick patients with possible cancer. The characteristics of the optimal pathway were: Early identification of potential cancer in sick patients, prevention of unnecessary emergency admissions, alert/tracking systems to drive responsive care, rapid access to assessment and diagnostics for sick patients with possible cancer (ideally within 6 – 12 hours), getting patients on the right pathway at the earliest opportunity (ideally within 12 – 24 hours) and supporting organisational factors
Notes	

Seve-2006

Methods	Retrospective cohort study
Participants and Country	389 patients entered in the Northern Alberta Cancer Registry, with histologically proven metastases from an unknown primary tumour, with epithelial histology. Patients belonging to sub-groups with well defined treatment were excluded.
Interventions	No treatment (55% of patients), chemotherapy (23% of patients), radiotherapy (16%), chemoradiotherapy (5%), hormone therapy (1%) and other treatments (3%)
Outcomes	257 patients were evaluated at cancer centres and 132 patients were not. **Referral to cancer centre (specialist oncologist)** Patients with poor prognosis tended not to be referred for evaluation at a cancer centre: univariate and multivariate analysis showed that age older than 75 years, comorbidity, peritoneal involvement, and poor performance status (PS 2 or more) were correlated with not being evaluated at a cancer centre. **Overall survival** Patients referred to cancer centres had better overall survival than those not referred (median survival 150 and 21 days respectively). This difference is probably explained by the much poorer prognosis of the patients not referred to cancer centres.

Treatment received

It was not clear whether patients not evaluated at cancer centres received treatment, the analysis focuses on the group referred to cancer centres.

Notes

References for included studies

GRILLI 1998
Grilli R, Minozzi S, Tinazzi A, Labianca R, Sheldon TA and Liberati A. Do specialists do it better? The impact of specialization on the process and outcomes of care for cancer patients. Annals of Oncology 1998; 9 () 365-374

GRUEN 2009
Gruen RL, Pitt V, Green S, Parkhill A, Campbell D, Jolley D. The effect of provider case volume on cancer mortality. CA: A Cancer Journal for Clinicians 2009; 59 () 192-211

NCEPOD 2008
National Confidential Enquiry into Patient Outcome and Death. Systemic Anti-Cancer Therapy: For better, for worse?. 2008; ()

NHSIII 2009
NHS Institute for Innovation and Improvement. Focus on: Cancer. 1 June, 2009; ()

SEVE 2006
Seve P, Sawyer M, Hanson J, Broussolle C, Dumontet C, Mackey JR. The influence of comorbidities, age, and performance status on the prognosis and treatment of patients with metastatic carcinomas of unknown primary site: a population-based study. Cancer 2006; 106 (9) 2058-66

2. Key workers for people with cancer

Last updated: 29/ 10/ 2009.

Short summary

Key workers have become a standard of care for people with cancer, but there is relatively little evidence about their effectiveness.

One trial found that palliative care coordinators had little effect on the severity of symptoms of terminally ill patients with cancer (Addington-Hall et al, 1992).

Two other trials looked at nurses who coordinated care or provided support for women undergoing radical therapy for breast cancer. McArdle et al, (1996) reported that psychological and physical symptoms were less severe when women received support from a specialist breast cancer nurse. Goodwin et al (2003) found that when care was coordinated by a nurse case manager women were more likely to receive breast conserving surgery and have better post operative arm function.

There was no evidence, however, about the effect of key workers on the diagnostic process in those with suspected cancer.

Rationale

Patients diagnosed with cancer, and their families / carers, commonly suffer significant psychological morbidity. The provision of support from a specialist nurse is now an accepted intervention for patients with the major common cancers. Patients with cancer of unknown primary, or those with undefined primary cancer undergoing investigations, are not currently provided with the support facilities offered to the majority of other cancer patients. This, combined with the additional concerns and uncertainties associated with this particular diagnosis, may result in unmet needs, and avoidable psychological morbidity. The objective of this question is to estimate the clinical and cost effectiveness of a single person to co-ordinate emotional and psychological support for a person with unknown primary cancer.

Methods

Study types

Any study design.

Participants

The literature search was initially restricted to studies in those with unknown primary cancer, but did not return any relevant studies. The search was widened to include studies in people with any cancer.

Interventions

An identified key worker appointed to remain as a patient's point of contact with throughout their clinical course. For example, the NICE Improving Outcomes Guidance for people with brain tumours defines the key worker as "[the] person who, with the patient's consent and agreement, takes a key role in coordinating the patient's care and promoting continuity, ensuring the patient knows whom to access for information and advice".

Outcomes

Patient satisfaction with care, patient enablement, time taken to establish diagnosis, number of investigations, cost of hospital stay, overall duration of pathway from diagnosis to treatment, referral to appropriate site-specific team at first attempt and reduced morbidity resulting from more rapid diagnosis (including psychological morbidity)

Study selection

An initial list of studies was selected by the information specialist (SA). One reviewer (NB) then selected potentially relevant papers from this list on the basis of their title and abstract. These studies were ordered and each paper was check against the inclusion criteria. Reference lists of included papers were also checked for other relevant studies.

Data extraction and synthesis

One reviewer (NB) extracted data. Data extraction and critical appraisals of studies included in existing service guidance were used verbatim.

Quality assessment

Study quality was assessed using the NICE checklists for critical appraisal.

Heterogeneity assessment

There was no statistical assessment of heterogeneity, differences in studies were recorded in the study characteristics tables.

Search results

When restricted to people with cancer of unknown primary, the literature search identified no potentially relevant studies. When broadened to include studies of people with cancer in general the search returned 44 studies.

Description of included studies

Two studies were identified from the literature reviews of the Improving Outcomes cancer service guidance series (see Table 1). A UK randomised trial of cancer care coordinators (Addington Hall et al, 1992) in patients with life expectancy of less than a year. The coordinators were nurses who continually assessed need for NHS and social services, provided a link between the patient these services if needed, and offered advice and help.

Another UK randomised trial examined the effectiveness of breast cancer specialist nurses (McArdle et al,1996) who acted as a continuing source of advice and reassurance to women with breast cancer

An additional American randomised trial was found in the current literature search. Goodwin et al (2003) examined the effect of nurse case managers who coordinated care for older women with breast cancer.

Study quality

The included studies were well conducted and considered at moderate to low risk of bias.

Evidence summary

All but one of the NICE Improving Outcomes series of cancer service guidance recommended that each person with cancer should have a named key worker (see Table 2.1). Earlier guidance (colorectal, lung, urological, haematological, head and neck cancer) identified the clinical nurse specialist as the ideal key worker. Later editions (brain tumours, children and young people with cancer, sarcoma and supportive and palliative care for people with cancer) recognised that other healthcare professionals might perform the key worker role. The key worker recommendations were usually based on guideline group consensus rather than published evidence.

The Department of Health Manual for Cancer Services (2004), incorporating recommendations from the Calman-Hine (1995) report and subsequent NICE Improving Outcomes guidance, lists measures for a named key worker as part of generic, site specific and palliative care multidisciplinary teams.

Outcome 1: Patient satisfaction with care.

Addington-Hall and co workers (Addington-Hall et al 1992) reported no difference between groups in satisfaction with care.

Outcome 2: Patient enablement.

In the Addington-Hall et al study (Addington-Hall et al 1992) the two groups were equally likely to need help. There were no differences between groups in the sources of help, in the proportions having unmet needs for help or in the proportions who had aids and appliances for use at home.

Goodwin et al (2003) observed that women in the nurse case management group were more likely to report that they had a real choice in their treatment than women receiving standard care.

Outcomes 3,4 and 5: Time taken to establish diagnosis, the number of investigations and the overall duration of pathway from diagnosis to treatment

No evidence was found. The studies included only patients with an established diagnosis.

Outcome 6: Referral to appropriate site-specific team at first attempt

There was no direct evidence, but some studies attempted to measure the quality of coordination of care between healthcare professionals and patients.

Addington-Hall et al (1992) reported that frequency of contact with agencies and satisfaction with services did not differ significantly between groups.

Goowdin et al (2003) reported that women in the nurse case management group were more likely to receive breast conserving surgery and radiotherapy than those in the standard care group.

Outcome 7: Morbidity

In the Addington-Hall et al (1992) trial patients in the care coordination group were significantly less likely to have been suffering from vomiting, but there were no other significant differences in the symptoms experienced in the 24 hours before interview. There were also few significant differences in severity of symptoms, concern about symptoms and effectiveness of treatment: coordination group patients were more likely to be receiving effective treatment for vomiting (OR=0.04, 95% CI: 0.02-0.79) and were less likely to be concerned about having itchy skin (OR=3.7, 95% CI: 1.12-12.1). The control group patients were more likely to have died by the end of the study (OR=1.90, 95% CI: 1.01-3.58), but the authors considered this a statistical artefact of multiple comparisons.

There were few between group differences in the carers' reports of the type, severity and effectiveness of treatment of the patient's symptoms in the last week of life; carers of coordination group patients were more likely to report that the patient had had a cough, less likely to rate the patient's difficulty with swallowing as severe, more likely to report effective treatment for constipation and less likely to report effective treatment for anxiety.

McArdle et al (1996) found that psychological morbidity scores (GHQ, HAD) were consistently better in patients offered routine care plus support from the breast care nurse compared with patients offered routine care from ward staff, routine care plus support from a voluntary organisation or routine care plus support from the nurse and the voluntary organisation.

Goodwin et al (2003) reported that, at two months after surgery, more women in the nurse case management group had normal arm function than those in the standard care group.

References

Addington-Hall JM, MacDonald LD, Anderson HR, Chamberlain J, Freeling P, Bland JM, et al. *Randomised controlled trial of effects of coordinating care for terminally ill cancer patients*. BMJ 1992; 305: (6865) 1317-22

Chumbler NR, Kobb R, Harris L, Richardson LC, Darkins A, Sberna M, et al. *Healthcare utilization among veterans undergoing chemotherapy: the impact of a cancer care coordination/home-telehealth program*. Journal of Ambulatory Care Management 2007; 30: (4) 308-17

Chumbler NR, Mkanta WN, Richardson LC, Harris L, Darkins A, Kobb R, et al. *Remote patient-provider communication and quality of life: empirical test of a dialogic model of cancer care*. Journal of Telemedicine & Telecare 2007; 13: (1) 20-5

Goodwin JS, Satish S, Anderson ET, Nattinger AB, Freeman JL. *Effect of nurse case management on the treatment of older women with breast cancer*. J Am Geriatr Soc 2003; 51: (9) 1252-9

McArdle JM, George WD, McArdle CS, Smith DC, Moodie AR, Hughson AV, et al. *Psychological support for patients undergoing breast cancer surgery: a randomised study*. BMJ 1996; 312: (7034) 813-6

The Expert Advisory Group on Cancer to the Chief Medical Officers of England and Wales. *A policy framework for commissioning cancer services. The Calman-Hine Report* 1995;

Department of Health. *Manual for Cancer Services*. 2004;

Table 2.1: Key workers in the Improving Outcomes cancer service guidance

Service Guidance	Issued	Key worker recommendation	Evidence base
Brain tumours	2006	Yes	None (no search for evidence).
Breast cancer	2002	Yes	None. No evidence found.
Children and young people with cancer	2005	Yes	No evidence found
Colorectal cancer	2004	Yes (clinical nurse specialist offering support and continuity of care)	No direct evidence about key workers.
Haemato-oncology	2003	Yes (clinical nurse specialist offering support and continuity of care)	Indirect evidence from RCTs of link nurses in other cancers
Head and neck cancer	2004	Named clinical nurse specialist	No direct evidence
Lung cancer	2005	Yes (clinical nurse specialist offering support and continuity of care)	No evidence found
Sarcoma	2006	Yes	None (no search for evidence).
Skin cancer	2006	No specific recommendations	-
Supportive and palliative care	2004	Yes	RCT evidence about nurses coordinating palliative care
Urological cancer	2002	Yes (clinical nurse specialist offering support and continuity of care)	No evidence reported

2. Key workers for people with cancer

Last updated: 29 / 10 / 2009.

Characteristics of included studies

Addington-Hall-1992

Methods	Randomised controlled trial (level 1b)
Participants and Country	203 terminally ill cancer patients with life expectancy of less than one year. 104 were randomised into the co-ordination group and 99 into the control group. UK
Interventions	The co-ordinators were based in the community and introduced themselves to patients as nursesproviding a link between the hospital, general practitioner and community services. Their role was to assess the need for services from NHS, local authority and voluntary sector agencies; to offer advice on how to obtain these services and to contact the agencies themselves if necessary; to ensure that services were provided and were well coordinated; and to monitor the changing needs of the patient andfamily for services. Patients were encouraged to contact the coordinators if they needed help or advice. Co-ordinators did not provide practical nursing care, specialist palliative care advice or counselling services.
Outcomes	Outcome measures included the presence and severity of physical symptoms, psychiatric morbidity, use of and satisfaction with services and carers' problems.
Notes	Data extraction and critical apprasial from NICE Improving Outcomes in Haematological Cancers guidance (2003)

Chumbler-2007

Methods	Matched case-control study
Participants and Country	125 patients receiving chemotherapy at Department of Veteran's Affairs hospitals. USA
Interventions	Cancer care coordination
Outcomes	Use of hospital services
Notes	

Goodwin-2003

Methods	Randomised controlled trial (level 1b).
Participants and Country	355 women, aged 65 or older with newly diagnosed breast cancer. America
Interventions	Patients were randomised to nurse case managers or usual care, both for 12 months. Nurse case managers received 40 hours training about cancer care, complications, cancer guidelines and case management. The case manager's roles were educator, counsellor, advocate and care coordinator.
Outcomes	Type and use of cancer treatment in the first six months after diagnosis, arm function, patient satisfaction
Notes	Randomisation was at the level of the surgeon (n=60) not by individual patient (cluster randomisation).

McArdle-1996

Methods	Randomised controlled trial (level 1b)
Participants and Country	272 women aged less than 70 years undergoing surgery for breast cancer. 67 patients were randomised to routine care, 70 to routine care and support from a specialist breast care nurse, 66 to routine care and support from a voluntary organisation (Tak Tent) and 69 to routine care and support fromboth the breast care nurse and the voluntary organisation.
Interventions	Breast care nurse providing support. The nurse gave information, listened sympathetically and gavereassurance. Patients were also given a contact telephone number for the nurse.
Outcomes	Prevalence of psychological morbidity as assessed by self rating scales: 28 item general health questionnaire (GHQ) and its subscales and the hospital anxiety and depression scale (HAD).
Notes	Data extraction and critical apprasial from NICE Improving Outcomes in Haematological Cancers guidance (2003)

References for included studies

ADDINGTON HALL 1992
Addington-Hall JM, MacDonald LD, Anderson HR, Chamberlain J, Freeling P, Bland JM, et al. Randomised controlled trial of effects of coordinating care for terminally ill cancer patients. BMJ 1992; 305 (6865) 1317-22

CHUMBLER 2007
Chumbler NR, Kobb R, Harris L, Richardson LC, Darkins A, Sberna M, et al. Healthcare utilization among veterans undergoing chemotherapy: the impact of a cancer care coordination/home-telehealth program. Journal of Ambulatory Care Management 2007; 30 (4) 308-17

Chumbler NR, Mkanta WN, Richardson LC, Harris L, Darkins A, Kobb R, et al. Remote patient-provider communication and quality of life: empirical test of a dialogic model of cancer care. Journal of Telemedicine & Telecare 2007; 13 (1) 20-5

GOODWIN 2003
Goodwin JS, Satish S, Anderson ET, Nattinger AB, Freeman JL. Effect of nurse case management on the treatment of older women with breast cancer. J Am Geriatr Soc 2003; 51 (9) 1252-9

MCARDLE 1996
McArdle JM, George WD, McArdle CS, Smith DC, Moodie AR, Hughson AV, et al. Psychological support for patients undergoing breast cancer surgery: a randomised study. BMJ 1996; 312 (7034) 813-6

3. Multidisciplinary teams for people with cancer

Last updated: 29/ 9/ 2008.

Short summary

The NICE Improving Outcomes series of cancer service guidance recommended that people with cancer should have their treatment managed by multidisciplinary teams (MDTs). Although largely lacking at the time, evidence about the clinical effectiveness of MDTs has since emerged.

There is evidence from observational studies, that management by MDT is associated with improved overall survival in people with cancer. Some small studies observed large improvements in overall survival associated with MDT management, but the weight of evidence suggests a more modest beneficial effect.

The limited evidence about patient satisfaction suggests that patients managed by MDT report greater satisfaction than those managed elsewhere.

There was some evidence that the time from diagnosis to treatment was shorter when patients were managed by an MDT although none of the studies addressed the diagnostic process directly.

Rationale

The management of the major common cancers has been revolutionised and improved by the introduction of the Multidisciplinary Team (MDT) approach. Designated specialist teams comprising all relevant disciplines provide better treatment than non-specialists, and the organisational arrangements in which such teams function can deliver improvements in the speed of investigation and diagnosis. Supportive care from a designated disease site-specific specialist nurse is an additional benefit provided by the MDT approach to these patients.

Patients with undefined primary cancer are not currently "owned" by a specific MDT, and hence their management and support is fragmented and poorly coordinated. Some patients are discussed at other site-specific MDTs, but experience shows that the lack of a defined policy for management of these cases results in limited benefits from this approach. Formal application of the MDT approach to patients with undefined primary cancer early in their clinical course may be advantageous.

Methods

Study types

Any comparative study.

Participants

Initial literature searches restricted to studies of people with cancer of unknown primary returned no studies, so the search was broadened to included people with any type of cancer.

Interventions

Multidisciplinary team (MDT) management. For the purpose of this review an MDT was defined as a group of health professionals meeting regularly to discuss the management of patients with cancer. Typical cancer MDTs include a surgeon, clinical oncologist, medical oncologist, radiologist, pathologist and specialist nurse. Other specialists might be included depending on the cancer site: the NICE Improving Outcomes cancer guidance series recommends membership for various cancer site specific MDTs.

Outcomes

Treatment outcomes, patient satisfaction with care, overall duration of pathway from initial presentation to treatment and the number and cost of investigations.

Study selection

An initial list of studies was selected by the information specialist (SA). One reviewer (NB) then selected potentially relevant papers from this list on the basis of their title and abstract. These studies were ordered and the reviewer checked each paper against the inclusion criteria. Reference lists of included papers were also checked for other relevant studies. The NICE Improving Outcomes cancer service guidance series was also searched for recommendations and evidence about MDTs.

Data extraction and synthesis

One reviewer (NB) extracted data.

Quality assessment

Study quality (risk of bias) was assessed using the NICE checklists for critical appraisal.

Heterogeneity assessment

There was no statistical assessment of heterogeneity, differences in studies were recorded in the study characteristics tables.

Search results

When restricted to people with cancer of unknown primary, the literature search identified no potentially relevant studies. When broadened to include studies of people with cancer in general the search returned 292 studies. 19 studies were included.

Description of included studies

Three systematic reviews were identified (Coory, 2008; Houssami et al, 2006 and Wright 2007). Houssami et al (2006) and Wright et al (2007) included few relevant studies, so the original studies from these reviews were appraised in their own right.

Stephens et al (2005, 2007) compared overall survival before and after the introduction of multidisciplinary team working in UK upper gastrointestinal cancer care. These studies tried to address the problem of using historical control groups (with generally poorer prognosis) by using multivariate analysis. Birchall et al (2004) used two UK audits to examine the effect of MDTs on the outcomes of people with head or neck cancer.

Morris et al (2006, 2008) used UK cancer registry data to compare cancer teams' adherence to the MDT standards in the Manual for Cancer services with overall survival, in people with colorectal cancer (Morris et al 2006) or breast cancer (Morris et al 2008). Compliance was rated from 0% (no standards were met) to 100% (all standards met).

Study quality

The majority of the included studies were observational: a single randomised controlled trial was included in the Coory et al (2008) systematic review. Many of the studies used a "before-and-after" design, comparing outcomes before and after the introduction of MDT cancer teams. The use of historical controls introduces bias in favour of MDTs, because there has been a general improvement in the outcomes of people with cancer over time.

Evidence summary

NICE Improving Outcomes guidance

All the service guidance publications recommended that people with cancer should have their treatment managed by MDTs. On the whole these recommendations were not based on direct evidence (see Table 3.1). This is not surprising since cancer MDTs were just beginning to emerge (sometimes as a result of the Improving Outcomes guidance).

Treatment outcomes

Overall survival

Morris et al (2006, 2008) found for each 25% increase in MDT adherence score there was a 3% reduction in the risk of death within five years of diagnosis for colorectal cancer patients and 4% reduction for breast cancer patients. This effect was statistically significant in the colorectal cancer cohort but not in the breast cancer cohort. According to these figures, colorectal cancer patients treated by a team meeting none of the standards would have a 12% greater risk of 5 year mortality than patients treated by a team with full adherence to MDT standards.

Coory (2008) reviewed the evidence from five studies about the effect of MDT management on the overall survival of people with lung cancer. Two studies noted a modest survival benefit for patients managed by MDTs, and three studies reported no significant difference in survival

Stephens et al (2005, 2006) attributed large improvements in survival to MDT management (54% and 66% for patients with gastric and oesophageal cancer respectively).

Birchall et al (2004) reported two audits of UK head and neck cancer outcomes. In the earlier time period there was no statistical effect of MDT management on patient survival, but in the later audit MDT management was associated with 30% reduction in the risk of death within 2 years of diagnosis.

Operative mortality

The rate of operative mortality was considerably lower in upper GI cancer patients managed by MDTs than in historical control groups, 2% versus 12% respectively for those with gastric cancer (Stephens et al, 2005) and 6% versus 26% for those with oesophageal cancer (Stephens et al 2006).

Patient satisfaction

Two studies measured patient satisfaction, using questionnaires. Gabel et al (1997) reported that patients managed by MDT were more likely to report carers were encouraged to attend consultations and that the consultations helped them make a treatment decision, than patients managed in non-MDT settings. Another study (included in Coory et al 2008) found control group (non-MDT) patients were more likely to report the diagnostic process as too slow and that MDT patients were more likely to report a better care experience.

Overall duration of pathway from initial presentation to treatment and number of investigations.

Little evidence about the diagnostic process because studies were of patients with known primary tumours.

Grabel et al (1997) reported that the mean time from diagnosis to treatment was 30 days in patients managed by MDT compared with 42 days in those managed elsewhere. Chang et al. (2001) reported that the MDT review of cases would sometimes also lead to deferred radical treatment while further staging investigations were done.

The Coory (2008) systematic review included three studies reporting time from presentation to treatment. In all three the mean (or median) time from presentation to treatment was reduced by at least two weeks in the MDT group when compared to the non MDT group. Evidence from a single phase II randomised trial suggested this was due to quicker diagnosis in patients managed by MDT.

NUMBER OF INVESTIGATIONS.

There was little evidence about this outcome. Two studies suggested that additional staging investigations after diagnosis were more likely in patients managed by MDTs. Back et al (2007) study reported that post-operative imaging was more likely in patients managed by MDT. Chang et al. (2001) noted that MDT review of cases would lead to additional staging investigations before treatment in 31% of those destined for radical therapy.

In a randomised phase II trial of 57 patients with lung cancer (reported in Coory et al 2008) those managed by MDT made significantly fewer GP visits than those managed in a non-MDT setting (88 versus 164 respectively).

References

Back MF, Ang EL, Ng WH, See SJ, Lim CC, Tay LL, et al. *Improvements in quality of care resulting from a formal multidisciplinary tumour clinic in the management of high-grade glioma*. Annals of the Academy of Medicine, Singapore 2007; 36: (5) 347-51

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Coory M, Gkolia P, Yang IA, Bowman RV, Fong KM. *Systematic review of multidisciplinary teams in the management of lung cancer*. Lung Cancer 2008; 60: (1) 14-21

Gabel M, Hilton NE, Nathanson SD. *Multidisciplinary breast cancer clinics. Do they work?*. Cancer 1997; 79: (12) 2380-4

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Morris E, Haward RA, Gilthorpe MS, Craigs C, Forman D. *The impact of the Calman-Hine report on the processes and outcomes of care for Yorkshire's colorectal cancer patients*. British Journal of Cancer 2006; 95: (8) 979-85

Morris E, Haward RA, Gilthorpe MS, Craigs C, Forman D. *The impact of the Calman-Hine report on the processes and outcomes of care for Yorkshire's breast cancer patients*. Annals of Oncology 2008; 19: (2) 284-91

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Stephens MR, Hopper AN, Blackshaw G, Barry JD, Edwards P, Hodzovic I, et al. *Multidisciplinary team management is associated with improved outcomes after surgery for gastric cancer*. Gut 2005; 54:A111

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Wright FC, De Vito C, Langer B, Hunter A, Expert Panel on Multidisciplinary Cancer Conference Standards. *Multidisciplinary cancer conferences: a systematic review and development of practice standards. [Review] [56 refs]*. European Journal of Cancer 2007; 43: (6) 1002-10

Table 3.1: Multidisciplinary team recommendations in Improving Outcomes service guidance

Cancer guidance	Year issued	MDT recommendation	Evidence
Brain tumours	2006	Yes	No direct evidence. Breast cancer evidence was cited.
Breast cancer	2002	Yes	Evidence is from observational studies of treatment by specialists rather than MDTs *per se*.
Children and young people with cancer	2005	Yes	Indirect evidence from other cancer studies.
Colorectal cancer	2004	Yes	No direct evidence. Breast cancer evidence was cited.
Haemato-oncology	2003	Yes	No direct evidence
Head and neck cancer	2004	Yes	No evidence found about effect of MDTs on survival or quality of life
Lung cancer	2005	Yes	Evidence from observational studies
Skin cancer	2006	Yes	No direct evidence
Urological cancer	2002	Yes	No direct evidence.

Table 3.2: Treatment outcomes

Study	N	Outcome	MDT	non-MDT	Statistical comparison
Coory 2008	5 studies (N not reported)	Overall survival			One study found that median survival of inoperable patients was 3.2 months longer after the introduction of MDT care. Another study found a modest increase in the survival of older patients, when managed by MDTs. Three other studies reported no statistical difference in survival outcomes between MDT and non-MDT groups.
Birchall 2004 (1996-1997 cohort)	566	Overall survival, 2 years after diagnosis	NR	NR	In a multivariate analysis of survival, assessment by an MDT was not a significant predictor of survival within 2 years of diagnosis [P=0.01, HR not reported]
Birchall 2004 (1999-2000 cohort)	727	Overall survival, 2 years after diagnosis	NR	NR	In a multivariate analysis of survival, assessment by an MDT was associated with a 30% reduction in the risk of death within two years of diagnosis [HR=0.70, P=0.02]
Stephens 2005	95	Operative mortality	2%	12%	NR
Stephens 2006	77	Operative mortality	6%	26%	NR
Stephens 2005	95	Overall survival, 5 years post-op	71%	35%	In a multivariate analysis of survival, MDT management was associated with a 54% reduction in the risk of death during the period of follow up [HR=0.46, 95% CI= 0.23 to 0.92]
Stephens 2006	77	Overall survival, 5 years post-op	52%	10%	In a multivariate analysis of survival, MDT management was associated with a 66% reduction in the risk of death during the period of follow up [HR=0.34, 95% CI= 0.20 to 0.56]
Morris 2008	11919	Overall survival, 5 years post-op	NA	NA	A quartile increase in MDT score was associated with a 4% reduction in the risk of death within 5 years of surgery, but this was not statistically significant [HR=0.96, 95% CI = 0.89 to 1.02].
Morris 2006	11548	Overall survival, 5 years post-op	NA	NA	A quartile increase in MDT score was associated with a 3% reduction in the risk of death within 5 years of surgery, this was statistically significant [HR=0.97, 95% CI = 0.94 to 0.99].

Study	N	Outcome	MDT	non-MDT	Statistical comparison
Back 2007	67	Median survival	18.7 months	11.9 months	Log rank, P=0.11.
Shylasree 2006	287	Overall survival, over the period of the study.	NA	NA	Chi Squared = 5.24, P=0.022 (unadjusted comparison).

Abbreviations: CI, confidence interval; HR, hazard ratio; MDT, multidisciplinary team; NA, not applicable; NR, not reported.

Table 3.3: Patient satisfaction with care

Study	N	Outcome	MDT	non-MDT	Statistical comparison
Gabel 1997	339	Patient satisfaction (6 questions)	NR	NR	Patients managed by MDT were more likely to report carers were encouraged to attend consultations (P<0.001) and that the consultations helped them make a treatment decision (P<0.001) than patients managed in non-MDT settings. There were no significant differences in the responses to the other four questions (about adequacy of time spent with each consultant and the nurse specialist's knowledge).
Coory et al 2008	57 (1 study)	Patient satisfaction	NR	NR	Control group (non-MDT) patients were more likely to report the diagnostic process as too slow (P=0.02). MDT patients were more likely to report a better care experience (P=0.01). Not all patients completed the questionnaires

Table 3.4: Overall duration of pathway from initial presentation to treatment

Study	N	Outcome	MDT	non-MDT	Statistical comparison
Gabel 1997	339	Mean time from diagnosis to treatment	30 days	42 days	P = 0.02
Chang 2001	75	Decision to defer radical treatment pending further diagnostic tests			Additional work-up before treatment was recommended by the MDT in 10/32 (31%) patients whom non-MDT recommended immediate radical treatment.
Coory 2008	3 studies (N not reported)	Time from presentation to treatment			In three studies the mean (or median) time from presentation to treatment was reduced by at least two weeks in the MDT group when compared to the non MDT group. Evidence from a single phase II randomised trial suggested this was due to quicker diagnosis in patients managed by MDT.

Table 3.5: Number and cost of investigations

Study	N	Investigations	MDT	non-MDT	Statistical comparison
Back 2007	67	Imaging within 5 days post-op	86%	59%	
Coory 2008	57 (1 study)	Visits to G.P.	88	164	P=0.002

3. Multidisciplinary teams for people with cancer

Last updated: 29 / 9 / 2008.

Characteristics of included studies

Back-2007

Methods	Non randomised comparative.
Participants and Country	67 patients with high grade glioma treated with radical radiotherapy,at 2 hospitals. Singapore.
Interventions	Management by a neuro-oncology multidisciplinary team at one hospital was compared with the traditional on-call referral pattern (non-MDT) at the other hospital. The MDT met every 2 weeks with neurosurgeon, radiation oncologist, neuro-oncologist, neuroradiologist and clinical nurse specialist in attendance.
Outcomes	Median overall survival, use of postoperative imaging, time from surgery to start of radiotherapy, use of adjuvant chemotherapy in those with glioblastoma multiforme.
Notes	Clinical characteristics appear similar between the two patient groups.

Birchall-2004

Methods	Cohort study
Participants and Country	1293 patients with head and neck cancer identified from the South West Audit of Head and Neck Cancer. UK
Interventions	Assessment in a multidisciplinary clinic compared with assessment elsewhere.
Outcomes	Two year overall survival, time from diagnosis to treatment.
Notes	

Chang-2001

Methods	Non randomised comparative study. Women with breast cancer had their cases evaluated by an MDT, with comprehensive history and physical examination and review of pathology and radiological imaging. Treatment recommendations made by the MDT were then compared to those made before.
Participants and Country	75 women with breast cancer. USA
Interventions	Multidisciplinary team evaluation of case at a University Hospital compared with treatment recommendations from other institutions.
Outcomes	Treatment recommendations
Notes	Unclear whether the referring institutions had MDTs

Coory-2008

Methods	Systematic review of MDTs for patients with lung cancer. Literature search dates were 1984 to 2007. Any study design was eligible. (Evidence level 2)
Participants and Country	Patients with lung cancer.
Interventions	MDTs (meeting of a group of people of different healthcare disciplines to discuss individual patients).
Outcomes	Survival, practice patterns, waiting times, satisfaction with care, visits to GPs and quality of life.
Notes	16 studies were included (1 randomised trial, 7 before and after studies and 8 case series).

Gabel-1997

Methods	Non-randomised before and after study. Compares outcomes in a single institution before and after the opening of an MDT breast cancer clinic.
Participants and Country	339 patients with breast cancer (162 before the opening of the MDT clinic and 177 after).USA
Interventions	MDT management. Team meetings included specialists from surgery, radiation oncology, medical oncology, pathology and radiology. The system before the introduction of the MDT is not specified in detail, but involved consultations with individual specialists.
Outcomes	Time between diagnosis and treatment. Patient satisfaction, measured using a patient questionnaire.
Notes	

Houssami-2006

Methods	Systematic review of MDTs for patients with breast cancer. Literature search dates were 1984 to 2007. Any study design was eligible. (Evidence level 2)
Participants and Country	Patients with breast cancer.
Interventions	Multidisciplinary care
Outcomes	Overall survival, change in treatment recommendations, time between diagnosis and treatment.
Notes	15 studies included, although only 2 were true MDT studies the remainder were about case volume.

Morris-2006

Methods	Cohort study
Participants and Country	11548 patient with colorectal cancer entered in the Northern and Yorkshire Cancer Registry, with complete medical management information. UK
Interventions	Implementation of the Calman-Hine recommendations (cancer MDTs and surgical site specialisation). The degree of implementation was measured using a questionnaire derived from the National Accreditation Standards in the NHS Manual of Cancer Service standards.
Outcomes	Use of chemotherapy in Dukes stage C and D patients, use of neoadjuvant radiotherapy, use of anterior resection in patients with rectal cancer and five year overall survival.
Notes	

Morris-2008

Methods	Cohort study
Participants and Country	11919 women with breast cancer entered in the Northern and Yorkshire Cancer Registry, with complete medical management information. UK
Interventions	Implementation of the Calman-Hine recommendations (breast cancer MDTs and surgical site specialisation). The degree of implementation was measured using a questionnaire derived from the National Accreditation Standards in the NHS Manual of Cancer Service standards.
Outcomes	Use of breast conserving surgery, use of adjuvant radiotherapy and five year overall survival.
Notes	

Shylasree-2006

Methods	Cohort study
Participants and Country	287 women with suspected ovarian cancer treated at any of 20 hospitals. UK
Interventions	Management by gynaecology oncology MDT compared with management at a peripheral unit.
Outcomes	Overall survival
Notes	

Stephens-2005

Methods	Before and after study (case series)
Participants and Country	95 patients with gastric cancer undergoing R0 gastrectomy with curative intent in a single cancer unit. UK
Interventions	MDT management (45 patients), compared with a historical control group (50 patients) treated immediately before the introduction of the MDT.
Outcomes	Treatment related morbidity and mortality, 5 year overall survival.
Notes	

Stephens-2006

Methods	Before and after study (case series)
Participants and Country	134 patients with esophogeal cancer undergoing surgery with curative intent in a single cancer unit. UK
Interventions	MDT management, compared with historical control group immediately before the introduction of the MDT.
Outcomes	Preoperative staging, treatment related morbidity and mortality, overall survival.
Notes	

Wright-2007

Methods	Systematic review. Literature search dates 1960 to 2005, unpublished studies were also sought.
Participants and Country	People with cancer or tuberculosis.

Interventions	Multidisciplinary cancer conferences (MDT meetings), specialist cancer care, high volume cancer teams.
Outcomes	Any reported patient outcomes. Key components of an MDT
Notes	Ten studies reported the effect of MDTs (or specialist/ high volume teams) on outcomes. Only three were studies of MDTs for cancer (Birchal et al 2004; Chang et al 2001 and Gabel et al 1997), these were included in the current review in their own right.

References for included studies

BACK 2007
Back MF, Ang EL, Ng WH, See SJ, Lim CC, Tay LL, et al. Improvements in quality of care resulting from a formal multidisciplinary tumour clinic in the management of high-grade glioma. Annals of the Academy of Medicine, Singapore 2007; 36 (5) 347-51

BIRCHALL 2004
Birchall M, Bailey D, King P. Effect of process standards on survival of patients with head and neck cancer in the south and west of England. Br J Cancer 2004; 91 (8) 1477-81

CHANG 2001
Chang JH, Vines E, Bertsch H, Fraker DL, Czerniecki BJ, Rosato EF, et al. The impact of a multidisciplinary breast cancer center on recommendations for patient management: the University of Pennsylvania experience. Cancer 2001; 91 (7) 1231-7

COORY 2008
Coory M, Gkolia P, Yang IA, Bowman RV, Fong KM. Systematic review of multidisciplinary teams in the management of lung cancer. Lung Cancer 2008; 60 (1) 14-21

GABEL 1997
Gabel M, Hilton NE, Nathanson SD. Multidisciplinary breast cancer clinics. Do they work?. Cancer 1997; 79 (12) 2380-4

HOUSSAMI 2006
Houssami N, Sainsbury R. Breast cancer: multidisciplinary care and clinical outcomes. [Review] [27 refs]. European Journal of Cancer 2006; 42 (15) 2480-91

MORRIS 2006
Morris E, Haward RA, Gilthorpe MS, Craigs C, Forman D. The impact of the Calman-Hine report on the processes and outcomes of care for Yorkshire's colorectal cancer patients. British Journal of Cancer 2006; 95 (8) 979-85

MORRIS 2008
Morris E, Haward RA, Gilthorpe MS, Craigs C, Forman D. The impact of the Calman-Hine report on the processes and outcomes of care for Yorkshire's breast cancer patients. Annals of Oncology 2008; 19 (2) 284-91

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Shylasree TS, Howells RE, Lim K, Jones PW, Fiander A, Adams M, et al. Survival in ovarian cancer in Wales: Prior to introduction of all Wales guidelines. International Journal of Gynecological Cancer 2006; 16 (5) 1770-6

STEPHENS 2005
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STEPHENS 2006
Stephens MR, Lewis WG, Brewster AE, Lord I, Blackshaw GR, Hodzovic I, et al. Multidisciplinary team management is associated with improved outcomes after surgery for esophageal cancer.[see comment]. Diseases of the Esophagus 2006; 19 (3) 164-71

WRIGHT 2007
Wright FC, De Vito C, Langer B, Hunter A, Expert Panel on Multidisciplinary Cancer Conference Standards. Multidisciplinary cancer conferences: a systematic review and development of practice standards. [Review] [56 refs]. European Journal of Cancer 2007; 43 (6) 1002-10

4. Initial tests for metastases of undiagnosed primary

Last updated: 30/ 10/ 2009.

Short summary

A number of expert reviews proposed diagnostic strategies for the identification of primary tumours in patients with metastatic presentation. Their aim was typically to identify treatable tumours as quickly as possible. However, no studies directly compared an expert diagnostic strategy with tests performed in arbitrary order.

Limited evidence, from case series, suggests that most primary tumours can be identified by a restricted panel of basic tests. This implies that the use of additional tests at an early stage will not add anything in most cases and the additional false positive diagnoses could delay diagnosis for some patients.

The consensus in the literature was if the basic panel of tests fails to reveal a primary tumour, further tests should be used selectively, guided by the patients signs and symptoms and with the aim of identifying treatable tumours.

Rationale

NICE Guidelines exist for initial investigation and referral of patients, who present with symptoms suggestive of a primary tumour, but these Guidelines do not deal with patients who present with symptoms due to metastatic disease, nor do they advise about the optimal diagnostic workup in such patient.

Special circumstances exist where extensive investigation of metastatic malignancy is not clinically appropriate, specifically when patients have extremely advanced disease, and / or where anti-cancer treatment is very unlikely to be beneficial. Identification of these patients and their optimal management is dealt with below (PICO question 5). For all other patients, a rational approach to investigation which achieves a definitive diagnosis in the shortest possible time (i.e. with the least redundant tests) is the standard clinical aim.

The initial diagnosis of metastatic cancer is usually made on the basis of detection of tumour masses or effusions on clinical examination or by imaging, often on a background of recognised but non-specific symptoms. Once metastatic cancer is suspected or proven, further tests are performed with the aim of identifying a primary site (where possible), and refining the histological nature and extent of the disease. In the period after the initial presentation, when metastatic cancer has been identified, but the outcome of further tests are awaited, it is useful to apply a diagnosis of “malignancy of undefined primary origin”.

There are numerous different clinical presentations of malignancy of undefined primary origin, and it is inappropriate to apply exactly the same panel of investigations in every patient. Conversely, there are tests which clinical experience has shown commonly make a useful contribution to the diagnostic process with minimal cost (either financially, or in terms of patient inconvenience), which can therefore be reasonably applied in almost every case. Traditionally, the literature regarding investigation of provisional Cancer of Unknown Primary (CUP) has emphasised the importance of avoiding certain tests which were perceived as invasive, or low-yield (for instance endoscopy, barium studies). However, the advent of more modern approaches to diagnosis (e.g. same-day upper- and lower-GI endoscopy), and the wider availability of complex yet high-yield tests (eg CT scanning) has altered this perception. These developments, combined with the premium which applies to early identification of certain newly treatable entities such as metastatic colon cancer mean that the “optimal” list of preliminary investigations for malignancy of undefined primary origin is difficult to define, and changes with time, clinical opinion, and clinical circumstances.

The published literature contains a list of initial investigations which are applied in the majority of cases of malignancy of undefined primary origin. These tests are:

- Comprehensive history and physical examination including rectal and pelvic examination
- FBC, U+E+creatinine, LFTs, Ca2+, Urinalysis
- Immunoglobulin levels (isolated or multiple lytic bone lesions)
- Symptom-directed endoscopy
- Mammography (women)
- Chest x-ray and CT scan chest / abdomen / pelvis

- ◦Marker tests (PSA in males > 50 years; CA125 in females with peritoneal malignancy or ascites; AFP + HCG (midline nodal disease, age <50 years)
- ◦Biopsy and standard histological examination including "basic" immunohistochemistry panel (CD20, CD7) and other immunohistochemistry as appropriate

Formal review of the evidence on initial investigation of malignancy of undefined primary origin may reveal an optimal strategy for managing this process. Such a strategy would maximise the number of diagnoses made for which specific valuable interventions could be offered, would identify as many primary tumours as possible, and would be rapidly and easily applied. It would also ensure that inappropriate over-investigation was avoided in patients for whom exhaustive testing stood no chance of improving the ultimate treatment outcome.

Given that one of the most controversial components of the widely used screening investigations is the use of mammography in women with no specific clinical or pathological features to suggest breast cancer, the evidence on this topic will be explored in a separate review (see section 7).

Methods

Study types
There was no restriction on study design.

Participants
People with malignancy of undefined primary origin undergoing initial investigations to establish a primary site

Interventions
Expert-selected panel of investigations undertaken with expert overview (i.e. a specific diagnostic strategy). The comparison is commonly used investigations performed in arbitrary order following baseline history and examination, within the current clinical structure.

Outcomes
Diagnostic yield, duration of diagnostic process, number investigations, appropriateness of investigations and patient satisfaction with care

Study selection
An initial list of studies was selected by SA. NB then selected potentially relevant studies from this list on the basis of their title and abstract. These studies were ordered and each paper was checked against the inclusion criteria.

Data extraction and synthesis
One reviewer (NB) extracted data. Only published data were included and authors were not contacted.

Quality assessment
Study quality was assessed by one reviewer (NB) using NICE checklists.

Heterogeneity assessment
There was no formal assessment of heterogeneity. Differences between studies, that could contribute to differences in their results were noted in the evidence tables.

Search results

Description of included studies
Fourteen studies were included: three case series of patients with metastatic presentation, five series of patients presenting with bone metastases and six expert reviews or clinical guidelines.

Study quality
The studies were generally of low quality, typically retrospective case series or reviews based on expert opinion. Two of the series (Kirsten et al 1987 and Le Chevalier et al 1988) probably excluded patients with primaries quickly identified via basic tests, and could underestimate the sensitivity of these basic tests. One of the case series (Losa Gaspa et al, 2002) was a prospective evaluation of a diagnostic strategy for metastatic presentation.

Evidence summary

Basic panel tests for patients presenting with metastases of undefined origin
A number of studies suggested a basic panel of diagnostic tests (see Table 4.1). There was consensus about the basic panel tests that all patients should receive: history, comprehensive physical examination, biopsy with histopathology and immunohistochemistry, complete blood count, chest X-ray (or chest CT) and biochemistry tests. Many studies included CT of the abdomen and pelvis There was disagreement about the inclusion of mammography for all women. Some studies suggested measuring serum PSA, AFP and β-HCG in all men, whereas others used these markers more selectively.

In the bone metastasis series biopsy was used selectively (often after the other initial tests), patients also received an X-ray of the affected bone and a technetium bone scan.

Diagnostic yield
The number of primary tumours identified by initial tests and further tests is summarised in Table 4.2. The proportion of treatable primary tumours identified at each stage is also summarised in Table 4.2. Breast, ovarian, prostate, head/neck, thyroid and germ cell primary tumours were considered treatable.

Of the 556 primary tumours identified overall 424 (76%) were identified by initial tests. The proportion of patients who had a primary tumour identified by initial tests (the diagnostic yield) ranged from 25% to 85% compared with 8% to 75% for those who went on to have further tests.

Losa Gaspa et al (2002) compared three levels of a diagnostic strategy in a prospective series of 221 patients presenting with metastatic cancer. The levels were: basic tests, additional tests and exhaustive tests. The diagnostic yield of basic tests was 138/221(62%), of additional tests was 24/83 (29%) and of exhaustive tests was 13/59 (22%). If CT-abdomen-pelvis were considered as part of the initial panel of tests (as is typically the case) the diagnostic yield of initial tests would have been 158/ 221 (71%).

For patients presenting with bone metastases there was good consistency in the relative yield of initial and further tests (see Table 4.2). More than 80% of primary tumours that were found were identified during initial tests . The pattern was the same for the subgroup of treatable tumours, with more than 80% of those eventually diagnosed found during the initial tests.

EXPERT STRATEGY VERSUS ARBITRARY TEST ORDER

Although no studies reported a comparison of an expert diagnostic strategy with arbitrary diagnostic test order, the evidence suggests that most primary tumours can be identified by a restricted panel of basic tests. It follows that the use of additional tests at an early stage will not add anything in most cases. Many of these additional tests have significant false positive rates, these additional false positive diagnoses could delay diagnosis in some patients.

DURATION OF DIAGNOSTIC PROCESS AND PATIENT SATISFACTION WITH CARE

These outcomes were not reported in the studies.

NUMBER AND APPROPRIATENESS OF INVESTIGATIONS

These outcomes were not reported in the studies.

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Table 4.1 Initial diagnostic tests (done in all patients)

Study	Biopsy of metastasis & histopathology	H&P	CBC	Biochemistry tests	Urinalysis	Faecal occult blood test	Chest X-ray	Bone X-ray	Bone scan	CT-abdomen	CT-pelvis	CT-thorax	Mammogram in women	serum b-HCG and AFP	serum PSA (in men)
Any presentation															
Abbruzzese 1995	X	X	X	X			X				X	X	X	In men	X
Bitran 1992		X	X	X	X		X			X	X				
Bugat 2003	X	X	X				X				In women		X	in men	X
Camara 1994	X	X	X	X		X							In women with adenocarcinoma	In patients with poorly differentiated or undifferentiated carcinoma	In men with adenocarcinoma
ESMO 2008	X	X	X	X	X	X				X	X	X	In women with axillary adenopathy	In patients with midline disease	In men with adenocarcinoma and bone metastases
Ghosh 2005	X	X	X	X	X					X		X	X		
Kirsten 1987	X	X					X								
Leonard 1993	X	X	X	X	X	X	X			X	X	X			
Losa Gaspa 2002	X	X	X	X	X		X							In men	X
NCCN 2008	X	X	X	X	X	X				X	X	X	In women with adenocarcinoma or unspecified carcinoma	In men with retroperitoneal presentation. AFP in patients with liver presentation.	In men with adenocarcinoma or unspecified carcinoma
Varadhachary 2004	X	X	X	X			X			X	X		In women with adenocarcinoma	In men with poorly differentiated or undifferentiated carcinoma. AFP when hepatocellular carcinoma is possible.	In men with adenocarcinoma and bone metastases
Bone metastasis series															
Alcalay 1995		X	X	X			X	X	X						
Jacobsen 1997	Done cautiously after other tests	X	X	X	X		X		X	X		X			X

Study	Biopsy of metastasis & histopathology	H&P	CBC	Biochemistry tests	Urinalysis	Faecal occult blood test	Chest X-ray	Bone X-ray	Bone scan	CT-abdomen	CT-pelvis	CT-thorax	Mammogram in women	serum b-HCG and AFP	serum PSA (in men)
Katigiri 1999		X	X	X	X		X	X	X						In men with osteosclerotic lesions.
Rougraff 1993	X	X	X	X				X	X	X	X	X			
Simon 1986	X	X	X	X	X		X	X	X						

Abbreviations: H&P, history and physical examination; CBC, complete blood count; CT, computed tomography; IVP, intravenous pyelogram

Table 4.2 Diagnostic yield of initial and further diagnostic tests

Study	N patients	Primaries identified	Primary tumour identified by initial tests*	Treatable cancers identified by initial tests**	Primary tumour identified by further tests*	Treatable cancers identified by further tests**
Any presentation						
Kirsten 1987	286	58/286 (20%)	-	-	58	29
Le Chevalier 1988	302	134/302 (44%)	81	not reported	53	not reported
Losa Gaspa 2002	221	175/221 (79%)	138	36	37	7
Bone metastases						
Alcalay 1995	350	109/350 (31%)	89	59	20	5
Jacobsen 1997	29	22/29 (76%)	18	6	4	1
Katigiri 1999	64	60/64 (94%)	48	17	12	1
Rougraff 1993	40	36/40 (90%)	34	2	2	0
Simon 1986	46	20/46 (43%)	16	5	4	1

* Initial tests are defined in table 1

** Treatable cancers defined as: breast, ovarian, germ cell, prostate, head/neck, thyroid,

4. Initial tests for metastases of undiagnosed primary

Last updated: 30 / 10 / 2009.

Characteristics of included studies

Abbruzzese-1995

Methods	Retrospective series of patients with suspected metastasis of unknown primary referred from community physicians to an unknown primary tumour clinic. Patients with inadequate initial diagnostic work up, obvious primary tumour or inappropriately referrals to the clinic were excluded.
Participants and Country	879 patients with suspected unknown primary tumour (including sarcoma, lymphoma and melanoma). 180 primary tumours were diagnosed in 179 patients.
Interventions	**Initial tests in all patients** Pathology review, H&P, CBC, biochemistry survey, chest x-ray, CT-abdomen-pelvis. Men: serum PSA, serum AFP and serum β-HCG Women: mammogram **Further tests according to signs, symptoms or results of initial tests** Sputum cytology, CT-chest, breast or pelvic ultrasound, bronchoscopy and GI-endoscopy.
Outcomes	**Diagnostic yield of initial tests (for identification of the primary tumour)** Pathology review 58 ,CT-abdomen-pelvis 35, Figures not reported for H&P, CBC, biochemistry survey, chest x-ray, or mammogram . **Diagnostic yield of further tests (for identification of the primary tumour)** Chest CT 20, bronchoscopy 7, breast-US 5, pelvic-US 1 **Comparison of limited versus additional evaluation** The authors argue that pathology review of outside slides, physical examination, chest radiography and mammography often provided the most information. Except for breast and pelvic ultrasound the additional studies were likely to identify only untreatable malignancies with short overall survival, such as lung or GI cancer. 55/122 of the diagnosed epithelial primary tumours were found by CT . Only 4 of these 55 were considered treatable (3 women with ovarian cancer and one patient with head/neck cancer). **Duration of diagnostic process** Not reported **Number of investigations** Not reported. **Appropriateness of investigations** Not reported **Patient satisfaction with care**

	Not reported.
Notes	Also compares the relative cost of limited and additional diagnostic evaluation. Incomplete reporting of the diagnostic yield of the individual tests: only goes into detail about CT.

Alcalay-1995

Methods	Retrospective case series of patients admitted to a single institution for the evaluation of skeletal metastasis of unknown primary between 1986 and 1995.
Participants and Country	350 patients. A primary tumour was identified in 109 patients.
Interventions	**Initial tests** H&P, CBC, biochemistry tests, bone X-ray,, chest X-ray and bone scan. **Further tests** Abdominal US, CT-abdomen, mammography, biopsy of metastasis, serum tumour markers
Outcomes	**Diagnostic yield initial tests** Bone X-ray (sclerotic appearance of metastasis): 350 tests done, 34 tumours identified (34 treatable -prostate cancer) H&P: 350 tests done, 34 tumours identified (25 treatable) Chest X-ray: 350 tests done, 21 tumours identified (none treatable). **Diagnostic yield further tests** Abdominal US: 6 tumours found (none treatable) CT-abdomen: 8 tumours found (one treatable) Mammography: 1 tumour found (treatable breast carcinoma) Biopsy of bone metastasis: 4 tumours found, (2 treatable) Serum tumour markers & mediastinal biopsy: 1 treatable tumour found **Duration of diagnostic process** **Number investigations** **Appropriateness of investigations** **Patient satisfaction with care**
Notes	

Bitran-1992

Methods	Expert review
Participants and Country	Patients with unknown primary malignancy
Interventions	**Initial tests in all patients** Minimal initial work-up is H&P, CBC, biochemistry tests, urinalysis, chest X-ray, CT abdomen-pelvis
Outcomes	No outcomes reported
Notes	

Briasoulis-2009

Methods	Expert consensus clinical guideline (European Society for Medical Oncology)
Participants and Country	Patients with CUP
Interventions	The ESMO guideline covers the diagnosis, treatment and follow-up of patients with CUP **Initial tests in all patients** Pathology review, H&P, CBC, biochemistry survey, urinalysis CT-abdomen-pelvis-thorax. **Further tests according to signs, symptoms or results of initial tests** *Patients with SCC cervical lymphadenopathy*: CT-head-neck or PET-CT Sign or symptom directed endoscopies. *Men with adenocarcinoma and bone metastases*: serum PSA *Patients with midline metastatic disease:* serum AFP and serum β-HCG. *Women with adenocarcinoma:* mammogram or breast MRI
Outcomes	Outcomes are not reported
Notes	

Bugat-2003

Methods	FNCLCC clinical guidelines, based on review of the literature and guideline group consensus.
Participants and Country	Patients with carcinoma of unknown primary site
Interventions	**Initial tests** Biopsy of metastasis and histopathology, H&P and chest X-ray. In men serum tumour markers (AFP, beta-HCG and PSA). In women mammography, CT-pelvis or pelvic US. **Further tests (depending on presentation)** CT thorax-abdomen-pelvis, testicular USD, breast US, breast MRI, serum tumour markers (AFP for liver tumours, beta-HCG in women), endoscopies, bone scan
Outcomes	No outcomes reported.
Notes	

Jacobsen-1997

Methods	Retrospective case series of patients with skeletal metastases as first sign of an unidentified primary tumour. All patients were evaluated at a single institution between 1983 and 1993.
Participants and Country	29 patients. Primary tumours were diagnosed antemortem in 22/29 patients and postmortem in 2/29.
Interventions	All patients were evaluated non- uniformly - there was no established diagnostic protocol although all had physical examination, chest X-ray and biochemistry tests.
Outcomes	**Diagnostic yield** Physical examination : done in all cases, 2 primary tumours identified (2 treatable tumour - breast carcinoma) Chest X-ray : Done in all cases, 10 primary tumours identified (none treatable)

	Abdominal US : 3 primary tumours identified (1 treatable) Intravenous pyelogram: done in 2 patients, 1 primary tumour identified (not treatable) Biopsy of metastasis: 6 primary tumours identified (4 treatable) **Duration of diagnostic process** Not reported **Number investigations** Not reported **Appropriateness of investigations** Not reported **Patient satisfaction with care** Not reported
Notes	The authors propose a diagnostic protocol, as a more efficient alternative to a disorganised approach. H&P, CBC, urinalysis, PSA (in men), chest X-ray (and/or chest-CT), bone scan, CT-abdomen or abdominal US and finally biopsy of the most accessible skeletal metastasis. Biopsy of skeletal metastasis should be done cautiously in the event that the tumour is a bone sarcoma - ill planned biopsy could comprise a later limb sparing surgery. Biopsy of metastases of renal cell carcinoma should be avoided if possible, due to abundant vascularized.

Katagiri-1999

Methods	Retrospective series of patients presenting with skeletal metastases as the first sign of unknown primary cancer, treated between 1990 and 1996 at a single institution.
Participants and Country	64 patients. The primary tumour was found antemortem in 56/64 patients (88%).
Interventions	**Initial tests (in all or almost all patients)** H&P, biochemical survey, urinalysis, chest X-ray, bone X-ray, bone scan, serum tumour markers (CEA, CA19-9, CA125, AFP), chest-CT, CT-abdomen, **Further tests** *In male patients with osteosclerotic lesions:* serum PAP and PSA *According to signs/symptoms:* Thyroid gland US, gastroscopy, colonoscopy or barium enema, mammography Bone biopsy, tissue biopsy.
Outcomes	**Some primary tumours were detected on both initial and further tests** **Diagnostic yield of initial tests** H&P: 64 tests, 17 with findings, 17 treatable tumours Lab tests did not help identify primary lesions Chest-CT: 57 tests, 39 with findings, no treatable tumours Abdominal-CT: 56 tests, 20 with findings, no treatable tumours Pelvic-CT: 56 tests, no findings **Diagnostic yield of further tests** Abdominal US: 49 tests, 12 with findings, no treatable tumours identified

	Thyroid gland US: 8 tests, 5 with findings, 1 treatable tumour Symptom directed endoscopy: 35 tests, 5 with findings, no treatable tumours. **Number investigations** Not reported **Appropriateness of investigations** Not reported **Patient satisfaction with care** Not reported
Notes	

Kirsten-1987

Methods	Retrospective series of patients presenting with adeno or undifferentiated carcinoma metastases with the primary site not apparent after careful H&P and chest X-ray. All patients presented to a single institution between 1977 and 1982. Patients presenting with upper neck node metastases were excluded, as this group were referred to the head and neck team and managed as head and neck primary cancer.
Participants and Country	286 patients.
Interventions	**Initial tests in all patients** H&P, CBC, biochemistry survey, chest x-ray, . **Further tests according to signs, symptoms or results of initial tests** Pathology review and IHC, intravenous pyelogram, mammogram, barium meal, barium enema, CT-abdomen-pelvis, CT-chest, abdominal pelvic ultrasound, bronchoscopy and GI-endoscopy, serum AFP, serum acid phosphatase and serum β-HCG.
Outcomes	**Diagnostic yield of further tests** Primary site was identified in 58/286 patients (20%). Treatable primary site was identified in 29/286 patients (10%) **Duration of diagnostic process** Not reported **Number investigations** Not reported for **Appropriateness of investigations** **Patient satisfaction with care**
Notes	Pre PSA study.

Le_x002d_Chevalier-1988

Methods	A retrospective consecutive case series of patients presenting with unknown primary cancer and metastases who also had an autopsy.
Participants and Country	302 patients.
Interventions	**Initial tests** All patients had chest X-ray, most (85%) had a biopsy of their metastasis

	Further tests Intravenous pyelogram, thyroid gland scan, barium enema, bronchoscopy, upper GI endoscopy, lower GI endoscopy, mammography and tumour markers (serum AFP. β-HCG and prostatic acid phosphatase).
Outcomes	A total of 82 primary tumours were found while the patient was still alive. **Diagnostic yield of initial tests (done in all cases)** Chest X-ray identified 31 primary tumours, histology 50 **Diagnostic yield of further tests (only done in selected patients)** Intravenous pyelogram 9, thyroid gland scan 4, barium enema 7, bronchoscopy 19, upper GI endoscopy 6, lower GI endoscopy 7 and mammography 1. Some primary tumours were evident on more than one diagnostic test **Duration of diagnostic process** Not reported **Number investigations** Not reported for individual patients **Appropriateness of investigations** Not reported **Patient satisfaction with care** Not reported
Notes	

Leonard-1993

Methods	The paper is an expert review about diagnosis of patients who presented with metastatic non-squamous carcinoma of unknown site Includes some data from: Nystrom JS, Weiner JM, Heffelfinger-Juttiner J, et al: Metastatic and histologic presentation of unknown primary cancer. Seminars in Oncology 4: 53-58, 1977
Participants and Country	266 patients
Interventions	Proposes a panel initial tests.
Outcomes	Outcomes not reported
Notes	

Losa-2002

Methods	Prospective series of consecutive patients presenting with metastatic cancer to a single institution between 1992 and 1997.
Participants and Country	221 patients.
Interventions	**Initial tests in all patients** Biopsy and histopathology of accessible lesions, H&P, CBC, biochemistry survey, chest x-ray, serum PSA, serum AFP and serum β-HCG **Further tests according to signs, symptoms or results of initial tests** CT-thorax, endoscopies, bronchoscopy, bone scan, MRI Women: mammogram, CT-abdomen.

Outcomes	**Diagnostic yield of initial tests for identification of the primary** 138 primary tumours diagnosed, out of 221 patients. Physical examination revealed 75 primary tumours, chest X-ray 83, histopathology 47 and tumour markers (PSA, AFP and β-HCG) 15. **Diagnostic yield of further tests for identification of the primary** An additional 21 primary tumours were diagnosed out of 83 patients. **Duration of diagnostic process** Not reported **Number investigations** Not reported **Appropriateness of investigations** Not reported **Patient satisfaction with care** Not reported
Notes	Additional information available in F. Losa-Gaspa's PhD thesis

Rougraff-1993

Methods	Prospective case series of consecutive patients presenting with skeletal metastases of unknown origin, presenting to a single orthopaedic surgery department.
Participants and Country	40 patients
Interventions	**Initial tests** H&P, biochemistry tests, CBC, X-ray of the involved bone, bone scan, chest X-ray, CT-chest-abdomen-pelvis, and finally open biopsy of the most accessible lesion. **Further tests** additional tests were ordered if the history or physical examination directed the search for a primary away from the chest and abdomen.
Outcomes	**Diagnostic yield of initial tests** 34/40 (85%) **Diagnostic yield of further tests** 2/6 (33%) **Duration of diagnostic process** Not reported **Number investigations** Not reported **Appropriateness of investigations** Not reported **Patient satisfaction with care** Not reported
Notes	

Simon-1986

Methods	Retrospective case series of patients with skeletal metastasis of unknown origin,referred to a single orthopaedic surgeon between 1976 and 1984.
Participants and Country	46 patients. Primary tumours were identified in 20 patients.
Interventions	**Intial tests in all patients** H&P, biochemistry tests, chest X-ray, bone scan, intravenous pyelogram, biopsy of metastasis **Further tests** Laparotomy, CT-abdomen
Outcomes	**Diagnostic yield of initial tests** In 46 patients initial tests identified 16 primary tumours (5 treatable) **Diagnostic yield of further tests** In 30 patients further tests identified 4 primary tumours (1 treatable) **Duration of diagnostic process** Not reported **Number investigations** Not reported **Appropriateness of investigations** Not reported **Patient satisfaction with care** Not reported
Notes	

Varadhachary-2004

Methods	Expert review
Participants and Country	Patients with a biopsy proven unknown primary cancer
Interventions	**Initial tests** H&P, biochemistry survey, CBC, chest X-ray, mammography (in women), PSA (in men), CT abdomen-pelvis **Further tests** Sign or symptom directed endoscopy *Patients with suspected occult head/neck cancer:* PET-CT *Women with adenocarcinoma:* mammography *Women with isolated axillary node metastases:* breast MRI *Men with adenocarcinoma and bone metastases:* PSA *Men with undifferentiated carcinoma or poorly differentiated carcinoma:* AFP and β-HCG
Outcomes	No outcomes reported.
Notes	

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5. Serum tumour marker tests for cancer of unknown primary

Last updated: 7 / 10 / 2009.

Short summary

There was very little evidence about the use of serum tumour markers in the diagnosis of primary tumours in patients with metastases of unknown primary.

Evidence suggests that elevated levels of the serum tumour markers AFP and PSA have reasonably high specificity for metastatic liver/germ cell and prostate tumours respectively. It follows that measurement of AFP and PSA could be useful in diagnosing these primary tumours in patients presenting with metastatic cancer.

One small study reported elevated β-hCG had intermediate sensitivity and specificity for the detection of metastatic germ cell tumours. Only three patients had confirmed germ cell tumours in this study.

Elevated serum CEA and CA 19-9 had a low specificity for the primary tumour site in patients with metastatic cancer, suggesting they would not be useful in diagnosing a primary tumour.

Evidence, from ten patients in a single study, suggests normal serum CA-125 could be used to rule out metastatic ovarian cancer. The low specificity of elevated serum CA-125 in this study suggests it would not be useful in diagnosing ovarian cancer.

Rationale

Identification of abnormally elevated levels of serum tumour markers can sometimes reinforce other evidence, to achieve a more secure diagnosis of the type of cancer present. Timely use of appropriate marker tests in some circumstances can therefore be associated with significant clinical gain.

In general however, tumour marker measurements are not generally recommended for diagnosis due to their low sensitivity and specificity. Nevertheless, their use for this purpose has increased in recent years, due to their routine availability on automated analysers in almost all clinical biochemistry laboratories. Inappropriately requested tumour marker results can lead to unnecessary and costly further investigations as well as causing needless distress and worry to patients. Inappropriate interpretation of tumour marker results (for instance, basing treatment decisions on particular patterns of markers, extrapolating from situations where the primary tumour site is known,) may result in incorrect management.

Clarifying which tumour markers, in what combination, should be measured and when, and what their limitations are, are important issues that are highly relevant to the diagnosis and management of cancers of unknown primary.

Methods

Study types

Any study design was considered for inclusion.

Target condition

Diagnosis of primary tumour and duration of the diagnostic process.

Participants

People with malignancy of undefined primary origin undergoing initial diagnostic tests.

Index tests

A panel of frequently used tumour markers: AFP, HCG, PSA, CEA, CA125,CA19-9.

Reference standard

The ideal reference standard was histopathologic confirmation of the primary tumour. In some cases, however, the definitive diagnosis of the primary was based on a combination of clinical and radiological following or the reference standard was not reported.

Study selection

An initial list of studies was selected by SA. NB then selected potentially relevant studies from this list on the basis of their title and abstract. These studies were ordered and each paper was checked against the inclusion criteria.

Data extraction and synthesis

One reviewer (NB) extracted data. Only published data were included and authors were not contacted. Data about the sensitivity and specificity of individual tumour markers were extracted into tables. Statistical meta-

analysis was not done, instead ranges of sensitivity and specificity were reported.

QUALITY ASSESSMENT

Study quality was assessed by one reviewer (NB) using the QUADAS checklist for diagnostic studies, incorporated in Cochrane Review Manager software.

HETEROGENEITY ASSESSMENT

Heterogeneity (variation between studies) was not investigated statistically.

Search results

The literature search identified 211 studies and nine were included in the final review. The studies were case series; two examining AFP, one β-hCG, three PSA, five CEA, two CA 19-9 and three CA-125.

STUDY QUALITY

Evidence about serum tumour markers to predict the primary tumour site in metastatic cancer was limited to series of patients presenting with metastases of initially undefined primary, or retrospective reviews of patients with metastases. Some studies used serum tumour markers as prognostic factors for survival or to predict treatment response: these studies will be included in the relevant review (topic 25).

In some of the included case series it was highly likely that serum tumour marker tests were targeted at patients with particular metastatic presentations, and not used in all patients. The numbers of patients receiving each tumour marker test did not always correspond with the total number of patients.

Summary of evidence

DIAGNOSIS OF THE PRIMARY TUMOUR

Studies typically used a single cut-off value to discriminate elevated from normal tumour marker levels. Some studies did not report this threshold value. Differences between studies in the reported sensitivity / specificity could be partly explained by the use of different cut-off values. Using lower cut-off values would give higher sensitivity and the expense of specificity. In practice multiple cut-off values could be used: for example a low cut-off value with high sensitivity would be useful in ruling out a diagnosis whereas a high cut-off value (with high specificity) could be used to rule in a diagnosis.

Usefulness of serum tumour markers

Guidelines for the management of CUP (see tables 5.1 and 5.2) recommend the measurement of serum β-hCG and AFP in both men and women as well as PSA in men and CA-125 in women (depending on presentation). Losa Gaspa et al (2002) reported that serum tumour markers (AFP, β-hCG and PSA) were elevated in 33/153 patients presenting with metastatic cancer and led to a primary tumour diagnosis in 15/153 (10%).

Alpha-fetoprotein (AFP)

Tsukushi et al (2006) reported relatively high sensitivity (81%) and specificity (98%) of elevated serum AFP for primary liver tumours in patients presenting with bone metastases . Losa Gaspa et al (2002) reported elevated serum AFP had a sensitivity and specificity of 50% and 96% respectively for primary germ cell or liver tumours in patients with metastatic cancer.

β-subunit of human chorionic gonadotrophin (β-hCG)

Losa Gaspa et al (2002) reported that elevated β-hCG had intermediate sensitivity (67%) and specificity (75%) for metastatic germ cell tumours. Only three patients in this series had germ cell tumours.

Prostate-specific antigen PSA

PSA had high sensitivity and specificity for primary prostate cancer in three studies. Estimates of sensitivity ranged from 85% to 92% (Losa Gaspa, 2002; Destombe et al 2007; Tsukushi et al 2006). A single study reported specificity of 98% (Losa Gaspa et al 2002). Only one of the studies reported the cut-off value used (4 ng/ml, Tsukushi et al 2006), although Destombe et al (2007) provided an PSA ROC curve, suggesting they had investigated a number of cut-off values.

NICE clinical guidelines for prostate cancer published in 2008 suggest that elevated serum PSA in men presenting with bone metastases is almost diagnostic of metastatic prostate cancer. The guidelines recommend that: *"If the clinical suspicion of prostate cancer is high, because of a high PSA value and evidence of bone metastases (identified by a positive isotope bone scan or sclerotic metastases on plain radiographs), prostate biopsy for histological confirmation should not be performed, unless this is required as part of a clinical trial."* The guideline does not define "high PSA value".

Carcinoembryonic antigen (CEA)

Three studies (Losa Gaspa et al, 2002; Tsukushi et al, 2006; Koch & McPherson, 1981; De Wit et al, 1991) examined elevated levels of serum CEA to discriminate between primary tumour sites in patients with metastatic cancer (using cut-off values from 5 to 10 ng/ml). CEA had low specificity for the primary tumour sites investigated, suggesting it is not useful identifying the primary site. Varachadry et al (2004) reported that measurement of CEA in a series of 147 patients with CUP did not help in establishing the primary tumour site.

Two of the studies (Tsukushi et al, 2006; Koch & McPherson 1981) reported reasonable sensitivity for colorectal tumours (76% to 82%), suggesting a potential role for CEA in ruling out a colorectal primary tumour if a low enough cut-off value were used.

Carbohydrate antigen 19-9 (CA 19-9)

Two studies examined the tumour marker CA 19-9 in patients presenting with metastatic cancer. Tsukushi et al (2006) did not in identify a primary tumour site consistently associated with elevated CA 19-9 patients presenting with bone metastases. Losa Gaspa et al (2002) reported that elevated CA 19-9 had a sensitivity of 80% for metastatic pancreatic cancer, suggesting a potential role for CA 19-9 in ruling out metastatic pancreatic cancer (CA 19-9 was raised in 4/5 patients with pancreatic cancer). Specificity was low however, CA 19-9 was raised in 30/77 (40%) patients without a pancreatic primary tumour, suggesting elevated CA 19-9 is not diagnostic of pancreatic primary tumour.

Cancer antigen 125 (CA-125)

Losa Gaspa et al (2002) reported elevated serum CA-125 in all ten women with metastatic ovarian cancer in their case series. This high sensitivity (100%) suggests normal serum CA-125 could rule out an ovarian primary tumour. The same study reported a low specificity (30%) of elevated CA-125 for ovarian cancer. According to this study serum CA-125 would not be useful in diagnosing an ovarian primary tumour, as elevated CA-125 was often seen in patients with other primary tumour sites.

De Wit et al (1991) reported low sensitivity and specificity (37% and 55% respectively) of CA-125 for breast cancer in a series of patients with metastatic adenocarcinoma.

Duration of the diagnostic process

None of the studies reported the duration of the diagnostic process.

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Table 5.1 Guideline recommendations for routine serum tumour markers - Men

Guideline	Last updated	β-hCG	AFP	PSA	CEA	CA 19-9	CA 125
NCCN* (USA)	2008	Mediastinal or retroperitoneal presentations	Mediastinal, retroperitoneal or liver presentations	In all cases except brain or liver presentations; not in men < 40 years with lymph node or retroperitoneal presentations	-	-	-
FNCLCC†	2006	In all cases	In all cases	In all cases	-	-	-
ESMO	2007	In those with midlinemetastatic disease	In those with midlinemetastatic disease	In men with bone metastases.	-	-	-

* For adenocarcinoma or carcinoma not otherwise specified, of unknown primary.
†For adenocarcinoma or undifferentiated carcinoma of unknown primary.

Table 5.2 Guideline recommendations for routine serum tumour markers - Women

Guideline	Last updated	β-hCG	AFP	PSA	CEA	CA 19-9	CA 125
NCCN*	2008	In those with mediastinal presentation	In those with mediastinal or liver presentations	-	-	-	In those with inguinal node, chest, pleural, peritoneal or retroperitoneal presentations
FNCLCC†	2006	In those with lung metastases	In those with undifferentiated liver metastases	-	-	-	-
ESMO	2007	In those with midlinemetastatic disease	In those with midlinemetastatic disease	-	-	-	-

* For adenocarcinoma or carcinoma not otherwise specified, of unknown primary.
†For adenocarcinoma or undifferentiated carcinoma of unknown primary.

Table 5.3 Diagnostic accuracy of serum AFP for primary tumour tissue of origin

Study	Population	N	cutoff value	Lung (Sn, Sp)	Breast (Sn, Sp)	Prostate (Sn, Sp)	Stomach (Sn, Sp)	Liver (Sn, Sp)	Germ cell or liver (Sn, Sp)	Colon (Sn,Sp)
Tsukushi 2006	Patients with presenting skeletal metastases	74	20 ng/ml	0%, 60%	6%, 68%	N.R.	11%, 72%	81%, 96%	N.R.	N.R.
Losa Gaspa 2002	Patients presenting with metastases and initially undefined tumour	87	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	50%, 96%	N.R.

Table 5.4 Diagnostic accuracy of serum β-hCG for the diagnosis of primary tumour tissue of origin

Study	Population	N	cutoff value	Lung (Sn, Sp)	Breast (Sn, Sp)	Prostate (Sn, Sp)	Stomach (Sn, Sp)	Liver (Sn, Sp)	Kidney (Sn, Sp)	Colon (Sn,Sp)	Germ cell tumour (Sn, Sp)
Losa Gaspa 2002	Patients presenting with metastases and initially undefined tumour	39	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	67%, 75%

Abbreviations: N.R. not reported; Sn, sensitivity; Sp, specificity;

Table 5.5 Diagnostic accuracy of serum PSA for primary tumour tissue of origin

Study	Population	N	cutoff value	Prostate (Sn, Sp)
Destombe 2006	Patients with bone metastases of unknown primary	32	N.R.	85%, Sp N.R.
Tsukushi 2006	Patients with presenting skeletal metastases	30	4 ng/ml	90%, Sp N.R.
Losa Gaspa 2002	Patients presenting with metastases and initially undefined tumour	70	N.R.	92%, 98%

Abbreviations: PSA, prostate specific antigen; N.R., not reported; Sp, specificity; Sn, Sensitivity;

Table 5.6 Diagnostic accuracy of serum CEA for primary tumour tissue of origin

Study	Population	N	cutoff value	Lung (Sn, Sp)	Breast (Sn, Sp)	Prostate (Sn, Sp)	Pancreas (Sn, Sp)	Liver (Sn, Sp)	Kidney (Sn, Sp)	Stomach (Sn, Sp)	Colon (Sn,Sp)	Rectosigmoid (Sn, Sp)	Ovary (Sn, Sp)
Tsukushi 2006	Patients with presenting skeletal metastases	238	5 ng/ml	64%, 54%	52%, 47%	35%, 46%	N.R.	17%, 45%	0%, 45%	48%, 47%	80%, 50%	N.R.	N.R.
De Wit 1991	Patients with adenocarcinoma metastases of known primary	87	5 ng/ml	N.R.	41%, 68%	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Koch 1981	Patients with metastases of known primary	432	10 ng/ml	39%, 37%	52%, 39%	N.R.	55%, 39%	N.R.	N.R.	52%, 39%	76%, 45%	82%, 44%	29%, 39%
Koch 1981	Patients with metastases of initially unknown primary	34	10 ng/ml	63%, 40%	0%, 40%	N.R.	29%, 40%	0%, 40%	0%, 40%	0%, 40%	N.R.	N.R.	67%, 40%
Losa Gaspa 2002	Patients presenting with metastases and initially undefined tumour	102	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.	Any GI cancer: 39%, 50%	Any GI cancer: 39%, 50%	Any GI cancer: 39%, 50%	N.R.

Abbreviations: N.R. not reported; Sn, sensitivity; Sp, specificity;

Table 5.7 Diagnostic accuracy of serum CA 125 for primary tumour tissue of origin

Study	Population	N	cutoff value	Ovary (Sn, Sp)	Lung (Sn, Sp)	Breast (Sn, Sp)	Stomach (Sn, Sp)	Liver (Sn, Sp)	Kidney (Sn, Sp)	Colon (Sn,Sp)
Tsukushi 2006	Patients with presenting skeletal metastases	238	35 U/ml	N.R.	63%, 65%	27%, 38%	60%, 57%	N.R.	N.R.	N.R.
Losa Gaspa 2002	Patients presenting with metastases and initially undefined tumour	49	N.R.	100%, 31%	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
De Wit 1991	Patients with adenocarcinoma metastases of known primary	83	35 U/ml	N.R.	N.R.	37%, 55%	N.R.	N.R.	N.R.	N.R.

Table 5.8 Diagnostic accuracy of serum CA 19-9 for primary tumour tissue of origin

Study	Population	N	cutoff value	Lung (Sn, Sp)	Breast (Sn, Sp)	Prostate (Sn, Sp)	Pancreas (Sn, Sp)	Stomach (Sn, Sp)	Liver (Sn, Sp)	Kidney (Sn, Sp)	Colon (Sn,Sp)
Tsukushi 2006	Patients with presenting skeletal metastases	182	37 U/ml	34%, 72%	23%, 68%	21%, 69%	N.R.	36%, 71%	35%, 70%	13%, 69%	37%, 71%
Losa Gaspa 2002	Patients presenting with metastases and initially undefined tumour	82	N.R.	N.R.	N.R.	N.R.	80%, 61%	N.R.	N.R.	N.R.	N.R.

5. Serum tumour marker tests for cancer of unknown primary

Last updated: 7 / 10 / 2009.

Characteristics of included studies

De-Wit-1991

Clinical setting	A consecutive series of patients with metastatic cancer being treated at a single institution.
Participants and Country	87 patients: 49 with breast cancer and 38 with metastatic adenocarcinoma of other primary site: lung (4 patients), pancreas(5), colon (7), stomach (3), ovary (10), prostate (3) and six others.
Study design	Retrospective case series
Target condition	Identification of breast cancer. Reference standard is not reported.
Tests	Serum tumour markers: CEA (threshold 5 µg/L) and CA 125 (35 U/ml).
Follow up	Not reported.
Notes	

Destombe-2007

Clinical setting	Patients referred to a single institution for evaluation of one or more bone metastases between1990 and 2000. All underwent bone scan, chest X-ray and abdominal ultrasound scan. CT and tumour marker tests were done if clinically indicated. 107/152 had bone biopsy, 80/152 had other biopsies.
Participants and Country	152 patients. France
Study design	Retrospective case series.
Target condition	Identification of the primary site, reference standard (available in a sub-set of cases) was the histopathology of the primary tumour.
Tests	PSA, CEA, CA 15-3
Follow up	Not reported
Notes	

Katagiri-1999

Clinical setting	Patients with bone metastasis of unknown primary treated at any of three institutions between 1990 and 1996. None had prior history of malignancy. 30/213 had biopsy of bone metastasis

Participants and Country	213 patients. 64/213 had a primary site detected and were included in the analysis. Japan
Study design	Retrospective case series
Target condition	Identification of the primary site, reference standard was: biopsy of the primary tumour (18), or combination of CT and biopsy of the bone lesion (15), evaluation of the GI tract (5), CT and tumour marker (AFP) elevation (3), autopsy (3), chest X-ray and lung biopsy (2), chest X-ray and skeletal biopsy (2), chest X-ray and skin biopsy (1), skeletal biopsy (1), physical examination and CT(1), and CT alone (1).
Tests	β-hCG (threshold >10 ng/ml) , AFP (threshold > 0.5 mIU/ml) , CEA (threshold > 5.0 ng/ml), CA 19-9 (threshold > 37 U/ml).
Follow up	Not reported.
Notes	

Kirsten-1987

Clinical setting	Patients referred to a medical oncology unit between 1977 and 1982, with undifferentiated or adenocarcinoma of unknown primary after careful H&P including pelvic examination and chest X-ray. Many had more extensive initial investigations.
Participants and Country	290 patients. Serum AFP and β-hCG levels were measured in 124 and 99 patients respectively. Australia.
Study design	Retrospective case series.
Target condition	Primary tumour site, overall survival. Primary site was histologically confirmed in a subset of patients.
Tests	β-hCG (groups: < 25 ng/ml, 25 to 50 ng/ml, > 50 ng/ml) , AFP (groups: < 25 mIU/ml, 25 to 50 mIU/ml, > 50 ng/ml)
Follow up	Not reported
Notes	

Koch-1981

Clinical setting	Patients registered as having CUP in a single cancer registry between 1975 and 1979. A second group of patients with metastases and histologically confirmed primary site were included for comparison
Participants and Country	34 patients with CUP, . Canada
Study design	Population based observational study.
Target condition	Location of the primary site. Primary site was eventually identified in all patients (30 at autopsy, 3 though surgery and 1 during prolonged follow up).
Tests	CEA (threshold > 10 ng/ml). Individual CEA levels are reported for each patient.
Follow up	Complete (all CUP patients had primary site discovered).
Notes	No colorectal primary tumours amongst the CUP group

Loi-2004

Clinical setting	All patients that had a tumour marker test ordered at a single major referral centre during a 3 month period.
Participants and Country	373 tumour marker tests in total, 71 for diagnosis. UK

Study design	Retrospective audit
Target condition	Appropriateness of tumour marker test. Usefullness of an abnormal test result
Tests	Serum tumour marker tests: CA 15-3, CA-125, CA 19-9, CEA and AFP.
Follow up	Not reported
Notes	

Losa-2002

Clinical setting	Patients admitted to a single institution with metastatic cancer without an identified primary ,between 1992 and 1997.
Participants and Country	221 patients. Spain
Study design	Retrospecitve case series.
Target condition	Primary tumour site. Referenence standard test was not specified.
Tests	Serum tumour marker tests (threshold values not reported): β-hCG, AFP, PSA, CEA, CA 125, CA 19-9.
Follow up	Not reported
Notes	Spanish language with English abstract, although data tables are self explanatory.

Tsukushi-2006

Clinical setting	Patients treated for skeletal metastases at either of two institution between 1992 and 2002.
Participants and Country	458 patients. 14/458 (3%) had CUP (no primary was ever identified). Japan
Study design	Retrospetive case series.
Target condition	Identification of the primary tumour organ of origin. Reference standard was not reported
Tests	serum tumour markers: PSA, CEA, CA 19-9, AFP and CA-125
Follow up	Not reported
Notes	

Varadhachary-2004

Clinical setting	A consecutive series of patients with CUP treated at a single cancer centre.
Participants and Country	147 patients.USA
Study design	Retrospective case series
Target condition	identification of the primary tumour site. The reference standard test was not reported.
Tests	Serum CEA levels (abnormal was defined as >10 ng/mL)
Follow up	Not reported
Notes	This paper is an expert review which mentions some of the authors' experiences at their own cancer centre. They report that CEA was raised in 41/147 of the patients in their series but it did not help establish the primary site.

Yonemori-2006

Clinical setting	Patients with CUP treated with platinum chemotherapy (plus taxanes in 66% of cases) at a single institution between 1997 and 2005
Participants and Country	93 patients. Most had lymph node metastasis (78%). Japan.
Study design	Retrospective case series.
Target condition	Response to chemotherapy, assessed using WHO criteria for treatment response. Overall survival
Tests	β-hCG (threshold >10 ng/ml) , AFP (threshold > 0.5 mIU/ml) , CEA (threshold > 5.0 ng/ml), CA 19-9 (threshold > 37 U/ml).
Follow up	Not reported. Survival was analysed up to 3 years after treatment, at the time of analysis 64/93 patients had died
Notes	

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6. Upper- and lower-GI endoscopy as an initial test in people with provisional diagnosis of CUP adenocarcinoma, without symptoms or signs suggesting a gut primary tumour

Last updated: 30 / 10 / 2009.

Short summary

Literature searches found no published evidence about the routine use of diagnostic gastrointestinal (GI) endoscopy in patients with metastatic adenocarcinoma of unknown primary and without GI signs or symptoms. Any estimate of the diagnostic yield of GI endoscopy depends heavily on the prior probability of GI tumours in this population, and there was no reliable source of this information.

Four studies reported the diagnostic yield of GI endoscopy in patients with CUP, but without specifying histology or presentation. Overall the yield was 17% for upper GI endoscopy and 7% for colonoscopy. It was unclear from these series what proportion of patients had signs or symptoms suggestive of a GI primary tumour.

Evidence from a systematic review suggests that mortality occurs as a result of diagnostic upper GI endoscopy in 1 in 12000 patients, with morbidity in 1 in 500 patients. For diagnostic colonoscopy the estimated mortality rate was 1 in every 5000 patients with morbidity approximately 1 in 420.

Rationale

Upper and lower gastrointestinal endoscopy (oesophagogastroduodenoscopy - OGD and colonoscopy) are standard investigations to detect possible primary cancer when well-recognised symptoms or signs are present. In the absence of symptoms or signs suggesting a gut origin for metastatic cancer, OGD and colonoscopy will sometimes reveal an occult primary tumour. There is uncertainty about whether the detection rate from universal OGD and colonoscopy (and subsequent possible benefit from site-specific treatment) is sufficiently high to justify the disadvantages of this approach, which include cost, delays in patient pathway, and morbidity.

Methods

Study types

No limits were placed on study design: any relevant study was considered for inclusion.

Target condition

Identification of primary tumours of the gastrointestinal tract. Data were extracted from studies abut the diagnostic rate and complications of GI endoscopy. Diagnostic rate was defined as the proportion of endoscopies that identified a primary tumour (the true positive rate).

Participants

People with provisional diagnosis of malignancy of undefined primary origin who are asymptomatic of GI symptoms and have histology showing adenocarcinoma undergoing initial diagnostic tests.

Index tests

Upper and lower gastrointestinal (GI) endoscopy: oesophagogastroduodenoscopy (OGD) and colonoscopy. Usually tumours identified on endoscopy would biopsied with histopathological examination.

Reference standard

This review was concerned with detection rate of GI endoscopy, rather than its sensitivity or specificity. It was assumed that the combination of GI endoscopy with biopsy and histopathology was 100% specific with unknown sensitivity. There was no reference standard test that was applied equally to patients regardless of the result of their endoscopy.

Study selection

An initial list of studies was selected by the information specialist (SA). One reviewer (NB) then selected potentially relevant papers from this list on the basis of their title and abstract. These studies were ordered and each paper was check against the inclusion criteria. Reference lists of included papers were also checked for other relevant studies. In the absence of good evidence

about complications of endoscopy in CUP, a high level search of MEDLINE was conducted for reviews of the safety of GI endoscopy in the general population. CUP case series, identified for other questions in the guideline, were also checked for data about the diagnostic rate of GI endoscopy.

Data extraction and synthesis

Two reviewers, NB and SOC, extracted data from the papers.

Quality assessment

The quality of the studies was appraised using the modified QUADAS checklist included the Cochrane Review Manager program.

Heterogeneity assessment

There was no statistical assessment of heterogeneity (differences between studies).

Search results

The literature search identified 34 papers.Twelve papers were included in the final review.

Study quality

No directly relevant studies were found. Indirect evidence about the potential diagnostic yield of endoscopy came from retrospective case series of patients with metastases of unknown primary. Evidence about the complications of GI endoscopy in general came from well conducted systematic reviews of large observational studies.

Summary of evidence

Probability of a GI primary tumour in patients without gastrointestinal signs or symptoms

Kirsten et al (1987) reported the diagnostic yield of various tests in a series of patients with metastatic adenocarcinoma or undifferentiated carcinoma of unknown primary site. Kirsten (1987) found the rate of detection of colon or gastric primary (by any means) in patients with CUP, without abdominal or hepatic presentation, was 6/191 (3%). In patients presenting with adenocarcinoma metastases histology, regardless of signs or symptoms, the probability of finding a gastrointestinal primary tumour (by any means) was 6/68 (9%) and in those with poorly differentiated adenocarcinoma histology it was 3/62 (5%). There was no information about the relationship between adenocarcinoma histology and gastrointestinal signs or symptoms.

The Kirsten et al (1987) study suggests a prior probability of 3% of a detectable GI primary tumour in patients without GI presentation, regardless of histology. The probability of finding a GI tumour in patients with adenocarcinoma histology and without GI symptoms cannot be estimated from Kirsten et al (1987).

In postmortem studies of patients with CUP, a primary tumour of the gastrointestinal tract was found in between 7% and 33% of patients (Chorneyko, 2008). Chorneyko (2008) did not report the proportion of patients with adenocarcinoma histology and gastrointestinal tract tumours, but from the reported figures this could have been as high as 47% (or as low as 0%).

Diagnostic yield of gastrointestinal endoscopy

In the absence of published evidence, an estimate of the diagnostic yield of routine GI endoscopy in patients without GI signs or symptoms is given by:

*Diagnostic yield = Prior probability of a detectable GI cancer * sensitivity of GI endoscopy*

Using the prior probability of 3% from Kirsten et al (1987) and arbitrary sensitivity of 92% (Whitlock et al 2008) gives a diagnostic yield of 2.7%. This estimate of diagnostic yield is heavily dependent upon the prior probability. Increasing this value to 47% (the upper value in postmortem studies) gives a diagnostic yield of around 43%.

Four small case series reported the diagnostic yield of upper and lower GI endoscopy in patients with metastatic cancer of unknown origin (Katagiri et al 1999 ; Kirsten et al 1987: Schapira et al 1995; Yamada et al, 1975), although these were probably symptom directed as only selected patients had GI endoscopy (see Tables 6.2 and 6.3). Only one of the series (Yamada et al, 1975) reported data for patients with CUP adenocarcinoma. For OGD the diagnostic rate was 17% (Katagiri et al 1999), for gastroscopy it ranged from 0 to 50% (Kirsten et al, 1987; Schapira et al, 1995; Yamada et al, 1975). For colonoscopy and flexible sigmoidoscopy the rates were 0 to 9% and 8% respectively. Combining the studies gives a diagnostic yield of 17% for upper GI endoscopy and 7% for colonoscopy.

Timing of gastrointestinal endoscopy

The PICO question for this review refers to endoscopy as part of initial diagnostic testing, but the timing of GI endoscopy was unclear in the included studies. Typically only a subset of the patients in each study had GI endoscopy (see Tables 6.2 and 6.3), which suggests it done as an additional test in selected patients.

Morbidity of gastrointestinal endoscopy

Froehlich et al (1999) published a systematic literature review of the complications of diagnostic gastrointestinal endoscopy (see tables 6.4 and 6.5). They included studies with a total of 576647 upper GI endoscopies and 103372 colonoscopies. For upper GI endoscopy mortality rates ranged from 0 to 0.04% (pooled estimate 0.008%) with total morbidity rates from 0.14% to 0.20% (pooled estimated 0.20%). A UK audit (Quine et al, 1994) of

upper GI endoscopy reported a higher mortality rate of 0.05% (or 1 in every 2000 procedures).

For diagnostic colonoscopy mortality rates ranged from 0 to 0.06% (pooled estimate 0.019%) with total morbidity rates from 0% to 0.25% (pooled evidence 0.24%). More than half of the reported adverse events were cardio-respiratory complications as a result of intra-venous sedation before the GI endoscopy. Evidence suggests that if both procedures were to be done routinely, upper GI endoscopy, being the less morbid procedure, should be done first.

DIAGNOSTIC DELAYS

There was no evidence about the effect of GI endoscopy on diagnostic delays.

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Table 6.1 GI signs and symptoms in CUP series

Study	N	Proportion with adenocarcinoma histology	GI primary tumour confirmed	Hepatic presentation	Peritoneal presentation / ascites	Abdominal distention	Diarrhoea / constipation	Nausea / vomiting	Abdominal / pelvic mass
Pavlidis 1990	30	67%	no primary tumours found	20%	10%	13%	7%	7%	10%
Kirsten 1987	286	Adenocarcinoma or poorly differentiated adenocarcinoma (56%)	14/286 (5%)	18%	6%	N.R.	N.R.	N.R.	4%
Culine 2002	150	Adenocarcinoma 51%, poorly differentiated adenocarcinoma 33%	N.R.	31%	12%	N.R.	N.R.	N.R.	N.R.
Hess 1999	1000	60%	N.R.	33%	9%	N.R.	N.R.	N.R.	N.R.
Lortholary 2001	311	53%	N.R.	16%	7%	N.R.	N.R.	N.R.	N.R.
Seve 2006	389	well differentiated adenocarcinoma (50%), poorly differentiated adenocarcinoma (30%)	N.R.	39%	23%	N.R.	N.R.	N.R.	N.R.
van de Wouw 2002	1285	47%	N.R.	24%	9%	N.R.	N.R.	N.R.	N.R.

Table 6.2 Diagnostic yield of upper GI endoscopy

Study	Population	Endoscopy details	Proportion of patients who had upper GI endoscopy	Proportion of adenocarcinoma histology in patients receiving endoscopy	Diagnostic yield (%)
Katagiri 1999	Bone metastases of unknown origin. It was not reported whether patients had GI symptoms, but it was probable as only selected patients had endoscopy.	OGD	24/64 (38%)	Not reported	4/24 (17%)
Kirsten 1987	Metastases of unknown primary .It was not reported whether patients had GI symptoms, but it was probable as only selected patients had endoscopy.	Gastroscopy	21/286 (7%)	Not reported	0/21 (0%)
Schapira 1995	Metastases of unknown primary .It was not reported whether patients had GI symptoms, but it was probable as only selected patients had endoscopy.	Gastroscopy	2/56 (4%)	Not reported	1/2 (50%)
Yamada 1975	Metastases of unknown primary .It was not reported whether patients had GI symptoms,	Gastroscopy	18/18 (100%)	100%	6/18 (30%)

Abbreviations: OGD, oesophagogastroduodenoscopy.

Table 6.3 Diagnostic yield of lower GI endoscopy

Study	Population	Endoscopy details	Proportion of patients who had lower GI endoscopy	Proportion of adenocarcinoma histology in patients receiving endoscopy	Diagnostic yield (%)
Katagiri 1999	Bone metastases of unknown origin. It was not reported whether patients had GI symptoms, but it was probable as only selected patients had endoscopy.	Colonoscopy or barium enema	11/64 (17%)	Not reported	1/11 (9%)
Kirsten 1987	Metastases of unknown primary. It was not reported whether patients had GI symptoms, but it was probable as only selected patients had endoscopy.	Sigmoidoscopy	26/286 (9%)	Not reported	2/26 (8%)

Study	Population	Endoscopy details	Proportion of patients who had lower GI endoscopy	Proportion of adenocarcinoma histology in patients receiving endoscopy	Diagnostic yield (%)
Schapira 1995	Metastases of unknown primary .It was not reported whether patients had GI symptoms, but it was probable as only selected patients had endoscopy.	Colonoscopy	7/56 (13%)	Not reported	0/7 (0%)

Table 6.4 Complications due to diagnostic upper gastrointestinal endoscopy

Study	Population	Number of procedures	Mortality	Overall complication rate	Peforation	Bleeding	Cardio-respiratory	Drug related	Other
Froehlich 1999	Systematic review of studies reporting complications in patients undergoing diagnostic upper gastrointestinal endoscopy	4 studies (576647 procedures)	0% to 0.04% in 4 studies. Pooled estimate: 0.008%	0.14% to 0.20% in 3 studies. Pooled estimate: 0.20%	0.008% to 0.04% in 3 studies	0.02% to 0.06% in 2 studies	0.05% to 0.73% in 3 studies	0.01% in one study	0.01% in one study
Quine 1994	Patients receiving diagnostic upper GI endoscopy East Anglia and North West regions	13036 procedures	0.05%	0.28%	0.05%	N.R.	0.24%	N.R.	N.R.

Table 6.5 Complications due to diagnostic colonoscopy

Study	Population	Number of procedures	Mortality	Overall complication rate	Peforation	Bleeding	Surgery	Other
Froehlich 1999	Systematic review of studies reporting complications in patients undergoing diagnostic colonoscopy	6 studies (103372 procedures)	0% to 0.06% in six studies. Pooled estimate: 0.019%	0% to 0.25% in 3 studies. Pooled estimate: 0.24%	0% to 0.20% in 5 studies	0% to 0.11% in 6 studies	0.05% in 1 study	0.03% to 0.11% in 3 studies
Whitlock 2008	Systematic review of studies reporting complications in patients undergoing screening colonoscopy	12 studies (57742 procedures)	N.R.	Pooled estimate: 0.28%	N.R.	N.R.	N.R.	N.R.

6. Upper- and lower-GI endoscopy as an initial test in people with provisional diagnosis of CUP adenocarcinoma, without symptoms or signs suggesting a gut primary tumour

Last updated: 30 / 10 / 2009.

Characteristics of included studies

Froehlich-1999

Clinical setting	Literature review of papers reporting complications of GI endoscopy, published up to 1997 (with limited search of 1998 articles).
Participants and Country	23 papers included: 4 papers reporting upper GI diagnostic endoscopy and 6 papers reporting diagnostic colonoscopy.
Study design	Literature review
Target condition	Complication rates associated with GI endoscopy
Tests	Upper GI endoscopy and colonoscopy.
Follow up	Not reported.
Notes	Does not the criteria for a systematic review (insufficient information about the searching and appraisal procedure).

Katagiri-1999

Clinical setting	Patients presenting with skeletal metastases, as the first sign of malignancy at any of three institutions between 1990 and 1996.
Participants and Country	64 patients. Japan
Study design	Retrospective case series
Target condition	Identification of the primary site, reference standard was: biopsy of the primary tumour (18), or combination of CT and biopsy of the bone lesion (15), evaluation of the GI tract (5), CT and tumour marker (AFP) elevation (3), autopsy (3), chest X-ray and lung biopsy (2), chest X-ray and skeletal biopsy (2), chest X-ray and skin biopsy (1), skeletal biopsy (1), physical examination and CT(1), and CT alone (1).
Tests	Gastroscopy (N=24) and colonoscopy or barium enema (N=11), amongst other tests
Follow up	Not reported.
Notes	Histology of metastases not reported, although 48/64 had biopsy of metastases.

Kirsten-1987

Clinical setting	Patients with metastatic adenocarcinoma or undifferentiated carcinoma whose primary had not been identified by clinical history, physical examination or chest x-ray. Patients presented to a single institution between 1977 and 1982.
Participants and Country	286 patients. 177 had metastases histology: 68 adenocarcinoma, 64 poorly differentiated adenocarcinoma and 54 undifferentiated carcinoma. Australia
Study design	Retrospective case series.
Target condition	Identification of the primary tumour. Primary site was histologically confirmed in a subset of patients.
Tests	Gastroscopy (N=21) and sigmoidoscopy (N=26) (amongst other tests)
Follow up	not reported
Notes	

Quine-1995

Clinical setting	No specific criteria given however the study looked at endoscopies performed within a four month period between February and June 1991 in 39 hospitals in the East Anglia and North West regions.
Participants and Country	14,149 upper GI endoscopies were performed with 92% being for diagnostic purposes and 8% for therapeutic purposes.
Study design	Prospective audit
Target condition	Complications associated with upper GI endoscopy
Tests	Upper GI endoscopy
Follow up	Morbidity and mortality within 30 days following endoscopy was reported
Notes	

Schapira-1995

Clinical setting	Patients presenting with metastases of unknown origin between 1990 and 1992 at a single institution.
Participants and Country	56 patients, 39 with CUP adenocarcinoma. USA
Study design	Retrospective case series
Target condition	Diagnostic yield of tests to find the primary tumour
Tests	Gastroscopy (N=2) and colonoscopy (N=7) (other tests were used but are not discussed here)
Follow up	Not reported, all patients had extensive tests to find the primary.
Notes	

Whitlock-2008

Clinical setting	systematic review of evidence for colorectal cancer screening, done for the 2008 update of the AHRQ guideline.
Participants and Country	Papers reporting colorectal cancer screening tests in patients of average risk. One relevant study (of 1233 patients) was found for the sensitivity of colonoscopy

Study design	Systematic review
Target condition	Sensitivity of colonoscopy for the detection of adeomas or colorectal cancer.
Tests	Colonoscopy
Follow up	not reported
Notes	Study is included only to provide a rough estimate of the sensitivity of colonoscopy in patients without signs or symptoms. Colonoscopy was often regarded as the gold standard test in these studies, so it is difficult to estimate its sensitivity.

Yamada-1975

Clinical setting	Patients referred for upper GI endoscopy for possible malignant conditions in a two year period in a single institution.
Participants and Country	215 patients in total. 23 with CUP, 18 with CUP adenocarcinoma. USA
Study design	Retrospective case series
Target condition	Identification of primary tumours of the upper GI tract. No reference standard diagnosis.
Tests	Gastroscopy and biopsy
Follow up	Not reported.
Notes	Significant complications were seen in two patients: aspiration pneumonia and bronchospasm.

References for included studies

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7. Mammography for the detection of occult breast tumours in women with metastases of unknown primary

Last updated: 7 / 10 / 2009.

Short summary

There was inconsistent evidence about the usefulness of mammography for as a routine test for women with metastases of undefined primary, without a palpable breast mass. In three studies the diagnostic yield in this population was zero, in two other studies it ranged from 6% to 14%. A primary breast tumour was eventually confirmed in between 5% and 22% of these women.

The diagnostic yield of mammography was not much higher in women presenting with axillary metastases (but without a palpable breast mass), ranging from 0% to 19%. A primary breast tumour was eventually confirmed in between 24% and 100% of these women.

There was no evidence about the influence of mammography on treatment outcome or the decision to offer breast cancer specific treatment.

Rationale

NICE Guidelines exist for initial investigation and referral of patients, who present with symptoms suggestive of a primary tumour, but these Guidelines do not deal patients who present with symptoms due to metastatic disease, nor do they advise about the optimal diagnostic workup in such patient.

Special circumstances exist where extensive investigation of metastatic malignancy is not clinically appropriate, specifically when patients have extremely advanced disease, and / or where anti-cancer treatment is very unlikely to be beneficial. Identification of these patients and their optimal management is dealt with below (PICO 5). For all other patients, a rational approach to investigation which achieves a definitive diagnosis in the shortest possible time (i.e. with the least redundant tests) is the standard clinical aim.

The initial diagnosis of metastatic cancer is usually made on the basis of detection of tumour masses or effusions on clinical examination or by imaging, often on a background of recognised but non-specific symptoms. Once metastatic cancer is suspected or proven, further tests are performed with the aim of identifying a primary site (where possible), and refining the histological nature and extent of the disease. In the period after the initial presentation, when metastatic cancer has been identified, but the outcome of further tests are awaited, it is useful to apply a diagnosis of “malignancy of undefined primary origin”.

Formal review of the evidence on initial investigation of malignancy of undefined primary origin may reveal an optimal strategy for managing this process. Such a strategy would maximise the number of diagnoses made for which specific valuable interventions could be offered, would identify as many primary tumours as possible, and would be rapidly and easily applied. It would also ensure that inappropriate over-investigation was avoided in patients for whom exhaustive testing stood no chance of improving the ultimate treatment outcome.

Given that one of the most controversial components of the widely used screening investigations is the use of mammography in women with no specific clinical or pathological features to suggest breast cancer, the evidence on this topic is explored separately in this review.

Methods

Study types

There was no restriction on study design.

Target condition

Identification of breast cancer.

Participants

Women with malignancy of undefined primary origin undergoing initial investigations to establish a primary site.

Index tests

Mammography in all patients. The comparator strategy was no mammography unless there was suspicion of breast cancer based on histology or clinical features.

REFERENCE STANDARD
Histological confirmation of breast cancer, or clinical and radiological follow-up in cases where women did not have breast biopsy or surgery.

STUDY SELECTION
An initial list of studies was selected by SA. NB then selected potentially relevant studies from this list on the basis of their title and abstract. These studies were ordered and each paper was checked against the inclusion criteria. The literature search results from other relevant questions in the guideline (local treatment for CUP-breast and breast MRI) were also searched for studies.

DATA EXTRACTION AND SYNTHESIS
One reviewer (NB) extracted data. Only published data were included and authors were not contacted.

QUALITY ASSESSMENT
Study quality was assessed by one reviewer (NB) using the QUADAS checklist for diagnostic studies.

HETEROGENEITY ASSESSMENT
There was no assessment of heterogeneity. Differences between studies, that could contribute to differences in their results were noted in the evidence tables.

Search results

Seven papers discussed mammography in women presenting with axillary metastases (Knapper, 1991; Merson et al, 1992; Galimberti et al, 2004; Panareo et al, 2006 and Wu, 2007) or axillary abnormalities (Leibman and Kossoff, 1992 and Muttarak et al, 2004).

Five papers reported mammography in women presenting with metastatic cancer of unidentified primary but without palpable breast mass(Kirsten et al, 1987; Le Chevalier et al, 1988; Leonard and Nystrom, 1993; Losa Gaspa et al 2002 and Stevens et al, 1999). Two of the studies performed mammography in all women (Stevens et al 1999 and Losa Gaspa et al 2002), in the other studies it was not reported how women were selected for mammography. It is possible two of the series (Le Chevalier et al, 1988; Leonard and Nystrom, 1993) included some patients from before the modern era of mammography.

STUDY QUALITY
The quality of the included studies was low. They were almost all retrospective series, and not designed to evaluate mammography and as a result they were at high risk of bias. There was often missing data about test results, and in a number of cases no primary site was ever found so the mammography findings could not be verified as true or false. One study (Losa Gaspa et al, 2002) was a prospective evaluation of a diagnostic strategy for patients presenting with metastatic cancer.

Summary of evidence

INCREASED IDENTIFICATION OF PRIMARY TUMOUR

In patients presenting with any metastases
The diagnostic yield of mammography, used regardless of metastatic presentation, is summarised in table 7.1. In these series the prevalence of breast cancer (the proportion of women eventually confirmed to have a primary breast tumour) ranged from 5% to 22%. The proportion of mammographies that led to a true positive diagnosis of breast cancer (diagnostic yield) ranged from 0% to 14%.

Kirsten et al (1987) noted that the analysis of the yield of mammography was necessarily biased by the referral to their medical oncology unit of patients with negative tests, those with positive tests were presumably referred to breast surgeons. This is probably also true of Leonard and Nystrom's (1993) retrospective series, the diagnostic yield of mammography as an initial test was zero in both these studies. Kirsten et al (1987), however, reported that mammography repeated at later stages of the illness contributed significantly to the diagnosis of five of the eight patients ultimately diagnosed with breast cancer in their series.

Stevens et al (1999) reported a series of 31 women with metastases of undefined primary referred for mammograms. Mammograms were negative in all five women eventually diagnosed with breast cancer. Mammograms were still negative for primary breast tumours when re-examined following the diagnosis of breast cancer in these patients. Four women had positive mammograms, three were eventually diagnosed with non-breast primary tumours and one diagnosis was indeterminate (as either breast or lung primary tumour).

Losa-Gaspa et al (2002) reported a prospective study of a diagnostic strategy for patients presenting with metastases of undefined primary. If initial tests failed to identify a primary tumour, women received mammography and CT of the abdomen and pelvis. In this study 4 breast tumours were identified on mammography in 29 women: a diagnostic yield of 14%.

In patients presenting with suspected breast cancer (axillary lymphadenopathy)
The diagnostic yield of mammography in women presenting with axillary metastases or axillary abnormalities is summarised in table 7.2. In women presenting with axillary metastases (but no palpable breast mass) between 65% to 100% were eventually diagnosed with a breast primary tumour. In patients with axillary abnormalities (including benign conditions) the prevalence was lower, ranging from 12% to 13%.

The diagnostic yield of mammography in women with axillary metastases ranged from 0% to 19%.

Figues in tables 7.1 and 7.2 suggest mammography has relatively high false negative and false positive rates in these populations. It follows that a negative mammography result does not rule out primary breast cancer and a positive mammography result needs to be confirmed by another test.

TREATMENT OUTCOMES AND BREAST CANCER CHEMOTHERAPY

Three of the studies reported treatment outcomes (Knapper et al, 1991; Merson et al, 1991 and Stevens et al, 1999). For women presenting with axillary metastases eventually diagnosed with breast cancer the 5 year survival rate was at least 75% (Knapper et al, 1991 and Merson et al, 1999). Stevens et al (1999) noted that overall survival was significantly higher in women diagnosed with breast cancer than the other patients in their series of women presenting with metastases and undefined primary tumours.

There was no evidence about the influence of mammography on treatment outcome or on the decision to offer breast cancer chemotherapy or hormone therapy. Both Knapper et al (1991) and Merson et al (1999) reported no statistically significant effect of adjuvant or systemic chemotherapy on survival in women treated with breast surgery or radiotherapy. Both these studies were non-randomised, however, and not designed to evaluate the effects of systemic treatment.

AVOIDANCE OF INAPPROPRIATE INVESTIGATIONS

None of the studies reported the avoidance of inappropriate investigations.

PATIENT SATISFACTION WITH CARE

None of the studies reported this outcome.

References

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Muttarak M, Chaiwun B, Peh WC. *Role of mammography in diagnosis of axillary abnormalities in women with normal breast examination*. Australasian Radiology 2004; 48: (3) 306-10

Panareo S. *Detection of occult breast cancer in patients with axillary lymph node metastases (CUP syndrome): Preliminary comparison of conventional diagnostic procedures and other imaging techniques*. European Journal of Oncology 2006; 11: (2) 121-32

Stevens KJ, Smith SL, Denley H, Pinder SE, Evans AJ, Chan SY. *Is mammography of value in women with disseminated cancer of unknown origin?*. Clinical Oncology (Royal College of Radiologists) 1999; 11: (2) 90-2

Wu B. *Diagnosis and treatment of occult breast cancer: Analysis of 36 cases*. Chinese Journal of Cancer Prevention and Treatment 2007; 14: (19) 1496-7

Table 7.1 Mammography results for women with any metastatic presentation

Study	N	Prevalence of primary breast cancer	TP	FP	FN	TN	Unevaluable results
Kirsten 1987*	40	9/40 (22%)	0	4	9	4	23 (primary site not found)
Leonard 1993*	65	3/65 (5%)	0	3	3	NR	NR
Le Chevalier 1988	18	NR	1	NR	NR	NR	NR
Losa Gaspa 2002	29	4/29 (14%)	4	NR	NR	NR	NR
Stevens 1999	31	5/31 (16%)	0	3	5	22	1 (primary site not found)

* Retrospective occult primary series
Abbreviations: FP, false positive; FN, false negative; NR, not reported; TP, true positive; TN, true negative;

Table 7.2 Mammography results for women presenting with axillary metastases or abnormalities

Study	N	Prevalence of primary breast cancer	TP	FP	FN	TN	Unevaluable results
Confirmed axillary metastases							
Galimberti 2004	50	12/50 (24%)	4	NR	8	NR	NR
Knapper 1991	32	21/32 (65%)	6	3	15	8	0
Merson 1992	55	37/55 (67%)	<10	NR	>27	NR	NR
Panareo 2006	6	6/6 (100%)	0	0	6	0	0
Axillary abnormalities (including benign conditions)							
Leibman 1992	17	2/17 (12%)	1	0	1	15	0
Muttarak 2004	40	5/40 (13%)	4	NR	1	NR	NR

Abbreviations: FP, false positive; FN, false negative; NR, not reported; TP, true positive; TN, true negative;

7. Mammography for the detection of occult breast tumours in women with metastases of unknown primary

Last updated: 7 / 10 / 2009.

Characteristics of included studies

Galimberti-et-al-2004

Clinical setting	Women presenting with axillary adenopathy with a diagnosis of metastatic adenocarcinoma compatible with breast cancer. All women were treated for primary breast cancer at a single institution between 1995 and 2004.
Participants and Country	50 women. In 23 patients imaging (mammogram, US, MRI or breast-scintigraphy) suggested a primary site . In 12 cases a primary breast tumour was found.
Study design	Retrospective case series
Target condition	Identification of primary breast tumour. The reference standard was histopathology of the surgical specimen in those who had breast surgery and clinical follow-up in those who did not have surgery.
Tests	Mammography The overall positivity rate for mammography was not reported, but in the 12 women with confirmed primary breast carcinoma mammography was true positive in 4 cases, false negative in 8 cases.
Follow up	Mean follow-up was 41.3 months (range 1 to 108 months).
Notes	

Kirsten-1987

Clinical setting	Patients presenting with metastatic adeno or undifferentiated carcinoma of unknown primary site, after H&P and chest X-ray. Patients presented to a single institution between 1977 and 1982.
Participants and Country	286 patients (143 male and 143 female). 40 had a mammogram.
Study design	Retrospective case series
Target condition	Identification of breast primary tumours. The reference standard was histopathological confirmation of the primary tumour (before death in 58 patients and postmortem in 30). Most patients did not have a primary tumour identified, however, so their mammography results could not be validated.
Tests	40 mammograms were done. Results were: Positive mammograms: no true positives, 4 false positives and 3 equivocal / unevaluable results. Negative mammograms: 4 true negatives, 9 false negatives and 20 unevaluable negatives. Mammography, repeated at later stages of the illness, contributed significantly to the diagnosis in 5 of the 8 patients with axillary metastases in whom primary breast cancer was ultimately identified.
Follow up	It is likely that follow up was to death in all cases.

Notes	The authors note that analysis of the yield of mammography in patients with isolated metastases and clinically normal breasts was necessarily biased by the referral to the medical oncology unit of patients with negative tests and the referral of those with positive tests to the surgeons.

Knapper-1991

Clinical setting	Women treated for primary operable breast cancer who presented with axillary metastases only between 1975 and 1988.
Participants and Country	35 women. 32 had preoperative mammograms, 28 had mastectomy.
Study design	Retrospective case series.
Target condition	Identification of the primary breast tumour. The reference standard was histopathology of the breast biopsy or surgical specimen.
Tests	Mammography 9/32 mammographs were suspicious for cancer.6 were true positive, 3 were false positive. 23/32 mammograms were negative for caner: 15 were false positive and 8 were true positive. This corresponds to sensitivity of 29% and specificity of 73% with accuracy of 44%. Treatment outcomes Five and ten year survival, for the group as a whole was 75% and 55% respectively. Five year survival was similar whether or not post-operative adjuvant chemotherapy and/or hormone therapy was given.
Follow up	Not reported, from the publication date the possible range was 1 to 13 years.
Notes	

Le-Chevalier-1988

Clinical setting	Retrospective consecutive series of patients who presented with metastases of unknown primary and had an autopsy between 1959 and 1980.
Participants and Country	302 patients (255 males and 77 females). 18 women had mammography.
Study design	Retrospective case series
Target condition	Target condition was the detection of the primary tumour. The reference standard was post-mortem examination.
Tests	Mammograhpy was done in 18 women (in whom clinical examination of the breast was normal). Two patients had abnormal results: one was a breast metastasis of unknown primary origin and another was a primary breast carcinoma.
Follow up	Complete follow up.
Notes	A subset of women (18/77) received mammography, suggesting either it was limited to those women with presentation consistent with breast cancer or was only introduced in the later years of the series. Most of the series predates CT, tumour markers, ultrasound etc.

Leibman-1992

Clinical setting	Patients with palpable axillary adenopathy of unknown origin referred for mammography at a single institution between 1981 and 1991. All patients had normal breasts on physical examination
Participants and Country	17 patients.

Study design	Retrospective case series
Target condition	The target condition was diagnosis of axillary lymphadenopathy and of primary breast tumours. Reference standard was clinical history and lab tests in 6 patients and cytopathology or histopathology in 11 patients.
Tests	Mammography
Follow up	Diagnosis of axillary lymphadenopathy 7/17 mammograms showed enlarged axillary nodes. In 4 patients lymph node biopsy showed cancer. Diagnosis of primary breast One patient showed a mass suggestive of breast carcinoma, confirmed at biopsy. Another patient, with metastatic lung cancer, had a benign-appearing breast mass that was not biopsied.
Notes	Patients did not have confirmed axillary metastases before mammography (most had non malignant adenopathy)

Leonard-1993

Clinical setting	Patients who presented with metastatic non-squamous carcinoma of unknown site
Participants and Country	266 patients, 133 female, 65 mammograms
Study design	The paper is an expert review but includes previously unpublished data about mammography from: Nystrom JS, Weiner JM, Heffelfinger-Juttiner J, et al: Metastatic and histologic presentation of unknown primary cancer. Seminars in Oncology 4: 53-58, 1977
Target condition	Identification of breast primary tumours. Reference standard for mammography was surgical biopsy for positive cases and autopsy for selected negative cases.
Tests	Mammography 65 tests were done: 3 were positive (suggesting a primary malignancy) - all of these were false positive. There were also three false negatives (three primary breast tumours not detected on mammogram).
Follow up	
Notes	It is unclear what proportion of the patients had axillary metastases, however the Authors suggest that routine mammography is futile in patients without evidence of axillary metastases or masses within the breast.

Losa-Gaspa-2002

Clinical setting	Consecutive series of patients presenting with malignancy of undefined primary
Participants and Country	221 overall.
Study design	Prospective series.
Target condition	Identification of the primary breast tumours. reference standard was not reported.
Tests	Three levels of diagnostic tests: basic, further tests and exhaustive tests. Mammography was reserved for women in whom basic tests failed to identify a primary tumour
Follow up	138 patients had a primary discovered by basic tests (including 10 patients with breast primary tumours). 83 went on to have further diagnostic tests: CT abdomen-pelvis and mammography. 29 women had mammography*. Mammography led to the diagnosis of breast cancer in four patients with unidentified primary tumour following basic tests.
Notes	* figure comes from F. Losa-Gaspa's 2004 PhD thesis.

Merson-1991

Clinical setting	Patients admitted to a single institution between 1945 and 1987 with unilateral axillary node enlargement or diagnosis of axillary metastatic breast cancer, but without clinical evidence of a primary tumour. Patients with metastases outside the axilla were excluded.
Participants and Country	56 patients. Mammography was done in 55 patients.52 patients had axillary dissection, and 4 had axillary biopsy only. 33/56 had breast surgery followed by radiotherapy, 6 had radiotherapy only and 17 had no local treatment to the breast.
Study design	Retrospective case series.
Target condition	Target condition was the identification of primary breast tumours. reference standard was histopathology of the surgical specimen or clinical follow up in those who did not have breast surgery.
Tests	Mammography Mammography was negative in 45/55 patients. Mammography showed some alterations in 10 cases, but no suspicious microcalcification. 27 primary breast tumours were discovered after surgery. Ten tumours became evidence with time in patients who then received surgery. In total 37 primary breast tumours were verified. Treatment outcomes Overall survival at 5 and 10 years was 77% and 58% respectively. Comparison of patients treated with or without systemic treatment showed no significant differences.
Follow up	Median follow up was 10 years and 3 months.
Notes	Paper does not analyse the diagnostic performance of mammography. It is unclear whether the alterations seen on the mammograms of ten patients correlated with primary breast tumours found at surgery.

Muttarak-2004

Clinical setting	Women presenting with palpable unilateral masses in the axilla but with normal breasts on physical examination, between 1995 and 2002 at a single institution.
Participants and Country	43 women.
Study design	Retrospective case series
Target condition	The target condition was diagnosis of the axillary mass, the reference standard was histopathological or cytopathological confirmation. The authors also report the rate of diagnosis of primary breast tumours in this group of patients, the reference standard was histopathological or cytopathological confirmation..
Tests	Mammography (a screen film mammographic unit LoRad MIII). 40/43 patients had axillary lymphadenopathy (22/40 malignant and 18/40 benign). Lymph node metastases were: from previous contralateral breast cancer in 9/22 cases, from non-mammary or unknown primary tumour in 8/22 cases. from an ipsilateral breast tumour in 5 cases. In 4 cases the primary breast tumour was detected on mammogram.The false positive rate of mammography (for primary breast carcinoma) was not reported.
Follow up	Not reported.
Notes	

Panareo-2006

Clinical setting	Women with biopsy proven adenocarcinoma in axillary lymph nodes and probable occult breast cancer. All patients had normal breasts on physical examination and no history of other primary cancer.
Participants and Country	6 women.

Study design	Case series
Target condition	The target condition was diagnosis of primary breast tumours. Reference standard was MRI guided breast biopsy with histopathology or histopathology of the surgical specimen.
Tests	Mammography Mammography was negative in all six cases. Mammography was false negative in all cases, as primary breast tumours were confirmed by other means. Ultrasound, MRI, PET and scintimammography were also done.
Follow up	Not reported
Notes	Italian language paper with English abstract.

Stevens-1999

Clinical setting	Women with a provisional diagnosis of metastatic carcinoma, with no palpable breast mass referred for mammography at a single centre between 1995 and 1997.
Participants and Country	31 women. Presentation was: lung metastases (45%), lymph node metastases (5%), abdominal metastases (5%), brain or neurological (4%), bone metastases (2%) and skin nodule (1%).
Study design	Retrospective case series
Target condition	The aim was to diagnose primary breast tumours and the reference standard was histopathological confirmation of the primary tumour, or histopathological and immunohistochemical diagnosis of the metastasis biopsy.
Tests	The index test was mammography. Diagnostic accuracy in all presentations Mammography was normal in 27 and abnormal in 4. In the 4 patients with abnormal mammograms three proved not to be breast carcinoma and in one the primary site remained indeterminate (as either breast or lung: probably breast given her good survival). 5 women had a confident diagnosis of breast cancer based on histopathology and IHC, but all of these 5 normal mammograms. Their mammograms were still normal after re-examining them once the diagnosis of breast cancer was known. The sensitivity of mammography was 0% (95% C.I. 0 to 52%). Diagnostic accuracy in women with axillary adenopathy No breast cancers were detected on mammography in the two women diagnosed with breast cancer and axillary adenopathy. Treatment outcomes 2 year overall survival in women with breast cancer was 80% compared with <10% in women with other presentations (Mantel-Cox test; P<0.001). One patient with an indeterminate primary tumour (either breast or lung) and brain metastases was still alive after 31 months. The authors suggest that given the length of survival, the primary site is very likely to be breast.
Follow up	Follow up was not reported, but form the survival analysis was probably less than 30 months.
Notes	The authors suggest that breast carcinoma that presents with metastatic disease is atypical and more likely to have be mammographically occult.

Wu-2007

Clinical setting	Patients with occult breast cancer treated in a single hospital between 1980 and 2006. It was unclear how patients were selected for inclusion.
Participants and Country	36 patients
Study design	Retrospective case series
Target condition	The target condition was the location of breast primary tumour, the reference standard was mastectomy.
Tests	Mammography, ultrasound. Mammography was positive in 2 cases and suspicious in 3; ultrasound was positive in 1 and suspicious in 3.
Follow up	30 patients were followed up and median survival was more than five years in these patients.
Notes	Chinese language with English abstract.

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WU 2007
Wu B. Diagnosis and treatment of occult breast cancer: Analysis of 36 cases. Chinese Journal of Cancer Prevention and Treatment 2007; 14 (19) 1496-7

8. Dynamic contrast enhanced breast MRI for patients with provisional CUP and axillary adenopathy

Last updated: 30 / 10 / 2009.

Short summary

In ten included case series of women with axillary adenopathy and unknown primary tumour between 25% and 100% were found to have occult breast cancer. In these series, most primary breast tumours were visible on breast MRI.

Limited evidence, from two studies, suggests a negative breast MRI could have a role in ruling out breast cancer in this population. However the high prevalence of breast cancer in this group means that a significant number of occult breast cancers would be missed.

Due to the uncertain specificity of breast MRI, further diagnostic tests would be needed (such as biopsy) before commencing treatment in women with lesions detected on MRI .

The evidence suggests MRI influences treatment decisions. Evaluation of the extent of disease on breast MRI has been used to plan breast surgery and select candidates for radiotherapy and neoadjuvant chemotherapy.

There is a lack of evidence comparing outcomes in patients who have breast MRI with those who do not have breast MRI.

Rationale

Women who present with provisional Cancer of Unknown Primary involving axillary nodes, and in whom histological findings in the nodes are compatible with a breast cancer, may harbour a small occult breast primary tumour. Given the potential therapeutic opportunities which follow the conclusive diagnosis of breast cancer, significant efforts should be made to achieve this in appropriate subgroups of women with provisional CUP. The best test for detecting occult breast cancer in women with Cancer of Unknown Primary involving axillary nodes has not been defined. The high sensitivity offered by contrast-enhanced breast MRI may be advantageous in this group.

Methods

Study types

Any study that evaluated the diagnostic utility of breast MRI for cancer of unknown primary.

Target condition

The identification of primary breast tumours.

Participants

Patients with axillary adenopathy and a provisional diagnosis of cancer of unknown primary (initial tests having failed to locate a breast tumour).

Index tests

Dynamic contrast enhanced breast MRI in addition to clinical evaluation, breast ultrasound and mammography.

Reference standard

The reference standard diagnosis was made using the histopathology of the breast lesion seen on MRI, following surgery or biopsy. Clinical follow up was a possible confirmatory test in patients with no lesions visible on breast MRI.

Study selection

An initial list of studies was selected by SA. NB then selected potentially relevant studies from this list on the basis of their title and abstract. These studies were ordered and checked against the inclusion criteria.

Data extraction and synthesis

One reviewer (NB) extracted data. Only published data were included and authors were not contacted. Patients who had no confirmatory tests or clinical follow-up after breast MRI were excluded from the analysis of sensitivity and specificity. Any patient with both false positive and true positive lesions on the same MRI was classed as true positive

Quality assessment

Study quality was assessed by one reviewer (NB) using the QUADAS checklist for diagnostic studies, incorporated in the Cochrane Review Manager software.

Heterogeneity assessment

Heterogeneity (variation between studies) was assessed by visual inspection of Forest plots. Sub-group analysis was done according to whether studies used mastectomy in those with negative breast MRI, as this might discover primary tumours not seen on MRI.

Search results

The literature search returned 129 studies, ten of which were included.

Study quality

All the studies were case series, ranging in size from six to 55 patients. All but one were retrospective. The studies were not designed to evaluate the diagnostic performance of breast MRI, and as a result many used different reference standard tests to confirm the findings of breast MRI depending on whether the MRI was positive or negative (so called differential verification). Women with tumours detected on MRI typically had a biopsy of the lesion and breast surgery if a primary cancer was found. Women with negative MRI often had clinical and radiological follow up only. Breast biopsy was directed at lesions seen on MRI, this incorporation of MRI findings into the reference standard test would tend to bias estimates of accuracy in favour of MRI.

Only in the two largest studies (Orel et 1999 and Bucanan et el 2005) did women with negative MRI receive mastectomy. These studies provide the best evidence of the diagnostic accuracy of breast MRI, as they had the potential to discover breast tumours missed on MRI.

Summary of evidence

In the ten included studies, the rate of histologically confirmed breast cancer ranged from 25% to 100%. Combing the data across studies the pre-test probability of a occult breast tumour was relatively high at 62%. The true figure is likely to be higher than this as a proportion women did not have histological confirmation of their breast cancer.

Diagnostic accuracy

The eight studies in which women with negative MRI did not have breast surgery tended to give high estimates of sensitivity and specificity (see Table 8.1 and Figure 8.1): with only a single breast tumour missed on MRI (false negative).

A better estimate of sensitivity and specificity comes from the combined results of Orel et al (1999) and Buchanan et al (2005), where the majority of women with negative MRI received mastectomy. This gives a sensitivity of breast MRI of 91% [95% C.I. 80 to 97%] for the detection of breast tumours with a corresponding specificity of 42% [95% CI 24 to 61%]. Using these figures breast MRI has a positive likelihood ratio of 1.57 and a negative likelihood ratio of 0.22, suggesting it is not useful for ruling in but moderately useful in ruling out breast cancer in this population.

Probability of breast cancer before and after breast MRI, using data from Orel et al (1999) and Buchanan et al (2005)

Pre-MRI probability	Post-MRI probability, positive MRI	Post-MRI probability, negative MRI
66%	75%	29%

Due to the high prevalence of breast cancer in this patient group, however, there was still a 29% probability of breast cancer in women with negative breast MRI.

The low specificity of breast MRI suggests it is insufficient on its own to rule in a diagnosis of breast cancer. Further diagnostic tests would be required before treatment. Studies typically verified the MRI diagnosis with an ultrasound (or MRI) guided breast biopsy directed to the lesions seen on breast MRI.

Change in management

Change in management is recorded in Table 8.2. Three studies reported that, in patients with MRI positive lesions who were candidates for breast surgery, the extent of the tumour on MRI was useful in selecting patients for breast conserving surgery or mastectomy. One study used breast MRI to inform the decision to offer neoadjuvant chemotherapy.

Lieberman et al (2008) considered the accuracy of extent-of-disease estimates from breast MRI. In nine patients who had breast surgery, MRI correctly estimated the extent of disease in six patients (67%), underestimated it in one patient (11%) and overestimated it in two patients (22%).

Treatment outcome

None of the studies compared treatment outcomes in patients who had and had not received breast MRI.

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Ko EY, Han BK, Shin JH, Kang SS. *Breast MRI for evaluating patients with metastatic axillary lymph node and initially negative mammography and sonography*. Korean Journal of Radiology 2007; 8: (5) 382-9

Lieberman S, Sella T, Maly B, Sosna J, Uziely B, Sklair-Levy M. *Breast magnetic resonance imaging characteristics in women with occult primary breast carcinoma*. Israel Medical Association Journal: Imaj 2008; 10: (6) 448-52

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Schorn C, Fischer U, Luftner-Nagel S, Westerhof JP, Grabbe E. *MRI of the breast in patients with metastatic disease of unknown primary*. European Radiology 1999; 9: (3) 470-3

Stomper PC. *Breast MRI in the evaluation of patients with occult primary breast carcinoma*. Breast Journal 1999; 5: (4) 230-4

Table 8.1 Diagnostic accuracy of breast MRI in women with axillary adenopathy and unknown primary tumour

Study	Population	N	Occult breast cancer	Reference standard test for patients with MRI positive lesions	MRI positive	True positives*	False positive†	Reference standard test for patients with negative MRI	MRI negative	True negatives¥	False negatives‡
Buchanan 2005	Women with axillary adenopathy and unknown primary	55	28/55 (51%)	MRI or US guided biopsy (N=38), none (N=4).	42/55 (76%)	26/38 (68%)	12/38 (32%)	Histopathology of mastectomy specimen (N=8), clinical follow up (N=3), none (N=2)	13/55 (24%)	9/11 (82%)	2/11 (18%)
Henry-Tillman 1999	Women with axillary or supraclavicular adenopathy and unknown primary	10	8/10 (80%)	MRI directed US core biopsy, MRI guided core biopsy or MRI guided lumpectomy (N=8)	8/10 (80%)	8/8 (100%)	0/8 (0%)	Primary tumours (lymphoma and ovary) found by unspecified means (N=2)	2/10 (20%)	2/2 (100%)	0/2 (0%)
Ko 2007	Patients with axillary adenopathy and unknown primary	12	10/12 (83%)	MRI directed US or mammography guided biopsy or mastectomy (N=10),	10/12 (83%)	10/10 (100%)	0/10 (0%)	Clinical and radiological follow up (N=2)	2/12 (17%)	2/2 (100%)	0/2 (0%)
Lieberman 2008	Women with metastatic disease consistent with breast cancer and unknown primary	16	14/16 (88%)	MRI directed US core biopsy (N=10), MRI guided needle location and lumpectomy (N=4) or lumpectomy (N=1).	15/16 (94%)	13/15 (87%)	2/15 (13%)	PET-CT and US guided core biopsy (N=1)	1/16 (6%)	0/1 (0%)	1/1 (100%)
McMahon 2005	Women with axillary adenopathy and unknown primary	18	11/18 (61%)	MRI directed US biopsy (N=11), random surgical biopsy (N=1), mastectomy (N=1), none (N=1).	14/18 (78%)	11/13 (85%)	2/13 (15%)	Clinical and radiological follow up (N=4)	4/18 (22%)	4/4 (100%)	0/4 (0%)
Obdein 2000	Women with axillary adenopathy and unknown primary	20	8/20 (40%)	MRI directed US biopsy (N=8)	8/20 (40%)	8/8 (100%)	0/8 (0%)	Clinical follow up (N=12)	12/20 (60%)	12/12 (100%)	0/12 (0%)
Orel 1999	Women with axillary adenopathy and unknown primary	22	19/22 (86%)	MRI, US or mammography guided lumpectomy (N=9), mastectomy (N=9), MRI tumour response to chemotherapy (N=1)	19/22 (86%)	17/19 (89%)	2/19 (11%))	Mastectomy (N=3)	3/22 (14%)	1/3 (33%)	2/3 (66%)
Panareo 2006	Women with axillary adenopathy and unknown primary	6	6/6 (100%)	MRI guided breast biopsy (N=6)	6/6 (100%)	6/6(100%)	0/6 (0%)	-	0/6 (0%)	-	-
Schorn 1999	Women with metastatic disease consistent with breast cancer and unknown primary	14	6/14 (43%)	Histopathology of the surgical specimen (N=9)	9/14	6/9 (67%)	3/9(33%)	Primary tumours (pancreas or colon) found by unspecified means (N=3), clinical follow up (N=2)	5/14 (36%)	5/5 (100%)	0/5 (0%)
Stomper 1999	Women with axillary	8	2/8 (25%)	Breast biopsy (MRI guided) (N=2)	2/8 (25%)	2/2 (100%)	0/2 (0%)	Clinical follow up (N=6)	6/8 (75%)	NR	NR

Study	Population	N	Occult breast cancer	Reference standard test for patients with MRI positive lesions	MRI positive	True positives*	False positive†	Reference standard test for patients with negative MRI	MRI negative	True negatives¥	False negatives‡
	adenopathy and unknown primary										
Total		181	112/181 (62%)		133/181 (73%)	107/128 (84%)			48/181 (27%)		

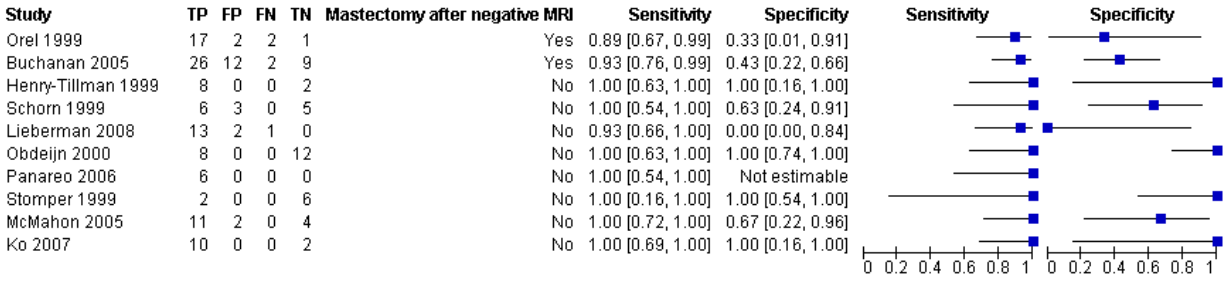
Abbreviations: MRI, magnetic resonance imaging; US, ultrasound;
* The breast lesion identified on MRI was confirmed using the reference standard test
† The breast lesion identified on MRI was not confirmed using the reference standard test
¥ No breast lesion identified on MRI and the reference standard test found no breast lesion (or primary tumour found outside the breast).
‡ No breast lesion identified on MRI, but breast primary tumour found by the reference standard test

Table 8.2 Change in management and treatment outcomes

Study	Change in management	Treatment outcome
Buchanan 2005	MRI helped to select candidates for breast conserving surgery or mastectomy in the group of 26/55 (47%) patients who had positive MRI and breast surgery	Not reported by MRI group
Henry-Tillman 1999	3/10 (30%) of patients had neoadjuvant chemotherapy before surgery, on the basis of an MRI showing multicentric disease.	Not reported
Ko 2007	MRI used to select candidates for lumpectomy, breast conserving surgery or modfied radical mastectomy in the group of 8/12 patients who had positive MRI and breast surgery. 2/12 patients received radiotherapy and chemotherapy as a result of MRI assessment of disease extent. Total change in management was 10/12 (83%)	Not reported
Lieberman 2008	Not reported. In 9 patients who had breast surgery, MRI correctly estimated the extent of disease in 6/9 (67%) patients, underestimated it in 1 patient (11%) and overestimated it in 2 patients (22%).	Not reported
McMahon 2005	MRI was used to select candidates for breast conserving surgery in a group of 9/18 (50%) patients with malignancy confirmed preoperatively and without haematologic metastatic disease.	Not reported by MRI group
Obdejin 2000	Not reported	Not reported
Orel 1999	Not reported	Not reported
Panareo 2006	Not reported in abstract*	Not reported in abstract*
Schorn 1999	Not reported	Not reported
Stomper 1999	Management decisions were influenced in two cases. One patient was able to have breast conserving surgery while mastectomy was indicated in the other. Patients with negative MRI received whole breast radiation.	Not reported

* Italian language paper with English abstract.

Figure 8.1 Forest plot of Breast MRI sensitivity and specifity for the identification of breast tumours in women with unknown primay and axillary adenopathy



8. Dynamic contrast enhanced breast MRI for patients with provisional CUP and axillary adenopathy

Last updated: 30 / 10 / 2009.

Characteristics of included studies

Buchanan-2005

Clinical setting	Women with axillary adenopathy and unknown primary presenting to a breast surgery service between 1995 and 2001.
Participants and Country	55 with stage II disease, and 14 with stage IV disease (data from stage IV patients were excluded from this review). USA
Study design	Retrospective case series
Target condition	Identification of breast primary tumour. Reference standard for those with positive MRI scans: MRI or US guided biopsy (N=38), none (N=4). Reference standard for those with negative MRI scans: Histopathology of mastectomy specimen (N=8), clinical follow up (N=3), none (N=2).
Tests	Dynamic contrast enhanced breast MRI.
Follow up	Median 4.5 years (range 2 to 8 years)
Notes	

Henry-Tillman-1999

Clinical setting	Women with axillary or supraclavicular adenopathy and unknown primary presenting to a single institution.
Participants and Country	10 patients. USA
Study design	Retrospective case series.
Target condition	Identification of breast primary tumour. Reference standard for those with positive MRI scans: MRI directed US core biopsy, MRI guided core biopsy or MRI guided lumpectomy (N=8) Reference standard for those with negative MRI scans: Primary tumours (lymphoma and ovary) found by unspecified means (N=2)
Tests	Dynamic contrast enhanced breast MRI. MRI used rotating delivery of excitation resonance (3D RODEO MRI)
Follow up	Not reported
Notes	

Ko-2007

Clinical setting	Women with axillary adenopathy and unknown primary tumour presenting to a single hospital between 2001 and 2006.
Participants and Country	12 women. Korea
Study design	Retrospective case series.
Target condition	Identification of primary breast tumour. Reference standard for those with positive MRI scans: MRI directed US or mammography guided biopsy or mastectomy (N=10)Reference standard for those with negative MRI scans: Clinical and radiological follow up (N=2)
Tests	Dynamic contrast enhanced breast MRI.
Follow up	3.25 to 3.66 years, in patients with negative MRI.
Notes	

Lieberman-2008

Clinical setting	Women with metastatic disease consistent with breast cancer and unknown primary, referred for MRI at a single institution between 2000 and 2006.
Participants and Country	16 women. Israel
Study design	Retrospective case series
Target condition	Identification of primary breast tumour. Reference standard for those with positive MRI scans: MRI directed US core biopsy (N=10), MRI guided needle location and lumpectomy (N=4) or lumpectomy (N=1).Reference standard for those with negative MRI scans: PET-CT and US guided core biopsy (N=1)
Tests	Dynamic contrast enhanced breast MRI.
Follow up	Not reported
Notes	

McMahon-2005

Clinical setting	Women with axillary adenopathy and unknown primary referred for a breast MRI at a single instution between 2000 and 2004.
Participants and Country	18 women. Australia
Study design	Retrospective case series.
Target condition	Identification of primary breast tumour. Reference standard for those with positive MRI scans: MRI directed US biopsy (N=11), random surgical biopsy (N=1), mastectomy (N=1), none (N=1).Reference standard for those with negative MRI scans: Clinical and radiological follow up (N=4)
Tests	Dynamic contrast enhanced breast MRI.

Follow up	Up to 3 years (minimum not reported)
Notes	

Obdeijn-2000

Clinical setting	Women with axillary adenopathy and unknown primary
Participants and Country	20 women. Netherlands
Study design	Prospective case series
Target condition	Identification of primary breast tumours. Reference standard for those with positive MRI scans: MRI directed US biopsy (N=8)Reference standard for those with negative MRI scans: Clinical follow up (N=12)
Tests	Breast MRI
Follow up	Not reported
Notes	

Orel-1999

Clinical setting	Women with axillary adenopathy and unknown primary who had breast MRI at a single institution between 1993 and 1997
Participants and Country	22 women. USA
Study design	Retrospective case series
Target condition	Identification of primary breast tumour. Reference standard for those with positive MRI scans: MRI, US or mammography guided lumpectomy (N=9), mastectomy (N=9), MRI tumour response to chemotherapy (N=1) Reference standard for those with negative MRI scans: Mastectomy (N=3)
Tests	Dynamic contrast enhanced breast MRI.
Follow up	Not reported
Notes	

Panareo-2006

Clinical setting	Women with axillary adenopathy and unknown primary.
Participants and Country	6 women. Italy.
Study design	Retrospective case series.
Target condition	Identification of primary breast tumour. Reference standard for those with positive MRI scans: MRI guided breast biopsy (N=6)Reference standard for those with negative MRI scans: (all had positive scans)
Tests	Breast MRI (not specified in detail in the English abstract)
Follow up	
Notes	Italian language, abstract only in English.

Schorn-1999

Clinical setting	Women with metastatic disease consistent with breast cancer and unknown primary. Presentation was metastatic disease of: bone (N=3), liver (N=3), lung (N=1), axillary nodes (N=6) and supraclavicular nodes (N=1).
Participants and Country	14 women. Germany
Study design	Retrospective case series
Target condition	Identification of primary breast tumour. Reference standard for those with positive MRI scans: Histopathology of the surgical specimen (N=9)Reference standard for those with negative MRI scans: Primary tumours (pancreas or colon) found by unspecified means (N=3), clinical follow up (N=2)
Tests	Dynamic contrast enhanced breast MRI.
Follow up	Up to 14 months. Minimum not reported
Notes	

Stomper-1999

Clinical setting	Women with axillary adenopathy and unknown primary, presenting to a single multidisciplinary breast clinic.
Participants and Country	8 women. USA
Study design	Retrospective case series
Target condition	Identification of primary breast tumour. Reference standard for those with positive MRI scans: Breast biopsy (MRI guided) (N=2)Reference standard for those with negative MRI scans: Clinical follow up (N=6)
Tests	Breast MRI
Follow up	Dynamic contrast enhanced breast MRI.
Notes	

References for included studies

BUCHANAN 2005

Buchanan CL, Morris EA, Dorn PL, Borgen PI, Van Zee KJ. Utility of breast magnetic resonance imaging in patients with occult primary breast cancer. Annals of Surgical Oncology 2005; 12 (12) 1045-53

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LIEBERMAN 2008
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SCHORN 1999
Schorn C, Fischer U, Luftner-Nagel S, Westerhof JP, Grabbe E. MRI of the breast in patients with metastatic disease of unknown primary. European Radiology 1999; 9 (3) 470-3

STOMPER 1999
Stomper PC. Breast MRI in the evaluation of patients with occult primary breast carcinoma. Breast Journal 1999; 5 (4) 230-4

9. PET/CT for the identification of the primary tumour in metastatic cancer with unidentified primary

Last updated: 29 / 10 / 2009.

Rationale

18-FDG PET-CT is a hybrid imaging modality which has developed in recent years and is being increasingly used in oncology. PET-CT is of proven value in improving the accuracy of cancer staging in patients with an identified primary tumour. This has a tangible impact on subsequent treatment decisions where interventions depend on the disease being localised rather than disseminated.

The rationale for use of PET-CT in patients with cancer of unknown primary (CUP) is different to that in patients with an identified primary. In CUP the purpose is still to identify occult disease, but in this case it is hoped that a previously undetected primary tumour will be revealed when all previous tests in an individual have failed to achieve this. Identification of an occult primary is presumed to result in improved treatment outcomes compared with empirical therapy for metastatic cancer of unknown primary origin. It is desirable to establish the nature and magnitude of any benefits of PET-CT in CUP. It is expected that these will vary by clinical subtype.

Methods

Study types

Eligible study designs were: randomised trials, diagnostic studies, or case series. Minimum study size was 5 patients.

Target condition

Identification of the primary tumour.Identification of true cancer of unknown primary. Identification of additional metastases.

Participants

Patients with histologically confirmed metastatic malignant disease whose primary tumour remains unknown after conventional diagnostic tests.

Index tests

FDG PET or PET-CT done after negative initial diagnostic work up.

Reference standard

The reference standard test was histologic analysis of tissue from the putative primary tumour, or radiological and clinical follow-up if biopsy is not possible.

Study selection

An initial list of studies was selected by SA. NB then selected potentially relevant studies from this list on the basis of their title and abstract. These studies were ordered and each paper was checked against the inclusion criteria.

Data extraction and synthesis

One reviewer (NB) extracted data. Only published data were included and authors were not contacted. Where possible, data about individual metastatic presentations (for example liver metastases) was extracted. Descriptive displays of sensitivity and specificity, as well as summary ROC curves where there were sufficient data. The following definitions were adopted: Sensitivity: the proportion people with identifiable primary tumours (by any reasonable means) correctly detected by PET Specificity: the proportion of people with unidentifiable primary tumours (by any reasonable means) with a negative PET result. According to these definitions, specificity for the location of the primary tumour corresponds to the sensitivity for the diagnosis of "true" CUP. In order to calculate sensitivity and specificity the review used the following definitions: True positive (TP) was when PET suggested a primary tumour site and the tumour location was confirmed False positive (FP) was when PET suggested a primary tumour site, but without confirmation of the location of the primary tumour True negative (TN) no primary tumour site is evident on PET, and no primary tumour is ever discovered during follow up False negative (FN) no primary tumour site is evident on PET, but a primary tumour is subsequently found by other means Trial reports of sensitivity and specificity were pooled, using the Mantel-Haensel fixed effects model in Meta-DiSc statistical software version 1.4 (Zamora et al, 2006). The Q* index was also calculated using Meta-Disc.The Q* index is defined by as the point where sensitivity equals specificity on the summary ROC curve, and is a more stable estimate of diagnostic performance when there is heterogeneity due to

threshold effects. Data about the rate of detection of additional metastases, the influence of PET on patient management and survival were also extracted.

QUALITY ASSESSMENT
Study quality was assessed by one reviewer (NB) using the QUADAS checklist for diagnostic studies, incorporated in Cochrane Review Manager software.

HETEROGENEITY ASSESSMENT
Heterogeneity (variation between studies) was assessed by visual inspection of Forest plots and by using the chi-squared test, with heterogeneity defined as P<0.10.

Search results

The literature search identified 274 studies. On the basis of their title and abstract 86 papers were ordered for further appraisal and 50 included in the final review. The studies were case series; 35 examining PET and 12 PET-CT, or meta-analyses. All studies included patients with unidentified primary tumour after initial diagnostic tests. The initial battery of diagnostic tests received by each patient varied, even within the same study, and appeared largely dependent on metastatic presentation. Nearly all had presentation dependent CT and histological confirmation of their metastasis (but in some cases MRI was substituted for CT and cytology for histology). Two of the studies were meta-analyses (Kwee and Kwee, 2009; Dong et al, 2008).

Studies included the following patient groups: any metastatic presentation (N= 18), cervical lymph node metastases (N=25), any extra-cervical metastases (N=2), brain metastases (N=2) and axillary lymph node metastasis (N=1).

STUDY QUALITY
The methodological quality of the included studies was generally poor. There was a lack of well designed diagnostic studies with defined protocols, instead the evidence came from largely retrospective case series of patients referred for PET or PET-CT.

Common flaws included:

- Differential verification of PET results. Patients with suggested primary tumour sites often had biopsies, whereas others didn't. For practical reasons, however, it was reasonable not to biopsy all patients (especially when no primary site was suggested) and sometimes biopsy was contraindicated or refused.
- Incorporation: the PET results influenced which subsequent diagnostic tests were done, and whether any further tests were done at all.

Both differential verification and incorporation would tend to overestimate the sensitivity and specificity of PET. There was also poor reporting of equivocal test results, only 5/45 studies reported indeterminate test results. It is possible that authors classified indeterminate test results as negative for the location of the primary tumour.

Summary of evidence

Diagnostic accuracy

The pooled data (see Table 9.1 and Figures 9.1 to 9.13) suggest relatively high sensitivity and specificity (of the order of 80%) for the detection of the primary tumour . PET-CT tended to have higher sensitivity and specificity than PET. Patient numbers were low for some metastatic presentations. There were fewer than 30 patients in the following presentation groups: peritoneum, bone, liver, lung, pleura or mediastinum and skin, and the corresponding pooled estimates are unlikely to be informative

Two systematic reviews conducted meta-analyses of the utility of PET-CT for the detection of unknown primary tumours. Kwee and Kwee (2009) reported pooled sensitivity and specificity of PET-CT of 84% (95% CI 78% to 88%) and 84% (95% CI 78% to 89%) respectively. Dong et al (2008) estimated the pooled sensitivity and specificity of PET-CT as 81% (95% CI 74% to 87%) and 83% (95% CI 78% to 87%) respectively. Both reviews identified

Five studies reported the rate of indeterminate PET or PET-CT results (where PET images could not be interpreted as either positive or negative for the primary tumour). The pooled rate of indeterminate results was 16% [95% CI 11 to 23%].

Timing of PET

No studies were designed to investigate the timing of PET. All the studies were of PET or PET-CT used after negative presentation specific diagnostic tests.

Survival

There were no studies designed to study the effect of a PET scan on a patient's survival. However, four studies compared overall survival in patients whose tumour was found on PET with those whose tumour was undetected. Two of these studies reported that overall survival was significantly lower in those patients with a primary tumour visible on PET (Guntinas-Lichius et al. 2006; Fencl et al. 2007), two other studies found no difference in overall survival between the groups (Delgado Bolton, 2004 ; Kole et al 1998).

Detection of additional metastases

Eighteen studies reported the rate at which PET or PET-CT revealed previously unknown metastases (see Table 9.2). Previously occult metastases were revealed by PET or PET-CT in approximately 28% of cases. The sensitivity and specificity for the detection of additional metastases is not considered in this review, and it is possible that a

proportion of these metastases were false positives. Also that a significant number of additional metastases were missed by PET.

Change in management

Twenty studies reported the proportion of patients whose management was changed as a result of PET or PET-CT findings (see Table 9.3). PET findings influenced management in approximately 38% of cases. Only one study considered whether these changes in management were correct in hindsight. Joshi et al. (2004) reported the rate of favourable and unfavourable changes in management as a result of PET findings (27% and 5% respectively).

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Table 9.1 Sensitivity and specificity [95% confidence intervals] pooled by metastatic presentation.

Metastatic presentation	Test	Studies	Participants	Q* index	Pooled Sensitivity [95% CI]	Pooled Specficity [95% CI]	Figures
Series including both cervical and extra-cervical presentations*	PET	14	485	0.83	0.88 [0.82 to 0.92]**	0.80 [0.75 to 0.85]**	9.1,9.2
	PET-CT	8	494	0.87	0.88 [0.83 to 0.92]**	0.87 [0.82 to 0.90]	
	PET or PET-CT	22	979	0.86	0.88 [0.84 to 0.91]**	0.83 [0.80 to 0.87]**	
Extracervical metastases	PET	9	225	0.81	0.74 [0.62 to 0.84]**	0.78 [0.70 to 0.85]**	9.3,9.4
	PET-CT	3	92	0.87	0.94 [0.80 to 0.99]**	0.90 [0.79 to 0.96]	
	PET or PET-CT	12	317	0.83	0.80 [0.72 to 0.87]**	0.82 [0.75 to 0.87]**	
Cervical lymph nodes	PET	26	613	0.77	0.79 [0.73 to 0.84]**	0.77 [0.73 to 0.81]**	9.5,9.6
	PET-CT	8	168	0.85	0.90 [0.82 to 0.95]**	0.78 [0.69 to 0.85]**	
	PET or PET-CT	34	781	0.78	0.82 [0.77 to 0.86]**	0.77 [0.74 to 0.81]**	
Axillary lymph nodes	PET	7	27	-	0.78 [0.55 to 0.91]†	0.56 [0.27 to 0.81]†	9.7
	PET-CT	1	6	-	0.67 [0.21 to 0.94]†	0.67 [0.21 to 0.94]†	
	PET or PET-CT	8	33	-	0.76 [0.55 to 0.89]†	0.58 [0.32 to 0.81]†	
Other lymph nodes	PET	3	20	-	0.50 [0.15 to 0.85]†	0.75 [0.51 to 0.90]†	9.8
	PET-CT	2	27	-	1.00 [0.51 to 1.00]†	0.90 [0.79 to 0.99]†	
	PET or PET-CT	5	47	-	0.75 [0.41 to 0.93]†	0.87 [0.73 to 0.94]†	
Peritoneum	PET	2	5	-	1.00 [0.34 to 1.00]†	1.00 [0.44 to 1.00]†	9.9
	PET-CT	3	17	-	1.00 [0.65 to 1.00]†	1.00 [0.72 to 1.00]†	
	PET or PET-CT	5	22	-	1.00 [0.70 to 1.00]†	1.00 [0.77 to 1.00]†	
Brain	PET	7	86	-	0.95 [0.84 to 0.98]†	0.53 [0.36 to 0.70]†	9.10
	PET-CT	3	9	-	1.00 [0.57 to 1.00]†	0.75 [0.30 to 0.95]†	
	PET or PET-CT	10	95	-	0.95 [0.87 to 0.98]†	0.56 [0.39 to 0.71]†	
Bone	PET	4	15	-	0.58 [0.32 to 0.81]†	0.33 [0.06 to 0.79]†	9.11
	PET-CT	3	10	-	1.00 [0.51 to 1.00]†	0.83 [0.44 to 0.97]†	
	PET or PET-CT	7	25	-	0.69 [0.44 to 0.86]†	0.67 [0.35 to 0.88]†	
Liver	PET	4	15	-	0.75 [0.30 to 0.95]†	0.75 [0.41 to 93]†	9.12
	PET-CT	2	6	-	1.00 [0.34 to 1.00]†	0.75 [0.30 to 0.95]†	
	PET or PET-CT	6	21	-	0.89 [0.57 to 0.98]†	0.75 [0.47 to 0.91]	
Lung, pleura or mediastinum	PET	5	26	-	0.54 [0.29 to 0.77]†	0.77 [0.50 to 0.92]†	9.13
	PET-CT	-	-	-	-	-	
	PET or PET-CT	5	26	-	0.54 [0.29 to 0.77]†	0.77 [0.50 to 0.92]†	

Metastatic presentation	Test	Studies	Participants	Q* index	Pooled Sensitivity [95% CI]	Pooled Specficity [95% CI]	Figures
Skin	PET	1	1	-	PET was false positive		
	PET-CT	1	1	-	PET-CT was false positive		
	PET or PET-CT	2	2	-	False positive in both patients		

*Series including both cervical and extra-cervical presentations was included as a category because it was not possible to separate the data into subgroups in some studies.
**Significant heterogeneity (Chi squared test, P<0.10)
†Estimate unlikely to be valid due to small subject numbers, heterogeneity and Q* index not calculated.

Table 9.2 Detection of previously occult metastases

Test	Studies	Participants	Pooled rate of detection of additional metastases [95% CI]
PET	16	608	29% [26 to 33%]
PET-CT	2	77	16% [9 to 25%]
PET or PET-CT	18	685	28% [24 to 31%]

Table 9.3 Change in management as a result of PET

Test	Studies	Participants	Pooled rate of change in management due to PET findings [95% CI]
PET	17	658	35% [32 to 39%]
PET-CT	3	140	52% [44 to 60%]
PET or PET-CT	20	798	38% [35 to 42%]

Table 9.4 Additional outcomes

Study	Test	Presentation	Indeterminate results	Survival outcomes	Detection of additional metastases	Changes in patient management influenced by PET(%)
Ambrosini 2006	PET-CT	Any	N.R.	N.R.	N.R.	N.R.
Au Yong 2005	PET-CT	Any	N.R.	N.R.	N.R.	N.R.
Bruna 2007	PET	Any	N.R.	Overall survival reported, but French language only	10/37 (27%)	14/37 (38%)
Fencl 2007	PET-CT	Any		Overall survival was lower in people with PET+ lesions compared with PET-. Follow-up was short, median O.S. not reached in either group.	N.R.	N.R.
Fleming 2007	PET-CT	Head/neck	N.R.	N.R.	N.R.	N.R.
Freudendberg 2005	PET-CT	Neck	N.R.	N.R.	N.R.	N.R.
Gutzeit 2005	PET-CT	Any	N.R.	N.R.	N.R.	N.R.

Study	Test	Presentation	Indeterminate results	Survival outcomes	Detection of additional metastases	Changes in patient management influenced by PET(%)
Pelosi 2006	PET-CT	Any	N.R.	N.R.	9/39 (23%)	33/68 (49%)
Nabili 2007	PET-CT	Neck (tonsil)	1/5 (20%)	N.R.	N.R.	N.R.
Nanni 2005	PET-CT	Any	N.R.	N.R.	N.R.	N.R.
Nassenstein 2007	PET-CT	Neck	N.R.	N.R.	N.R.	N.R.
Wu 2007	PET-CT	Any	1/34 (3%)	N.R.	N.R.	17/34 (50%)
Wartski 2007	PET-CT	Neck	N.R.	N.R.	3/38 (8%)	23/38 (60%)
Aassar 1999	PET	Neck	N.R.	N.R.	N.R.	N.R.
Albertini 2003	PET	Any	N.R.	N.R.	N.R.	11/41 (27%)
Bohuslavizki 2000	PET	Any	N.R.	N.R.	30/53 (57%)	N.R.
Braams 1997	PET	Neck	N.R.	N.R.	N.R.	N.R.
Delgado Bolton 2004	PET	Any	N.R.	No significant differences (figures not reported)	33/77 (43%)	46/77 (60%)
Ekberg 2007	PET	Neck	N.R.	N.R.	2/18 (11%)	N.R.
Fogarty 2003	PET	Neck	N.R.	N.R.	9/21 (43%)	12/21 (57%)
Garin 2007	PET	Any	N.R.	N.R.	21/51 (41%)	12/51 (24%)
Greven 1999	PET	Neck	N.R.	N.R.	N.R.	N.R.
Guntinas-Lichius 2006	PET	Neck	N.R.	Median OS was approximately 18 months for those with a diagnosed primary tumour versus approximately 70 months for those whose primary remained undetected. Difference in OS was statistically significant using Kaplan Meier test	N.R.	N.R.
Gupta	PET	Cerebral	N.R.		12/22 (55%)	N.R.
Hasasono 1999	PET	Head/neck	N.R.	N.R.	N.R.	N.R.
Junehulsing 2000	PET	Head/neck	N.R.	OS was 64% at 5 years. Median OS not reached	7/27 (26%)	13/27 (48%)
Johansen 2002	PET	Head/neck	N.R.	OS was 57% at 2 years. Median OS not reached		10/42 (24%)
Johansen 2008	PET	Neck	17/62 (27%)	OS was 55% at 3 years [95% C.I. 42 to 68%], disease free survival at 3 years was 65% [95% C.I. 51 to 78%]	4/60 (7%)	15/60 (25%)
Joshi 2004	PET	Extracervical	N.R.	N.R.	12/63 (19%)	favourable 17/63 (27%) unfavourable 3/63 (5%)
Kole 1998	PET	Any	2/29 (7%)	OS was not significantly different between those with a diagnosed primary and those whose primary remained undetected after PET. Median survival OS after PET was approximately 25 months for those with detected primary tumours and 28 months for those with undetected tumours.	5/29 (17%)	4/29 (14%)

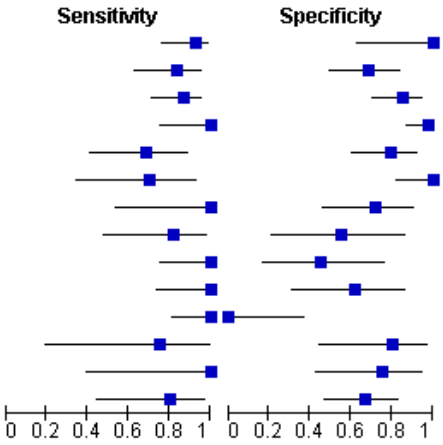
Study	Test	Presentation	Indeterminate results	Survival outcomes	Detection of additional metastases	Changes in patient management influenced by PET(%)
Kolesnikov-Gauthier 2005	PET	Any	4/25 (16%)	N.R.	5/25 (20%)	2/25 (8%)
Klee 2002	PET	Cerebral	N.R.	N.R.	N.R.	N.R.
Lassen 1999	PET	Any	N.R.	N.R.	N.R.	4/20 (20%)
Lonneux 2000	PET	Any	N.R.	N.R.	N.R.	10/24 (42%)
Mantaka 2003	PET	Any	N.R.	Median overall survival not reached. Survival data reported by individual patient.	N.R.	11/25 (44%)
Mevio 2004	PET	Neck	N.R.	N.R.	N.R.	N.R.
Miller 2005	PET	Neck	N.R.	N.R.	N.R.	N.R.
Miller 2008	PET	Neck	N.R.	N.R.	N.R.	N.R.
Monoo 2003	PET	Head/neck	N.R.	5 year OS survival was 46% (from Kaplan Meier curve)	N.R.	N.R.
Panareo 2006	PET	Axillary nodes	N.R.	N.R.	1/6 (17%)	N.R.
Paul 2007	PET	Neck	N.R.	N.R.	N.R.	N.R.
Rades 2001	PET	Any	N.R.	OS at 1 year was 71% for the whole series; 87% and 47% for localised and disseminated disease respectively.	16/42 (38%)	29/42 (69%)
Regelink 2002	PET	Neck	N.R.	N.R.	7/50 (14%)	10/50 (20%)
Safa 1999	PET	Neck	N.R.	N.R.	N.R.	N.R.
Schipper 1996	PET	Neck	N.R.	German language paper		
Scott 2005	PET	Extracervical	N.R.	N.R.	15/31 (48%)	12/31 (39%)
Stoeckli 2003	PET	Neck	N.R.	N.R.	0/18 (0%)	N.R.
Wong 2003	PET	Neck	N.R.	N.R.	N.R.	9/17 (53%)

Abbreviations NR, not reported; PET-CT, fused positon emission tomography/ computed tomography; PET positon emission tomography; OS, overall survival

Figure 9.1 Sensitivity and specificity of PET and PET/CT in studies that included both cervical and extra-cervical presentations

PET Mixed cervical and extra-cervical presentations

Study	TP	FP	FN	TN	Sensitivity	Specificity
Alberini 2003	26	0	2	8	0.93 [0.76, 0.99]	1.00 [0.63, 1.00]
Bohuslavizki 2000	20	10	4	22	0.83 [0.63, 0.95]	0.69 [0.50, 0.84]
Delgado-Bolton 2004	32	6	5	34	0.86 [0.71, 0.95]	0.85 [0.70, 0.94]
Garin 2007	13	1	0	39	1.00 [0.75, 1.00]	0.97 [0.87, 1.00]
Gutzeit 2005	11	6	5	23	0.69 [0.41, 0.89]	0.79 [0.60, 0.92]
Kole 1998	7	0	3	19	0.70 [0.35, 0.93]	1.00 [0.82, 1.00]
Kolesnikov-Gauthier 2005	6	5	0	13	1.00 [0.54, 1.00]	0.72 [0.47, 0.90]
Lassen 1999	9	4	2	5	0.82 [0.48, 0.98]	0.56 [0.21, 0.86]
Lonneux 2000	13	6	0	5	1.00 [0.75, 1.00]	0.45 [0.17, 0.77]
Mantaka 2003	12	5	0	8	1.00 [0.74, 1.00]	0.62 [0.32, 0.86]
Rades 2001	18	8	0	0	1.00 [0.81, 1.00]	0.00 [0.00, 0.37]
Safa 1999	3	2	1	8	0.75 [0.19, 0.99]	0.80 [0.44, 0.97]
Schipper 1996	4	3	0	9	1.00 [0.40, 1.00]	0.75 [0.43, 0.95]
Scott 2005	8	10	2	20	0.80 [0.44, 0.97]	0.67 [0.47, 0.83]



PET-CT Mixed cervical and extra-cervical presentations

Study	TP	FP	FN	TN	Sensitivity	Specificity
Ambrosini 2006	20	1	1	16	0.95 [0.76, 1.00]	0.94 [0.71, 1.00]
Au 2005	33	3	0	26	1.00 [0.89, 1.00]	0.90 [0.73, 0.98]
Bruna 2007	13	1	1	17	0.93 [0.66, 1.00]	0.94 [0.73, 1.00]
Fencl 2007	31	26	19	118	0.62 [0.47, 0.75]	0.82 [0.75, 0.88]
Gutzeit 2005	15	3	2	25	0.88 [0.64, 0.99]	0.89 [0.72, 0.98]
Kaya 2008	24	1	0	18	1.00 [0.86, 1.00]	0.95 [0.74, 1.00]
Nanni 2005	12	1	0	8	1.00 [0.74, 1.00]	0.89 [0.52, 1.00]
Pelosi 2006	24	5	0	39	1.00 [0.86, 1.00]	0.89 [0.75, 0.96]
Wu 2007	17	3	0	14	1.00 [0.80, 1.00]	0.82 [0.57, 0.96]

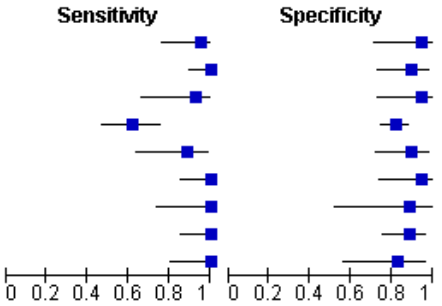


Figure 9.2 Summary ROC Plot of tests: PET and PET-CT for studies including both cervical and extra-cervical presentations.

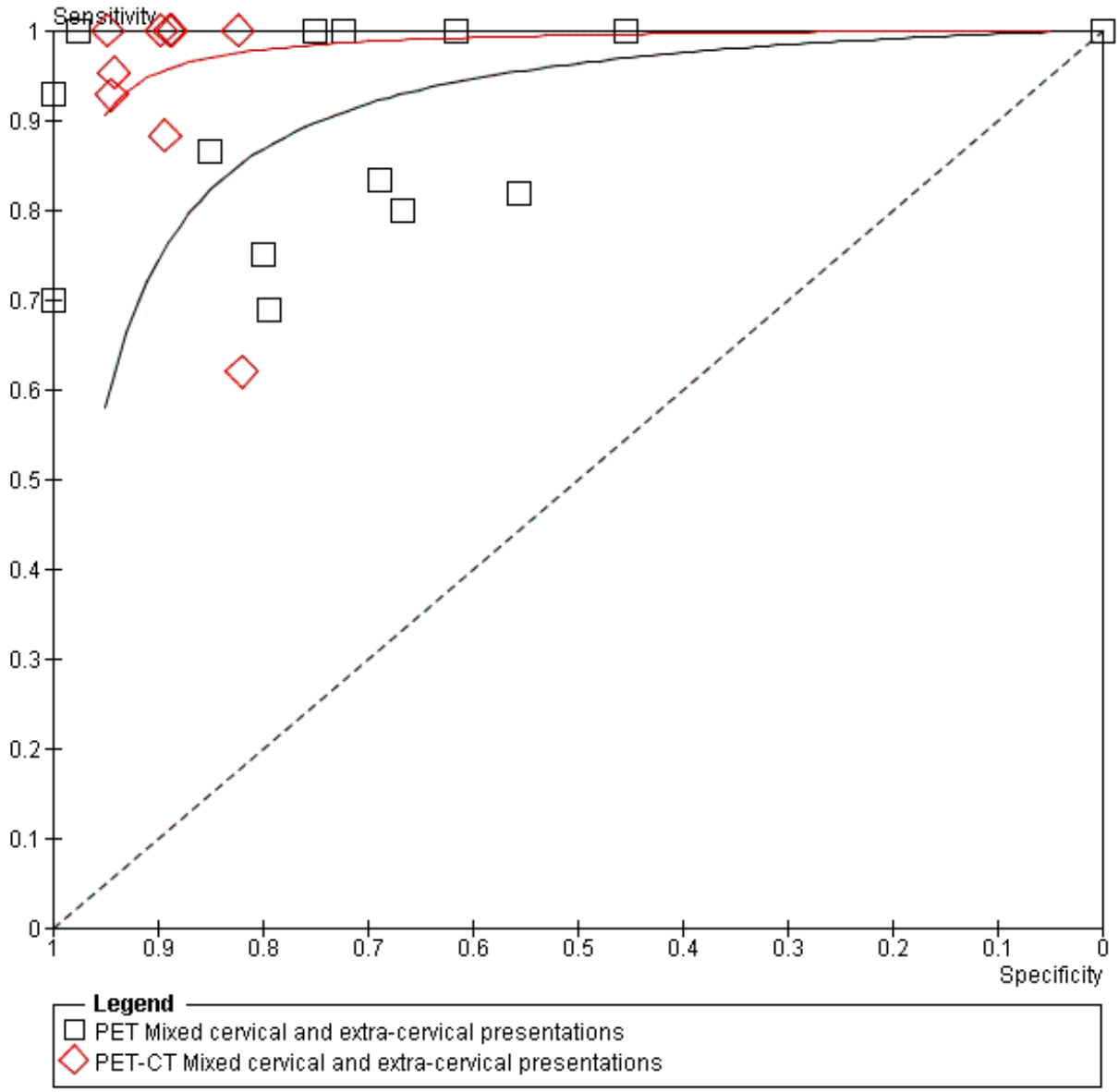
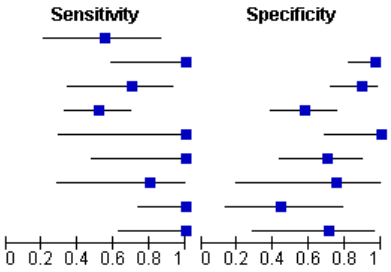


Figure 9.3 Sensitivity and specificity of PET and PET-CT in patients with any extra-cervical presentation.

PET Extra-cervical presentation

Study	TP	FP	FN	TN	Study type	Sensitivity	Specificity
Bohuslavizki 2000	5	0	4	0	Non-comparitive	0.56 [0.21, 0.86]	Not estimable
Garin 2007	7	1	0	28	Non-comparitive	1.00 [0.59, 1.00]	0.97 [0.82, 1.00]
Gutzeit 2005	7	3	3	25	Comparitive	0.70 [0.35, 0.93]	0.89 [0.72, 0.98]
Joshi 2004	16	13	15	18	Non-comparitive	0.52 [0.33, 0.70]	0.58 [0.39, 0.75]
Kole 1998	3	0	0	10	Non-comparitive	1.00 [0.29, 1.00]	1.00 [0.69, 1.00]
Kolesnikov-Gauthier 2005	5	5	0	12	Non-comparitive	1.00 [0.48, 1.00]	0.71 [0.44, 0.90]
Lassen 1999	4	1	1	3	Non-comparitive	0.80 [0.28, 0.99]	0.75 [0.19, 0.99]
Lonneux 2000	12	5	0	4	Non-comparitive	1.00 [0.74, 1.00]	0.44 [0.14, 0.79]
Mantaka 2003	8	2	0	5	Non-comparitive	1.00 [0.63, 1.00]	0.71 [0.29, 0.96]



PET-CT Any extra-cervical presentation

Study	TP	FP	FN	TN	Study type	Sensitivity	Specificity
Gutzeit 2005	9	2	2	14	Comparitive	0.82 [0.48, 0.98]	0.88 [0.62, 0.98]
Nanni 2005	7	1	0	7	Non-comparitive	1.00 [0.59, 1.00]	0.88 [0.47, 1.00]
Pelosi 2006	16	3	0	31	Non-comparitive	1.00 [0.79, 1.00]	0.91 [0.76, 0.98]

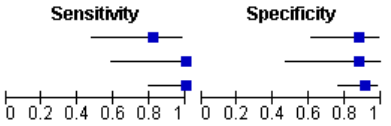


Figure 9.4 Summary ROC Plot of tests: PET and PET-CT, any extra-cervical presentation.

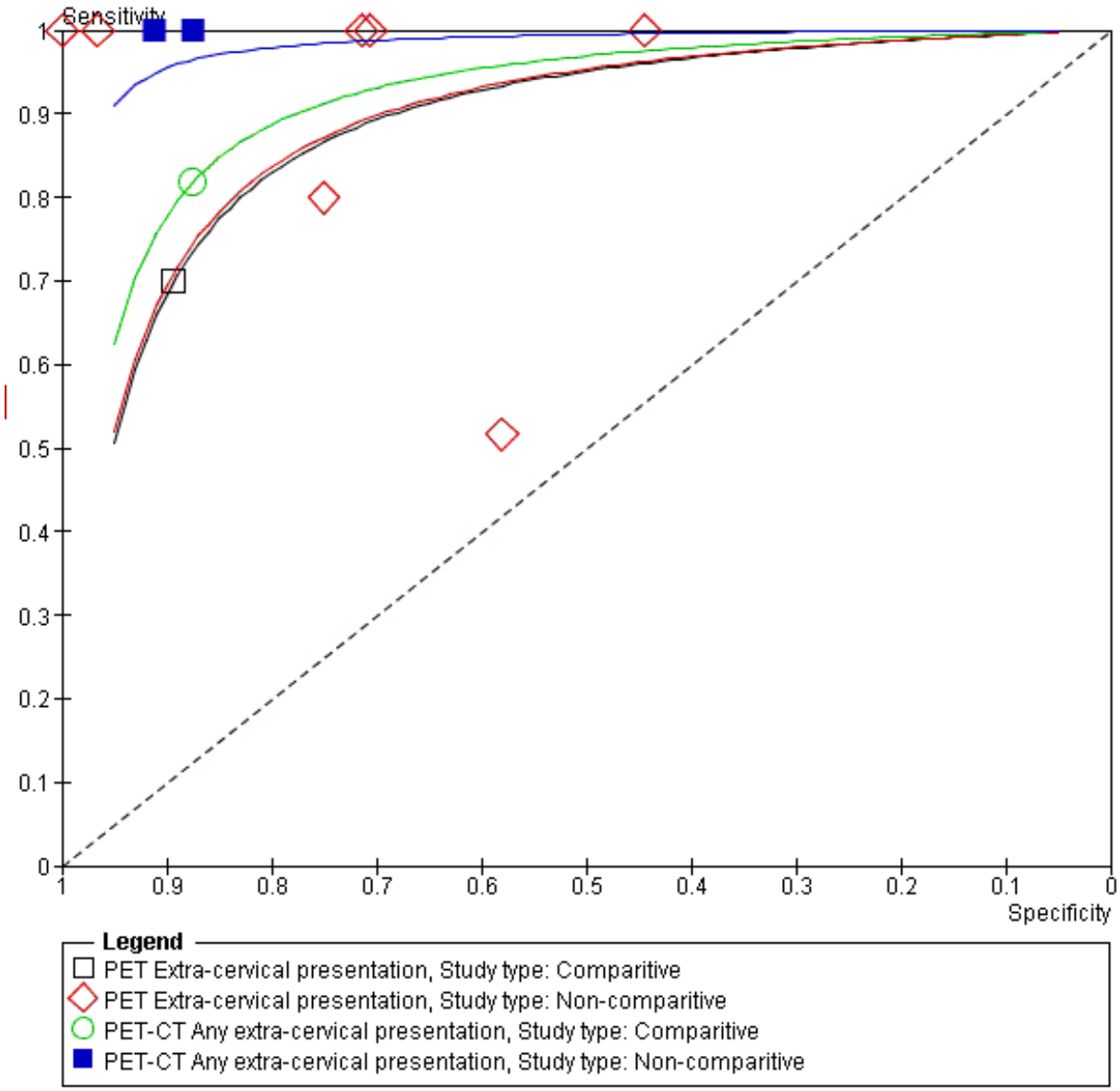
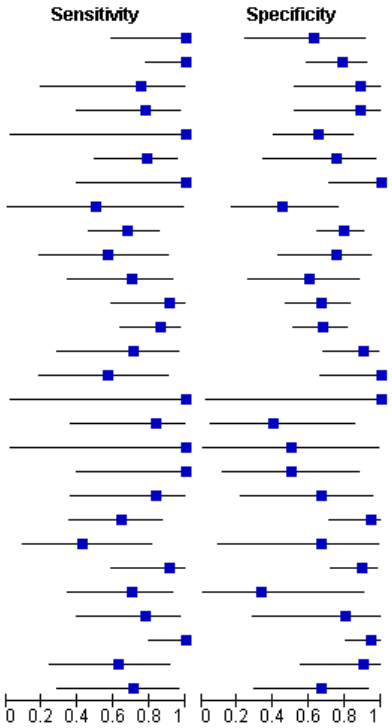


Figure 9.5 Sensitivity and specificity of PET and PET-CT in patients presenting with metastatic cervical lymph nodes

PET Cervical LN

Study	TP	FP	FN	TN	Study type	Sensitivity	Specificity
Aassar 1999	7	3	0	5	Comparitive	1.00 [0.59, 1.00]	0.63 [0.24, 0.91]
Bohuslavizki 2000	15	6	0	22	Non-comparitive	1.00 [0.78, 1.00]	0.79 [0.59, 0.92]
Braams 1997	3	1	1	8	Non-comparitive	0.75 [0.19, 0.99]	0.89 [0.52, 1.00]
Ekberg 2007	7	1	2	8	Non-comparitive	0.78 [0.40, 0.97]	0.89 [0.52, 1.00]
Fogarty 2003	1	7	0	13	Non-comparitive	1.00 [0.03, 1.00]	0.65 [0.41, 0.85]
Freudenberg 2005	11	2	3	6	Comparitive	0.79 [0.49, 0.95]	0.75 [0.35, 0.97]
Garin 2007	4	0	0	11	Non-comparitive	1.00 [0.40, 1.00]	1.00 [0.72, 1.00]
Greven 1999	1	6	1	5	Comparitive	0.50 [0.01, 0.99]	0.45 [0.17, 0.77]
Guntinas-Lichius 2006	17	9	8	35	Comparitive	0.68 [0.46, 0.85]	0.80 [0.65, 0.90]
Gutzeit 2005	4	3	3	9	Comparitive	0.57 [0.18, 0.90]	0.75 [0.43, 0.95]
Hanasono 1999	7	4	3	6	Comparitive	0.70 [0.35, 0.93]	0.60 [0.26, 0.88]
Johansen 2002	10	10	1	20	Non-comparitive	0.91 [0.59, 1.00]	0.67 [0.47, 0.83]
Johansen 2008	18	13	3	27	Non-comparitive	0.86 [0.64, 0.97]	0.68 [0.51, 0.81]
Jungehulsing 2000	5	2	2	18	Non-comparitive	0.71 [0.29, 0.96]	0.90 [0.68, 0.99]
Kole 1998	4	0	3	9	Non-comparitive	0.57 [0.18, 0.90]	1.00 [0.66, 1.00]
Kolesnikov-Gauthier 2005	1	0	0	1	Non-comparitive	1.00 [0.03, 1.00]	1.00 [0.03, 1.00]
Lassen 1999	5	3	1	2	Non-comparitive	0.83 [0.36, 1.00]	0.40 [0.05, 0.85]
Lonneux 2000	1	1	0	1	Non-comparitive	1.00 [0.03, 1.00]	0.50 [0.01, 0.99]
Mantaka 2003	4	3	0	3	Non-comparitive	1.00 [0.40, 1.00]	0.50 [0.12, 0.88]
Mevio 2004	5	2	1	4	Comparitive	0.83 [0.36, 1.00]	0.67 [0.22, 0.96]
Miller 2008	9	1	5	16	Non-comparitive	0.64 [0.35, 0.87]	0.94 [0.71, 1.00]
Monoo 2003	3	1	4	2	Non-comparitive	0.43 [0.10, 0.82]	0.67 [0.09, 0.99]
Nassenstein 2007	10	3	1	25	Comparitive	0.91 [0.59, 1.00]	0.89 [0.72, 0.98]
Padovani 2009	7	2	3	1	Comparitive	0.70 [0.35, 0.93]	0.33 [0.01, 0.91]
Paul 2007	7	1	2	4	Non-comparitive	0.78 [0.40, 0.97]	0.80 [0.28, 0.99]
Regelink 2002	16	2	0	32	Comparitive	1.00 [0.79, 1.00]	0.94 [0.80, 0.99]
Stoeckli 2003	5	1	3	9	Non-comparitive	0.63 [0.24, 0.91]	0.90 [0.55, 1.00]
Wong 2003	5	3	2	6	Comparitive	0.71 [0.29, 0.96]	0.67 [0.30, 0.93]



PET-CT Cervical LN

Study	TP	FP	FN	TN	Study type	Sensitivity	Specificity
Fleming 2007	16	0	1	5	Non-comparitive	0.94 [0.71, 1.00]	1.00 [0.48, 1.00]
Freudenberg 2005	12	0	2	7	Comparitive	0.86 [0.57, 0.98]	1.00 [0.59, 1.00]
Gutzeit 2005	6	1	0	11	Comparitive	1.00 [0.54, 1.00]	0.92 [0.62, 1.00]
Nabili 2007	1	1	4	0	Non-comparitive	0.20 [0.01, 0.72]	0.00 [0.00, 0.97]
Nanni 2005	5	0	0	1	Non-comparitive	1.00 [0.48, 1.00]	1.00 [0.03, 1.00]
Nassenstein 2007	11	4	0	24	Comparitive	1.00 [0.72, 1.00]	0.86 [0.67, 0.96]
Pelosi 2006	8	2	0	8	Non-comparitive	1.00 [0.63, 1.00]	0.80 [0.44, 0.97]
Roh 2009	14	5	2	23	Non-comparitive	0.88 [0.62, 0.98]	0.82 [0.63, 0.94]
Wartski 2007	13	13	1	11	Non-comparitive	0.93 [0.66, 1.00]	0.46 [0.26, 0.67]

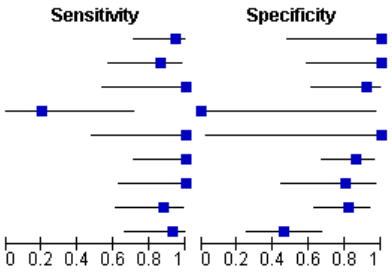


Figure 9.6 Summary ROC Plot of tests: PET and PET-CT for patients presenting with metastatic cervical lymph nodes

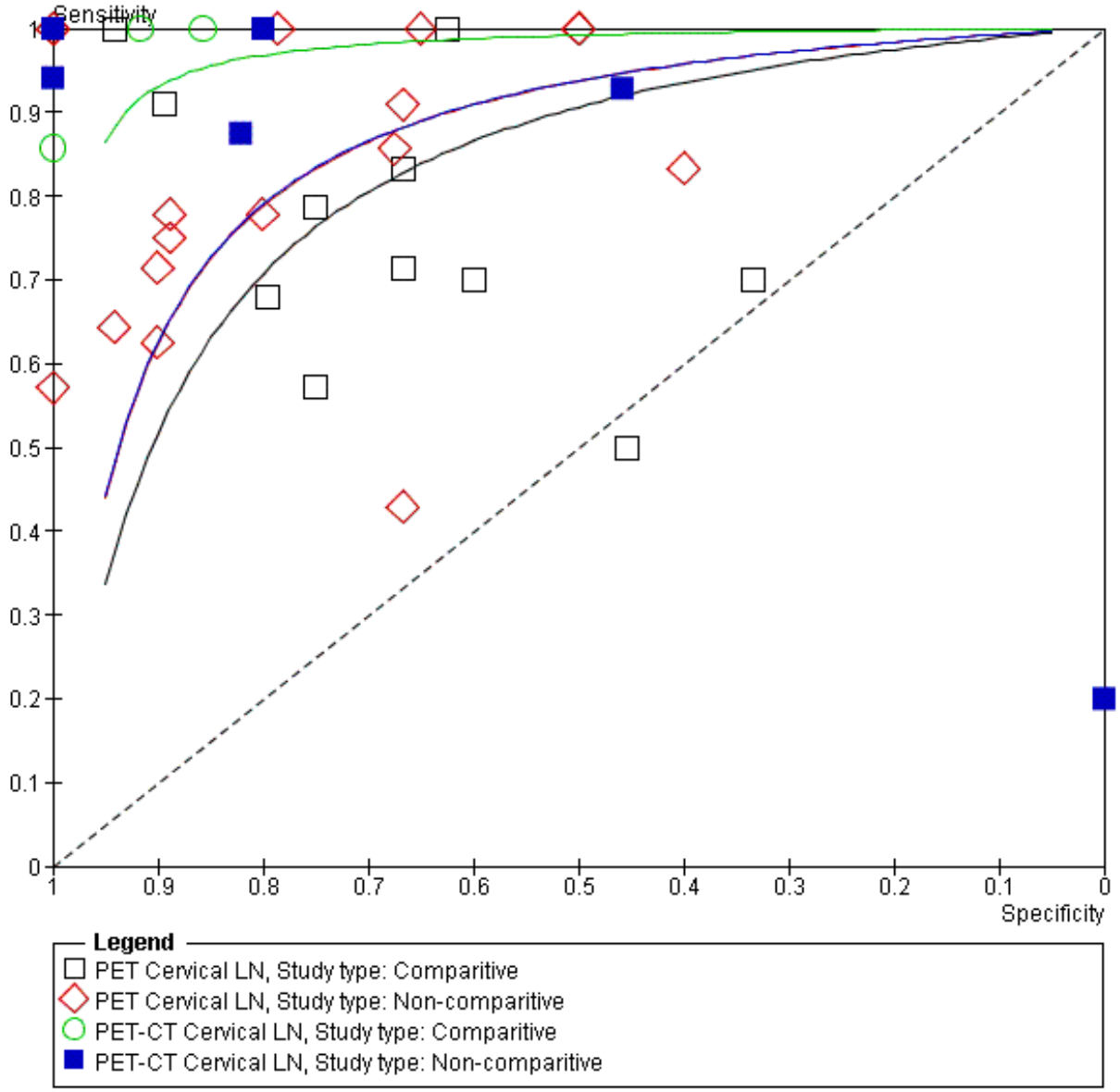


Figure 9.7 Sensitivity and specificity of PET and PET-CT in patients presenting with metastatic axillary lymph nodes

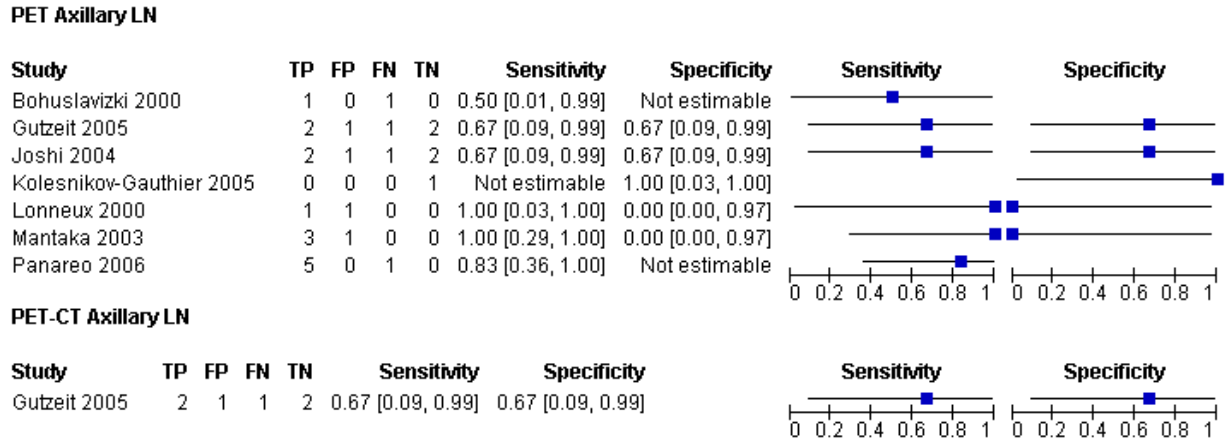


Figure 9.8 Forest plot of tests: PET and PET-CT in patients presenting with metastatic other (not axillary or cervical) lymph nodes.

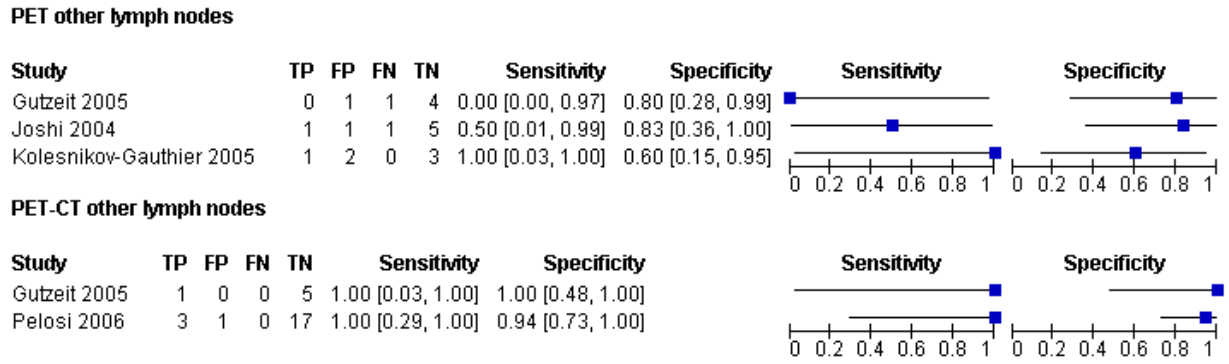


Figure 9.9 Sensitivity and specificity of PET and PET-CT in patients presenting with peritoneal metastases.

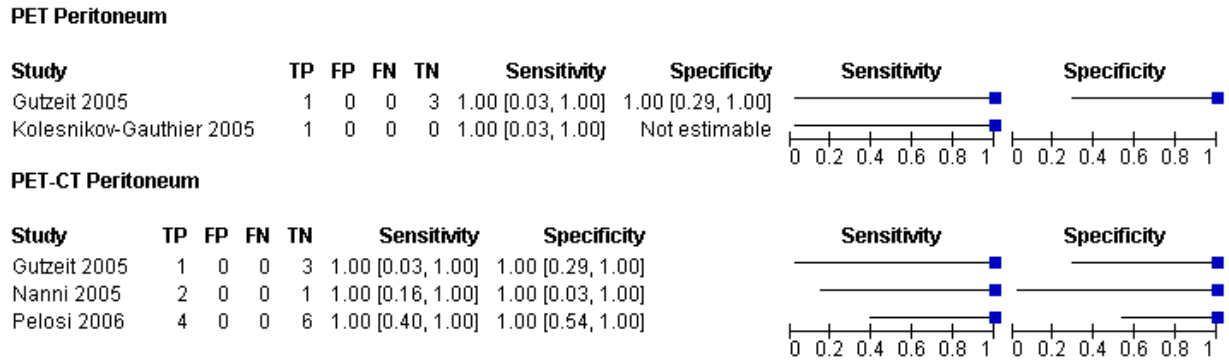


Figure 9.10 Sensitivity and specificity of PET and PET-CT in patients presenting with brain metastases.

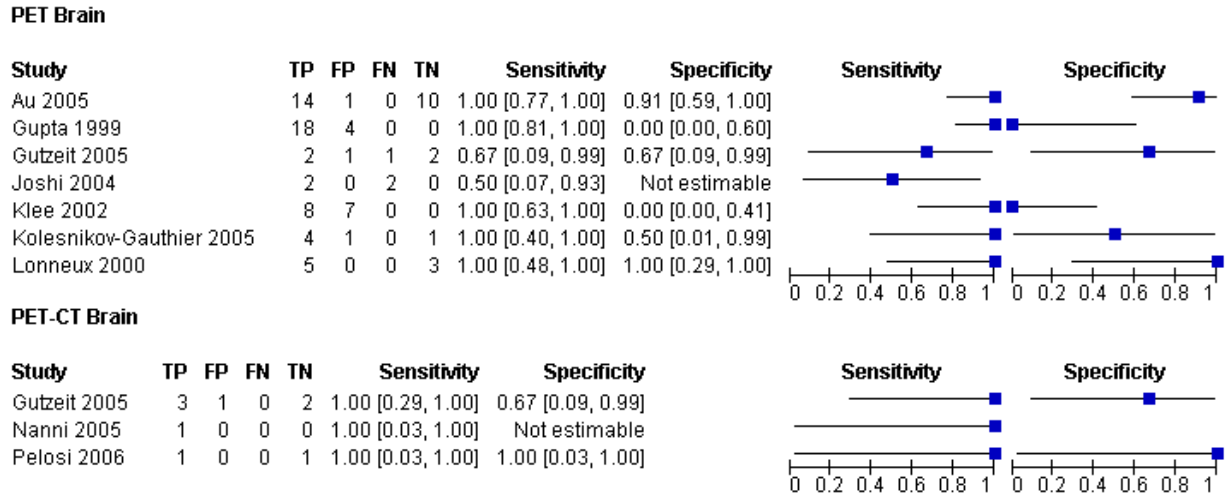


Figure 9.11 Sensitivity and specificity of PET and PET-CT in patients presenting with bone metastases

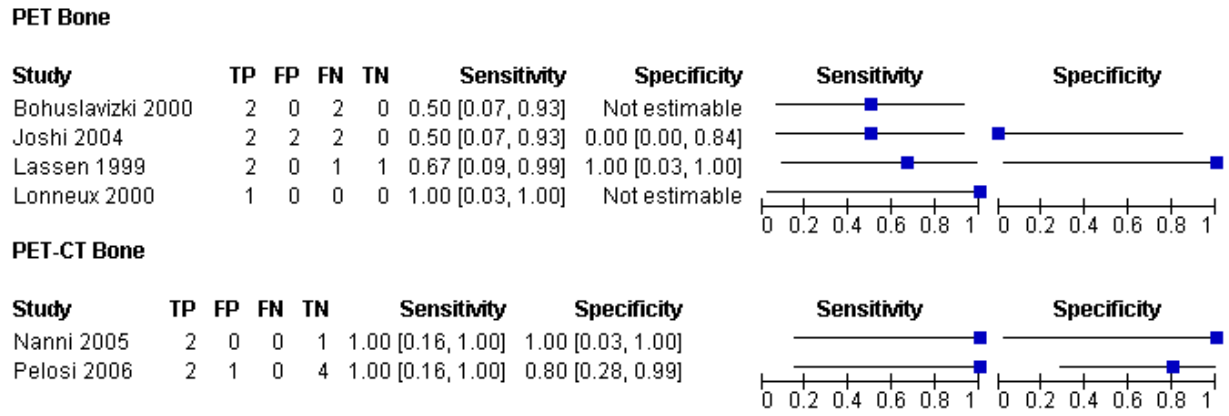


Figure 9.12 Sensitivity and specificity of PET and PET-CT in patients presenting with liver metastases.

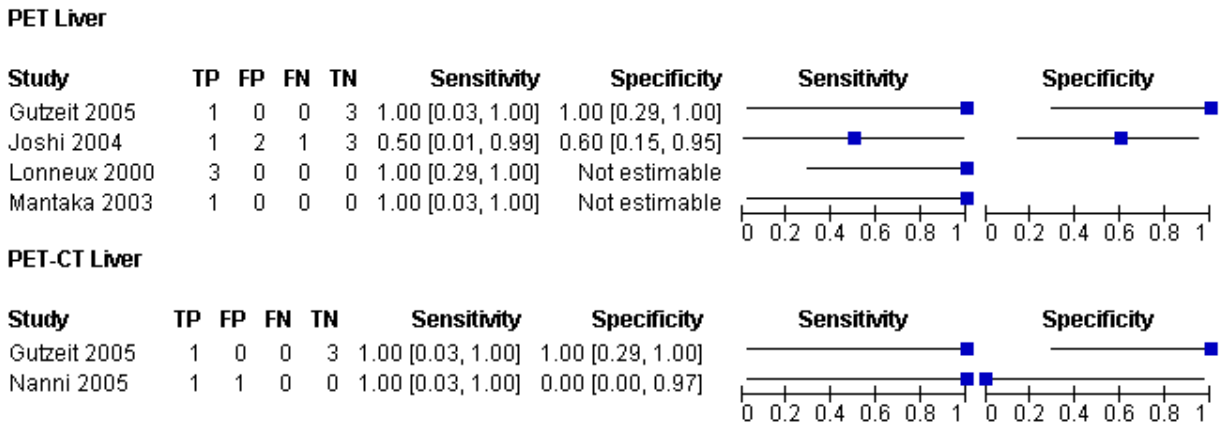
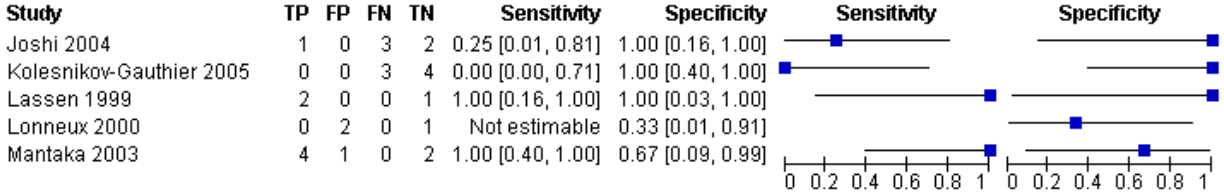


Figure 9.13 Sensitivity and specificity of PET and PET-CT in patients presenting with metastases of the lung, pleura or mediastinum.



9. PET/CT for the identification of the primary tumour in metastatic cancer with unidentified primary

Last updated: 29 / 10 / 2009.

Characteristics of included studies

Aassar-1999

Clinical setting	Patients with metastatic cervical adenopathy (non lymphomatous) and unknown primary tumour. Before PET patients received CT and or MRI, 4/17 had endoscopy before PET.
Participants and Country	17 patients, age 43 to 87. 2 were excluded from the analysis because they had lung primary tumours. FNA of the affected cervical nodes suggested squamous cell carcinoma in 14/15 cases and adenocarcinoma in 1 case. USA
Study design	Retrospective case series
Target condition	Endoscopy with biopsy of any presumed primary tumour (or panendoscopy when there was no putative tumour) and clinical follow-up.
Tests	FDG PET. HR Exact, Siemens. 370 MBq FDG. Attenuation corrected. PET images were evaluated alongside MRI or CT imaging studies.
Follow up	8 to 42 months (mean 29 months)
Study Type	II
PET imaging field	Head, thorax (skull base to thoracic inlet)
Biopsy of metastasis	17/17 (100%) FNA or biopsy. squamous cell carcinoma (16/17, 94%) and adenocarcinoma (1/17, 6%).
Notes	

Alberini-2003

Clinical setting	Patients with histologically confirmed metastases, unidentified primary tumour and no previous history of cancer. Before PET all had biopsy & histology, H&P, lab tests (unspecified), CT, bone scan and IHC. Some had CXR, US, gastric endoscopy and colonoscopy
Participants and Country	41 patients with metastases: bone (n=14), brain (9), lymph nodes (8), liver (6), skin (2), pleura (1) and epidural space (1). Belgium
Study design	Retrospective, case series.
Target condition	Identification of the primary tumour. Reference standard was histology (30/41) and clinical/radiological follow-up (11/41).
Tests	FDG PET. Penn 240H. 220 MBq FDG. No attenuation correction. Comparator tests: chest X-ray, chest CT, CT of abdomen, US of abdomen, gastroscopy and colonoscopy.

Follow up	Minimum 6 months, mean was 24 months
Study Type	II
PET imaging field	Whole body (no brain images)
Biopsy of metastasis	41/41 (100%). adenocarcinoma (20/41, 49%), poorly differentiated carcinoma (5/41, 12%), squamous cell carcinoma (4/41, 10%), small cell carcinoma(5/41, 12%), clear cell carcinoma(1/41, 2%) and neuroendocrine carcinoma(2/41, 5%).
Notes	

Ambrosini-2006

Clinical setting	Patients with histologically confirmed metastases at any site, unidentified primary tumour. Before PET/CT all had biopsy & histology of the metastasis, H&P, lab tests, CT, MRI.
Participants and Country	38 patients with metastases, mean age 59 years (S.D. 11 years; range 41 to 77 years). Italy
Study design	Retrospective case series
Target condition	Identification of the primary tumour. Reference standard was surgery or biopsy of the presumed primary tumour site (20/38) or clinical and radiological follow-up (18/38 patients).
Tests	FDG PET/CT. General Electric Discovery LS & Siemens Biograph Sensation 16. 370 MBq FDG. Attenuation correction
Follow up	Not reported
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	All had biopsy. Histology showed: adenocarcinoma (13/38, 34%), undifferentiated carcinoma (2/38, 5%), epithelial carcinoma (8/38, 21%), squamous cell carcinoma (5/38, 13%), mucoid carcinoma (2/38, 5%), poorly differentiated carcinoma (2/38, 5%) and others (6/38,19%)
Notes	

Au-2005

Clinical setting	Patients with presumed metastases (following biopsy, CT/MRI or tumour marker studies), referred for FDG-PET/CT to locate a primary tumour.
Participants and Country	62 patients with presumed metastases. Presumed metastasis site was brain 25/62 (40%), cervical LN 13/62 (21%), multiple sites 9/62 (15%), bone 3/62 (5%), liver 2/62 (3%), skin 1/62 (2%) and lung 1/62 (2%). 7/62 (11%) were referred for raised CEA or CA125 levels. Hong Kong.
Study design	Retrospective, consecutive case series.
Target condition	Detection of primary tumour site. Reference standard was biopsy of the presumed primary tumour site or clinical follow up.
Tests	FDG-PET/CT. General Electric Discovery LS. Attenuation correction. 370 to 555 MBq FDG.
Follow up	Not reported
Study Type	I

PET imaging field	Whole body
Biopsy of metastasis	Partial, the biopsy rate is not reported. Carcinoma types not reported.
Notes	

Bohuslavizki-2000

Clinical setting	Patients with confirmed metastases but unidentified primary tumour after initial diagnostic work-up. Patients with cervical adenopathy had negative ultrasound, panendoscopy and biopsies.
Participants and Country	Patients with malignant cervical adenopathy 44/53 (83%) or extra-cervical metastases 9/53 (17%). Germany
Study design	Retrospective case series
Target condition	Primary tumour site. Reference standard was clinical/radiological follow up and biopsy of presumed primary site in some cases.
Tests	FDG-PET, Siemens ECAT EXACT model 921 scanner. 370 MBq FDG. No attenuation correction.
Follow up	Not reported
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	All had FNA or biopsy. Cytology or histology was squamous cell carcinoma (30/53, 53%), adenocarcinoma (3/53, 7%), undifferentiated carcinoma (8/53, 15%) and indecisive (11/53, 21%). 1 patient had lymphoepitheilomatous carcinoma.
Notes	Unclear whether patients had CT or MRI before PET

Braams-1997

Clinical setting	Patients with metastatic cervical lymph nodes and unidentified primary tumour. Before PET all patients had negative MRI and/or CT of the head and neck area.
Participants and Country	13 patients with metastatic cervical lymph nodes. Netherlands
Study design	Retrospective case series
Target condition	Identification of the primary tumour. Reference standard was panendoscopy with biopsy of suspicious areas.
Tests	FDG-PET Siemens ECAT 951/31 scanner.185 to 370 MBq FDG.
Follow up	Not reported
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	All had FNA or biopsy. squamous cell carcinoma (10/13, 77%) and one case each (8%) of adenocarcinoma, plasmocytoma and papillary thyroid carcinoma/
Notes	

Bruna-2007

Clinical setting	Patients with metastatic cancer of unidentified primary. Patients had a negative initial diagnostic evaluation (five tests on average).
Participants and Country	37 patients with metastases. Location was cervical or mediastinal lymph nodes (10/37, 27%), inguinal or retroperitoneal nodes (5/37, 14%), axillary nodes (6/37, 16%), bone (5/37, 14%). 14/37 (27%) had multiple sites of metastasis.
Study design	Retrospective case series
Target condition	Identification of the primary tumour. Reference was clinical/radiological follow up and biopsy in selected cases.
Tests	FDG-PET/CT, Siemens Biograph. 5.5 MBq FDG per kilogramme (to a maximum of 550MBq). Attenuation correction.
Follow up	Not reported
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	All had biopsy. adenocarcinoma (17/37, 46%), squamous cell carcinoma (14/37, 38%) and poorly differentiated carcinoma (6/37, 16%).
Notes	French language article with English abstract.

Delgado_x002d_Bolton-2004

Clinical setting	People with metastatic cancer with unidentified primary tumour.
Participants and Country	77 patients. Spain.
Study design	Retrospective case series
Target condition	Reference standard was histology of the primary tumour site biopsy, or clinical follow up.
Tests	FDG-PET (not specified in detail).
Follow up	9 months.
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	Not reported
Notes	Abstract only

Dong-2008

Clinical setting	Patients diagnosed with CUP after conventional diagnostic work-up failed to diagnose a primary tumour
Participants and Country	28 studies were included, with 910 patients. 21 studies evaluated PET (10 prospective). 8 studies evaluated PET/CT (3 prospective).
Study design	Systematic review. Study exclusion criteria were: less than 4 patients, inability to extract sensitivity and specificity, grey literature .
Target condition	Target condition was identification of the primary tumour. The reference standard was histology or follow-up.

Tests	FDG-PET Pooled sensitivity 78% [95%CI 72% to 84%] Pooled specificity 79% [95%CI 74% to 83%] Sensitivity by location was: tonsil 77%, base of tongue 68%, pharynx 100%, breast 100%, thyroid 60%, pelvis 86% and others 67%. Tumours from the base of the tongue accounted for 6/29 false positive FDG-PET scans. Likelihood ratio of a positive test for primary tumour site was 2.95 [95%CI 2.08 to 4.17] Likelihood ratio of a negative test for primary tumour site was 0.36 [95%CI 0.27 to 0.46] Diagnostic odds ratio was 2.56 [95%CI 1.96 to 3.15] FDG-PET/CT Pooled sensitivity 81% [95%CI 74% to 87%] Pooled specificity 83% [95%CI 78% to 87%] Likelihood ratio of a positive test for primary tumour site was 4.19 [95%CI 2.27 to 7.73] Likelihood ratio of a negative test for primary tumour site was 0.22 [95%CI 0.10 to 0.49] Diagnostic odds ratio was 3.19 [95%CI 1.88 to 4.50]
Follow up	Not reported
Study Type	I
PET imaging field	Any
Biopsy of metastasis	Not reported
Notes	

Ekberg-2007

Clinical setting	People with head or neck cancer referred for PET for initial staging, re-staging or unidentified primary tumour.
Participants and Country	18 patients with unidentified primary tumour and head or neck metastases.
Study design	Retrospective consecutive case series.
Target condition	Identification of the primary tumour. Reference standard was not specified, but some patients had biopsy of the presumed primary tumour.
Tests	FDG-PET, General Electric 4096 or Siemens CTI ECAT HR plus. Approximately 400 MBq FDG. Patients also had CT, MRI or both
Follow up	Not reported
Study Type	I
PET imaging field	Head-neck in all cases, in most cases the thorax and abdomen were included.
Biopsy of metastasis	All had biopsy. squamous cell carcinoma (10/18, 56%), adenocarcinoma (3/18,17%), poorly differentiated carcinoma (3/18, 17%), malignant melanoma (1/18, 6%) and carcinosarcoma (1/18, 6%).
Notes	Unclear what cross sectional imaging was done before PET

Fencl-2007

Clinical setting	Patients with suspected malignancy and unidentified primary, referred for PET/CT at a single institution. Initial tests (diagnostic imaging, medical history, clinical examination and lab tests) had not revealed a primary tumour.
Participants and Country	190 patients with Czech Republic.
Study design	Retrospective case series.
Target condition	Identification of the primary tumour site. Reference standard was the histology of the primary tumour and/or clinical/ radiological follow up.

Tests	FDG PET/CT, Siemnens Biograph Duo LSO PET/CT. 350 to 450 MBq FDG.
Follow up	
Study Type	
PET imaging field	
Biopsy of metastasis	82/190 (43%) had histologically proved metastases: poorly differentiated carcinoma (35/82, 43%), adenocarcinoma (24/82, 29%), squamous cell carcinoma (5/82, 6%), mucinous carcinoma (10/82, 12%), spinocellular carcinoma (7/82, 9%) and 1 small cell carcinoma. 108/190 (57%) there was only clinical suspicion of malignancy.
Notes	

Fleming-2007

Clinical setting	Patients with untreated head/neck cancer referred for PET-CT at one of 2 institutions.
Participants and Country	22 patients with unknown primary cancer,
Study design	Retrospective case series
Target condition	Identification of the primary tumour site. Reference standard was histopathology of the putative tumour site.
Tests	FDG PET/CT, Siemens Biograph 16 hi-Rez, 550 MBq FDG. SUV level greater than 2.5 was considered abnormal, hypermetabolic activity in primary, regional and distant disease.
Follow up	Not reported
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	All 22 patients had biopsy of metastasis, histology not reported separately for this subgroup.
Notes	

Fogarty-2003

Clinical setting	People with malignant cervical lymph nodes and unidentified primary tumour. All patients had negative CT, MRI and endoscopy examinations before the PET study.
Participants and Country	21 patients, all with metastatic cervical lymph nodes. Australia.
Study design	Retrospective case series.
Target condition	Identification of primary tumour. Reference standard was biopsy of the presumed primary tumour or clinical follow up.
Tests	FDG-PET, General Electric. 74 to 111 MBq FDG. Attenuation correction.
Follow up	At least 24 months when there was no histological confirmation of the primary tumour.
Study Type	I
PET imaging field	Whole body

Biopsy of metastasis	Histologpathology of the metastatic cervical lymph nodes was reported. squamous cell carcinoma (10/21, 48%), undifferentiated carcinoma (9/21, 43%), adenocarcinoma (1/21, 5%) and small cell carcinoma(1/21. 5%).
Notes	

Freudenberg-2005

Clinical setting	Patients with cervical lymph node metastases of unknown primary tumour. None had received head & neck CT before.
Participants and Country	21 patients.
Study design	Case series
Target condition	Identification of the primary tumour site. Reference standard was histology of the primary site or clinical follow up.
Tests	FDG PET/CT, Siemens Biograph. 360 MBq FDG CT alone, PET alone, PET - CT side by side were also compared.
Follow up	Not reported
Study Type	II
PET imaging field	Whole body
Biopsy of metastasis	All had histology or cytology of the metastasis available: 14/21 squamous cell carcinoma, adenocarcinoma 4/21 and undifferentiated malignancy 3/21
Notes	Possible overlap with Gutzeit 2005

Garin-2007

Clinical setting	Patients with metastatic cancer of unidentified primary tumour. Those with cervical lymph node metastases had panendoscopy, and cervical-thoracic CT. The other patients had CT of the thorax, abdomen and pelvis as well as thyroid US and mammography (for women). Symptom directed endoscopy was also done in some cases.
Participants and Country	51 patients with metastatic cancer of unidentified primary tumour. Presentation was cervical lymph nodes (15/51, 29%), extra-cervical lymph nodes (8/51, 16%), brain (3/51, 6%), and 1/51(2%) each in bone, pleura, oesophagus, pancreas, pericardium and skin. 19 of the patients had multiple metastases.
Study design	Retrospective case series
Target condition	Identification of the primary tumour site. Reference standard was histopathology of the primary tumour site or clinical and radiological follow up.
Tests	FDG-PET (24/51, 41% of patients), General Electric Advance. FDG-PET-CT (37/51, 59% of patients), General Electric Discovery LS. 197 to 540 MBq FDG. Attenuation correction.
Follow up	Average 13 months (range 1 to 32 months).
Study Type	I
PET imaging field	Not reported
Biopsy of metastasis	Biopsy method not reported. Histology of the metastasis was : squamous cell carcinoma (19/51, 37%), adenocarcinoma (20/51, 39%), undifferentiated carcinoma (11/51, 22%) and one sarcomatoid carinoma (2%).
Notes	Mixed PET and PET/CT

Greven-1999

Clinical setting	Patients with metastatic squamous cell carcinoma in cervical lymph nodes, but unidentified primary. All had CT or MRI evaluation of the upper aerodigestive tract, negative for primary tumour.
Participants and Country	13 Patients with metastatic cervical lymph nodes. USA
Study design	Prospective case series
Target condition	Identification of the primary tumour site. Reference standard was panendoscopy, and directed biopsies (sometimes directed by the PET findings).
Tests	FDG-PET Siemens ECAT 951. 370 MBq FDG.
Follow up	Not reported
Study Type	I
PET imaging field	Head-neck
Biopsy of metastasis	All had histopathology confirmed metastasis, squamous cell carcinoma in all cases.
Notes	

Guntinas_x002d_Lichius-2006

Clinical setting	Patients with metastatic cervical lymphadenopathy, but unidentified primary. All had CT scan of the neck, bone scan, US of neck and abdomen and panendoscopy. Only a subset of the patient group (46/69, 67%) had PET, if the other diagnostic tests were negative.
Participants and Country	46 patients. Germany.
Study design	Retrospective case series
Target condition	Identification of the primary tumour. Reference standard was a combination of all the diagnostic tests and clinical follow up.
Tests	FDG-PET (details not reported). Results for MRI, CT, panendoscopy and biopsy are also reported.
Follow up	0.4 to 170 months (mean 29 months)
Study Type	II
PET imaging field	Whole body
Biopsy of metastasis	67/69 patients had FNA. If cytology was inconclusive patients had an open lymph node biopsy (17/69, 25%).squamous cell carcinoma (51/69, 74%), undifferentiated carcinoma (12/69, 17%), adenocarcinoma (2/69, 3%) and miscellaneous (4/69, 6%).
Notes	

Gupta-1999

Clinical setting	Patients with documented or suspected radiographic (CT or MRI) evidence of intracranial metastases, with unknown primary tumour. Only those with histological confirmation of metastases (22/31) had work-up for detection of the primary tumour.

Participants and Country	31 patients, 9 with a history of malignancy.
Study design	Retrospective case series. USA
Target condition	Extra cranial tumours were confirmed using clinical and CT/MRI follow up.
Tests	FDG-PET, General Electric Advance. 10 mCi FDG
Follow up	At least 1 year
Study Type	II
PET imaging field	Whole body
Biopsy of metastasis	22/31 had histological confirmation of brain metastasis.
Notes	The main focus of the study is diagnosis of brain metastasis

Gutzeit-2005

Clinical setting	Patients with metastatic cancer and unidentified primary tumour. All had been extensively tested with conventional diagnostic tests including labs tests, CT, X-ray and endoscopy (where appropriate).
Participants and Country	45 patients. Germany
Study design	Retrospective case series
Target condition	Identification of the primary tumour site. Reference standard was
Tests	FDG PET-CT Siemens Biograph. 350 MBq FDG. No attenuation correction. Comparator tests: PET, CT, PET-CT side by side
Follow up	Not reported
Study Type	II
PET imaging field	Whole body
Biopsy of metastasis	All had biopsy of at least one metastasis: adenocarcinoma 25/45 (56%), squamous cell carcinoma 15/45 (33%) and undifferentiated carcinoma 5/45 (11%).
Notes	Possible overlap with Freundenberg 2005 series

Hanasono-1999

Clinical setting	Patients with head and neck cancer referred for PET scans to identify a primary tumour. Most (18/20, 90%) had CT or MR imaging, but 2/20 had no other imaging.
Participants and Country	20 patients with unidentified metastatic head/neck squamous cell carcinoma.
Study design	Retrospective case series. USA
Target condition	Identification of the primary tumour. Reference standard was clinical follow up or histology of surgical specimen or biopsy.
Tests	FDG-PET, Siemens CTI ECAT EXACT. Attenuation corrected. 10 to 15 millicuries FDG.

Follow up	A minimum of one year in surviving patients
Study Type	II
PET imaging field	Whole body
Biopsy of metastasis	Histology or cytology was squamous cell carcinoma in all cases.
Notes	

Johansen-2002

Clinical setting	Patients with metastatic neck disease (excluding adenocarcinoma) and unidentified primary after negative initial tests. Intial diagnostic tests were: biopsy of lymph nodes, CT/MRI/US of neck, CT-chest, CT-neck, chest X-ray, pan endoscopy with random biopsy of likely sites including tonsillectomy.
Participants and Country	42 patients. Denmark
Study design	Prospective consecutive case series.
Target condition	Identification of the primary tumour. Reference standard was histopathology of the presumed tumour site or clinical follow up.
Tests	FDG-PET, General Electric Advance or 4096 PET scanner. 333 to 565 MBq FDG.
Follow up	Median 22 months (range 3 to 83 months). At least 6 months in surviving patients
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	Most had FNA then excisional biopsy of neck nodes. squamous cell carcinoma (36/42, 86%), undifferentiated carcinoma (5/42, 12%) and 1 large cell carcinoma.
Notes	

Johansen-2008

Clinical setting	Patients with metastatic neck disease and unidentified primary, with histopathology compatible with a head-neck primary tumour. Other diagnostic tests were: biopsy of lymph nodes, CT/MRI/US of neck, CT-chest, CT-neck, chest X-ray, pan endoscopy with random biopsy of likely sites.
Participants and Country	64 patients. Denmark
Study design	Prospective case series.
Target condition	Identification of primary tumour. Reference standard was biopsy of primary tumour site or clinical/radiological follow up.
Tests	FDG-PET, General Electric Advance PET or General Electric Discovery LS PET/CT or Siemens ECAT EXACT. 281 to 534 MBq FDG. Attenuation correction.
Follow up	Median 22 months (range 2 to 47 months).
Study Type	I

PET imaging field	Whole body (43/64, 67%), half body (21/64, 33%).
Biopsy of metastasis	squamous cell carcinoma (44/60, 73%), undifferentiated carcinoma (12/60, 20%) and others (4/60, 7%).
Notes	Some (11/64, 17%) patients had PET/CT scans. Compares PET before or after panendoscopy in terms of delay.

Joshi-2004

Clinical setting	Patients with unknown primary tumours presenting with metastases outside the cervical lymph nodes. None had received systemic treatment for the metastases.
Participants and Country	62 patients. Mean age 57 years (SD 12 years). 52% were female. 8/62 (13%) had a previously diagnosed primary tumour (pathologically incompatible with the metastases). Netherlands.
Study design	Case series. Retrospective. Single group. Patients were identified from the records of a PET scanning department
Target condition	Identification of primary tumour site.Reference standard was histopathology or radiological and clinical follow-up.
Tests	PET specification: Siemens ECAT EXACT. FDG 370 MBq. Visual interpretation by 2 nuclear medicine physicians, blinded to clinical history. PET scans were coded as positive, negative or equivocal No comparator tests.
Follow up	Patients were followed until death or for a minimum of 11 months. Median follow-up in surviving patients was 28 months (range 11 to 51 months).
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	Histopathology of metastasis was available for all 59/62 (94%). adenocarcinoma 40/62 (64%), large cell carcinoma(7/62), squamous cell carcinoma (2/62).
Notes	Supraclavicular nodes included. Unclear what diagnostic tests were done before PET.

Jungehulsing-2000

Clinical setting	Patients with metastatic cervical lymphadenopathy but unidentified primary tumour after initial diagnostic tests. Intial tests were: medical history, physical examination, chest X-ray, complete blood count, cervical and abdominal ultrasound and panendoscopy. If these were negative for the primary tumour then patients had MRI or CT.
Participants and Country	27 patients. Germany.
Study design	Retrospective case series
Target condition	Identification of primary tumour. Reference standard was FNA, biopsy or surgery.
Tests	FDG-PET, Siemens CTI ECAT EXACT. 370 MBq FDG.
Follow up	Not reported
Study Type	I
PET imaging field	Whole body

Biopsy of metastasis	Lymph node specimen was obtained by: excisional biopsy (13/27, 48%), functional or radical neck dissection (3/27, 11%), FNA (10/27, 37%) and 1 by brain surgery. Histology or cytology was squamous cell carcinoma (18/27, 67%), adenocarcinoma (3/27, 11%), undifferentiated carcinoma (3/27, 11%) and others (3/27, 11%).
Notes	

Kaya-2008

Clinical setting	Patients with biopsy confirmed metastasis and unknown primary tumour following physical examination, lab tests and conventional diagnostic tests (CT chest-abdomen-thorax and or MRI, mammography in women, PSA in men and endoscopies).
Participants and Country	43 patients. Turkey
Study design	Retrospective case series
Target condition	Identification of the primary tumour. Reference standard was biopsy of FDG-PET avid lesions. No reference standard was reported for PET-negative patients.
Tests	FDG-PET/CT (GE Discovery ST PET-CT scanner). 18F-FDG dose was 0.14 mCI per kg of body weight, administered 45 minutes before the scan.
Follow up	Median duration of follow up was 9 months (range 2 to 34 months)
Study Type	II
PET imaging field	Whole body
Biopsy of metastasis	The histology of the metastases was not reported
Notes	

Klee-2002

Clinical setting	Patients with cerebral metastases and unknown primary tumour. Before PET patients received various combinations of: chest X-ray, mammography, bronchoscopy, US, abdominal/chest/pelvic CT and lab tests.
Participants and Country	16 patients.
Study design	Retrospective case series.
Target condition	Identification of the primary tumour site. Reference standard was histology from biopsy or resection of the primary tumour or appearance of the lesion on CT / X-ray during follow up.
Tests	FDG PET, General Electric Advance. 370 to 470 MBq.
Follow up	Not reported
Study Type	II
PET imaging field	Whole body
Biopsy of metastasis	Metastasis was confirmed histologically in all cases. adenocarcinoma 14/16, 1 each of malignant melanoma and carcinoma.
Notes	Relatively few had CT before PET, 2/16

Kole-1998

Clinical setting	Patients with metastatic disease with unidentified primary tumour, after conventional diagnostic tests. Intial diagnostic work up depended on clinical presentation, CT was done in those with adenocarcinoma metastases (7/29) or those with symptoms suggesting a primary site.
Participants and Country	27 patients. Netherlands
Study design	Retrospective case series.
Target condition	Primary tumour site. Reference standard was additional diagnostic tests suggested by PET results and clinical follow up.
Tests	FDG PET, Siemens ECAT 951/31. 370 MBq FDG. No attenuation correction.
Follow up	Not reported
Study Type	I
PET imaging field	Whole body.
Biopsy of metastasis	All had histology of metastasis: Melanoma (8/29), squamous cell carcinoma (11/29), adenocarcinoma (7/29) and others (3/29).
Notes	

Kolesnikov_x002d_Gauthier-2005

Clinical setting	Patients with metastatic cancer and unidentified primary, after conventional diagnostic work up. All were at least 18 years old with adenocarcinoma or undifferentiated carcinoma histology. Before PET all patients had H&P, CBC, CT of chest-abdomen-pelvis, mammography for women, gastroscopy, coloscopy and bronchoscopy.
Participants and Country	25 patients. France
Study design	Prospective case series.
Target condition	Identification of the primary tumour. Reference standard was clinical follow up and any histology of biopsy or surgical specimen.
Tests	FDG PET, Siemens ECAT EXACT or General Electric Advance. Mean dose 370 Mbq FDG.
Follow up	Ranged from 10 to 20 months in surviving patients.
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	Histology was available for all patients. adenocarcinoma (well diff. 13/25, poorly diff., 11/25) undifferentiated carcinoma (1/25).
Notes	

Kwee-2009

Clinical setting	Patients with
Participants and Country	11 studies were included
Study design	Systematic review
Target condition	Identification of the primary tumour. Reference standard was histopathology or follow up.
Tests	FDG-PET/CT Sensitivity ranged from 55% to 100% Pooled sensitivity 84% [95%CI 78% to 88%], but there was significant heterogeneity between studies in their estimates of sensitivity. Pooled specificity 84% [95%CI 78% to 89%] (no significant heterogeneity).
Follow up	Variable: depending on the results of FDG-PET/CT
Study Type	I
PET imaging field	Any
Biopsy of metastasis	Hisotology of metastasis was reported in 10/11 studies.
Notes	QUADAS checklist was used (two items were removed since histopathological verification is dependent on the FDG-PET/CT results). Study quality ranged from 42% to 75%, where 100% was the maximum possible quality score.

Lassen-1999

Clinical setting	Patients with metastatic cancer but unidentified primary tumour. Before PET all patients had H&P, X-ray and/or CT and lab tests.
Participants and Country	20 patients. Age between 18 and 75 years. Denmark
Study design	Retrospective case series
Target condition	Identification of the primary tumour. Reference standard was further diagnostic tests guided by PET and/or clinical follow up.
Tests	FDG PET, General Electric Advance. 300 to 400 MBq FDG. No attenuation correction.
Follow up	Not reported
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	All had biopsy of metastasis. squamous cell carcinoma (6/20), poorly diff. adenocarcinoma (8/20), well diff. adenocarcinoma (4/20) and poorly diff. carcinoma (2/20).
Notes	

Lonneux-2000

Clinical setting	Patients with referred for PET to find an unidentified primary tumour. Prior to PET. all patients had a physical examinaton, blood chemistry, liver ultrasound, and presentation dependent tests (breast US, mammography, CT, MRI, cervical US, and panendoscopy).
Participants and Country	24 patients. Belguim
Study design	Retrospective case series.
Target condition	To identify the location of the primary tumour. Reference standard was biopsy (in cases where therapuetic or palliative benefit was expected) or further imaging.
Tests	FDG-PET, Seimens ECAT EXACT. 370 MBq FDG
Follow up	At least six months.
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	Histology of metastasis was known in 22/24 patients. Adenocarcinoma (18/22), squamous cell carcinoma (2/22) and poorly differentiated carcinoma (2/22).
Notes	

Mantaka-2003

Clinical setting	Patients with metastatic cancer and unidentified primary tumour. Before PET patients had H&P, lab tests, most had presentation dependent CT and or MRI and endoscopies.
Participants and Country	25 patients. Germany
Study design	Retrospective case series
Target condition	Identification of the primary tumour. Reference standard was clinical follow up and biopsy/surgery in selected cases.
Tests	FDG PET, Siemens ECAT Exact. 185 to 750 MBq FDG.
Follow up	Ranged from 6 months to 3 years.
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	All metastases were biopsied
Notes	

Mevio-2004

Clinical setting	Patients with metastatic cervical nodes and unidentified primary. Before PET patients typical received panendoscopy and CT.

Participants and Country	11 Patients. Italy
Study design	Retrospective case series.
Target condition	Identification of the primary tumour site. Reference standard was clinical follow up.
Tests	FDG PET, General Electric Advance. Comparator tests were CT, and endoscopy.
Follow up	
Study Type	II
PET imaging field	Whole body
Biopsy of metastasis	
Notes	

Miller-2008

Clinical setting	Patients with metastatic cervical lymph nodes and unknown primary tumour. Before PET all received head and neck examination and CT and/or MRI. Pandendoscopy was done after PET.
Participants and Country	31 Patients. USA
Study design	Retrospective case series
Target condition	Identification of the primary tumour. Reference was panendoscopy with biopsies influenced by PET results.
Tests	FDG PET, 544 MBq FDG.
Follow up	Ranged from 7 to 60 months
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	All squamous cell carcinoma (fine needle aspiration cytology)
Notes	

Monoo-2003

Clinical setting	patients with metastatic cervical nodes and unidentified primary tumour.
Participants and Country	17 patients. Japan
Study design	Retrospective case series
Target condition	Identification of the primary site. Reference standard was not specified in detail.
Tests	FDG PET.
Follow up	Not reported
Study Type	I
PET imaging field	Not reported - probably whole body given putative tumour sites

Biopsy of metastasis	Histopathology of metastasis was: squamous cell carcinoma (12/17), adenocarcinoma (2/17) and one each of adenoid cystic carcinoma, salivary duct carcinoma and malignant melanoma.
Notes	Japanese language, appraised using English abstract.

Nabili-2007

Clinical setting	Patients with occult primary tumours of the tonsil, referred for PET/CT.
Participants and Country	6 patients. USA
Study design	Retrospective case series
Target condition	Location of the primary tumour. Reference standard was histology of tonsillectomy specimen.
Tests	FDG PET/CT, not specified in detail.
Follow up	Not reported
Study Type	I
PET imaging field	not reported
Biopsy of metastasis	not reported
Notes	Unclear what investigations patients had before PET/CT.

Nanni-2005

Clinical setting	Patients with metastatic cancer but unidentified primary after conventional diagnostic procedures (including CT).
Participants and Country	21 patients. Italy
Study design	Retrospective case series.
Target condition	Primary tumour site. Biopsy or surgical specimen of primary tumour site, or clinical follow-up.
Tests	FDG PET/CT, General Electric Discovery LS. 370 MBq FDG.
Follow up	Ranged from 2 to 19 months
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	All had biopsy. Histology was 8/21 (38%) adenocarcinoma, 7/21 (33%) squamous cell carcinoma, 1 (5%) each of poorly differentiated Ca, melanoma, transitional cell Ca, germ cell tumour, spindle cell tumour and flat cell tumour.
Notes	

Nassenstein-2007

Clinical setting	Patients with cervical lymph node metastases of unknown origin. Before PET/CT patients had H&P, US, chest X-ray, complete endoscopic investigation with blind biopsies. 7/39 had ipsilateral or bilateral neck dissection before PET/CT
Participants and Country	39 patients. Germany
Study design	Retrospective case series.

Target condition	Identification of primary tumour. Reference standard was the final diagnosis - but this is not specified further.
Tests	FDG PET/CF Siemens Biograph. 350 MBq FDG. Comparator tests: CT, MRI, PET, PET-CT side by side.
Follow up	Not reported
Study Type	II
PET imaging field	Whole body
Biopsy of metastasis	Histology of excised nodes was: squamous cell carcinoma 27/39, adenocarcinoma 5/39, undifferentiated carcinoma 2/39 and 5/39 others.
Notes	Possible overlap with Freundenberg 2005

Padovani-2009

Clinical setting	Patients with biopsy confirmed malignancy of cervico-cephalic lymph nodes and unknown primary tumour following panendoscopy and conventional imaging. Patients were investigated between 2001 and 2006.
Participants and Country	13 patients. Italy
Study design	Prospective case series
Target condition	Identification of the primary tumour. Reference standard was histopathology of lesions seen on PET and ten random biopsies of other likely sites (5 to the base of the tongue, three to the nasopharynx and two to the tonsillar fossa).
Tests	FDG-PET (Marconi IRIX coincidence detection gamma camera). 370 MBq of 18F-FDG, administered 1 hour before the images were acquired. Comparator tests: CT/MRI
Follow up	No follow-up beyond the random biopsies is reported.
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	Histology of the metastasis was not reported. FNAC was used to confirm malignancy.
Notes	

Panareo-2006

Clinical setting	Patients with axillary lymph node metastases, but unidentified primary tumour after conventional diagnostic procedures. PET was done relatively early.
Participants and Country	6 women. Italy
Study design	Retrospective case series
Target condition	Identification of the primary tumour site. Reference standard was histopathology of MRI guided breast biopsy, surgical specimen and axillary node clearance.
Tests	FDG PET. Comparators CT, MRI, US and Scintigraphy.
Follow up	Not reported.
Study Type	II
PET imaging field	Unclear

Biopsy of metastasis	All had biopsy proven adenocarcinoma.
Notes	Italian, appraised using English abstract.

Paul-2007

Clinical setting	Patients with neck metastases from an unidentified primary tumour. Before PET patients had at least a chest X-ray. US, CT and MRI was done before or after PET.
Participants and Country	14 patients.
Study design	Retrospective case series.
Target condition	Identification of the primary tumour. Reference standard was clinical follow up and histology of the primary tumour in some cases.
Tests	FDG PET or PET/CT General Electric Adavance or Discovery LS
Follow up	Not reported
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	Cytology or histology of metastasis was non-squamous cell carcinoma in all cases: 9/14 adenocarcinoma, 3/14 undifferentiated carcinoma and one each of undifferentiated neuroendocrine tumour and low grade sarcoma.
Notes	Possible overlap with Stoeckli 2003

Pelosi-2006

Clinical setting	Patients with unidentified primary tumour. Before PET/CT patients received lab tests, chest X-ray, abdominal CT, chest CT, MRI, US, mammography and endoscopy (depending on presentation).
Participants and Country	68 patients. Italy
Study design	Retrospective case series.
Target condition	Identfication of the primary tumour. Reference standard was imaging, clinical follow up and/or histology of biopsy or surgery.
Tests	FDG PET/CT, General Electric Discovery ST or Philips Gemini. 222 to 370 MBq
Follow up	Minimum 3 months
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	All had biopsy of metastasis. Histology was adenocarcinoma (18/68, 27%), squamous cell carcinoma (8/68, 12%), undefined carcinoma(32/68, 47%), poorly differentiated carcinoma(5/68, 7%), melanoma (4/68, 6%).
Notes	

Rades-2001

Clinical setting	Patients with metastatic cancer of unknown primary (presentation was lymph nodes 34/42 patients). Before PET patients received a median of 7 diagnostic tests (range 3 to 11), most had CT. Some had MRI and endoscopy (dependent on presentation).

Participants and Country	42 patients. Germany
Study design	Retrospective case series.
Target condition	Indentification of the primary tumour. Reference standard was clinical follow up.
Tests	FDG PET Siemens ECAT. 370 to 740 MBq FDG.
Follow up	Median follow up 15 months (range 4 to 36 months).
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	Histology was available: squamous cell carcinoma (24/42), adenocarcinoma (10/42), anaplastic carcinoma(7/42) and small cell carcinoma(1/42).
Notes	

Regelink-2002

Clinical setting	Patients with cervical metastases of unidentified primary tumour. Before PET patients had received H&P (50/50), CT (30/50) and MRI (24/50) of the head/neck, and panendoscopy (45/50)
Participants and Country	50 patients. The Netherlands
Study design	Retrospective case series
Target condition	Identification of the primary tumour. Reference standard was histology of biopsies taken during panendoscopy or histology of neck dissection. In patients treated with RT only, reference was cytology.
Tests	FDG PET Siemens ECAT or Siemens HR+. 370 to 490 MBq PET. Comparators: CT/MRI imaging, panendoscopy
Follow up	Not reported
Study Type	II
PET imaging field	Whole body, and head/neck
Biopsy of metastasis	Cytology or histology was squamous cell carcinoma (30/50), large cell carcinoma(18/50), adenocarcinoma (1/50) and neuroendocrine (1/50)
Notes	

Roh-2009

Clinical setting	Patients with FNA confirmed cervical metastases of unknown primary, following physical and endoscopic examinations of the upper aerodigestive tract, but before head/neck CT, PET/CT and panendoscopy.
Participants and Country	44 patients. South Korea.
Study design	Case series.
Target condition	identification of the primary tumour. Reference standard was histopathology of lesions identified by PET/CT, CT or panendoscopy, or clinical follow up.

Tests	PET/CT (Siemens Biograph Sensation 16 scanner). Scans done 1 hour after IV injection of 555MBq FDG. Contrast enhanced head/neck CT was the comparator test, using either GE lightspeed QXi or Siemens Somatom Sensation 16 scanners.
Follow up	Median 28 months (range 12 to 48 months).
Study Type	II
PET imaging field	Whole body (skull base to upper thigh).
Biopsy of metastasis	Histology of the metastasis was not reported, but the identified primary tumours were consistent with squamous cell carcinoma.
Notes	

Safa-1999

Clinical setting	Patients with cervical metastases of unidentified primary tumour. Before PET patients had CT (13/14) and MRI (1/14) of the head/neck, and panendoscopy with random biopsies (14/14).
Participants and Country	14 men. USA
Study design	Retrospective case series.
Target condition	Identification of primary tumour site. Reference standard was clinical follow up and biopsy in selected cases.
Tests	FDG PET, Siemens ECAT-953. 370 MBq FDG.
Follow up	Not reported
Study Type	I
PET imaging field	whole body
Biopsy of metastasis	All had biopsy proven squamous cell carcinoma
Notes	

Schipper-1996

Clinical setting	Patients with cervical metastases of unidentified primary tumour.
Participants and Country	16 Patients. Germany
Study design	Prospective case series
Target condition	Location of the primary tumour
Tests	FDG PET, Siemens ECAT. 350 MBq FDG.
Follow up	Follow up ranged from 2 to 22 months
Study Type	I
PET imaging field	
Biopsy of metastasis	
Notes	German language, English abstract appraised.

Scott-2005

Clinical setting	Patients with biopsy proven metastases from unidentified primary tumour, not isolated to the head and neck. Before PET 94% had CT, 19% had presentation directed endoscopy.
Participants and Country	31 patients. Australia
Study design	Retrospective case series.
Target condition	Location of the primary tumour. Reference standard histologic or radiologic confirmation of the primary tumour site.
Tests	FDG PET, General Electric GE
Follow up	Minimum of 1 month
Study Type	I
PET imaging field	Whole body.
Biopsy of metastasis	Histology was adenocarcinoma in 22/31, undifferentiated carcinoma in 6/31 and the remainder were squamous cell carcinoma, small cell or neuroendocrine tumour.
Notes	

Stoeckli-2003

Clinical setting	Patients with cervical metastases of unidentified primary tumour, squamous cell carcinoma cytology. Before PET patients had CT,, chest X-ray and FNA of lymph node metastases. Patients had panendoscopy the day after PET.
Participants and Country	18 patients. Switzerland.
Study design	Retrospective case series
Target condition	Location of primary tumour. Reference standard was panendoscopy, with or without tonsillectomy, with additional PET directed biopsies.
Tests	FDG PET, General Electric Trace 2000 or FDG PET/CT General Electric Discovery LS. 300 to 400 MBq FDG.
Follow up	Not reported
Study Type	I
PET imaging field	Whole body (pelvis to head)
Biopsy of metastasis	Cytology was squamous cell carcinoma in all
Notes	

Wartski-2007

Clinical setting	Patients with metastatic cervical nodes, but unidentified primary tumour after conventional diagnostic procedures. Before PET/CT patients had H&P,US, laryngoscopy, pharyngostomy, random biopsy of likely sites, CT and or MRI. No prior history of head/neck cancer, no radiotherapy or chemotherapy before PET/CT.
Participants and Country	38 patients. France

Study design	Retrospective case series.
Target condition	Identification of the primary tumour. Reference standard was a second panendoscopy with biopsy of the putative tumour site.
Tests	FDG PET/CT General Electric Discovery LS. 4 to 5 MBq FDG per kg.
Follow up	Not reported
Study Type	I
PET imaging field	Whole body
Biopsy of metastasis	Histology was available for all patients: squamous cell carcinoma 32/38, poorly differentiated carcinoma 4/38, mucoepidermoid carcinoma2/38
Notes	

Wong-2003

Clinical setting	Patients with metastatic head or neck cancer and unidentified primary. Before PET all patients received, CT and/or MRI, examination under anaesthesia with random biopsies as well as directed biopsies at suspicious sites.
Participants and Country	17 Patients. UK
Study design	Retrospective case series
Target condition	Location of primary tumour. Reference standard was clinical follow up or histological confirmation of the primary tumour
Tests	FDG PET, Siemens ECAT EXACT. 350 MBq FDG.
Follow up	Minimum of 8 months follow up (to declare true negative).
Study Type	II
PET imaging field	Head, neck and chest
Biopsy of metastasis	Histology of metastasis was: 16/17 squamous cell carcinoma and 1/17 undifferentiated carcinoma.
Notes	Restricted field. PET was read with image registration or alongside anatomical imaging.

Wu-2007

Clinical setting	Patients with metastatic cancer of unidentified primary tumour after conventional diagnostic work-up
Participants and Country	34 patients. China
Study design	Case series
Target condition	Identification of the primary tumour. Reference standard was histology/cytology of primary tumour and/or clinical follow up.
Tests	FDG PET/CT
Follow up	Not reported
Study Type	I

PET imaging field	Not reported, but likely to be whole body
Biopsy of metastasis	Not reported.
Notes	Chinese language study, appraised from abstract only.

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10. Immunohistochemistry for adenocarcinoma of unknown primary

Last updated: 29 / 10 / 2009.

Short summary

There was consistent evidence, in patients with tumours of known primary to support the use of CK7, CK20, TTF-1, ER and PSA in narrowing the differential diagnosis of metastatic adenocarcinoma.

Immunohistochemistal markers with particularly good sensitivity and specificity included: TTF-1 positivity for lung cancer, PSA positivity for prostate cancer and CK7-/CK20+ for colorectal cancer.

Rationale

Basic H+E staining can lead to a firm histological diagnosis in many instances, based on morphological appearances of tumour tissue alone. In some circumstances however, appearances are suggestive of several possible organs of origin. In this situation, IHC analysis of the expression of two antigens, (CD20 and CD7), can result in greater certainty about the likely tissue of origin. These findings have been validated in patients in whom the primary site of malignancy is identified.

For patients with malignancy of undefined primary origin with a basic histological diagnosis of adenocarcinoma, CD20 and CD7 staining is employed with the aim of predicting the organ of origin, (and hence tumour behaviour) but it is uncertain whether basing further diagnostic tests and treatment on this approach is valid. There is also uncertainty about the optimal panel of IHC tests, and the order in which they should be applied.

This PICO is intended to examine the optimal use of IHC in patients found to have adenocarcinoma of undefined primary origin after initial standard histological examination which has excluded melanoma, lymphoma, sarcoma, squamous carcinoma, teratoma. IHC specifically for hormone receptor expression and expression of EGFR etc is included in the potential "panel" of tests.

Methods

Study types

Any study design.

Target condition

Identification of the primary tumour organ of origin.

Participants

People with adenocarcinoma of undefined primary origin, (who have a tissue biopsy of their metastasis).

Index tests

Immunohistochemistry, including the following antibodies:- CK7, CK20, TTF-1, PLAP, Oestrogen receptor, EGFR and PSA in the first instance.

Reference standard

Histopathological confirmation of the primary tumour.

Study selection

An initial list of papers was selected by the information specialist (SA). One reviewer then selected potentially relevant papers from this list, based on their titles and abstracts. These were ordered and checked against the inclusion criteria.

Data extraction and synthesis

One reviewer (NB) extracted data into an Excel spreadsheet and then into the Cochrane Review Manager program. Only published data were included. The positivity for each of the tumour markers was calculated for each study of the primary sites: biliary, breast, colon, endometrium, kidney, lung, oesophagus, ovary mucinous, ovary non-mucinous, pancreas, prostate, salivary gland, stomach and urothelium. The figures from the individual studies were pooled to give an overall estimate. For each study the sensitivity and specificity of each marker for individual primary tumour sites were calculated (for tumour sites with at least five cases in the study).

Quality assessment

Heterogeneity assessment

There was no statistical assessment of heterogeneity, but plots of sensitivity and specificity were examined to identify inconsistency between studies. Potential sources of such inconsistency were: immunohistochemistry

technique, sample type (cell block or tissue) and study population.

Search results

The literature searches found 160 papers of which 32 were included. Studies were retrospective reviews of surgical pathology archives. Tot (2002) was a review article summarising evidence about CK7 and CK20 as bio markers in primary and metastatic adenocarcinoma. Studies already included in this review were excluded from the CK7 and CK20 analyses to avoid double counting of patients.

The original literature search identified a single paper about PLAP for the differential diagnosis of metastatic adenocarcinoma and metastatic germ cell tumours (DeYoung and Wick, 2000). Two additional studies were identified from the reference list of this paper, and a broader MEDLINE search, combining the MESH term "Neoplasm Metastasis" with "placental alkaline phosphatase", returned 40 papers of which two were included.

STUDY QUALITY

The studies were retrospective reviews of tumour samples selected on the basis of their histopathological analysis. Many studies excluded patients who never had a primary tumour identified, this would tend to inflate the specificity of immunohistochemistry markers.

Some studies examined highly selected populations (for example patients with mucinous adenocarcinomas, brain metastases, liver metastases, ovary metastases or bladder metastases) and may not reflect the diagnostic utility of IHC markers in the general CUP population. Data were sparse for certain primary tumour types (salivary gland and oesophagus).

There were methodological differences between studies in the details of the immunohistochemical technique (such as fixation time and antibody type), which could contribute to variability between study results. As a result some of the studies used cell blocks prepared from serous effusions or fine needle aspirates rather than tissue samples.

The definition of marker positivity also varied between studies. Some considered any staining as positive, whereas others specified a minimum percentage of stained cells (ranging from 5% to 50%) or used a staining intensity criterion.

In some cases studies reported results by tumour site only, but not the tumour histology, so it was sometimes unclear whether tumours were adenocarcinoma or not.

Summary of evidence

IMMUNOHISTOCHEMICAL MARKERS FOR THE DIAGNOSIS OF UNKNOWN PRIMARY TUMOURS

Individually the immunohistochemical markers were not specific enough to be used in isolation. The exceptions were for TTF-1 and PSA which had high specificity for lung and prostate adenocarcinoma respectively. The proportion of metastases staining positive for each of the IHC markers was estimated by combining the figures from the individual studies for each primary tumour site (see Figure 10.1).

The immunoreactivity to each of the IHC markers for each primary site are summarised in Figures 10.3 to 10.18. Only studies with at least five patients for a given primary site are included, so sensitivity/specificity data are lacking for some combinations of IHC marker and primary tumour site.

Cytokeratin 7 (CK7)

CK7 was widely expressed and as a result CK7 positivity was not very specific for any tumour type. Kidney, colon and prostate primary tumours tended to CK7 negative. Due to the large proportion of patients with colorectal adenocarcinoma CK7 negativity was reasonably sensitive and specific for a colorectal primary (see Figure 10.6).

Cytokeratin 20 (CK20)

CK20 was commonly positive in colon and urothelial tumours. Approximately half biliary, stomach and pancreatic tumours were also positive for CK20.

CK7 and CK20 profiles

A number of studies reported the distribution of CK7 / CK20 phenotype according to the primary tumour site. Data from these studies were pooled in Figure 2. Primary tumour sites tended to fall into groups depending on their combined CK7/CK20 immunoreactivity. Adenocarcinomas of the oesophagus, ovary mucinous, and urothelium tended to be CK7+CK20+. Colorectal tumours tended to be CK7-CK20+ as were around 20% of stomach adenocarcinomas. Breast, endometrium, ovary non-mucinous, lung and salivary gland adenocarcinomas tended to be CK7+CK20-. Prostate and kidney adenocarcinomas tended to be CK7-CK20-. Pancreatic, biliary and stomach adenocarcinomas tended to be CK7+ with either CK20+ or CK20-.

CK7 and CK20 immunoreactivity was highly variable for stomach primary tumours (see Figure 10.16). It is possible that tumours coded as stomach primary were really a heterogeneous group.

Prostate Specific Antigen (PSA)

PSA was sensitive and highly specific for prostate primary tumours (see Figure 10.15).

Thyroid transcription factor (TTF-1)
Positive immunostaining for TTF-1 was highly sensitive and specific for lung primary tumours. Metastases or effusions from breast or colon primary tumours were always negative for TTF-1. Data were lacking for thyroid tumours, however, and these are also known to positive for TTF-1.

Oestrogen Receptor (ER)
About half of breast, endometrium and ovarian primaries were ER positive. ER positivity was reasonably specific for breast primary tumours, however, because these other ER+ primary cancers were less common than breast cancer.

Progesterone Receptor (PR)
Positive in about half of breast, endometrium and ovarian primaries. Again PR was reasonably specific for breast primary tumours, however, because these other PR+ primary cancers were less common than breast cancer. Compared with other studies, Perry et al (1997) reported relatively high levels of PR immunostaining. The authors suggested it might related to necrosis or an electrocautery artefact.

Placental alkaline phosphatase (PLAP)
DeYoung and Wick (2000) combined data from two studies (Wick et al , 1987; Hamilton-Dutoit et al, 1990) to estimate the rate of PLAP immunoreactivity in various primary tumours. Their evidence suggests placental alkaline phosphatase expression is highly sensitive for germ cell tumours: 90% of embryonal carcinomas and 95% of seminomas showed immunoreactivity for PLAP. A number of other tumour types, however were also positive for PLAP. Rates of immunoreactivity were: ovarian (both serous and mucinous adenocarcinoma), breast, gastric , colon , carcinomas.

This high sensitivity suggests that PLAP is a useful screen for germ cell tumours, but immunoreactivity for PLAP alone is not sufficient to make diagnosis of metastatic germ cell tumour.

Evidence from case reports suggests that PLAP is useful in identifying curable germ cell tumours in patients with presentations suggestive of incurable metastatic carcinoma. Shek et al (1996) described two patients with metastatic germ cell tumours presenting with cervical lymphadenopathy. PLAP was positive in both cases, although serum β-HCG and AFP were negative in one patient. Wehrshutz et al (2002) reported a patient whose clinical presentation was consistent with incurable pancreatic cancer but histopathology and PLAP immunoreactivity confirmed metastatic seminoma which completely responded to treatment.

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Figure 10.1 Proportion of metastases from each primary tumour sites that were positive for each IHC marker. The figures were calculated using pooled data from studies.

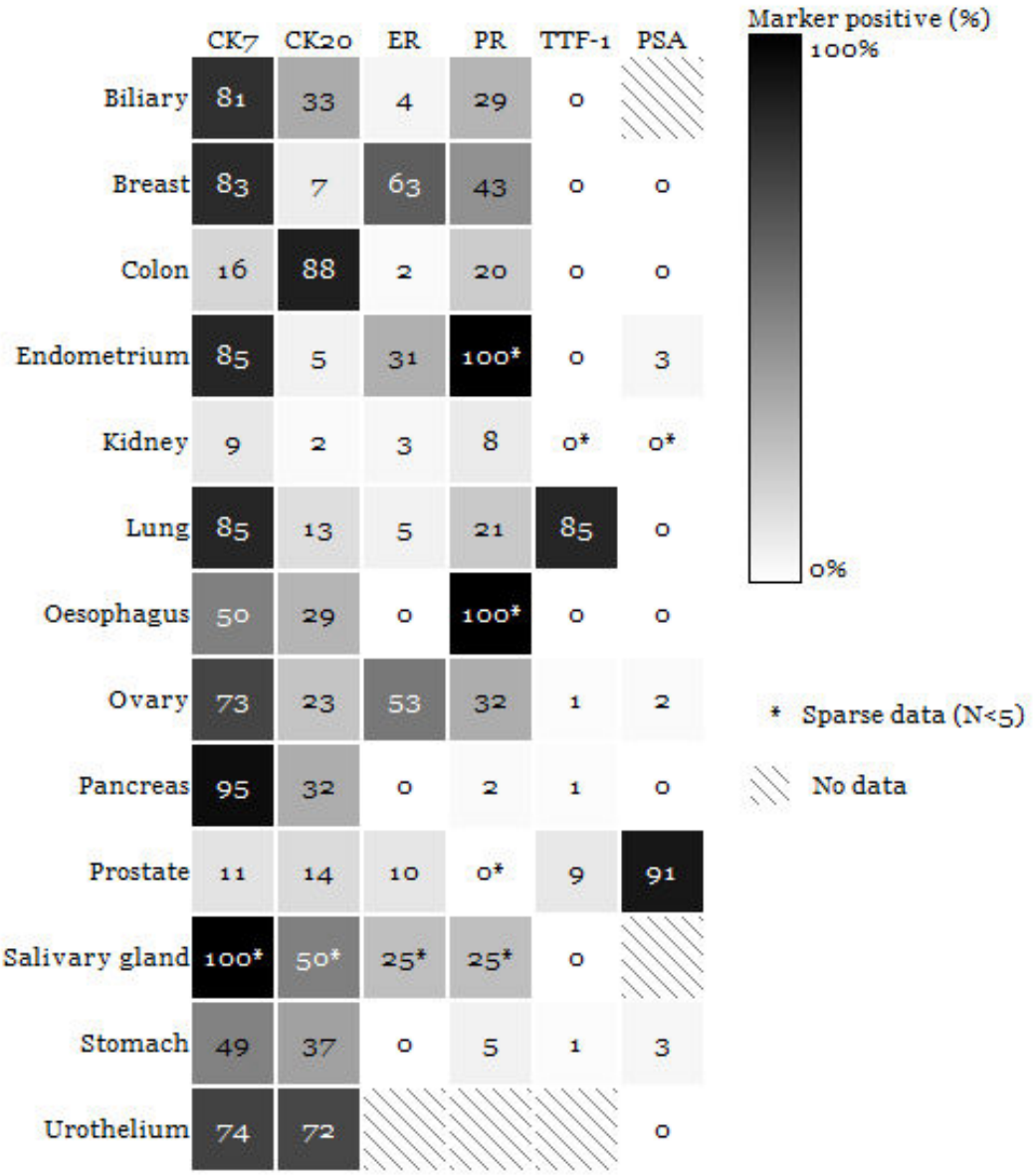
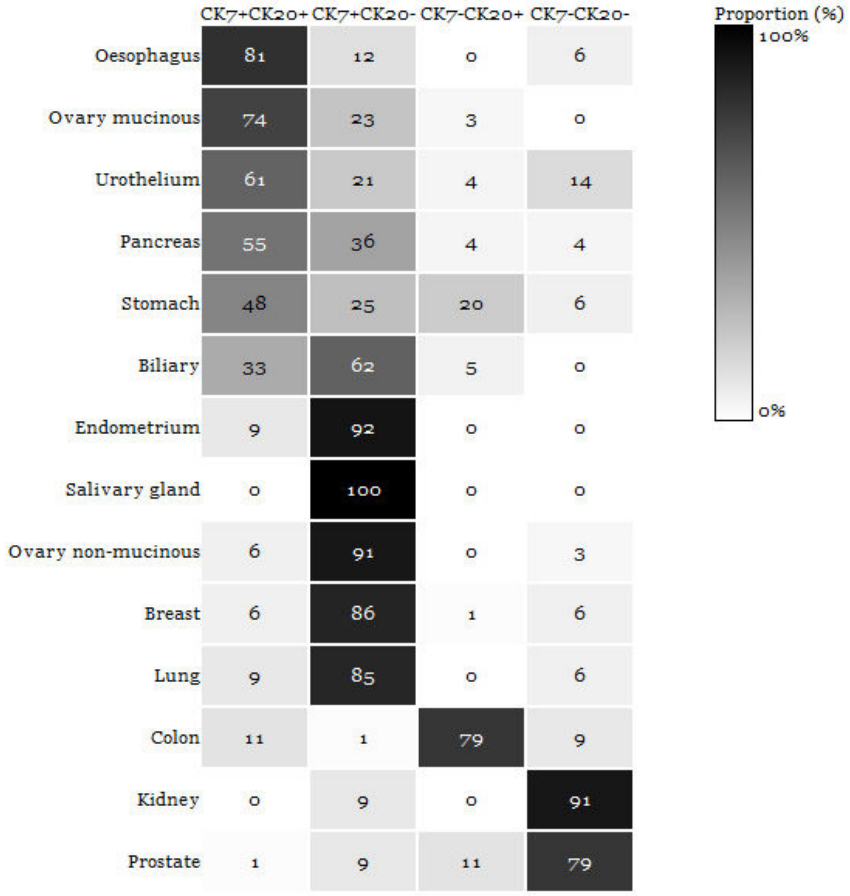


Figure 10.2 CK7 and CK20 expression profile for each primary tumour site. The figures were calculated using pooled data from studies.

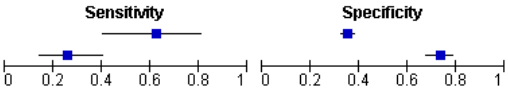


Not all studies reported all possible combinations of CK7 and CK20 for all possible tumour sites, as a result row totals do not necessarily sum to 100%

Figure 10.3 Biliary primary tumours.

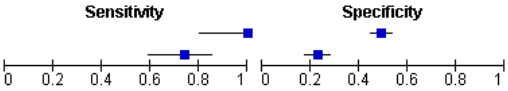
Negative CK20 for biliary primary tumour

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Tot 2002	15	710	9	391	Histopathology	Biliary	0.63 [0.41, 0.81]	0.36 [0.33, 0.38]
Park 2007	13	70	37	194	Histopathology	Biliary	0.26 [0.15, 0.40]	0.73 [0.68, 0.79]



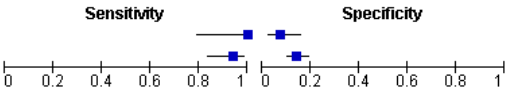
Positive CK7 for biliary primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Tot 2002	17	281	0	275	Histopathology	Biliary	1.00 [0.80, 1.00]	0.49 [0.45, 0.54]
Park 2007	37	203	13	61	Histopathology	Biliary	0.74 [0.60, 0.85]	0.23 [0.18, 0.29]



Negative ER for biliary primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Nash 2003	16	70	0	6	Histopathology	Biliary	1.00 [0.79, 1.00]	0.08 [0.03, 0.16]
Park 2007	47	225	3	39	Histopathology	Biliary	0.94 [0.83, 0.99]	0.15 [0.11, 0.20]



CK7+/CK20- for biliary primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Tot 2002	13	269	4	407	Histopathology	Biliary	0.76 [0.50, 0.93]	0.60 [0.56, 0.64]

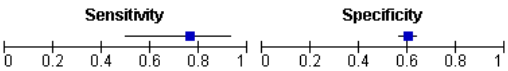
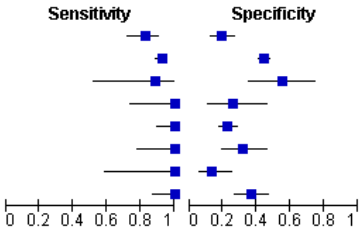


Figure 10.4 Breast primary tumours, CK7 and CK20

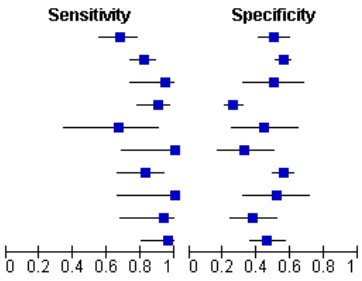
Negative CK20 for breast primary tumours

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Longatto 1997	58	106	12	25	Cytopathology	Breast	0.83 [0.72, 0.91]	0.19 [0.13, 0.27]
Tot 2002	254	471	21	379	Histopathology	Breast	0.92 [0.89, 0.95]	0.45 [0.41, 0.48]
Wauters 1995	8	12	1	15	Histopathology	Breast	0.89 [0.52, 1.00]	0.56 [0.35, 0.75]
Azoulay 2005	12	20	0	7	Histopathology	Breast	1.00 [0.74, 1.00]	0.26 [0.11, 0.46]
Dennis 2005	35	198	0	59	Histopathology	Breast	1.00 [0.90, 1.00]	0.23 [0.18, 0.29]
Perry 1997	15	36	0	17	Histopathology	Breast	1.00 [0.78, 1.00]	0.32 [0.20, 0.46]
Giordana 2001	7	50	0	8	Histopathology	Breast	1.00 [0.59, 1.00]	0.14 [0.06, 0.25]
Chu 2000	26	59	0	34	Histopathology	Breast	1.00 [0.87, 1.00]	0.37 [0.27, 0.47]



Positive CK7 for breast primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Longatto 1997	48	65	23	66	Cytopathology	Breast	0.68 [0.55, 0.78]	0.50 [0.42, 0.59]
Tot 2002	100	198	22	253	Histopathology	Breast	0.82 [0.74, 0.88]	0.56 [0.51, 0.61]
Scarpatetti 2002	18	17	1	17	Histopathology	Breast	0.95 [0.74, 1.00]	0.50 [0.32, 0.68]
Park 2007	45	195	5	69	Histopathology	Breast	0.90 [0.78, 0.97]	0.26 [0.21, 0.32]
Azoulay 2005	8	15	4	12	Histopathology	Breast	0.67 [0.35, 0.90]	0.44 [0.25, 0.65]
Strickland-Marmol 2007	10	23	0	11	Histopathology	Breast	1.00 [0.69, 1.00]	0.32 [0.17, 0.51]
Dennis 2005	29	114	6	143	Histopathology	Breast	0.83 [0.66, 0.93]	0.56 [0.49, 0.62]
Wauters 1995	9	13	0	14	Histopathology	Breast	1.00 [0.66, 1.00]	0.52 [0.32, 0.71]
Perry 1997	14	33	1	20	Histopathology	Breast	0.93 [0.68, 1.00]	0.38 [0.25, 0.52]
Chu 2000	25	50	1	43	Histopathology	Breast	0.96 [0.80, 1.00]	0.46 [0.36, 0.57]



CK7+/CK20- for breast primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Jang 2001	7	35	1	13	Cytopathology	Breast	0.88 [0.47, 1.00]	0.27 [0.15, 0.42]
Chu 2000	25	59	1	72	Histopathology	Breast	0.96 [0.80, 1.00]	0.55 [0.46, 0.64]
Drlicek 2004	4	25	0	21	Histopathology	Breast	1.00 [0.40, 1.00]	0.46 [0.31, 0.61]
Azoulay 2005	8	2	4	7	Histopathology	Breast	0.67 [0.35, 0.90]	0.78 [0.40, 0.97]
Fernandez 2001	10	37	4	27	Histopathology	Breast	0.71 [0.42, 0.92]	0.42 [0.30, 0.55]
Tot 2002	57	225	8	403	Histopathology	Breast	0.88 [0.77, 0.95]	0.64 [0.60, 0.68]

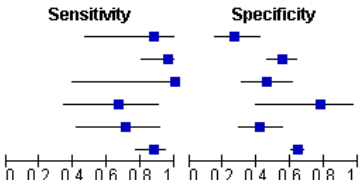
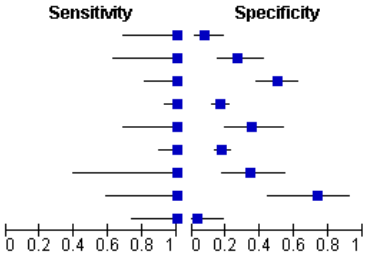


Figure 10.5 Breast primary tumours, TTF-1, ER and PR

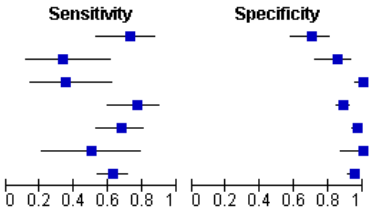
Negative TTF-1 for breast primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Saad 2004	10	48	0	4	Cytopathology	Breast	1.00 [0.69, 1.00]	0.08 [0.02, 0.19]
Jang 2001	8	35	0	13	Cytopathology	Breast	1.00 [0.63, 1.00]	0.27 [0.15, 0.42]
Hecht 2001	18	35	0	35	Cytopathology	Breast	1.00 [0.81, 1.00]	0.50 [0.38, 0.62]
Park 2007	50	220	0	44	Histopathology	Breast	1.00 [0.93, 1.00]	0.17 [0.12, 0.22]
Strickland-Marmol 2007	10	22	0	12	Histopathology	Breast	1.00 [0.69, 1.00]	0.35 [0.20, 0.54]
Dennis 2005	35	211	0	46	Histopathology	Breast	1.00 [0.90, 1.00]	0.18 [0.13, 0.23]
Roh 2002	4	19	0	10	Histopathology	Breast	1.00 [0.40, 1.00]	0.34 [0.18, 0.54]
Srodon 2002	7	4	0	11	Histopathology	Breast	1.00 [0.59, 1.00]	0.73 [0.45, 0.92]
Azoulay 2005	12	26	0	1	Histopathology	Breast	1.00 [0.74, 1.00]	0.04 [0.00, 0.19]



Positive ER for breast primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Lee 2002	21	20	8	47	Cytopathology	Breast	0.72 [0.53, 0.87]	0.70 [0.58, 0.81]
Perry 1997	5	8	10	45	Histopathology	Breast	0.33 [0.12, 0.62]	0.85 [0.72, 0.93]
Nash 2003	6	0	11	75	Histopathology	Breast	0.35 [0.14, 0.62]	1.00 [0.95, 1.00]
Dennis 2005	27	29	8	228	Histopathology	Breast	0.77 [0.60, 0.90]	0.89 [0.84, 0.92]
Park 2007	34	8	16	256	Histopathology	Breast	0.68 [0.53, 0.80]	0.97 [0.94, 0.99]
Azoulay 2005	6	0	6	27	Histopathology	Breast	0.50 [0.21, 0.79]	1.00 [0.87, 1.00]
Kaufmann 1996	81	10	48	189	Histopathology	Breast	0.63 [0.54, 0.71]	0.95 [0.91, 0.98]



Positive PR for breast primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Lee 2002	15	15	14	52	Cytopathology	Breast	0.52 [0.33, 0.71]	0.78 [0.66, 0.87]
Azoulay 2005	5	1	7	26	Histopathology	Breast	0.42 [0.15, 0.72]	0.96 [0.81, 1.00]
Perry 1997	13	39	2	14	Histopathology	Breast	0.87 [0.60, 0.98]	0.26 [0.15, 0.40]
Nash 2003	5	9	12	66	Histopathology	Breast	0.29 [0.10, 0.56]	0.88 [0.78, 0.94]
Kaufmann 1996	49	6	80	193	Histopathology	Breast	0.38 [0.30, 0.47]	0.97 [0.94, 0.99]

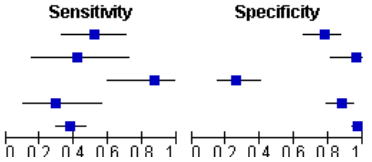
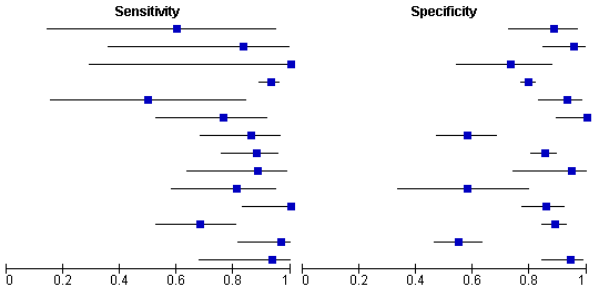


Figure 10.6 Colorectal primary tumours, CK7 and CK20

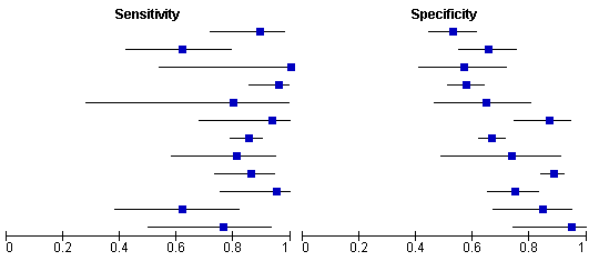
Positive CK20 for colon primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Azoulay 2005	3	4	2	30	Histopathology	Colon	0.60 [0.15, 0.95]	0.88 [0.73, 0.97]
Drlicek 2004	5	2	1	42	Histopathology	Colon	0.83 [0.36, 1.00]	0.95 [0.85, 0.99]
Roh 2002	3	8	0	22	Histopathology	Colon	1.00 [0.29, 1.00]	0.73 [0.54, 0.88]
Tot 2002	217	183	16	709	Histopathology	Colon	0.93 [0.89, 0.96]	0.79 [0.77, 0.82]
Giordana 2001	4	4	4	53	Histopathology	Colon	0.50 [0.16, 0.84]	0.93 [0.83, 0.98]
Scarpatetti 2002	16	0	5	32	Histopathology	Colon	0.76 [0.53, 0.92]	1.00 [0.89, 1.00]
Torenbeek 1998	25	39	4	54	Histopathology	Colon	0.86 [0.68, 0.96]	0.58 [0.47, 0.68]
Park 2007	44	39	6	225	Histopathology	Colon	0.88 [0.76, 0.95]	0.85 [0.80, 0.89]
Wauters 1995	15	1	2	18	Histopathology	Colon	0.88 [0.64, 0.99]	0.95 [0.74, 1.00]
Shimonishi 2000	17	8	4	11	Histopathology	Colon	0.81 [0.58, 0.95]	0.58 [0.33, 0.80]
Chu 2000	20	14	0	85	Histopathology	Colon	1.00 [0.83, 1.00]	0.86 [0.77, 0.92]
Dennis 2005	32	27	15	218	Histopathology	Colon	0.68 [0.53, 0.81]	0.89 [0.84, 0.93]
Vang 2006	27	68	1	83	Histopathology	Colon	0.96 [0.82, 1.00]	0.55 [0.47, 0.63]
Perry 1997	14	3	1	50	Histopathology	Colon	0.93 [0.68, 1.00]	0.94 [0.84, 0.99]



Negative CK7 for colon primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Vang 2006	25	71	3	80	Histopathology	Colon	0.89 [0.72, 0.98]	0.53 [0.45, 0.61]
Torenbeek 1998	18	32	11	61	Histopathology	Colon	0.62 [0.42, 0.79]	0.66 [0.55, 0.75]
Drlicek 2004	6	19	0	25	Histopathology	Colon	1.00 [0.54, 1.00]	0.57 [0.41, 0.72]
Dennis 2005	45	104	2	141	Histopathology	Colon	0.96 [0.85, 0.99]	0.58 [0.51, 0.64]
Azoulay 2005	4	12	1	22	Histopathology	Colon	0.80 [0.28, 0.99]	0.65 [0.46, 0.80]
Perry 1997	14	7	1	46	Histopathology	Colon	0.93 [0.68, 1.00]	0.87 [0.75, 0.95]
Tot 2002	138	137	24	274	Histopathology	Colon	0.85 [0.79, 0.90]	0.67 [0.62, 0.71]
Shimonishi 2000	17	5	4	14	Histopathology	Colon	0.81 [0.58, 0.95]	0.74 [0.49, 0.91]
Park 2007	43	31	7	233	Histopathology	Colon	0.86 [0.73, 0.94]	0.88 [0.84, 0.92]
Chu 2000	19	25	1	74	Histopathology	Colon	0.95 [0.75, 1.00]	0.75 [0.65, 0.83]
Scarpatetti 2002	13	5	8	27	Histopathology	Colon	0.62 [0.38, 0.82]	0.84 [0.67, 0.95]
Wauters 1995	13	1	4	18	Histopathology	Colon	0.76 [0.50, 0.93]	0.95 [0.74, 1.00]



CK7-/CK20+ for colon primary tumour

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Jang 2001	5	0	3	56	Cytopathology	Colon	0.63 [0.24, 0.91]	1.00 [0.94, 1.00]
Kende 2003	23	3	6	46	Histopathology	Colon	0.79 [0.60, 0.92]	0.94 [0.83, 0.99]
Drlicek 2004	5	1	1	41	Histopathology	Colon	0.83 [0.36, 1.00]	0.98 [0.87, 1.00]
Vang 2006	23	4	5	35	Histopathology	Colon	0.82 [0.63, 0.94]	0.90 [0.76, 0.97]
Chu 2000	19	3	1	134	Histopathology	Colon	0.95 [0.75, 1.00]	0.98 [0.94, 1.00]
Tot 2002	161	29	45	458	Histopathology	Colon	0.78 [0.72, 0.84]	0.94 [0.92, 0.96]
Azoulay 2005	2	0	3	16	Histopathology	Colon	0.40 [0.05, 0.85]	1.00 [0.79, 1.00]

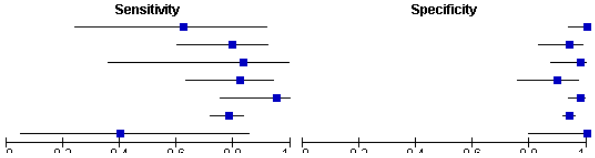
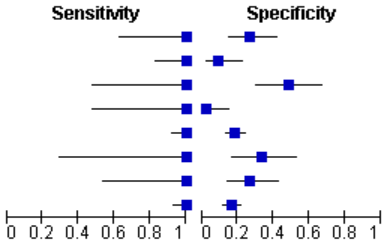


Figure 10.7 Colorectal primary tumours, TTF-1, ER, PR and PSA

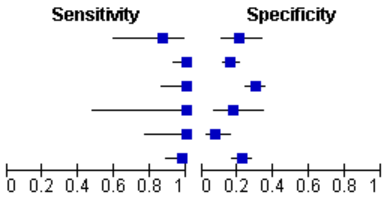
Negative TTF-1 for colon primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Jang 2001	8	35	0	13	Cytopathology	Colon	1.00 [0.63, 1.00]	0.27 [0.15, 0.42]
Saad 2004	20	38	0	4	Cytopathology	Colon	1.00 [0.83, 1.00]	0.10 [0.03, 0.23]
Ng 2002	5	16	0	15	Cytopathology	Colon	1.00 [0.48, 1.00]	0.48 [0.30, 0.67]
Azoulay 2005	5	33	0	1	Histopathology	Colon	1.00 [0.48, 1.00]	0.03 [0.00, 0.15]
Dennis 2005	47	199	0	46	Histopathology	Colon	1.00 [0.92, 1.00]	0.19 [0.14, 0.24]
Roh 2002	3	20	0	10	Histopathology	Colon	1.00 [0.29, 1.00]	0.33 [0.17, 0.53]
Drlicek 2004	6	32	0	12	Histopathology	Colon	1.00 [0.54, 1.00]	0.27 [0.15, 0.43]
Park 2007	50	220	0	44	Histopathology	Colon	1.00 [0.93, 1.00]	0.17 [0.12, 0.22]



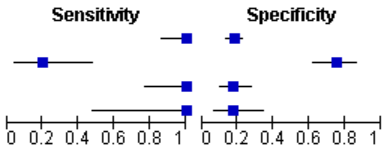
Negative ER for colon primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Perry 1997	13	42	2	11	Histopathology	Colon	0.87 [0.60, 0.98]	0.21 [0.11, 0.34]
Park 2007	50	222	0	42	Histopathology	Colon	1.00 [0.93, 1.00]	0.16 [0.12, 0.21]
Kaufmann 1996	25	212	0	91	Histopathology	Colon	1.00 [0.86, 1.00]	0.30 [0.25, 0.36]
Azoulay 2005	5	28	0	6	Histopathology	Colon	1.00 [0.48, 1.00]	0.18 [0.07, 0.35]
Nash 2003	14	72	0	6	Histopathology	Colon	1.00 [0.77, 1.00]	0.08 [0.03, 0.16]
Dennis 2005	46	190	1	55	Histopathology	Colon	0.98 [0.89, 1.00]	0.22 [0.17, 0.28]



Negative PR for colon primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Kaufmann 1996	25	248	0	55	Histopathology	Colon	1.00 [0.86, 1.00]	0.18 [0.14, 0.23]
Perry 1997	3	13	12	40	Histopathology	Colon	0.20 [0.04, 0.48]	0.75 [0.62, 0.86]
Nash 2003	14	64	0	14	Histopathology	Colon	1.00 [0.77, 1.00]	0.18 [0.10, 0.28]
Azoulay 2005	5	28	0	6	Histopathology	Colon	1.00 [0.48, 1.00]	0.18 [0.07, 0.35]



Negative PSA for colon primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Giordana 2001	8	52	0	5	Histopathology	Colon	1.00 [0.63, 1.00]	0.09 [0.03, 0.19]
Torenbeek 1998	29	74	0	19	Histopathology	Colon	1.00 [0.88, 1.00]	0.20 [0.13, 0.30]
Dennis 2005	47	224	0	21	Histopathology	Colon	1.00 [0.92, 1.00]	0.09 [0.05, 0.13]

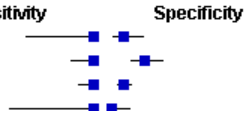
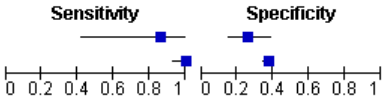


Figure 10.8 Kidney primary tumours

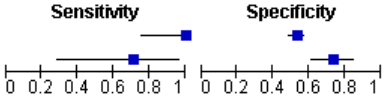
Negative CK20 for kidney primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Perry 1997	6	45	1	16	Histopathology	Kidney	0.86 [0.42, 1.00]	0.26 [0.16, 0.39]
Tot 2002	53	672	0	400	Histopathology	Kidney	1.00 [0.93, 1.00]	0.37 [0.34, 0.40]



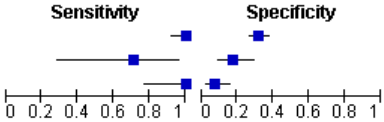
Negative CK7 for kidney primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Tot 2002	13	262	0	298	Histopathology	Kidney	1.00 [0.75, 1.00]	0.53 [0.49, 0.57]
Perry 1997	5	16	2	45	Histopathology	Kidney	0.71 [0.29, 0.96]	0.74 [0.61, 0.84]



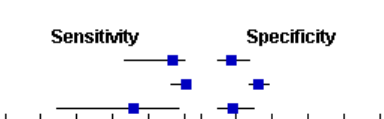
Negative ER for kidney primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Kaufmann 1996	45	192	0	91	Histopathology	Kidney	1.00 [0.92, 1.00]	0.32 [0.27, 0.38]
Perry 1997	5	50	2	11	Histopathology	Kidney	0.71 [0.29, 0.96]	0.18 [0.09, 0.30]
Nash 2003	14	72	0	6	Histopathology	Kidney	1.00 [0.77, 1.00]	0.08 [0.03, 0.16]



Negative PR for kidney primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Nash 2003	13	65	1	13	Histopathology	Kidney	0.93 [0.66, 1.00]	0.17 [0.09, 0.27]
Kaufmann 1996	45	192	0	91	Histopathology	Kidney	1.00 [0.92, 1.00]	0.32 [0.27, 0.38]
Perry 1997	5	50	2	11	Histopathology	Kidney	0.71 [0.29, 0.96]	0.18 [0.09, 0.30]



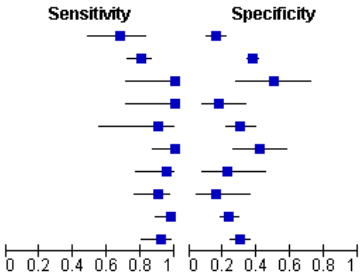
CK7-/CK20- for kidney primary tumour

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity

Figure 10.9 Lung primary tumours, CK7 and CK20

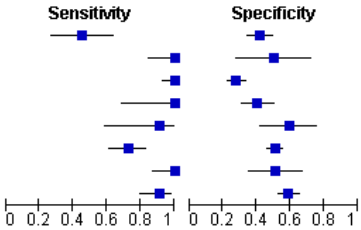
Negative CK20 for lung primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Longatto 1997	21	143	10	27	Cytopathology	Lung	0.68 [0.49, 0.83]	0.16 [0.11, 0.22]
Tot 2002	115	610	29	371	Histopathology	Lung	0.80 [0.72, 0.86]	0.38 [0.35, 0.41]
Roh 2002	11	11	0	11	Histopathology	Lung	1.00 [0.72, 1.00]	0.50 [0.28, 0.72]
Drlicek 2004	11	32	0	7	Histopathology	Lung	1.00 [0.72, 1.00]	0.18 [0.08, 0.34]
Chu 2000	9	76	1	33	Histopathology	Lung	0.90 [0.55, 1.00]	0.30 [0.22, 0.40]
Perry 1997	27	24	0	17	Histopathology	Lung	1.00 [0.87, 1.00]	0.41 [0.26, 0.58]
Strickland-Marmol 2007	21	17	1	5	Histopathology	Lung	0.95 [0.77, 1.00]	0.23 [0.08, 0.45]
Giordana 2001	36	21	4	4	Histopathology	Lung	0.90 [0.76, 0.97]	0.16 [0.05, 0.36]
Dennis 2005	45	188	1	58	Histopathology	Lung	0.98 [0.88, 1.00]	0.24 [0.18, 0.29]
Park 2007	46	185	4	79	Histopathology	Lung	0.92 [0.81, 0.98]	0.30 [0.24, 0.36]



Positive CK7 for lung primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Longatto 1997	14	99	17	72	Cytopathology	Lung	0.45 [0.27, 0.64]	0.42 [0.35, 0.50]
Strickland-Marmol 2007	22	11	0	11	Histopathology	Lung	1.00 [0.85, 1.00]	0.50 [0.28, 0.72]
Park 2007	50	190	0	74	Histopathology	Lung	1.00 [0.93, 1.00]	0.28 [0.23, 0.34]
Chu 2000	10	65	0	44	Histopathology	Lung	1.00 [0.69, 1.00]	0.40 [0.31, 0.50]
Drlicek 2004	10	15	1	22	Histopathology	Lung	0.91 [0.59, 1.00]	0.59 [0.42, 0.75]
Tot 2002	51	247	19	256	Histopathology	Lung	0.73 [0.61, 0.83]	0.51 [0.46, 0.55]
Perry 1997	27	20	0	21	Histopathology	Lung	1.00 [0.87, 1.00]	0.51 [0.35, 0.67]
Dennis 2005	42	101	4	145	Histopathology	Lung	0.91 [0.79, 0.98]	0.59 [0.53, 0.65]



CK7+/CK20- for lung primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Jang 2001	16	26	0	14	Cytopathology	Lung	1.00 [0.79, 1.00]	0.35 [0.21, 0.52]
Chu 2000	9	75	1	72	Histopathology	Lung	0.90 [0.55, 1.00]	0.49 [0.41, 0.57]
Tot 2002	126	156	26	385	Histopathology	Lung	0.83 [0.76, 0.89]	0.71 [0.67, 0.75]
Fernandez 2001	34	13	9	22	Histopathology	Lung	0.79 [0.64, 0.90]	0.63 [0.45, 0.79]
Drlicek 2004	10	19	1	18	Histopathology	Lung	0.91 [0.59, 1.00]	0.49 [0.32, 0.66]
Taweevisit 2003	23	5	1	3	Histopathology	Lung	0.96 [0.79, 1.00]	0.38 [0.09, 0.76]

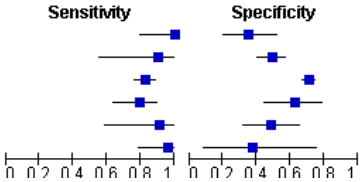
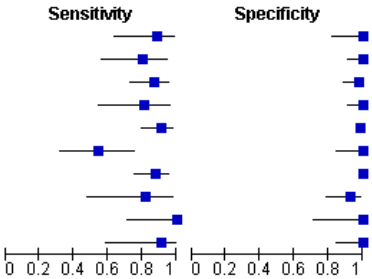


Figure 10.10 Lung primary tumours, TTF-1, ER, PR and PSA

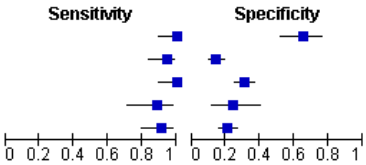
Positive TTF-1 for lung primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Ng 2002	15	0	2	19	Cytopathology	Lung	0.88 [0.64, 0.99]	1.00 [0.82, 1.00]
Saad 2004	16	0	4	42	Cytopathology	Lung	0.80 [0.56, 0.94]	1.00 [0.92, 1.00]
Hecht 2001	34	1	5	48	Cytopathology	Lung	0.87 [0.73, 0.96]	0.98 [0.89, 1.00]
Jang 2001	13	0	3	40	Cytopathology	Lung	0.81 [0.54, 0.96]	1.00 [0.91, 1.00]
Dennis 2005	42	4	4	242	Histopathology	Lung	0.91 [0.79, 0.98]	0.98 [0.96, 1.00]
Strickland-Marmol 2007	12	0	10	22	Histopathology	Lung	0.55 [0.32, 0.76]	1.00 [0.85, 1.00]
Park 2007	44	0	6	264	Histopathology	Lung	0.88 [0.76, 0.95]	1.00 [0.99, 1.00]
Drlicek 2004	9	3	2	36	Histopathology	Lung	0.82 [0.48, 0.98]	0.92 [0.79, 0.98]
Srodon 2002	11	0	0	11	Histopathology	Lung	1.00 [0.72, 1.00]	1.00 [0.72, 1.00]
Roh 2002	10	0	1	22	Histopathology	Lung	0.91 [0.59, 1.00]	1.00 [0.85, 1.00]



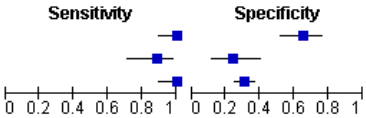
Negative ER for lung primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Lee 2002	33	22	0	41	Cytopathology	Lung	1.00 [0.89, 1.00]	0.65 [0.52, 0.77]
Park 2007	47	225	3	39	Histopathology	Lung	0.94 [0.83, 0.99]	0.15 [0.11, 0.20]
Kaufmann 1996	35	202	0	91	Histopathology	Lung	1.00 [0.90, 1.00]	0.31 [0.26, 0.37]
Perry 1997	24	31	3	10	Histopathology	Lung	0.89 [0.71, 0.98]	0.24 [0.12, 0.40]
Dennis 2005	42	194	4	52	Histopathology	Lung	0.91 [0.79, 0.98]	0.21 [0.16, 0.27]



Negative PR for lung cancer

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Lee 2002	33	22	0	41	Cytopathology	Lung	1.00 [0.89, 1.00]	0.65 [0.52, 0.77]
Perry 1997	24	31	3	10	Histopathology	Lung	0.89 [0.71, 0.98]	0.24 [0.12, 0.40]
Kaufmann 1996	35	202	0	91	Histopathology	Lung	1.00 [0.90, 1.00]	0.31 [0.26, 0.37]



Negative PSA for lung primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Giordana 2001	40	20	0	5	Histopathology	Lung	1.00 [0.91, 1.00]	0.20 [0.07, 0.41]
Dennis 2005	46	225	0	21	Histopathology	Lung	1.00 [0.92, 1.00]	0.09 [0.05, 0.13]
Drlicek 2004	11	38	0	1	Histopathology	Lung	1.00 [0.72, 1.00]	0.03 [0.00, 0.13]

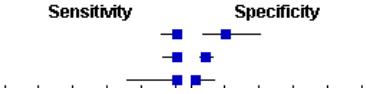
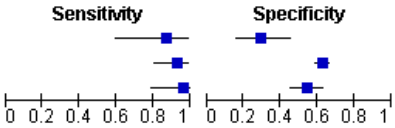


Figure 10.11 Ovarian tumours, CK7 and CK20

CK7+/CK20- for ovarian non-mucinous primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Jang 2001	13	29	2	12	Cytopathology	Ovary	0.87 [0.60, 0.98]	0.29 [0.16, 0.46]
Tot 2002	39	243	3	408	Histopathology	Ovary	0.93 [0.81, 0.99]	0.63 [0.59, 0.66]
Chu 2000	23	61	1	72	Histopathology	Ovary	0.96 [0.79, 1.00]	0.54 [0.45, 0.63]



CK7+/CK20+ for ovarian mucinous primary tumour

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Tot 2002	13	105	4	571	Histopathology	None	0.76 [0.50, 0.93]	0.84 [0.82, 0.87]
Vang 2006	39	28	14	98	Histopathology	None	0.74 [0.60, 0.85]	0.78 [0.70, 0.85]

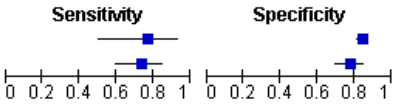
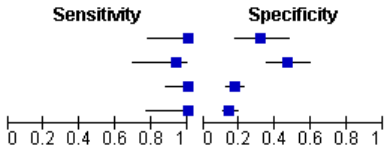


Figure 10.12 Ovarian primary tumours, TTF1, ER and PR

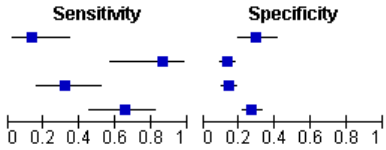
Negative TT-1 for ovarian primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Jang 2001	15	28	0	13	Cytopathology	Ovary	1.00 [0.78, 1.00]	0.32 [0.18, 0.48]
Hecht 2001	15	38	1	34	Cytopathology	Ovary	0.94 [0.70, 1.00]	0.47 [0.35, 0.59]
Dennis 2005	28	218	0	46	Histopathology	Ovary	1.00 [0.88, 1.00]	0.17 [0.13, 0.23]
Park 2007	14	256	0	44	Histopathology	Ovary	1.00 [0.77, 1.00]	0.15 [0.11, 0.19]



Negative ER for ovary primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Lee 2002	3	52	19	22	Cytopathology	Ovary	0.14 [0.03, 0.35]	0.30 [0.20, 0.41]
Park 2007	12	260	2	40	Histopathology	Ovary	0.86 [0.57, 0.98]	0.13 [0.10, 0.18]
Dennis 2005	9	227	19	37	Histopathology	Ovary	0.32 [0.16, 0.52]	0.14 [0.10, 0.19]
Kaufmann 1996	19	218	10	81	Histopathology	Ovary	0.66 [0.46, 0.82]	0.27 [0.22, 0.33]



Negative PR for ovarian primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Lee 2002	11	55	11	19	Cytopathology	None	0.50 [0.28, 0.72]	0.26 [0.16, 0.37]
Kaufmann 1996	23	250	6	49	Histopathology	None	0.79 [0.60, 0.92]	0.16 [0.12, 0.21]

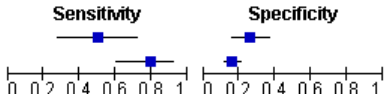
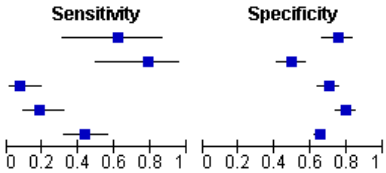


Figure 10.13 Pancreatic primary tumours, CK7 and CK20

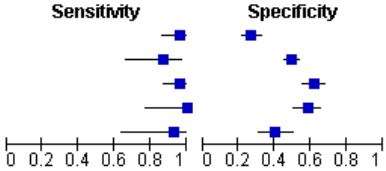
Positive CK20 for pancreatic primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Chu 2000	8	26	5	80	Histopathology	Pancreas	0.62 [0.32, 0.86]	0.75 [0.66, 0.83]
Vang 2006	11	84	3	81	Histopathology	Pancreas	0.79 [0.49, 0.95]	0.49 [0.41, 0.57]
Park 2007	4	79	46	185	Histopathology	Pancreas	0.08 [0.02, 0.19]	0.70 [0.64, 0.76]
Dennis 2005	10	49	43	190	Histopathology	Pancreas	0.19 [0.09, 0.32]	0.79 [0.74, 0.84]
Tot 2002	31	369	40	685	Histopathology	Pancreas	0.44 [0.32, 0.56]	0.65 [0.62, 0.68]



Positive CK7 for pancreatic primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Park 2007	48	192	2	72	Histopathology	Pancreas	0.96 [0.86, 1.00]	0.27 [0.22, 0.33]
Tot 2002	20	278	3	272	Histopathology	Pancreas	0.87 [0.66, 0.97]	0.49 [0.45, 0.54]
Dennis 2005	51	92	2	147	Histopathology	Pancreas	0.96 [0.87, 1.00]	0.62 [0.55, 0.68]
Vang 2006	14	69	0	96	Histopathology	Pancreas	1.00 [0.77, 1.00]	0.58 [0.50, 0.66]
Chu 2000	12	63	1	43	Histopathology	Pancreas	0.92 [0.64, 1.00]	0.41 [0.31, 0.51]



CK7+/CK20+ for pancreatic primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Tot 2002	22	96	24	551	Histopathology	Pancreas	0.48 [0.33, 0.63]	0.85 [0.82, 0.88]
Chu 2000	8	4	5	140	Histopathology	Pancreas	0.62 [0.32, 0.86]	0.97 [0.93, 0.99]
Vang 2006	11	56	3	109	Histopathology	Pancreas	0.79 [0.49, 0.95]	0.66 [0.58, 0.73]

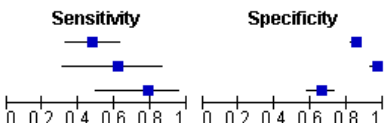
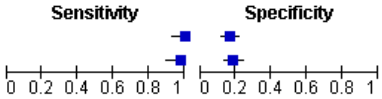


Figure 10.14 Pancreatic primary tumours, TTF-1, ER and PR

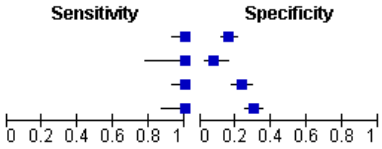
Negative TTF-1 for pancreatic primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Park 2007	50	220	0	44	Histopathology	Pancreas	1.00 [0.93, 1.00]	0.17 [0.12, 0.22]
Dennis 2005	52	194	1	45	Histopathology	Pancreas	0.98 [0.90, 1.00]	0.19 [0.14, 0.24]



Negative ER for pancreatic primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Park 2007	50	222	0	42	Histopathology	Pancreas	1.00 [0.93, 1.00]	0.16 [0.12, 0.21]
Nash 2003	15	71	0	6	Histopathology	Pancreas	1.00 [0.78, 1.00]	0.08 [0.03, 0.16]
Dennis 2005	53	183	0	56	Histopathology	Stomach	1.00 [0.93, 1.00]	0.23 [0.18, 0.29]
Kaufmann 1996	26	211	0	91	Histopathology	Pancreas	1.00 [0.87, 1.00]	0.30 [0.25, 0.36]



Negative PR for pancreatic primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Kaufmann 1996	26	211	0	91	Histopathology	Pancreas	1.00 [0.87, 1.00]	0.30 [0.25, 0.36]
Nash 2003	14	64	1	13	Histopathology	Pancreas	0.93 [0.68, 1.00]	0.17 [0.09, 0.27]

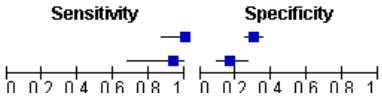
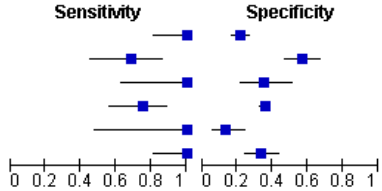


Figure 10.15 Prostate primary tumours

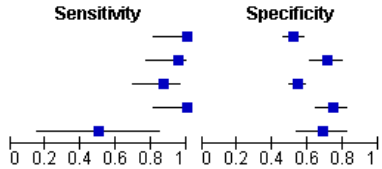
Negative CK20 for prostate primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Dennis 2005	18	215	0	59	Histopathology	Prostate	1.00 [0.81, 1.00]	0.22 [0.17, 0.27]
Torenbeek 1998	15	43	7	57	Histopathology	Prostate	0.68 [0.45, 0.86]	0.57 [0.47, 0.67]
Scarpatetti 2002	8	29	0	16	Histopathology	Prostate	1.00 [0.63, 1.00]	0.36 [0.22, 0.51]
Tot 2002	24	701	8	392	Histopathology	Prostate	0.75 [0.57, 0.89]	0.36 [0.33, 0.39]
Giordana 2001	5	52	0	8	Histopathology	Prostate	1.00 [0.48, 1.00]	0.13 [0.06, 0.25]
Chu 2000	18	67	0	34	Histopathology	Prostate	1.00 [0.81, 1.00]	0.34 [0.25, 0.44]



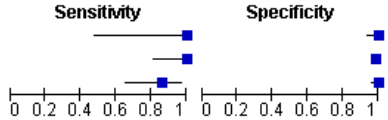
Negative CK7 for prostate primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Dennis 2005	18	131	0	143	Histopathology	Pancreas	1.00 [0.81, 1.00]	0.52 [0.46, 0.58]
Torenbeek 1998	21	29	1	71	Histopathology	Prostate	0.95 [0.77, 1.00]	0.71 [0.61, 0.80]
Tot 2002	26	249	4	294	Histopathology	Prostate	0.87 [0.69, 0.96]	0.54 [0.50, 0.58]
Chu 2000	18	26	0	75	Histopathology	Prostate	1.00 [0.81, 1.00]	0.74 [0.65, 0.82]
Scarpatetti 2002	4	14	4	31	Histopathology	Prostate	0.50 [0.16, 0.84]	0.69 [0.53, 0.82]



Positive PSA for prostate primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Giordana 2001	5	0	0	60	Histopathology	Prostate	1.00 [0.48, 1.00]	1.00 [0.94, 1.00]
Dennis 2005	18	3	0	271	Histopathology	Prostate	1.00 [0.81, 1.00]	0.99 [0.97, 1.00]
Torenbeek 1998	19	0	3	100	Histopathology	Prostate	0.86 [0.65, 0.97]	1.00 [0.96, 1.00]



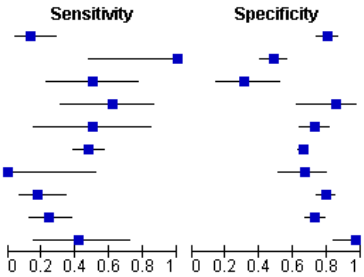
CK7-/CK20- for prostate primary tumour

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Chu 2000	18	21	0	118	Histopathology	Prostate	1.00 [0.81, 1.00]	0.85 [0.78, 0.90]

Figure 10.16 Stomach primary tumours, CK7 and CK20

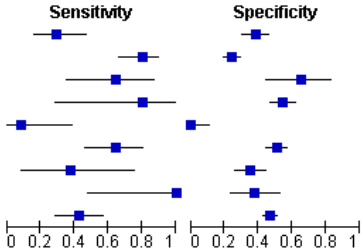
Positive CK20 for stomach primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Longatto 1997	5	32	32	132	Cytopathology	Stomach	0.14 [0.05, 0.29]	0.80 [0.74, 0.86]
Vang 2006	5	90	0	84	Histopathology	Stomach	1.00 [0.48, 1.00]	0.48 [0.41, 0.56]
Shimonishi 2000	7	18	7	8	Histopathology	Stomach	0.50 [0.23, 0.77]	0.31 [0.14, 0.52]
Roh 2002	8	3	5	17	Histopathology	Stomach	0.62 [0.32, 0.86]	0.85 [0.62, 0.97]
Chu 2000	4	30	4	81	Histopathology	Stomach	0.50 [0.16, 0.84]	0.73 [0.64, 0.81]
Tot 2002	61	339	66	659	Histopathology	Stomach	0.48 [0.39, 0.57]	0.66 [0.63, 0.69]
Scarpatetti 2002	0	16	5	32	Histopathology	Stomach	0.00 [0.00, 0.52]	0.67 [0.52, 0.80]
Dennis 2005	6	53	28	205	Histopathology	Stomach	0.18 [0.07, 0.35]	0.79 [0.74, 0.84]
Park 2007	12	71	38	193	Histopathology	Stomach	0.24 [0.13, 0.38]	0.73 [0.67, 0.78]
Strickland-Marmol 2007	5	1	7	31	Histopathology	Stomach	0.42 [0.15, 0.72]	0.97 [0.84, 1.00]



Negative CK7 for stomach primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Longatto 1997	11	102	26	63	Cytopathology	Stomach	0.30 [0.16, 0.47]	0.38 [0.31, 0.46]
Park 2007	40	200	10	64	Histopathology	Stomach	0.80 [0.66, 0.90]	0.24 [0.19, 0.30]
Shimonishi 2000	9	9	5	17	Histopathology	Stomach	0.64 [0.35, 0.87]	0.65 [0.44, 0.83]
Vang 2006	4	79	1	95	Histopathology	Stomach	0.80 [0.28, 0.99]	0.55 [0.47, 0.62]
Strickland-Marmol 2007	1	32	11	0	Histopathology	Stomach	0.08 [0.00, 0.38]	0.00 [0.00, 0.11]
Dennis 2005	22	127	12	131	Histopathology	Stomach	0.65 [0.46, 0.80]	0.51 [0.45, 0.57]
Chu 2000	3	72	5	39	Histopathology	Stomach	0.38 [0.09, 0.76]	0.35 [0.26, 0.45]
Scarpatetti 2002	5	30	0	18	Histopathology	Stomach	1.00 [0.48, 1.00]	0.38 [0.24, 0.53]
Tot 2002	22	276	30	245	Histopathology	Stomach	0.42 [0.29, 0.57]	0.47 [0.43, 0.51]



CK7+/CK20+ for stomach primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Jang 2001	3	2	6	45	Cytopathology	Stomach	0.33 [0.07, 0.70]	0.96 [0.85, 0.99]
Tot 2002	13	105	26	549	Histopathology	Stomach	0.33 [0.19, 0.50]	0.84 [0.81, 0.87]
Kende 2003	27	15	11	25	Histopathology	Stomach	0.71 [0.54, 0.85]	0.63 [0.46, 0.77]
Chu 2000	1	11	7	138	Histopathology	Stomach	0.13 [0.00, 0.53]	0.93 [0.87, 0.96]
Vang 2006	4	63	1	111	Histopathology	Stomach	0.80 [0.28, 0.99]	0.64 [0.56, 0.71]

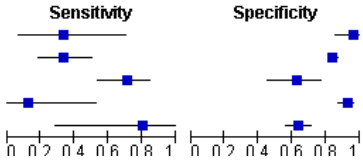
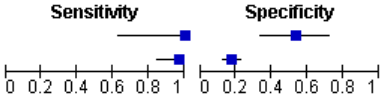


Figure 10.17 Stomach primary tumours, TTF-1, ER and PR

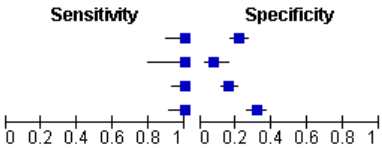
Negative TTF-1 for stomach primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Ng 2002	8	13	0	15	Cytopathology	Stomach	1.00 [0.63, 1.00]	0.54 [0.34, 0.72]
Dennis 2005	33	213	1	45	Histopathology	Stomach	0.97 [0.85, 1.00]	0.17 [0.13, 0.23]



Negative ER for stomach primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Dennis 2005	34	202	0	56	Histopathology	Stomach	1.00 [0.90, 1.00]	0.22 [0.17, 0.27]
Nash 2003	16	70	0	6	Histopathology	Stomach	1.00 [0.79, 1.00]	0.08 [0.03, 0.16]
Park 2007	50	222	0	42	Histopathology	Stomach	1.00 [0.93, 1.00]	0.16 [0.12, 0.21]
Kaufmann 1996	39	198	0	91	Histopathology	Stomach	1.00 [0.91, 1.00]	0.31 [0.26, 0.37]



Negative PR for stomach primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Kaufmann 1996	39	198	0	91	Histopathology	Stomach	1.00 [0.91, 1.00]	0.31 [0.26, 0.37]
Nash 2003	14	64	2	12	Histopathology	Stomach	0.88 [0.62, 0.98]	0.16 [0.08, 0.26]

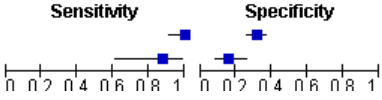
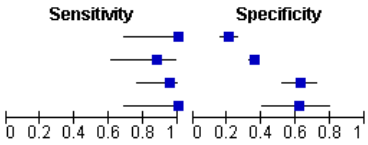


Figure 10.18 Other primary tumours: endometrial, oesophageal, salivary gland and urothelial

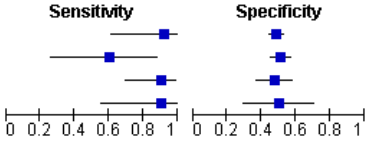
Negative CK20 for endometrial primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Dennis 2005	10	223	0	59	Histopathology	Endometrium	1.00 [0.69, 1.00]	0.21 [0.16, 0.26]
Tot 2002	14	711	2	398	Histopathology	Endometrium	0.88 [0.62, 0.98]	0.36 [0.33, 0.39]
Torenbeek 1998	20	38	1	63	Histopathology	Endometrium	0.95 [0.76, 1.00]	0.62 [0.52, 0.72]
Wauters 1995	10	10	0	16	Histopathology	Endometrium	1.00 [0.69, 1.00]	0.62 [0.41, 0.80]



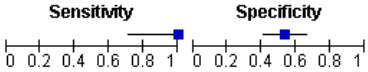
Positive CK7 for endometrial primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Tot 2002	11	287	1	274	Histopathology	Endometrium	0.92 [0.62, 1.00]	0.49 [0.45, 0.53]
Dennis 2005	6	137	4	145	Histopathology	Endometrium	0.60 [0.26, 0.88]	0.51 [0.45, 0.57]
Torenbeek 1998	19	53	2	48	Histopathology	Endometrium	0.90 [0.70, 0.99]	0.48 [0.37, 0.58]
Wauters 1995	9	13	1	13	Histopathology	Endometrium	0.90 [0.55, 1.00]	0.50 [0.30, 0.70]



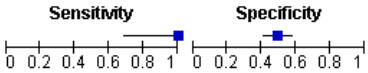
CK7+/CK20+ for oesophageal primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Kende 2003	11	31	0	36	Histopathology	Oesophagus	1.00 [0.72, 1.00]	0.54 [0.41, 0.66]



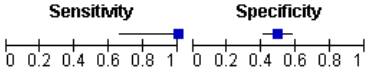
CK7+/CK20- for endometrial primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Chu 2000	10	74	0	73	Histopathology	Endometrium	1.00 [0.69, 1.00]	0.50 [0.41, 0.58]



CK7+/CK20- for salivary gland primary

Study	TP	FP	FN	TN	Sample type	Primary	Sensitivity	Specificity
Chu 2000	9	75	0	73	Histopathology	Salivary gland	1.00 [0.66, 1.00]	0.49 [0.41, 0.58]



CK7+/CK20+ for urothelial primary tumour

10. Immunohistochemistry for adenocarcinoma of unknown primary

Last updated: 29 / 10 / 2009.

Characteristics of included studies

Azoulay-2005

Clinical setting	Patients with skin metastases, retrieved from the files of a single institution
Participants and Country	44 patients. The primary site was found in 34 cases.
Study design	Retrospective case series
Target condition	Primary tumour site. Primary tumour site was determined retrospectively from pathology reports and/or clinical notes.
Tests	IHC, including: CK 7, CK 20, ER, PR, TTF1
Follow up	Not reported
Proportion with adenocarcinoma	Not reported, although primary sites were consistent with adenocarcinoma.
Primary or metastatic tumour?	Metastases
Sample type	Parafin embedded tissue
Notes	

Blumenfeld-1999

Clinical setting	Patients with malignant cytology. Samples identified from the records of a single pathology department
Participants and Country	51 patients. USA
Study design	Retrospective case series.
Target condition	Identification of the primary tumour organ of origin. Reference standard not reported.
Tests	IHC markers: CK7 and CK20
Follow up	Not reported
Proportion with adenocarcinoma	Not reported (all were described as carcinoma)
Primary or metastatic tumour?	Metastatic
Sample type	Cell blocks prepared from fine needle aspirates or malignant effusions
Notes	

Chu-2000

Clinical setting	Cases of carcinoma selected from the files of a single pathology department.
Participants and Country	435 patients.USA
Study design	Retrospective case series
Target condition	Identification of primary site. The paper states the diagnoses were reconfirmed but not how.
Tests	IHC markers: CK7 and CK20, and all possible combinations thereof.
Follow up	Not reported
Proportion with adenocarcinoma	CK7 data were available for 93 patients with adenocarcinoma and CK20 data for 109 patients. All other cases were excluded from this analysis.
Primary or metastatic tumour?	Primary
Sample type	Paraffin embedded tissue sample from primary tumour
Notes	

Dennis-2005

Clinical setting	Cases of adenocarcinoma (or tumour types included in the differential diagnosis of adenocarcinoma) selected from the records of a single pathology department. Sample numbers of specific primary tumours were chose to reflect the frequency of presentation with metastatic disease, rather than their overall incidence.
Participants and Country	352 primary tumour samples were included. 261 adenocarcinomas: 35 breast, 47 colon, 46 lung A validation set of 100 tumour samples and 30 paired metastases was used to test the diagnostic algorithm.
Study design	Cross sectional study
Target condition	The target condition was identification of the primary tumour organ of origin. The reference standard diagnosis was taken from the original pathology records of the sample.
Tests	The expression profiles of 27 candidate markers were measured using tissue micro-arrays and immunohistochemistry. Data were analysed using the Rosetta program, to derive a decision tree to classify tumours based on their IHC profile. This analysis led to a smaller panel of 10 markers: CA125, CDX2, CK7, CK20, oestrogen receptor, PSA, GCDFP-15, lysozyme, mesothelin and TTF1. A decision tree was also included, which gives the a primary tumour classification algorithm based on these ten markers. Correct assignment of primary tumour site was obtained in 87% of primary and metastatic tumours using a diagnostic table, and 89% using the decision tree.
Follow up	All primary tumour diagnoses were known at the outset of the study.
Proportion with adenocarcinoma	For the training set 261/352 (74%)
Primary or metastatic tumour?	The algorithm was developed using primary tumours, but tested with a validation set of 100 primary tumours and 30 paired metastases
Sample type	Histopathology
Notes	

DeYoung-2000

Clinical setting	Patients with cancer of unknown primary
Participants and Country	Not applicable

Study design	Expert review
Target condition	Identification of primary tumour origin.
Tests	IHC markers: Keratin-mixed, CK20, ERP, MOC31, PSA, TGB, B72.3, GCDFP, CEA-M,S100, PLAP, CA125, CA19-9, EMA and VIM
Follow up	Not applicable
Proportion with adenocarcinoma	The review is not limited to adenocarcinoma
Primary or metastatic tumour?	Metastatic
Sample type	Tissue sample from metastasis
Notes	

Drlicek-2004

Clinical setting	Samples of brain metastases submitted over a one year period , selected from the surgical pathology files of a single institution.
Participants and Country	54 patients. Primary tumour site was known before surgery or discovered after in 40 patients. Austria
Study design	Retrospective case series.
Target condition	Primary site correlation with immunohistochemistry. reference standard was not reported.
Tests	Immunohistochemistry: antibodies to CK7, CK20, TTF-1, PSA and others: CK AE1/AE3, CK 10/13, CK 18, S100, CA 15-3, CA-125 and CA 19-9.
Follow up	Not reported.
Proportion with adenocarcinoma	Only the primary tumour site was reported: 4 patients had melanoma and 2 soft tissue tumours, these were excluded from analysis. 2 patients wih mouth / tongue cancer were also excluded as these were probably squamous cell cancers.
Primary or metastatic tumour?	Metastases
Sample type	Paraffin embedded tissue
Notes	

Fernandez-2001

Clinical setting	Patients with cerebral metastases identified from the records of a single institution between 1995 and 2000.
Participants and Country	78 patients. France
Study design	Retrospective case series
Target condition	Identification of primary tumour. Reference standard was unclear, and some patients (8/78) never had a primary tumour diagnosed,
Tests	IHC markers: CK7 and CK20
Follow up	Not reported
Proportion with adenocarcinoma	100%

Primary or metastatic tumour?	Metastatic.
Sample type	Tissue from biopsy or resected brain metastasis
Notes	French language.

Giordana-2001

Clinical setting	Patients presenting with single brain metastases treated at a single neurosurgery department between 1985 and 1997.
Participants and Country	181 patients 99 patients had unidentified primary (35 patients had a primary identified within 2 months of presentation. 14 later than 2 months). 82 patients had a existing known primary tumour
Study design	Retrospective case series
Target condition	Correlation of the primary tumour site and the IHC of the surgical brain metastasis specimen. Reference standard was not defined, although the study states that the primary site was known
Tests	IHC, including CK20.
Follow up	Not reported
Proportion with adenocarcinoma	Adenocarcinoma (64.4%) and undifferentiated carcinoma (35.6%).
Primary or metastatic tumour?	Metastases
Sample type	Surgical specimen of brain metastasis
Notes	

Hecht-2001

Clinical setting	Cell blocks from lung tumours identified from the files of a single institution
Participants and Country	122 patients (85 with metastatic adenocarcinoma). USA
Study design	Retrospective case series
Target condition	Locatio of primary site. Distinction between primary and metastatic lung cancer.
Tests	IHC markers: TTF-1.
Follow up	Not reported
Proportion with adenocarcinoma	85/122 had metastatic adenocarcinoma. All others were excluded from this analysis
Primary or metastatic tumour?	Primary lung cancer (14/122) and malignant effusions (108/122), primary tumours were excluded from this analysis.
Sample type	Cell blocks prepared from effusions or FNA biopsies
Notes	

Jang-2001

Clinical setting	Cytologic specimens from 56 patients with malignant effusions collected between 1997 and 2000, obtained from the files of a single pathology department.

Participants and Country	56 patients. Korea
Study design	Retrospective series
Target condition	IHC marker reactivity according to primary site. The primary site was determined based on clinical, radiologic and histopathologic findings.
Tests	IHC markers: TTF-1, CK7 and CK20
Follow up	
Proportion with adenocarcinoma	100% adenocarcinoma
Primary or metastatic tumour?	Metastases (effusions)
Sample type	Paraffin fixed cell blocks from malignant effusions
Notes	

Kaufmann-1996

Clinical setting	Patients with metastatic adenocarcinoma and confirmed primary site identified form the surgical pathology files of a single institution
Participants and Country	328 patients. Germany
Study design	Retrospective case series
Target condition	Identification of the primary tumour. Reference standard not reported (although the primary tumour sites were described as "well established").
Tests	IHC markers: GCDFP, ER, PR, CK20, CEA1, VIM , CSA, CA19-9, CEA2, CEA3, Transthyretin and Vimentin.
Follow up	Not reported.
Proportion with adenocarcinoma	100%
Primary or metastatic tumour?	Metastases
Sample type	paraffin embedded tissue blocks from metastases.
Notes	CK7 and CK20 data included in the Tot (2002) review.

Kende-2003

Clinical setting	Cases with GI cancer referred to a single pathology department
Participants and Country	105 patients.
Study design	Prospective case series
Target condition	Identification of the primary tumour organ of origin. Primary diagnosis was based on the consensus opinion of three pathologists.
Tests	IHC markers: CK7 and CK20
Follow up	Not reported
Proportion with adenocarcinoma	85/120. Only patients with adenocarcinoma were included in this analysis.

Primary or metastatic tumour?	Primary.
Sample type	Paraffin embedded tissue or unstained slides
Notes	

Lee-2002

Clinical setting	Malignant effusion specimens identified from the records of a single institution.
Participants and Country	96 patients. USA
Study design	Retrospective case series
Target condition	Identification of the primary tumour site. Primary site was biopsy proven in all cases.
Tests	IHC markers: ER, PR, WT1 and GCDFP.
Follow up	Not reported
Proportion with adenocarcinoma	100%
Primary or metastatic tumour?	Metastases
Sample type	Cell blocks prepared from serous effusions.
Notes	

Longatto-1997

Clinical setting	Women with adenocarcinoma detected in serous effusions, selected from the records of a single institution. Patients had clinical, radiological and histological evidence of the primary tumour. Only cases with representative and well fixed effusion samples were included.
Participants and Country	208 patients
Study design	Retrospective series
Target condition	Identification of the primary tumour site. Reference standard was clinical, radiological and histological evidence of the primary tumour
Tests	Immunocytochemical reactivity of CK7 and CK20. Reactions were quantified on a five point scale - to ++++
Follow up	Not reported
Proportion with adenocarcinoma	100%
Primary or metastatic tumour?	Metastases (effusions)
Sample type	Cytologic smears fixed in ethanol. immuncytochemical reactions were performed after removing the coverslips and rehydrating the smears.
Notes	

Nash-2003

Clinical setting	Patients with confirmed hepatic neoplasms (primary or secondary) were identified from the files of a single pathology department.

Participants and Country	92 patients
Study design	Retrospective case series. USA
Target condition	Correlation of IHC marker reactivity and primary tumour site: specifically the distinction of metastatic breast cancer from other liver tumours. The reference standard diagnosis was not reported.
Tests	IHC markers: ER and PR
Follow up	Not reported
Proportion with adenocarcinoma	100% adenocarcinoma
Primary or metastatic tumour?	30 primary and 66 metastatic tumours
Sample type	Formalin fixed paraffin embedded tissue from liver tumour.
Notes	

Ng-2002

Clinical setting	Effusion cytology samples identified from the files of a single institution.
Participants and Country	36 patients. Hong Kong
Study design	Retrospective case series
Target condition	Identification of primary site, differentiation of metastatic pulmonary adenocarcinoma from metastatic extrapulmonary adenocarcinoma. Evidence of primary site came from radiology, endoscopic biopsy, or surgical specimen
Tests	IHC marker: TTF-1.
Follow up	Not reported
Proportion with adenocarcinoma	100%
Primary or metastatic tumour?	Metastases.
Sample type	Cell block from effusion sample.
Notes	

Park-2007

Clinical setting	Cases selected from the surgical pathology files of a single institution
Participants and Country	314 primary adenocarcinomas and 60 metastatic adenocarcinomas. Korea
Study design	Retrospective case series.
Target condition	Correlation of IHC with primary tumour site.
Tests	IHC markers: antibodies to: TT1-1, CK7, CK20 and ER. Also CEA, CDX, MUC2, MUC5AC, SMAD4 and GCDFP-15
Follow up	Not reported

Proportion with adenocarcinoma	100% adenocarcinoma
Primary or metastatic tumour?	Sensitivity and specificity of indidividual IHC markers was only reported for the primary adenocarcinomas.
Sample type	Paraffin embedded tissue
Notes	

Perry-1997

Clinical setting	Biopsies of metastatic adenocarcinoma to the brain of known primary retrieved from the files of a single pathology department.
Participants and Country	68 patients. USA
Study design	Retrospective case series
Target condition	Identification of the primary site. Primary site was confirmed by biopsy in 65/68 cases, the remainder were confirmed using radiology and histopathology of the metastasis.
Tests	IHC markers: CK7, CK20, ER, PR, CFAP, CAM 5.2, WSK and GCDFP-15
Follow up	Not reported
Proportion with adenocarcinoma	100%
Primary or metastatic tumour?	Metastases
Sample type	Tissue from biopsy of brain metastasis.
Notes	

Roh-2002

Clinical setting	Patients with metastatic cervical lymph nodes, were identified from the files of a single pathology department
Participants and Country	68 patients. Korea
Study design	Retrospective case series.
Target condition	Identification of the primary tumour (correlation of tumour site with immunoreactivity). Reference standard was the histologic features of the primary tumour and metastases.
Tests	IHC markers: TTF-1 and CK20.
Follow up	Not reported
Proportion with adenocarcinoma	33/68 (49%). Only these patients were included in this present evidence review
Primary or metastatic tumour?	Metastases
Sample type	Formalin fixed paraffin embedded tissue from cervical lymph node metastasis.
Notes	

Saad-2004

Clinical setting	Patients with metastatic adenocarcinoma and adequate cell block material were identified from the pathology files of a single institution.
Participants and Country	62
Study design	Retrospective case series
Target condition	Identification of the primary tumour. Reference standard was any combination of clinical follow-up, endoscopy, imaging findings and tumour resection with histopathologic confirmation.
Tests	IHC markers: TTF-1 and CDX2
Follow up	Not reported
Proportion with adenocarcinoma	100%
Primary or metastatic tumour?	Metastases
Sample type	Cell block prepared from fine needle aspirate.
Notes	

Scarpatetti-2002

Clinical setting	Pateints with lung metastases who were identified from the pathology records of a single institution.
Participants and Country	82 patients (53 metastatic adenocarcinoma). Austria
Study design	Retrospective case series
Target condition	Primary tumour site (correlation with immunoreactivity). Reference standard was not reported, although the study states that all primary tumours were proven.
Tests	IHC markers: CK4, Ck5, CK6, CK7, Ck8, Ck10, Ck13, Ck14, CK17, CK18, CK19 and CK20
Follow up	Not reported.
Proportion with adenocarcinoma	53/85 (62%) adenocarcinoma
Primary or metastatic tumour?	Metastases
Sample type	Tissue from open or transbronchial biopsies as well as lobectomies
Notes	

Shek-1996

Clinical setting	Patients presenting with cervical lymphadenopathy who were found to have germ cell tumours.
Participants and Country	2 patients. Hong Kong
Study design	Case report
Target condition	Metastatic germ cell tumour. Reference standard was a combination of all diagnostic tests, a primary tumour was histopathlogically confirmed in one case.

Tests	IHC markers: PLAP, MAK-6, S-100 . Serum tumour markers: beta-HCG, AFP.
Follow up	Not reported
Proportion with adenocarcinoma	None: both had germ cell tumours
Primary or metastatic tumour?	Metastatic
Sample type	Cell block made from fine needle aspirate of cervical lymph node.
Notes	

Shimonishi-2000

Clinical setting	Patients with metastatic adenomacarcinoma of the liver identified from the pathology records of a single institution.
Participants and Country	40 patients.Japan
Study design	Retrospective case series
Target condition	Identification of the primary site. Reference standard was not reported.
Tests	IHC markers: CK7, CK19, CK8 and Ck20
Follow up	Not reported
Proportion with adenocarcinoma	100%
Primary or metastatic tumour?	Metastatic
Sample type	Formalin fixed paraffin embedded tissue: obtained from surgical liver resection or autopsy.
Notes	Study also included patients with primary intrahepatic cholangiocarcinoma but these are not included in this evidence review.

Srodon-2002

Clinical setting	Patients with brain metastases confirmed as metastatic carcinoma identified from the surgical pathology records of a single institution between 1990 and 2000.
Participants and Country	75 patients. USA
Study design	Retrospective case series
Target condition	Primary tumour organ of origin. Reference standard was the diagnosis obtained from review of clinical and radiological records of each patient
Tests	IHC markers: TTF-1
Follow up	Not reported
Proportion with adenocarcinoma	22/75, all others were excluded from this evidence review.
Primary or metastatic tumour?	Metastases
Sample type	Tissue from brain biopsy

Notes	

Strickland-Marmol-2007

Clinical setting	Consecutive patients with brain metastases from an adenocarcinoma primary, identified from the records of a single institution.
Participants and Country	38 patients. USA
Study design	Retrospective series
Target condition	Identification of primary site. Reference standard not reported.
Tests	IHC markers: CK7, CK20 and CDX-2
Follow up	Not reported
Proportion with adenocarcinoma	100%
Primary or metastatic tumour?	Metastases
Sample type	Formalin fixed paraffin embedded tissue from brain metastasis.
Notes	

Taweevisit-2003

Clinical setting	Patients with craniospinal metastases identified from the pathology records of a single institution between 1998 and 2002
Participants and Country	66 patients. Thailand
Study design	Retrospective case series
Target condition	Identification of the primary site.
Tests	IHC makers: CK7 and CK20.
Follow up	Not reported
Proportion with adenocarcinoma	Not reported
Primary or metastatic tumour?	Metastatic
Sample type	Tissue from brain metastasis
Notes	

Torenbeek-1998

Clinical setting	Patients with adenocarcinomas of the urinary bladder, prostate, urachus, colon, cervix, ovary or endometrium. Cases were selected from the records of a single pathology department.
Participants and Country	122 patients. Netherlands.
Study design	Retrospective case series.

Target condition	Identification of the primary tumour site. The primary tumour was confirmed using any combination of clinical, radiological and histological evidence
Tests	IHC markers: CK7, E48, PSA, PSAP, CK20, Vimentin, OC125 and HER-2/neu
Follow up	Not reported.
Proportion with adenocarcinoma	100%
Primary or metastatic tumour?	Primary
Sample type	Formalin fixed paraffin embedded tissue
Notes	

Tot-2002

Clinical setting	Patients with primary or metastatic adenocarcinoma.
Participants and Country	Studies reporting CK7 or CK20 immunoreactivity according to the primary site of adenocarcinoma. 35 papers were included
Study design	Review of diagnostic studies
Target condition	Correlation of CK7 / Ck20 immunoreactivity with primary tumour site. reference standard was not reported.
Tests	IHC markers: combinations CK7 and CK20 immunoreactivity
Follow up	Not reported
Proportion with adenocarcinoma	Review was specifically concerned with adenocarcinoma, but it is possible that some of the primary studies included other tumours
Primary or metastatic tumour?	The proportion with metastatic tumours is reported for each tumour site. It ranged from 13% for the prostate to 100% for lobular breast and biliary tumours.
Sample type	Histopathology
Notes	

Vang-2006

Clinical setting	Patients with primary ovarian mucinous tumours or metastatic mucinous tumours of other sites, identified from the surgical pathology files of three institutions between 1978 and 2006
Participants and Country	179 patients. USA
Study design	Retrospective case series
Target condition	Correlation between primary tumour and marker immunoreactivity. Reference standard diagnosis was
Tests	IHC markers: CK7, CK20 and all combinations of the two.
Follow up	Not reported
Proportion with adenocarcinoma	100%
Primary or metastatic tumour?	84/179 primary (45%)
Sample type	Formalin fixed paraffin embedded tissue.

Notes

Wauters-1995

Clinical setting	Patients with metastatic ovarian tumours identified from the pathology records of a single institution
Participants and Country	37 patients.
Study design	Retrospective case series
Target condition	Identification of the primary tumour. Reference standard was the histopathological diagnosis
Tests	IHC markers: CK7, CK8 and CK20
Follow up	Not reported.
Proportion with adenocarcinoma	100%
Primary or metastatic tumour?	adenocarcinoma
Sample type	Paraffin embedded tissue from ovarian metastases.
Notes	Patients in this study with primary ovarian cancer or with non-adenocarcinoma (N= metastases were exlcuded from the evidence review

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11. Bronchoscopy versus video-assisted thoracic surgery for the diagnosis of intra-pulmonary nodules not amenable to percutaneous biopsy in patients with undefined primary cancer.

Last updated: 30 / 10 / 2009.

Short summary

Evidence from case series suggests that bronchoscopy can yield a diagnosis in approximately 64% of patients with suspected lung metastases.

Evidence about the diagnostic yield of video-assisted thoracic surgery (VATS) was limited to one case series, reporting a 100% yield of tissue adequate for diagnosis in patients with lung metastases.

Both these estimates come from series which selected patients with proven lung metastases, and probably overestimates the diagnostic yield of both procedures in practice.

There was little evidence was about the complications of VATS or bronchoscopy for the diagnosis of suspected lung metastases. Evidence from literature reviews suggests that both procedures carry a risk of complications. For example the reported rates of perioperative mortality were between 1 and 2% for VATS compared with 0.1 to 0.2% for bronchoscopy.

Rationale

The lung is a common site for metastatic malignancy. Most intra-pulmonary metastases are due to common cancers, including primary lung cancer, colorectal (sometimes solitary), breast (often with effusion), and renal cell (often large or “cannonball”). Rarer tumours metastasising to lung include thyroid (usually multiple), testicular, melanoma, osteo-sarcoma and choriocarcinoma. Cavitating metastases are most likely to be of squamous cell type. Although these patterns can be helpful in directing attention to candidate primary sites, in the absence of an identified primary, (or a more accessible site of metastatic disease) it is logical to seek to obtain tissue from the parenchymal lung deposits.

Bronchoscopy is the investigation of choice for patients with intra-pulmonary nodules who have clinical features to suggest either endobronchial involvement with tumour (lung collapse or significant haemoptysis), or central node involvement. In both these cases there is a significant chance of visualising tumour and obtaining tissue by forceps biopsy.

Percutaneous biopsy is the investigation of choice when intrapulmonary tumour deposits are sufficiently large, and sufficiently close to the chest wall to allow this to be performed safely.

Where intra-pulmonary nodules are the sole finding, bronchoscopy is less likely to visualise tumour and the likelihood of a positive biopsy is correspondingly reduced. In this group of patients it is necessary to define whether bronchoscopy and biopsy is worthwhile, in terms of diagnostic yield, or whether video-assisted thoracic surgery (VATS) and lung biopsy is superior.

Methods

Study types

There was no restriction on study design.

Target condition

The diagnostic yield (true positive rate) for lung metastases.

Participants

Patients with undefined primary cancer (without histology, and without a strong presumptive diagnosis of primary lung cancer) presenting with intra-pulmonary nodules not easily accessible for percutaneous biopsy.

Index tests

Bronchoscopy (and its ancillary procedures: biopsy and cytology), video-assisted thoracic surgery and biopsy (VATS).

Reference standard

This review was concerned with diagnostic yield of bronchoscopy and VATS, rather than their sensitivity or

specificity. It was assumed that the combination of either procedure with biopsy and histopathology was 100% specific with unknown sensitivity.

STUDY SELECTION

An initial list of studies was selected by SA. NB then selected potentially relevant studies from this list on the basis of their title and abstract. These studies were ordered and each paper was checked against the inclusion criteria.

DATA EXTRACTION AND SYNTHESIS

Two reviewers (NB and AM) extracted data. Only published data were included and authors were not contacted. Data about diagnostic yield were extracted into tables, and where individual results were combined to give an average diagnostic yield for each procedure.

QUALITY ASSESSMENT

Study quality was assessed by one reviewer (NB) using the QUADAS checklist for diagnostic studies, incorporated in Cochrane Review Manager software.

HETEROGENEITY ASSESSMENT

There was no statistical analysis of heterogeneity.

Search results

The literature search identified 103 studies and six were included. In the absence of good evidence about complications associated with VATS and bronchoscopy in these six case series, a high level search of MEDLINE for reviews of complications was done and two additional review papers were included.

STUDY QUALITY

All the included case series were retrospective. These series also tended to select only patients with confirmed metastases which could bias their estimates of the diagnostic usefulness of bronchoscopy or VATS.

Summary of evidence

DIAGNOSTIC YIELD

Diagnostic yield of bronchoscopy

In five case series bronchoscopy was done for diagnosis of suspected lung metastases in a total of 431 patients (Argyro et al, 1994; Diaz et al, 2003; Mohsenifar et al 1978; Oshikawa et al, 1998; Poe et al, 1985). A lesion or other abnormality was visible on bronchoscopy in 45% of these patients. The overall diagnostic yield of bronchoscopy was 65%, in three series with a total of 252 patients. The overall diagnostic yield of bronchoscopic biopsy was 46% in four series with 311 patients. The yield of bronchoscopic brush cytology was 44% (4 studies, 263 patients) and the corresponding yield of washing cytology was 35% (4 studies, 310 patients).

Three of the series reported the results of bronchoscopy separately for patients presenting with solitary or multiple nodules on chest X-ray (Argyros et al, 1994; Diaz et al, 2003; Poe et al, 1985). It was unclear, however, whether pulmonary nodules were the sole finding. A lesion or other abnormality was visible on bronchoscopy in 44% of these patients. The overall diagnostic yield of bronchoscopy was 64%, in two series with a total of 112 patients. Only Diaz et al (2003) reported the individual diagnostic yield of biopsy, brushing cytology and washing cytology: 56%,44% and 40% respectively in a series of 88 patients.

One of the studies (Poe et al 1985) calculated the sensitivity and specificity of fibreoptic bronchoscopy. Bronchoscopy had a sensitivity of 67% and corresponding specificity of 100%.

Most of the included studies retrospectively selected only patients with proven metastases, thus the prevalence of lung metastases in these series was very high, ranging from 86% to 100%. In patients with only a presumptive diagnosis of lung metastases, the corresponding prevalence of lung metastases and diagnostic yield of bronchoscopy could be lower.

Diagnostic yield of VATS

Lin et al (1999) performed VATS for diagnosis of pulmonary metastases in 78 patients when percutaneous needle biopsy was unfeasible or unsuccessful. They reported a that VATS resection obtained adequate tissue for diagnosis in all cases. Again this was a series where only patients with confirmed metastases were retrospectively selected, so in patients with only suspected metastases the diagnostic yield could be lower.

COMPLICATIONS

Complications of bronchoscopy

None of the included case series reported complications associated with bronchoscopy. Geraci et al (2007) reviewed complication rates in 107969 flexible fibreoptic bronchoscopy procedures reported in the literature. The rate of complications of local anaesthesia ranged from 0.3-0.5%; hypoxaemia 0.2-21%; arrhythmia 1-10%; post-biopsy bleeding 0.12-7.5%; pneumothorax or pneumomediastinum 1-6%; fever 0.9-2.5% and mortality 0.1-0.2%.

Complications of VATS

In the diagnostic VATS series reported by Lin et al (1999) there were no major complications or conversions to thoracotomy in the 78 included patients. Imperatori et al (2009) reviewed the literature about complications in patients undergoing VATS for diagnosis or treatment. Peri-operative mortality occurred in between 1 and 2% of procedures, other complications included: prolonged air leak (3 to 6%), conversion to thoracotomy (8% to 11%), port site recurrence (0.3 to 0.6%) and post-operative bleeding (0.5 to 1.9%)

EXISTING NICE GUIDANCE

The current NICE clinical guideline on the diagnosis and treatment of lung cancer (2005) recommends that, following chest CT, bronchoscopy should be performed for the diagnosis of indeterminate central pulmonary nodules in patients who are able and willing to undergo the procedure. Surgical biopsy should be performed for diagnosis where other less invasive methods of biopsy have not been successful or are not possible.

These recommendations were based on evidence suggesting a relatively high sensitivity (around 88%) for bronchoscopy and its ancillary procedures in the detection of central bronchogenic carcinoma. The complication rate of bronchoscopy was not reported. The evidence was mixed for the accuracy of video assisted thoracic surgery in the diagnosis of solitary pulmonary nodules (sensitivity ranged from 41 to 100%), but suggested a moderately low complication rate.

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Table 11.1 Diagnostic yield and complications of bronchoscopy - regardless of presentation

Study	Population	N	Prevalence of lung metastases	Lesion visible on bronchoscopy	Overall diagnostic yield	Diagnostic yield biopsy*	Diagnostic yield brush cytology	Diagnostic yield washing cytology	bronchoscopy related mortality	bronchoscopy related morbidity
Diaz 2003	Patients with suspected lung metastases (eventually confirmed)	113	113/113 (100%)	57/113 (50%)	82/113 (73%)	69/113 (61%)	57/113 (50%)	50/113 (50%)	not reported	not reported
Oshikawa 1998	Patients with suspected lung metastases (eventually confirmed)	65	65/65 (100%)	45/65 (70%)	not reported	not reported	not reported	not reported	not reported	not reported
Agyros 1994	Patients with known malignancy and pulmonary symptoms or abnormal chest X-ray	111	Not reported	44/111 (40%)	not reported	27/75 (36%)	1/8 (13%)	1/55 (2%)	not reported	not reported
Poe 1985	Patients with known malignancy and abnormal chest X-ray, or patients presenting with an abnormal chest X-ray and suspected metastases (later confirmed)	105	90/105 (86%)	33/105 (31%)	60/105 (57%)	41/105 (40%)	brush or washing 40/105 (38%)	brush or washing 40/105 (38%)	not reported	not reported
Mohsnifar 1978	Patients with suspected lung metastases (eventually confirmed)	37	37/37 (100%)	14/37 (39%)	20/37 (54%)	7/18 (39%)	17/37 (46%)	17/37 (46%)	not reported	not reported
Geraci 2007	Studies reporting complications of bronchoscopy (107969 procedures included)		not reported	-	-	-	-	-	0.1-0.2%	complication of local anaesthesia was 0.3-0.5%; hypoxaemia 0.2-21%; arrhythmia 1-10%; post-biopsy bleeding 0.12-7.5%; pneumothorax or pneumomediastinum 1-6%; fever 0.9-2.5%
Total		431		193/431 (45%)	162/255 (64%)	144/311 (46%)	115/263 (44%)	108/310 (35%)	-	-

* Combines biopsy of visible endobronchial lesions and transbronchial biopsy under fluoroscopic guidance.

Table 11.2 Diagnostic yield and complications of bronchoscopy in patients presenting with solitary or multiple nodules on chest X-ray

Study	Population	N	Prevalence of lung metastases	Lesion visible on bronchoscopy	Overall diagnostic yield	Diagnostic yield biopsy*	Diagnostic yield brush cytology	Diagnostic yield washing cytology	bronchoscopy related mortality	bronchoscopy related morbidity
Diaz 2003	Patients with suspected lung metastases (eventually confirmed)	88	88/88 (100%)	39/88(44%)	60/88 (68%)	49/88 (56%)	39/88 (44%)	35/88 (40%)	not reported	not reported
Agyros 1994	Patients with known malignancy and pulmonary symptoms or abnormal chest X-ray	43	Not reported	19/43 (44%)	not reported	not reported	not reported	not reported	not reported	not reported
Poe 1985	Patients with known malignancy and abnormal chest X-ray, or patients presenting with an abnormal chest X-ray and suspected metastases (later confirmed)	24	Not reported	Not reported	12/24 (50%)	not reported	not reported	not reported	not reported	not reported
Total		155		58/131 (44%)	72/112 (64%)	49/88 (56%)	39/88 (44%)	35/88 (40%)	-	-

Table 11.3 Diagnostic yield and complications of video-assisted thoracic surgery (VATS)

Study	Population	N	Prevalence of lung metastases	Diagnostic yield	Peri-operative mortality	Prolonged air leak	Conversion to thoracotomy	Port site recurrence	Postoperative bleeding
Lin 1999	Patients undergoing VATS for diagnosis of suspected lung metastases when percutaneous biopsy was unsuccessful or unfeasible. Lesions were in the outer third of the parenchyma and less than 3cm in diameter.	78	78/78 (100%)	78/78 (100%)	0/78 (0%)	N.R.	0/78 (0%)	0/78 (0%)	N.R.
Imperatori 2009 - literature review	Studies reporting VATS complications	-	N.R.	N.R.	No intraoperative deaths, perioperative mortality was 1 to 2% in 2 studies (N=2451)	3.2 to 6.7% in 4 studies (N=N.R.)	8% to 11% in 2 studies (N=731)	0.3% to 0.6% in 3 studies (N=1772)	0.5% to 1.9% in 2 studies (N= N.R.)

Abbreviations: N.R. not reported;

11. Bronchoscopy versus video-assisted thoracic surgery for the diagnosis of intra-pulmonary nodules not amenable to percutaneous biopsy in patients with undefined primary cancer.

Last updated: 30 / 10 / 2009.

Characteristics of included studies

Argyros-1994

Clinical setting	Patients with extra pulmonary malignancy receiving a fibreoptic bronchoscopy for suspected lung metastases at a single institution between 1987 and 1991.
Participants and Country	111 patients. USA
Study design	Retrospective case series
Target condition	Diagnostic biopsy rate.
Tests	Fibreoptic bronchoscopy with endobronchial biopsy, transbronchial biopsy, brush biopsy, bronchial wash, transbronchial needle biopsy and flow cytometry.
Follow up	Not reported.
Notes	Includes only patients with confirmed primary tumours. Did not exclude haematological malignancies.

Diaz-2003

Clinical setting	Patients referred to a single bronchoscopy unit between 1993 and 2000 due to abnormal chest X-ray, and confirmed primary tumour (or confirmed extra pulmonary metastases in the case of unknown primary tumour). Patients with bronchogenic carcinoma, haematological malignancy and uncontrolled oesophageal or larynx carcinoma were excluded.
Participants and Country	153 patients. 11/153 had CUP. Spain
Study design	Retrospective case series.
Target condition	Diagnostic yield. All cases were histopathologically or cytopathologically proven: (washing 44%, brushing 50%, endobronchial biopsy 61%, surgery 11% and postmortem 17%)
Tests	Fibreoptic bronchoscopy (Oympus BF-T30 or BF-P20), brush cytology, washing cytology, bronchial biopsy in patients with visible endobronchial lesions and transbronchial biopsy under fluoroscopic guidance.
Follow up	
Notes	

Geraci-2007

Clinical setting	Patients receiving fibreoptic bronchoscopy for any indication
Participants and Country	Evidence from 107969 flexible fibreoptic bronchoscopy procedures was included.
Study design	Literature review
Target condition	Complications related to fibreoptic bronchoscopy
Tests	Fibreoptic bronchoscopy.
Follow up	
Notes	Italian language paper.

Imperatori-2009

Clinical setting	A case series of 1093 VATS procedures between 1996 and 2008 at a single institution. A literature review of other case series (24 papers) is included.
Participants and Country	1093 procedures (num ber of patients not reported). Italy
Study design	Case series and expert review of the literature.
Target condition	Peri-operative complications: overall morbidity and mortality, prolonged air leak, bleeding, infection, pain, port site tumour recurrence, and conversion to thoracotomy
Tests	VATS for biopsy or with curative intent.
Follow up	Not reported: case series reports perioperative morbidity (the perioperative period is not defined further)
Notes	

Lin-1999

Clinical setting	Patients who recived VATS wedge resection of pulmonary metastases at a multiple hospitals between 1991 and 1998. Inclusion criteria for VATS were: control of the primary tumour, no evidence of extra-pulmonary metastases, lesions in the outer third of the parenchyma, fitness for surgery and lesions of less than 3 cm in diameter. Lesions were identified and localised using high resolution CT.
Participants and Country	177 patients: VATS for diagnosis 78 patients (percutaneous biopsy was unfeasible or unsuccessful). VATS for therapeutic or curative intent in 99 patients. USA, ITALY and HONG KONG.
Study design	Retrospective case series.
Target condition	Yield of tissue adequate for diagnosis. Perioperative mortality and major complications. Conversion to thoracotomy. Survival. Intercostal or port site tumour recurrence.
Tests	VATS, lesions were excised stapled wedge resection using endoscopic stapling devices. Some patients received a combination of the Nd:YAG laser and endoscopic stapling. A 1-cm gross margin was obtained and frozen sections were performed to confirm a disease free staple line.
Follow up	Mean follow up interval was 37 months.
Notes	

Mohsenifar-1978

Clinical setting	Patients with confirmed extrapulmonary primary tumours with pulmonary nodules on chest X-ray.
Participants and Country	37 patients. USA
Study design	Retrospective case series.
Target condition	Diagnostic yield.
Tests	Fibreoptic bronchoscopy with forceps biopsy, brush cytology, and washing cytology. Sputum specimens were collected before bronchoscopy. Lesions not visible on bronchoscopy were biopsied with fluoroscopic guidance.
Follow up	Not reported.
Notes	Old paper: lesions identified on chest X-rays (CT not mentioned).

Oshikawa-1998

Clinical setting	Patients with cytologically or histologically confirmed metastatic disease who received fibreoptic bronchoscopy at a single institution.
Participants and Country	65 patients. Japan.
Study design	Retrospective case series.
Target condition	Visibility of lesions on bronchoscopy, diagnostic yield. Cases with no bronchoscopic findings were diagnosed with: transbronchial lung biopsy (13), autopsy (4) and 3 by percutaneous US guided biopsy.
Tests	Fibreoptic bronchoscopy with transbronchial tumour biopsy.
Follow up	Not reported
Notes	

Poe-1985

Clinical setting	Patients with either: 1) a history of extra-pulmonary malignancy and an abnormal chest X-ray or 2) patients presenting with chest X-rays susgesitve of malignancy, later confirmed as metastases. Patients were referred to any of five hospitals between 1979 and 1984.
Participants and Country	102 patients (105 bronchoscopies). 4 patients had CUP. USA
Study design	Retrospective case series.
Target condition	Diagnostic yield and accuracy of bronchoscopy.
Tests	Fibreoptic bronchoscopy with various ancillary procedures (not in all cases): transbronchial biopsy, brush cytology, washing cytology, fluoroscopy and forceps biopsy.
Follow up	Not reported.
Notes	Old case series: chest X-rays not CT identification of lesions.

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MOHSENIFAR 1978
Mohsenifar Z, Chopra SK, Simmons DH. Diagnostic value of fiberoptic bronchoscopy in metastatic pulmonary tumors. Chest 1978; 74 (4) 369-71

OSHIKAWA 1998
Oshikawa K, Ohno S, Ishii Y, Kitamura S. Evaluation of bronchoscopic findings in patients with metastatic pulmonary tumor. Internal medicine (Tokyo, Japan) 1998; 37 (4) 349-53

POE 1985
Poe RH, Ortiz C, Israel RH, Marin MG, Qazi R, Dale RC, et al. Sensitivity, specificity, and predictive values of bronchoscopy in neoplasm metastatic to lung. Chest 1985; 88 (1) 84-8

12. Cytological examination of ascitic fluid versus histological examination of malignant peritoneal tissue for ascites in patients with unknown primary tumour

Last updated: 27 / 10 / 2009.

Short summary

Cytomorphology had a very low rate of definitive diagnosis of primary tumour site in malignant effusions of unknown origin. When combined with immunocytochemistry the reported rates increased to between 57% and 87%. In comparison histopathology plus immunohistochemistry had a diagnostic rate between 93% and 97%.

There was no data about complications of cytology. Percutaneous core biopsy was associated with minor local bruising and discomfort. Minor complications were reported in less than two percent of laparoscopies from four series with 1284 patients (including cases with non-malignant aetiology). Major complications occurred at a rate of less than one percent, although Chu et al (1994) reported intestinal perforation due to laparoscopy in six percent of patients with peritoneal tuberculosis.

Percutaneous core biopsy had to be repeated in three to seven percent of cases due to sample inadequacy.

There was no useful data on the duration of diagnostic process. One study (Karoo et al, 2003) reported that the hope placed in cytology for the definitive diagnosis delayed radiological imaging by up to 5 days in patients with false negative cytology results.

In summary there is low quality evidence that percutaneous core biopsy has better rate of definitive diagnosis than cytology, possibly at the cost of minor local bruising and discomfort. It is debatable whether the patient groups from the percutaneous core biopsy studies and those from the cytology studies are sufficiently similar to allow direct comparisons.

Rationale

Ascites is a common manifestation of Cancer of Unknown Primary involving the peritoneum. Some patients have definite peritoneal or omental-based metastases which are amenable to percutaneous cutting needle biopsy under ultrasound control. Others have no (or minimal) bulk tumour, but instead have diffuse peritoneal disease which causes the ascites. Tumour cells shed from the peritoneal disease can commonly be detected in the ascitic fluid. It is common practice to examine cells obtained from ascitic fluid, and sometimes a diagnosis can be made on this basis. When there are inadequate numbers of malignant cells in the ascitic fluid, no diagnosis can be made, and a formal biopsy requiring laparoscopy is required. In some instances the accuracy of the diagnosis which can be made on cytology alone is insufficient, and once again, formal laparoscopic biopsy is required.

It is necessary to determine whether the diagnostic yield from a simple procedure, ascites cytology, is adequate, or whether formal biopsy, either by laparoscopy or percutaneous biopsy, is superior. Answering this question may allow the diagnostic pathway to be shortened if ascitic cytology is adequate, or may accelerate the decision to perform a biopsy if cytology is sub optimal.

Methods

Study types

Any study design.

Target condition

Identification of the primary tumour site.

Participants

Patients presenting with malignant ascites of unknown origin. Studies of patients presenting with any ascites of unknown origin, or patients with malignant ascites and known primary tumour were included for background information.

INDEX TESTS
Cytology of ascitic fluid.

REFERENCE STANDARD
Histological examination of malignant peritoneal tissue obtained through percutaneous core biopsy or laparoscopic biopsy.

STUDY SELECTION
An initial list of studies was selected by the information specialist (SA). One researcher (NB) the selected potentially relevant papers from the list, based on their titles and abstracts. These papers were ordered and each one was checked against the inclusion criteria.

DATA EXTRACTION AND SYNTHESIS
One reviewer (NB) extracted data. Only published data were included and authors were not contacted. Outcomes were summarised in tables, but not combined in statistical

QUALITY ASSESSMENT
The study design was noted. Observational studies were classified as prospective or retrospective. Study quality was assessed using the QUADAS checklist.

HETEROGENEITY ASSESSMENT
Differences between studies were noted, but heterogeneity was not investigated statistically.

Search results

The literature search found 55 potentially relevant studies, and 12 other studies were identified from the reference lists of included papers. 20 studies were included in the review.

Evidence was from observational studies and relatively few patients had ascites of unknown origin. Evidence about immunocytochemistry came from studies which combined malignant effusions. The histological evidence came largely from percutaneous core biopsy in women with peritoneal carcinomatosis. There was a complete lack of data about histology in men with malignant ascites of unknown origin, and about laparoscopy for the diagnosis of unknown primary.

Six studies report included only patients with unknown primary after initial diagnostic work up. One study included only patients with malignant ascites of unknown origin (Ringenberg, 1989), two studies malignant effusions of unknown origin (Mottolese et al 1988; Mottolese et al, 1992; Pomjanski et al 2005) and two studies women with peritoneal carcinomatosis of unknown origin (Hewitt et al, 2007; Spencer et al, 2001).

Retrospective reviews of malignant ascites were included for prior probabilities of primary tumour sites (Ayantunde and Parsons, 2007; DiBonito, 1993; Jha et al 2006; Sears, 1987) or data about diagnostic accuracy of immunocytochemistry (Longatto-Filho et al, 1997;) Studies reporting cytology (Gerbes et al, 1991; Karoo et al., 2003; Motherby, 1999; Metzgeroth et al, 2007) or laparoscopy (Chu et al, 1994; Orlando, 1996;Yoon et al 2007) to diagnose malignancy (but not the site of the primary tumour) in patients with ascites were included for information about complications.

STUDY QUALITY
No studies directly compared cytology and histology in the same group of patients, with consistent use of a reference standard diagnostic test. All studies were observational studies: of which 3/20 (15%) were prospective.

Summary of evidence

In a UK series of patients presenting with ascites, 35% of cases were found to have malignant aetiology (Karoo, 2003).

In women with malignant ascites, primary tumours of the ovary, endometrium or other gynaecologic site accounted for between 42% and 50% of cases (see Table 12.3). The other main primary tumour sites were: breast (range 5% to 24%), colorectal (5% to 6%), stomach (3% to 17%), and pancreas (3% to 9%).

In women presenting with malignant ascites of unknown origin (Ringenberg, 1985) or peritoneal carcinomatosis of unknown origin (Spencer 2001; Hewitt, 2007) the proportion eventually diagnosed with ovarian or other gynaecologic tumours was somewhat higher, ranging from 77% to 81%.

In men with malignant ascites, the most common primary tumour sites were stomach, colon or rectum and pancreas (see Table 12.4). Data about men presenting with malignant ascites of unknown origin was limited to a series of 25 cases (Ringenberg, 1985), but the pattern of primary tumours was similar.

The ratio of females to males in the included case series of malignant ascites was approximately 2:1 (see Tables 12.3 and 12.4).

DEFINITVE DIAGNOSIS OF HISTOTYPE IN ASCITES POSITIVE FOR MALIGNANCY
See Table 12.1.

Cytomorphology
Most studies did not report predictions of the primary tumour site on the basis of cytomorphology alone, instead it was used only to detect malignancy. When used for the detection of malignancy in ascites, cytology had high specificity (92 to 100%) but relatively low sensitivity (44 to 70%).

Longatto-Filho et al (1995) conducted a blinded study of serous effusions from 208 women with metastatic adenocarcinoma. They examined the ability of 11 cytomorphologic parameters to discriminate between

breast, ovary, stomach and lung primary tumours. No combination of morphological parameters was specific enough to allow the diagnosis of the primary site of adenocarcinoma.

Spencer et al (2001) reported a blinded cytological analysis of malignant ascites of unknown origin, in which a definitive diagnosis of ovarian cancer was made on the basis of cytology in 3/19 cases (two were confirmed by histopathological analysis, one was false positive).

Cytomorphology plus immunohistochemistry

All but one of the studies reporting the combined use of cytomorphology and immunocytochemistry included patients with any malignant serous effusion (peritoneal, pleural and sometimes pericardial effusions). Therefore these studies included a wider range of primary tumour sites which in turn is likely to inflate the estimates of diagnostic accuracy.

Mottolese et al (1988) reported the use of immunocytochemistry in patients with pleural or peritoneal effusions and unknown primary tumour. Using a panel of 5 monoclonal antibodies a definitive diagnosis was made in 56/60 cases (87%), confirmed by clinical follow up in 53/60 cases. In a follow up to their earlier Mottolese et al (1992) used a panel of ten monoclonal antibodies and reported a definitive diagnosis rate of 103/125 (82%).

Pomjanski et al (2005) reported a correct diagnosis of primary tissue of origin in 86/101 (85%) of patients with effusions and cancer of unknown primary syndrome.

In Longatto-Filho et al (1997), cytomorphology plus immunocytochemistry (panel of 2 monoclonal antibodies) led to a correct diagnosis of the primary tissue of origin adenocarcinoma in 119/208 (57%) women with metastatic serous effusions.

DiBonito et al (1993) reported that the cytologic prediction of histotype was correct in 12/15 (80%) patients with pancreatic primary tumour, and in 25/36 (69%) patients with ovarian primary. For other tumour types cytology was less accurate, but no figures were provided.

Histology plus immunohistochemistry

There was no data about laparoscopic biopsy for the diagnosis of primary tumour site in malignant ascites of unknown origin. Some studies reported laparoscopy for the diagnosis of malignancy in ascites of unknown origin.

Two studies originating from the same UK gynaecologic oncology centre (Hewitt et al, 2007 and Spencer et al, 2001) reported the use of image guided percutaneous biopsy in women with peritoneal carcinomatosis of unknown origin. A definitive diagnosis was made on the basis of histopathology and immunohistochemistry in 97% of cases in Spencer et al (2001) and in 93% of cases in Hewitt et al (2007).

There was no data about percutaneous biopsy for definitive diagnosis of primary tumour in men presenting with ascites.

RATE OF SECONDARY INTERVENTION TO OBTAIN TISSUE FOR DIAGNOSIS

No cytology papers explicitly reported this outcome, see Table 12.1. If tissue biopsies were required in cases when cytology and immunocytochemistry failed to give a definitive diagnosis the secondary biopsy rate would have ranged from 13 to 43 percent. Percutaneous core biopsies were repeated in between three and seven percent of cases, due to technical failure.

COMPLICATIONS

See Table 12.2.

Cytology

No data about complications, (not reported in the cytology studies).

Histology

Minor complications were reported in less than two percent of laparoscopies from four series with 1284 patients (including cases with non-malignant aetiology). Major complications occurred at a rate of less than one percent, although one series (Chu et al, 1994) observed intestinal perforation due to laparoscopy in six percent of patients with peritoneal tuberculosis.

Percutaneous core biopsy was associated with minor local bruising and discomfort (data from three studies with 225 patients in total). A theoretical complication of needle biopsy is tumour seeding in the needle tract. Spencer et al (2001) reported no clinically apparent needle tract metastases during follow up. Hewitt et al (2007) reported that the rate of subcutaneous tumour deposits was unchanged since the introduction of image guided core biopsy in their institution, but no supporting figures were given.

DURATION OF DIAGNOSIS

See Table 12.2. There was very little data about the effect on duration of diagnosis. One study mentions that cytology delayed radiological imaging in patients with false negative cytology results (Karoo et al , 2003).

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Table 12.1 Definitive diagnosis of primary site of tumour

Study	Test	Sensitivity for diagnosis of primary site of tumour	Rate of secondary intervention to obtain tissue for diagnosis
Hewitt 2007	Percutaneous core biopsy + immunohistochemistry (panel of at least 4 antibodies)	139/149 (93%)	10/149 (7%)
Spencer 2001	Percutaneous core biopsy (H&E staining only)	27/35 (77%)	1/35 (3%)
Spencer 2001	Percutaneous core biopsy + immunohistochemistry (panel of at least 4 antibodies)	34/35 (97%)	1/35 (3%)
Pombo 1997	Percutaneous core biopsy (pathological analysis not reported)	Diagnosis was not more detailed than metastatic adenocarcinoma	1/25 (4%) required a repeat biopsy procedure.
Spencer 2001	Cytology	2/19 (11%)	N.R.
Longato-Filho 1995	Cytology + immunocytochemistry (2 antibodies)	119/208 (57%)	N.R.
Mottolese 1988	Cytology + immunocytochemistry (6 antibodies)	52/60 (87%)	N.R.
Mottolese 1992	Cytology + immunocytochemistry (10 antibodies)	103/125 (82%)	N.R.
Pomjanski 2005	Cytology + immunocytochemistry (6 antibodies)	86/101 (85%)	N.R. Only specimens with sufficient tumour cells included in the study.

Table 12.2 Complications and diagnostic delay

Study	Test	N	Duration of diagnostic process	Minor Complications	Major Complications	Mortality due to the test
Bedioui 2007	Laparoscopy	90	N.R.	1/90 (1%) leakage of ascites	None	None
Chu 1994	Laparoscopy	129	N.R.	2/129 (2%) leakage of ascites 2/129 (2%) subcutaenous emphysema 1/129 (1%) wound infection	Intestinal perforation in 2/31 (6%) patients with tuberculous peritonitis	None
Yoon 1997	Laparoscopy	855	N.R.		6/855 (0.7%) biopsy site bleeding 2/855 (0.2%) liver laceration 1/855 (0.1%) spleen laceration 1/855 (0.1%) pneumothorax	None
Orlando 1996	Laparoscopy and guided liver/ peritoneal biopsies	210	N.R.	None	None	None
Pombo 1997	Percutaneous core needle biopsy (CT guided)	25	N.R.	0/25 within 24 hours of biopsy.	None	None

Study	Test	N	Duration of diagnostic process	Minor Complications	Major Complications	Mortality due to the test
Hewitt 2006	Percutaneous core biopsy (CT or ultrasound guided)	149	N.R.	Minor local bruising and discomfort. 1/149 (<1%) rectus sheath haematoma.	None	None
Spencer 2001	Percutaneous core biopsy (CT or ultrasound guided)	35	N.R.	None	None	None
Karoo 2003	Cytology	239	Authors report that the hope placed in cytology for the definitive diagnosis delayed radiological imaging by up to 5 days in patients with false negative cytology results.	N.R.		
Longatto-Filho 1997	Cytology	208	N.R.	N.R.	N.R.	N.R.
DiBonito 1992C	Cytology	153	N.R.	N.R.	N.R.	N.R.
Mottolese 1988	Cytology and immunocytochemistry	60	N.R.	N.R.	N.R.	N.R.
Mottolese 1992	Cytology and immunocytochemistry	135	N.R.	N.R.	N.R.	N.R.
Pomjanski 2005	Cytology and immunocytochemistry	180	N.R.	N.R.	N.R.	N.R.
Motherby 1999	Cytology	300	N.R.	N.R.	N.R.	N.R.
Sears 1987	Cytology	1165	Interval between cytology and tissue diagnosis of the primary tumour was one month or less in all but two patients (in those whose primary was identified).			

Abbreviations: CT, computed tomography; N.R., not reported

Table 12.3 Probabilities of primary tumour site, in female patients with malignant ascites

Definitive diagnosis of primary tumour	DiBonito 1993	Sears 1986	Ayantunde 2006*	Rigenberg 1989**	Hewitt 2006**	Spencer 2001**
Ovary	36 (35%)	90 (40%)	52 (37%)	20 (50%)	-	27 (77%)
Endometrium	7 (7%)	17 (7%)	7 (5%)	8 (20%)	-	-
Fallopian tube	1 (1%)	2 (1%)	-	-	-	-
Cervix	2 (2%)	5 (2%)	-	2 (5%)	-	-
Ovary, endometrium or other gynaecologic site	49 (48%)	114 (50%)	59 (42%)	31 (78%)	121 (81%)	27 (77%)
Stomach	17 (17%)	10 (4%)	-	1 (3%)	-	-
Colorectal	6 (6%)	8 (4%)	-	2 (5%)	-	2 (6%)
Pancreas	9 (9%)	7 (3%)	-	1 (3%)	-	-
Breast	5 (5%)	40 (18%)	33 (24%)	-	4 (3%)	2 (6%)
Hepatobiliary	7 (7%)	0 (0%)	-	-	1 (1%)	-
Lung	0 (0%)	4 (2%)	-	0 (0%)	-	-
Adenocarcinoma of unknown primary	0 (0%)	19 (8%)	-	5 (13%)	-	-
Sarcoma	6 (6%)	4 (2%)	-	-	-	-

Definitive diagnosis of primary tumour	DiBonito 1993	Sears 1986	Ayantunde 2006*	Rigenberg 1989**	Hewitt 2006**	Spencer 2001**
Benign (false positives)	0 (0%)	0 (0%)	-	-	4 (2%)	-
Lymphoma	(<1%)	10 (4%)	-	0 (0%)	3 (2%)	1 (3%)
Melanoma	(<2%)	2 (1%)	-	-	-	-
Mesothelioma	1 (1%)	1 (<1%)	-	-	-	-
Germ cell tumour	0 (0%)	2 (1%)	-	-	-	-
Total	103	227	140	40	138	35

* Figures for males and females are not presented separately, so only prior probabilities of certain tumour sites can be extracted (e.g. ovarian, prostate). Patients with breast cancer were assumed to be female.
**These studies contained women presenting with peritoneal carcinomatosis of unknown origin (Hewitt 2006; Spencer 2001) or malignant ascites of unknown origin (Ringenberg 1985)

Table 12.4 Probabilities of primary tumour site in male patients with malignant ascites

Primary tumour	Di Bonito 1993	Sears 1986	Ayantunde 2006*	Ringenberg 1989**
Stomach	17 (34%)	9 (11%)	-	4 (16%)
Colorectal	8 (16%)	9 (11%)	-	5 (20%)
Pancreas	6 (12%)	6 (7%)	-	2 (8%)
Head-neck	-	-	-	1 (4%)
Lung	0 (0%)	8 (10%)	-	2 (8%)
Kidney	0 (0%)	2 (2%)	-	-
Prostate	0 (0%)	3 (4%)	1 (1%)	1 (4%)
Adenocarcinoma unknown primary	0 (0%)	14 (17%)	-	9 (36%)
Liver	4 (8%)	2 (2%)	-	-
Gallbladder	2 (4%)	0 (0%)	-	-
Lymphoma	(<1%)	13 (15%)	-	1 (4%)
Melanoma	(<3%)	3 (4%)	-	-
Sarcoma	0%	5 (6%)	-	-
Mesothelioma	10 (20)%	2 (2%)	-	-
Total	72	84	69	25

* Figures for males and females are not presented separately, so only prior probabilities of certain tumour sites can be extracted (e.g. ovarian, prostate). Patients with breast cancer were assumed to be female.
**This study contained men presenting with malignant ascites of unknown origin

12. Cytological examination of ascitic fluid versus histological examination of malignant peritoneal tissue for ascites in patients with unknown primary tumour

Last updated: 27 / 10 / 2009.

Characteristics of included studies

Ayantunde-2007

Clinical setting	All patients diagnosed with malignant ascites over a one year period at a single hospital. Ascites malignancy was usually confirmed using cytology, imaging, laparoscopy or laparotomy.
Participants and Country	209 patients. 140 (67%) females 69 (33%) males. UK
Study design	Retrospective case series.
Target condition	Not applicable
Tests	Not applicable
Follow up	Not applicable
Propotion of patients with malignancy	100%
Pathology techniques	Not reported
Notes	Study is included because it provides information about primary tumour sites in patients with ascites

Bedioui-2007

Clinical setting	Patients presenting with isolated ascites of unknown etiology who had laparoscopy, over a 10 year period (1996 to 2006). Before laparoscopy patients received tests for tuberculosis including chest X-ray, and direct examination of sputum, urine, gastric products and ascites. Women received gynaecological examination with pelvic ultrasound. In patients with suspected carcinomatosis work-up included CT scan. All had aspiration of ascitic fluid for cytochemistry and bacteriology.
Participants and Country	90 patients. Tunisia
Study design	Prospective case series
Target condition	Diagnosis of peritoneal tuberculosis versus carcinomatosis. Reference standard was histology of the laparoscopic biopsies.
Tests	Index test was diagnostic laparoscopy including visual inspection and biopsies of peritoneum and liver where possible. The predictive values of atypical cells on cytology and of individual symptoms are also reported.

Follow up	Not reported
Propotion of patients with malignancy	31/90 (34%)
Pathology techniques	Not reported
Notes	

Chu-1994

Clinical setting	Patients with ascites of unknown origin, following ultrasound and CT.
Participants and Country	129 Patients. Taiwan
Study design	Retrospective case series.
Target condition	Diagnosis of the origin of ascites. Visual diagnoses of carcinomatosis peritonei were confirmed by either histology or ascitic cytology. Tuberculous peritonitis was confirmed variously by histology, response to chemotherapy or focus of tuberculosis elsewhere. Patients with visual diagnosis of liver cirrhosis or normal looking peritoneum were not biopsied.
Tests	Laparoscopic visual and histological evaluation of ascites. Ascitic cytology.
Follow up	Not reported
Propotion of patients with malignancy	67/129 (52%)
Pathology techniques	Not reported
Notes	

DiBonito-1993

Clinical setting	Patients with cytology of ascitic fluid positive for malignancy.
Participants and Country	153 patients. 50 males 103 females. Italy
Study design	Retrospective review of cytopathology specimens.
Target condition	Primary tumour site, reference standard was histology of tissue specimens from autopsy or surgery.
Tests	Ascitic cytology.
Follow up	Not reported
Propotion of patients with malignancy	100%
Pathology techniques	Fluid was centrifuged, smeared on slides and stained using the Papanicolauo technique.
Notes	Study reports that cytology was used to predict histotype, but figures are incomplete. Useful for prior probability of tumour location in patients with malignant ascites.

Gerbes-1991

Clinical setting	Patients with confirmed non-malignant ascites or malignancy related ascites (confirmed by ultrasound, CT, autopsy or follow-up).
Participants and Country	99 patients. Germany
Study design	Retrospective series
Target condition	Malignant ascites versus non-malignant ascites. Reference standard was ultrasound, CT, autopsy or clinical follow-up.
Tests	Cytology.
Follow up	Not reported.
Propotion of patients with malignancy	54/99, 55%
Pathology techniques	Sample was centrifuged then the sediment was smeared and stained with Papanicolaou and Giesma stains. Immunohistochemistry (CEA). Other lab tests: cholesterol, LDH, fibronectin, albumin gradient, total protein.
Notes	

Hewitt-2007

Clinical setting	Women with peritoneal carcinomatosis of unknown origin.
Participants and Country	149 women (32 had a previous history of malignancy). UK
Study design	Case series, retrospective.
Target condition	Identification of the primary site. Histopathology of the core sample was considered the definitive diagnosis.
Tests	Percutaneous core needle biopsy of peritoneum, guided by ultrasound or CT.
Follow up	Not reported
Propotion of patients with malignancy	145/149 (97%)
Pathology techniques	Biopsy material was embedded in paraffin, sectioned, and H&E stained. Immunohistochemical analysis was performed using monoclonal antibodies to CAE, CK 7, CK 20 and CA125. Additional monoclonal antibodies were used at the discretion of the pathologist.
Notes	Not diagnostic accuracy study, since histopathology of the core sample was considered definitive

Jha-2006

Clinical setting	Patients whose ascitic fluid samples were sent for cytological examination in 2003, at a single teaching hospital.
Participants and Country	65 patients. Nepal
Study design	Prospective case series
Target condition	Malignant ascites versus non-malignant ascites. Reference standard was biopsy, direct visualisation, radiological imaging or clinical follow up.
Tests	Cytology.

Follow up	Not reported
Propotion of patients with malignancy	37/65
Pathology techniques	Sample was centrifuged then the sediment was smeared and stained with Papanicolaou and Giesma stains.
Notes	

Karoo-2003

Clinical setting	Patients presenting with ascites, whose fluid samples were sent for cytology and recorded in the Histopathology APEX database.
Participants and Country	239 patients, 276 specimens. UK
Study design	Retrospective case series
Target condition	Malignancy, tissue of origin of malignant cells. Reference standard was radiological imaging in some patients whose cytology results were false negative.
Tests	Ascitic cytology (not specified in detail).
Follow up	Not reported
Propotion of patients with malignancy	83/239 (35%)
Pathology techniques	Not reported.
Notes	Unclear whether the tissue of origin of malignant cells was diagnosed on ascitic cytology. Unclear at what stage of the diagnostic work-up cytology was done.

Longatto-1997

Clinical setting	Women with metastatic serous effusions and primary adenocarcinoma, selected from the hospital records of a single cancer hospital.
Participants and Country	208 women. Brazil
Study design	Retrospective case series.
Target condition	Histotype of the primary tumour (breast, ovary, lung or stomach). Reference standard was clinical, radiologic and histologic evidence of primary tumour.
Tests	Cytomorphology (11 parameters considered) and immunocytochemistry (CK7 and CK20 reactivity).
Follow up	Not reported
Propotion of patients with malignancy	100%
Pathology techniques	The smeared sample was stained with Papanicolaou stain for morphological analysis. immunocytochemistry (CK7 and CK20 reactivity).
Notes	Known cases were selected for inclusion, likely to bias results in favour of the index test.

Metzgeroth-2007

Clinical setting	Serous effusion samples sent to a cytopathology department between 1999 and 2006.
Participants and Country	1234. Germany

Study design	Retrospective case series.
Target condition	Malignant or non-malignant. Reference standard was clinical follow up and treatment response.
Tests	Cytology
Follow up	Not reported
Propotion of patients with malignancy	610/1234 (50%)
Pathology techniques	The sample was centrifuged then the sediment was smeared and stained with Giesma stain. Immunocytochemistry (3 antibodies: pancytokeratin, HEA125, and calretinin).
Notes	

Motherby-1999

Clinical setting	Effusions analysed by a single cytopathology department between 1994 and 1995.
Participants and Country	300 pleural effusions and 300 peritoneal effusions, from 244 and 253 patients respectively. Germany
Study design	Retrospective, case series.
Target condition	Diagnosis of malignancy. The reference standard was the histologically or clinically proven diagnosis recorded in the patient's medical records.
Tests	Ascitic cytology.
Follow up	29 to 36 months
Propotion of patients with malignancy	93/293 (32%)
Pathology techniques	The sample was centrifuged then the sediment was smeared and Giesma stained.
Notes	Unclear at what stage of the diagnostic work-up cytology was done.

Mottolese-1988

Clinical setting	Patients with malignant effusions of unknown origin. Patients with known malignancy and patients with benign effusions were also included, to develop the immunocytochemical protocol.
Participants and Country	60 patients with unknown primary cancer. 23 with proven benign effusions and 65 with known malignancy. Italy.
Study design	Retrospective case series.
Target condition	Primary tumour site (organ of origin). Reference standard was clinical follow up
Tests	Cytology plus immunocytochemistry (6 antibodies: B72.3, B6.2, MBRI, MOv19, OC-125, KS1/4).
Follow up	Not reported
Propotion of patients with malignancy	125/148 (85%)
Pathology techniques	The sample was centrifuged then the sediment was smeared and stained with Papanicolaou and Giesma stains. Immunocytochemistry (6 antibodies: B72.3, B6.2, MBRI, MOv19, OC-125, KS1/4).
Notes	Known cases and controls would tend to bias in favour of the index test

Mottolese-1992

Clinical setting	Patients with malignant effusions (pleural and/or peritoneal)
Participants and Country	135 patients with unknown primary tumour (44 men and 91 women). 179 patients with known primary tumour (not included in this appraisal). Italy
Study design	Retrospective case series
Target condition	Identification of the primary tumour. Reference standard is not reported
Tests	Cytology and immunocytochemistry (panel of 10 monoclonal antibodies)
Follow up	Not reported
Propotion of patients with malignancy	125/135 (93%)
Pathology techniques	The sample was centrifuged then the sediment was smeared and Papanicolaou stained. Immunocytochemistry (panel of 10 monoclonal antibodies). Samples with a low proportion of tumour cells were also short-term cultured for 6 to 8 days.
Notes	Short term culture of the tumour cells improved the sensitivity of cytology + ICC

Orlando-1996

Clinical setting	Patients with ascites not due to renal or cardiac failure. All patients had previous evaluation of ascitic fluid that proved non-diagnostic.
Participants and Country	210 patients. Italy
Study design	Unclear, probably case series.
Target condition	Reference standard was a combination of all clinical, laboratory and imaging studies.
Tests	Laparoscopy, histology
Follow up	Not reported
Propotion of patients with malignancy	42/210 (20%)
Pathology techniques	Histopathology, not specified in detail.
Notes	

Pombo-1997

Clinical setting	Patients referred for CT guided biopsy of omental lesions and with no clinical or radiological of primary tumour or infectious or inflammatory condition that could be responsible.
Participants and Country	25 patients with focal (N=2) or diffuse (N=23) omental pathology. Spain
Study design	Retrospective case series.
Target condition	Specific diagnosis of malignancy. Reference standard was either histopathology of the resected tumour, laparoscopic biopsy or endoscopic biopsy; or clinical follow up.
Tests	CT guided biopsy of omental lesions: core biopsy (N=16) and other biopsy (N=9).
Follow up	Patients monitored for 24 hours for acute complications. Longer term follow up not reported

Propotion of patients with malignancy	19/25 (76%)
Pathology techniques	Histopathology, not specified in detail
Notes	

Pomjanski-2005

Clinical setting	Patients with cytologically positive effusions, with sufficient tumour cells in effusion and non-small cell carcinoma morphology.
Participants and Country	180 patients. Effusions were: pleural (118/180, 66%), peritoneal (53/180, 29%) and pericardial (5%). Germany
Study design	Retrospective case series
Target condition	Identification of the primary tumour site (breast, ovary, lung, colon, stomach, pancreas or other). Reference standard was clinical follow up or histology.
Tests	Cytology plus immunocytochemistry with 6 tumour markers (CK 5/6, CK 7, CK 20, CA 125, TTF1, Cdx 2)
Follow up	Not reported
Propotion of patients with malignancy	100%
Pathology techniques	The sample was centrifuged then the sediment was smeared and stained according to May-Grunewald Giesma and Papanicolaou.
Notes	Only patients with sufficient tumour cells were included: bias in favour of cytology. Algorithm for use of tumour markers is presented.

Ringenberg-1989

Clinical setting	Patients with malignant ascites, identified from the records of cytopathological service.
Participants and Country	65 patients, 40 female, 25 male. 14 patients had malignant ascites of unknown origin. USA.
Study design	Retrospective case series.
Target condition	Not applicable
Tests	Most had cytology. Laparotomy, autopsy, chest X-ray, CT, barium enema, upper GI endoscopy, lower GI endoscopy, mammography were done in selected cases.
Follow up	Not reported
Propotion of patients with malignancy	100%
Pathology techniques	Not specified
Notes	Not a diagnostic accuracy study, included for prior probability information

Sears-1987

Clinical setting	Specimens of pleural or peritoneal effusions sent to a cytopathology department between 1982 and 1984.
Participants and Country	3011 pleural or peritoneal effusions were examined, and 846 patients found to have malignant effusions. 53 patients presented with malignant peritoneal effusions and unknown primary tumour. USA
Study design	Retrospective case series.

Target condition	Positive or negative for malignancy. Epithelial versus nonepithelial neoplasm. Reference standard was histology of primary tumour (it cases where it was found).
Tests	Cytology of peritoneal effusions
Follow up	Not reported
Propotion of patients with malignancy	423/1165 (36%) peritoneal specimens were positive for malignancy
Pathology techniques	Not specified
Notes	No effort was made to predict the primary site of adenocarcinoma by effusion cytology.

Spencer-2001

Clinical setting	Women with peritoneal carcinomatosis (on the basis of clinical and imaging features) treated by a single gynaecological oncology team during a 2 year period.
Participants and Country	35 women. 8/35 had previous tumours known to metastasize to the peritoneal cavity. 25/35 had suspected ovarian cancer (on the basis of clinical and imaging features).UK
Study design	Prospective case series
Target condition	Diagnosis of tumour type. Reference standard was multidisciplinary review of all clinical information, findings of any subsequent surgery and response to therapy.
Tests	Image guided core needle biopsy. Immunohistochemistry, cytology in selected cases.
Follow up	Not reported
Propotion of patients with malignancy	100%
Pathology techniques	Histological analysis, H&E staining. Immunohistochemistry using antibodies to : CEA, CK-7, CK-20 and CA125. Additional breast cancer specific antibodies were used in women with a history of breast cancer. Ascites was drained in 19/35 women and analysed cytologically.
Notes	

Yoon-2007

Clinical setting	Patients referred for a diagnostic laparoscopy in a single gastroenterology unit. Only results for patients with ascites of unknown origin are included in this appraisal.
Participants and Country	142 diagnostic laparoscopy procedures were done for ascites of unknown origin. Korea
Study design	Retrospective case series.
Target condition	Diagnosis of metastatic carcinoma, peritoneal tuberculosis, no disease, or mesothelioma. Reference standard was
Tests	Laparoscopy with biopsy
Follow up	Not reported
Propotion of patients with malignancy	46/142 (32%)
Pathology techniques	Not reported
Notes	

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13. Investigations to find the primary tumour in people with cancer of unknown primary, when clinical benefit is unlikely

Last updated: 30/ 10/ 2009.

Short summary

There is evidence that people with CUP sometimes receive excessive diagnostic evaluation (Shaw et al, 2007). Diagnostic investigations limited to fewer tests would not affect survival in most patients, but this could have a negative impact on patients' psychological well being.

Very few studies reported the psychological effect of diagnosis of the primary tumour in people with CUP. The best evidence came from a qualitative study of a small group of people with CUP (Boyland and Davis, 2008). There was evidence that people with cancer of unknown primary experience uncertainty and distress. Patients have to deal with the uncertainty about the origin of their disease, its future course and the benefit of treatment.

In most cases finding a primary is unlikely to significantly improve outcome, but this appears contrary to patients' beliefs. Some patients felt that they were missing the chance of targeted therapy if their primary is not found. Patients with at least a suspected primary site gained some benefit in being able to focus on their treatment plan.

No studies directly compared minimal versus exhaustive diagnostic evaluation in terms of patients' quality of life.

Rationale

Conventional medical management of patients with malignancy of undefined primary origin concentrates on undertaking a minimum set of investigations to try and define a primary tumour site, with a view to providing rationally based treatment. A specific aim is to avoid "futile" or protracted investigations when the likelihood of further clarifying the diagnosis has become very low. This approach neglects an important priority for some patients, which is to gain the highest possible certainty about the nature of their illness, regardless of the extent of investigations which have to be performed.

In some instances, an explanation of the strategy, and the limitations of further tests will satisfactorily allay a patient's concerns. In other cases there may be remaining uncertainty, causing psychological morbidity, which in the patient's mind can only adequately be addressed by further tests seeking a possible primary, regardless of the low yield and additional inconvenience. To optimise the care of patients with malignancy of undefined primary origin it is necessary to try and define the optimal point for ceasing diagnostic tests, based on a balance between standard clinical benefit and individual psychological need.

Methods

Study types

There was no restriction on study design.

Participants

People with malignancy of undefined primary origin in the initial diagnostic phase and people with confirmed cancer of unknown primary origin at the completion of standard investigations.

Interventions

Further investigations to try and find the primary, compared with no further diagnostic tests.

Outcomes

Patient's psychological adjustment. Clinicians confidence in their ability.

Study selection

An initial list of studies was selected by the information specialist (SA). One reviewer (NB) then selected potentially relevant papers from this list on the basis of their title and abstract. These studies were ordered and each paper was check against the inclusion criteria.

Data extraction and synthesis

One reviewer (NB) extracted data. Qualitative data was summarised by listing the themes identified in the studies. Patient's first hand experiences about uncertainty and the diagnostic process were also included when available.

Search results

The literature search identified 14 studies, six of which were included. An additional study (Shaw et al, 2007) was included as evidence of the typical diagnostic evaluation of people with CUP in the UK.

DESCRIPTION OF INCLUDED STUDIES

The studies included a qualitative study of ten patients with CUP (Boyland and Davies, 2008), a study of psychological adjustment in a group of 72 patients with CUP (Lenzi et al, 2004) and three expert reviews (Chorost el al, 2004; Ettinger 2005; Symons, 2008).

Evidence summary

Shaw et al (2007) reviewed the investigation and management of carcinoma of unknown primary in a single UK cancer network during 2003. A wide variety of tests were used in the diagnostic evaluation of these patients, either before or after referral to the cancer centre. Nineteen different investigations were used in the cohort of patients with liver or multiple metastases, 13 different tests were used in the cohort with bone metastases. Shaw et al (2007) concluded that the number of diagnostic investigations could be reduced substantially, suggesting tests should be limited to those affecting clinical management.

QUALITATIVE EVIDENCE (BOYLAND AND DAVIS, 2008)

Boyland and Davis (2008) identified six main themes in their study: poor understanding, struggling with uncertainty (contrasting with stoical acceptance), undergoing multiple investigations, inability to treat, healthcare professionals not having the answers and difficulty explaining to others.

Understanding of CUP

All patients with an entirely unknown primary reported being told they had cancer but that the primary site could not be found. Some patients did not fully understand this.

"This kind of non-specific kind of ... they haven't found the primary tumour but it is spreading all over the place."

Uncertainty about diagnosis

Patients clearly struggled with the unknown nature of the primary tumour. This seemed to increase the unpredictability of the disease, with patients not knowing what to expect, feeling an ominous sense that it might be "spreading" or "lurking".

"I think that if there is a secondary and it can cause you that much jip, if there is is a primary it could do you double the damage. I just don't understand how it can hide away somewhere...it's the not knowing is the horrible thing...the uncertainty of it all...[if I knew] I would be more at ease."

Others wanted the understanding and feeling of control attached to a diagnostic label.

"Its confusion because you don't know what to expect. I know there are loads of cancers around and they know where most of them are, well why I am so different? Why are these unknown primaries? So ... I feel like screaming, literally screaming. [If] they said where they are ... well, for me it would be peace of mind."

One man had been diagnosed with leukaemia 20 years earlier and was able to compare the experiences of having known and unknown cancer.

"I've got no feeling where the actual cancer is and (my wife) quite often has a prod to see if she can find it. With the cancer I had before I knew exactly where it came from, but not knowing with this cancer makes me like unaware and I would like to know where it has come from."

Some patients accepted that their primary was unknown and that there was no point in thinking about finding it.

"... if it is there it is there. I mean it doesn't make any difference to me no ... so trying to think about it is to me a bit of a waste of time."

One patient, with a possible ovarian primary, found it useful to believe it was an ovarian primary.

"As far as I'm concerned it is in my ovaries ... because I'm being treated for ovarian cancer. I'm not looking for anything else at the moment. It would be much more difficult if I didn't know where it was."

Multiplie diagnostic tests

All participants experienced a series of unsuccessful tests to find the primary tumour:

"...a whole series of tests, CT scans, MRI - you name it I had it...and in the end they said well, we can't trace it."

"They seem to have covered the whole of my body with tests and things."

Finding the primary and targeting treatment

Many patients believed that finding the primary tumour would lead to more effective treatment.

"If they knew where it was they'd be doing something about it. I mean they have told me that they cannot do anything about it at all, it's only palliative and I can accept that."

Several patients felt that they were receiving untried and untested treatment.

"She said... they have not done that mixture before, so the side effects might cancel each other out or make it worse ... not sure about long-term effects ... very high dosage."

In contrast the patient with suspected ovarian cancer was more reassured by her treatment plan.

"They said we're going to treat you for ovarian cancer as that is the direction the tests are pointing, so as far as I was concerned that was it, a plan was in place. Because I've got a plan I'm concentrating on that, not on the negative."

The uncertainty of healthcare professionals

All patients referred to the uncertainty of the healthcare professionals involved in their care.

"I do understand they are in the dark as much as me...They don't know enough about this unknown primary situation. Perhaps that's why they don't tell you much because they are not sure of what they are telling you."

One patient was worried that the consultants were "baffled", but another acknowledged the difficulty faced by healthcare professionals in the diagnosis and treatment of patients with CUP.

PSYCHOLOGICAL ADJUSTMENT

In their study, Lenzi et al (2004) reported that people with CUP had higher levels of uncertainty than other patients with cancer , but did not present supporting data. They also reported over 40% of patients showed signs of depression. Other expert reviews (Symons, 2008; Ettinger, 2005) suggest that increasing patient's knowledge about their diagnosis can help dispel some of these fears.

In their questionnaire study, Pirian et al (2005) asked 45 American patients to imagine they had metastatic cancer of unknown origin. Patients were willing to pay a average of $1900 for ancillary immunohistochemical tests to identify a primary tumour, even when these tests would not affect their survival.

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13. Investigations to find the primary tumour in people with cancer of unknown primary, when clinical benefit is unlikely

Last updated: 30 / 10 / 2009.

Characteristics of included studies

Boyland-2008

Methods	Mixed method study (both qualitative and quantitative).
Participants and Country	Ten patients were recruited from 2 NHS trusts. Any patient with CUP, who was well enough to take part, was eligible for inclusion in the study. Purpositive sampling of patients continued until no new themes were identified
Interventions	No treatment interventions were studied (although 7/10 patients received chemotherapy), instead questionnaires and semi structured interviews were used to identify important themes in patients' experience of CUP. Observation, patient notes and field notes were also used to collect data.
Outcomes	The study aimed to: explore patients understanding of their cancer; to identify any concerns, especially relating to the uncertainty of the diagnosis and to measure quality of life (using the McGill QOL questionnaire). Six main themes were identified: poor understanding, struggling with uncertainty (contrasting with stoical acceptance), undergoing multiple investigations, inability to treat, healthcare professionals not having the answers and difficulty explaining to others. **Understanding of CUP** All patients with an entirely unknown primary reported being told they had cancer but that the primary site could not be found. Some patients did not fully understand this. *"This kind of non-specific kind of ... they haven't found the primary tumour but it is spreading all over the place."* **Uncertainty about diagnosis** Patients clearly struggled with the unknown nature of the primary tumour. This seemed to increase the unpredictability of the disease, with patients not knowing what to expect, feeling an ominous sense that it might be "spreading" or "lurking". *"I think that if there is a secondary and it can cause you that much jip,if there is is a primary it could do you double the damage. I just don't understand how it can hide away somewhere...it's the not knowing is the horrible thing...the uncertainty of it all...[if I knew] I would be more at ease."* Others wanted the understanding and feeling of control attached to a diagnostic label. *"Its confusion because you don't know what to expect. I know there are loads of cancers around and they know where most of them are, well why I am so different? Why are these unknown primaries? So ... I feel like screaming, literally screaming. [If] they said where they are ... well, for me it would be peace of mind."* One man had been diagnosed with leukaemia 20 years earlier and was able to compare the experiences of having known and unknown cancer. *"I've got no feeling where the actual cancer is and (my wife) quite often has a prod to see if she can find it. With the cancer I had before I knew exactly where it came from, but not knowing with this cancer makes me like unaware and I would like to know where it has come from."* Some patients, however, accepted that their primary was unknown and that there was no point in thinking about finding it.

"... if it is there it is there. I mean it doesn't make any difference to me no ... so trying to think about it is to me a bit of a waste of time."

One patient, with a possible ovarian primary, found it useful to believe it was an ovarian primary.

"As far as I'm concerned it is in my ovaries ... because I'm being treated for ovarian cancer. I'm not looking for anything else at the moment. It would be much more difficult if I didn't know where it was."

Multiplie diagnostic tests

All participants experienced a series of unsuccessful tests to find the primary tumour:

"...a whole series of tests, CT scans, MRI - you name it I had it...and in the end they said well, we can't trace it."

"They seem to have covered the whole of my body with tests and things."

Finding the primary and targeting treatment

Many patients believed that finding the primary tumour would lead to more effective treatment.

"If they knew where it was they'd be doing something about it. I mean they have told me that cannot do anything about it at all, it's only palliative and I can accept that."

Several patients felt that they were receiving untried and untested treatment.

"She said... they have not done that mixture before, so the side effects might cancer each other out or make it worse ... not sure about long-term effects ... very high dosage."

In contrast the patient with suspected ovarian cancer was more reassured by her treatment plan.

"They said we're going to treat you for ovarian cancer as that is the direction the tests are pointing, so as far as I was concerned that was it, a plan was in place. Because I've got a plan I'm concentrating on that, not on the negative."

The uncertainty of healthcare professionals

All patients referred to the uncertainty of the healthcare professionals involved in their care.

"I do understand they are in the dark as much as me...They don't know enough about this unknown primary situation. Perhaps that's why they don't tell you much because they are not sure of what they are telling you."

One patient was worried that the consultants were "baffled", but another acknowledged the difficulty faced by healthcare professionals in the diagnosis and treatment of patients with CUP.

Quality of life

QOL score ranged from 3 (in a patient with Parkinson's disease) to 10, where 10 was the highest possible score. The median score was 5/10.

Notes	

Chorost-2004

Methods	Expert review
Participants and Country	Patients with CUP
Interventions	Diagnosis
Outcomes	The authors estimated cost of diagnostic evaluation (in the USA 2004), as between $4500 and $18000. Given a 1 year survival of 18%, they suggest that minimalist approach to diagnosis (beyond ruling out treatable cancers). Literature suggests that even with exhaustive diagnostic evaluation relatively few primary tumours are found.
Notes	

Ettinger-2005

Methods	Clinical guidelines
Participants and Country	Patients with CUP
Interventions	Presents a clinical guideline for people with CUP
Outcomes	Makes several points about continued diagnostic tests when clinical benefit is unlikely. In general finding a primary tumour does not significantly improve survival, as the effectiveness of chemotherapy is limited in patients with advanced disease. The uncertainties surrounding CUP and the generally poor prognosis of this group of patients, means people with CUP experience significant psychosocial distress. This distress increases the difficulty in accepting the CUP diagnosis and treatment options. Empathatic discussion about the natural history, treatment and prognosis of CUP with patient and carers is required. Referral to psychosocial services may also be appropriate for some patients.
Notes	Consensus guideline developed by the National Comprehensive Cancer Network (NCCN)

Lenzi-2004

Methods	Observational study.
Participants and Country	72 patients with CUP. An unknown number of patients with other cancer were also included for comparison.
Interventions	No interventions, the study was purely observational.
Outcomes	Psychosocial adjustment measured using: CES-D for depressive symptoms, state-trait anxiety inventory (STAI-state) for anxiety, MUIS for illness uncertainty and SOC for sense of coherence. **Depression** Mean CES-D scores were 15.8 (standard deviation 10.1). 41% of patients were above the clinical cut-off score of 16: indicating further assessment of depression is appropriate. **Anxiety** Anxiety scores ranged from 20 to 70, mean 39.5 (standard deviation 14.2) **Illness uncertainty** Authors report that patient's anxiety scores were higher than other cancer populations: mean for CUP patients was 93.6 (standard deviation 10.4), however the mean for other cancer populations is not reported. **Sense of coherence** Comprehensibility mean 50.8 (S.D. 6.1), manageability mean 65.7(S.D. 6.9), and meaningfulness mean 46.0 (S.D. 7.2).
Notes	Abstract only, no details of any comparison group of cancer patients with known primary tumours. The authors concluded that people with CUP experience significant levels of difficulty in psychological adjustment. They suggest that the advanced stage of the disease at presentation coupled with the uncertainty involved may be detrimental to the patients' psychological adjustment.

Pirain-2005

Methods	Cross sectional questionnaire study
Participants and Country	45 patients presenting to a obstetrics and gynaecology outpatient clinic

Interventions	Ancillary immunohistochemistry tests to identify a primary tumour in CUP. Patients were asked to imagine they had either CUP or a previously diagnosed and treated breast cancer with a newly identified primary. after receiving information about the diagnostic performance of IHC, patients were asked how much they would be willing to pay for IHC analysis of their tumour when it would influence their survival, and also when it would not.
Outcomes	**Willingness to pay for additional immunohistochemistry tests** For both the CUP and breast cancer scenarios patients were willing to pay an average of $1900 for ancillary IHC tests. Respondents were willing to pay whether or not it made a difference to their clinical outcome, if it allowed them to know the origin of their tumour. Patients were willing to pay more for IHC tests with high diagnostic performance.
Notes	Private healthcare setting. Patient group was not cancer of unknown primary

Shaw-2007

Methods	Retrospective case series
Participants and Country	166 patients with CUP. All patients recorded to have a diagnosis of CUP in a single UK cancer centre during 2003 were included.
Interventions	Diagnostic investigations (carried out either before or after referral to the cancer centre).
Outcomes	A wide variety of tests were used in the diagnostic evaluation of these patients, either before or after referral to the cancer centre. Nineteen different investigations were used in the cohort of patients with liver or multiple metastases, 13 different tests were used in the cohort with bone metastases.
Notes	Shaw et al (2007) concluded that the number of diagnostic investigations could be reduced substantially, suggesting tests should be limited to those affecting clinical management.

Symons-2008

Methods	Expert review
Participants and Country	Overview of cancer of unknown primary targeted at nurses.
Interventions	Gives some suggestions how nurses can help patients with CUP and their families.
Outcomes	**Uncertainty about primary tumour site** "Not knowing where cancer has originated accentuates fear and anxiety" **Specific information needs for people with CUP** "It can seem incomprehensible to [people with CUP] that in this scientific age, with all the sophisticated diagnostic imaging techniques available, a primary tumour is invisible and that there are no clearly defined treatment paths." "Knowledge can help dispel the fear of this diagnosis, and a social network that offers patients emotional support, information and practical assistance has been shown to prolong and enhance life."
Notes	

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SYMONS 2008
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Cancer of Unknown Primary clinical guideline

14. Prognostic and predictive factors in CUP

Last updated: 30/ 10/ 2009.

Short summary

There was evidence that certain factors are associated with response to chemotherapy and overall survival in people with CUP.

While many prognostic factors appeared important on univariate analysis, few remained so on multivariate analysis. Independent adverse prognostic factors included: presence of liver metastases, low serum albumin and elevated serum lactate dehydrogenase. Good performance status was the only independent favourable prognostic factor consistently reported in studies.

Several authors have developed simple prognostic models incorporating some of these factors to which can classify people with CUP into low and high risk groups. These risk groups have statistically significant differences in overall survival, but their clinical significance is unclear: there are no studies evaluating whether these prognostic models influence treatment decisions. There is inconsistency between the factors included in the prognostic models, suggesting differences between the populations used to develop them

There was a lack of prognostic models to estimate the absolute survival probability of a given patient with CUP.

Rationale

For all cancer patients, the decision to introduce treatment is based on the balance of costs (toxicity, inconvenience) and benefits (relief of symptoms, prolongation of survival). The same principle applies to confirmed Cancer of Unknown Primary, though the more limited efficacy of treatment means that the greatest care should be taken in weighing the factors in these patients. In confirmed CUP, accurate prognostic predictors are potentially of great value in clinical decision making, allowing optimal treatment to be used in those most likely to gain the greatest benefit, while avoiding the unnecessary toxicity of futile treatment in those unlikely to benefit.

Individual physiological factors influence the likelihood that an individual will tolerate chemotherapy toxicity, and to a certain degree also influence the likelihood of benefit. These factors include organ function, performance status and co-morbidity. Tumour-specific factors (e.g. chemosensitivity, tumour burden, specific organ involvement) partly govern the likelihood of a satisfactory outcome of treatment. In many instances the factors referred to are unknown, or difficult to measure.

Defining major prognostic factors governing treatment outcomes in confirmed CUP would be of considerable benefit, both in terms of individual patient care, and more widely in terms of avoiding unnecessary treatment costs where such treatment could be predicted to be futile.

Methods

Study types

Any studies reporting prognostic analysis in patients with CUP, there was no restriction on study design.

Participants

People with confirmed Cancer of Unknown Primary in whom systemic therapy is being considered. Studies restricted to patients with a single specific presentation (such as squamous cell carcinoma in cervical lymph nodes) were excluded.

Interventions

Prognostic factors with an established role in general cancer treatment including: performance status, age, LDH, tumour burden and critical organ involvement.

Outcomes

Treatment outcomes: overall survival, treatment response. Change in management and avoidance of inappropriate treatment

Study selection

An initial list of studies was selected by the information specialist (SA). One reviewer (NB) then selected potentially relevant papers from this list on the basis of their title and abstract. These studies were ordered and the reviewer checked each paper against the inclusion criteria. Studies ordered for previous questions about chemotherapy were also checked for prognostic factor analysis.

Data extraction and synthesis

One reviewer (NB) extracted outcome data from the papers. Treatment response was treated as a dichotomous variable: any response or no response, and summarised using risk ratios. Overall survival data

include both the event (death from any cause) and the time at which the event occurs. Time-to-event outcomes are most appropriately analysed using hazard-ratios (HRs) which incorporate both the number and the timing of events. Overall survival was analysed using methods outlined in Tierney et al (2007). In most cases the log-rank P value and the overall death rate were the only data available to estimate the hazard ratio. The data from each study were pooled using the generic inverse variance method in the Cochrane RevMan software package.

QUALITY ASSESSMENT

Study quality (risk of bias) was assessed using the NICE checklists for critical appraisal.

HETEROGENEITY ASSESSMENT

Heterogeneiety was assessed in Forest plots using the I-squared statistic.

Search results

The literature searches identified 103 potentially relevant studies, of which 50 were included.

DESCRIPTION OF INCLUDED STUDIES

Six studies reported prognostic factor analyses in patients with CUP, regardless of their treatment (Abbruzzese et al, 1994; Hess et al, 1999; Ponce Lorenzo et al, 2007; Seve et al, 2006; Trivanovic et al, 2009; Van de Wouw et al 2004) . The remaining papers described case series or clinical trials in which the majority of patients received chemotherapy. Data about predictive factors for treatment response were drawn from these chemotherapy studies.

The studies typically excluded patients with cancer of unknown primary belonging to a subgroup with well defined treatment. In most cases histology was well, moderately well or poorly differentiated adenocarcinoma or poorly differentiated carcinoma. Abruzzesse et al (1994), Hess et al (1999), Jentsh-Ullrich et al (1998) and Hainsworth (1997), however, included patients with other histology. Van der Gast et al (1995) included only patients with undifferentiated carcinoma or poorly differentiated adenocarcinoma of unknown primary.

Most studies reported at univariate analysis of prognostic factors and many also reported multivariate analysis. Univariate analyses consider a single prognostic factor at a time, often splitting the patient group into two and comparing the outcomes of patients with and without the factor. Prognostic factors are not necessarily independent, for example elevated serum alkaline phosphatase and bone metastases are probably correlated. For this reason relative risks associated with multiple individual prognostic factors from univariate analyses cannot be combined to give an overall risk score.

Multivariate analysis is more useful as it estimates the independent effect of each factor. Thus several prognostic factors can be combined to estimate the absolute risk or probability than an event will occur in a given patient. Multivariate analysis form the basis for the prognostic models developed in some of the studies (see table 14.3).

Some chemotherapy trials reported individual patient data for those who responded to chemotherapy, allowing univariate analysis of predictors of treatment response.

STUDY QUALITY

Some studies using multivariate analyses only reported prognostic factors that were statistically significant. This reporting bias could lead to an overestimation of the effect of a given prognostic factor when pooling the results of these studies.

Continuous or ordinal prognostic variables (such as age, LDH level, performance status or number of involved sites) were typically dichotomised into high or low groups using an arbitrary cut-point. This could underestimate the effect of these prognostic factors. The location of the cut point can also be influenced post-hoc by the data, by choosing a cut point which maximises the effect of the prognostic factor.

Evidence summary

PROGNOSTIC FACTORS

Prognostic factors for overall survival and predictive factors for treatment response are summarised in tables 14.1 to 14.3, and in figures 14.1 to 14.31.

Lactate dehydrogenase (LDH)

Elevated serum LDH was an adverse prognostic factor for overall survival on univariate analysis. Elevated LDH was an independent prognostic factor in five of the nine studies that considered it in multivariate analysis. In these five studies patients with elevated serum LDH had almost twice the risk of death of those with normal serum LDH levels, HR=1.94 [95% C.I. 1.54 to 2.44].

Elevated serum LDH did not significantly affect response to platinum based chemotherapy, RR = 0.98 [0.68 to 1.41], however 95% confidence intervals were wide and included both appreciable benefit and harm .

Serum albumin

Low serum albumin was an independent adverse prognostic factor for overall survival in all three studies that considered it (Assersoh et al 2003; Seve et al 2006a and Munoz et al 2004). Munoz et al 2004 reported that patients with low serum albumin were at greatly increased risk of death, HR = 4.31 [95% C.I. 1.56 to 11.85]. Seve et al (2006a) also found low serum albumin to be an independent risk factor, HR = 2.70 [95% C.I. 1.79 to 4.07]

Serum alkaline phosphatase
Elevated serum alkaline phosphatase was an independent adverse prognostic factor for overall survival in three of the nine studies that examined it in multivariate analysis.

Performance status
Studies of performance status divided people into groups of good performance status and poor performance status. Some studies defined good performance status as 0 on the WHO/ECOG scale, while others defined it as 0 to 1 on the WHO/ECOG scale. Poor PS was everything else. Good performance status (however defined) was a favourable prognostic factor for overall survival in nine of the ten studies that analysed it in multivariate analysis, The pooled hazard ratio in these nine studies was 0.62 [95% C.I. 0.53 to 0.73].

Patients with good performance status were more likely to respond to chemotherapy, RR = 1.60 [1.09 to 2.35] on univariate analysis.

Number of metastatic sites
Studies divided patients into two groups according to the number of metastatic sites. Typically patients with either one or one to two metastatic sites were compared with everyone else. Fewer metastatic sites was a favourable prognostic factor for overall survival, HR = 0.82 [95% C.I. 0.73 to 0.92] on multivariate analysis. Patients with fewer sites were more likely to respond to chemotherapy, RR = 1.64 [95% C.I. 1.18 to 2.29] on univariate analysis.

Age
Studies split patients into two age groups, the cut-point defining older and younger varied between studies from 50 years to 65 years. In chemotherapy series younger age was not a prognostic factor for treatment response or overall survival. In univariate analysis from series of patients not selected by treatment, however, younger age was a favourable prognostic factor for overall survival HR = 0.69 [0.58 to 0.81]. Multivariate analyses suggested age was not an independent prognostic factor.

Histology
Studies were typically restricted to patients with adenocarcinoma, poorly differentiated carcinoma or undifferentiated carcinoma. On univariate analysis adenocarcinoma histology was an adverse prognostic factor for treatment response, RR=0.71 [0.59 to 0.86], and overall survival, HR = 1.32 [1.18 to 1.47]. Multivariate analyses, however, suggested adenocarcinoma histology was not an independent prognostic factor.

Poorly differentiated adenocarcinoma or poorly differentiated carcinoma histology was an positive prognostic factor for treatment response, RR = 1.44 [1.16 to 1.78], and overall survival, HR = 0.78 [0.67 to 0.91].

Evidence from two studies (Van der Gaast el al 1990; Pavlidis et al, 1992), suggests that patients with undifferentiated carcinoma are more than twice as likely to respond to platinum based chemotherapy than patients with other histology. The relative risk for response to treatment was 2.10 [95% C.I. 1.21 to 3.66]

Liver metastases
People with liver metastases tended to have poorer overall survival than people without. On multivariate analysis seven of the twelve studies that considered it found liver metastases to be an adverse prognostic factor for survival. The pooled hazard ratio in these seven studies was 1.40 [95% C.I. 1.24 to 1.57].

The presence of liver metastases was the factor most strongly associated with lack of response to chemotherapy, RR = 0.56 [0.45 to 0.69]

Lung metastases
The presence of lung metastases was an adverse prognostic factor for overall survival, HR=1.40 [1.24 to 1.57] on univariate analysis. It was unlikely that presence of lung metastases was an independent prognostic factor, however, as no studies retained this factor in their multivariate models.

People with lung metastases were also less likely to respond to chemotherapy, RR = 0.70 [0.53 to 0.93].

Peritoneal metastases
Presentation with peritoneal metastases was a favourable prognostic factor for treatment response, RR = 1.45 [95% C.I. 1,12 to 1.88]. There was imprecision and inconsistency in the estimate of the effect on peritoneal metastases on overall survival, and it was unclear whether peritoneal metastasis was a prognostic factor for overall survival.

Lymph node metastases
Lymph node metastases were a independent favourable prognostic factor for overall survival in only two of the nine studies that considered it. The presence of lymph node metastases was the factor most strongly associated with response to chemotherapy, RR = 2.68 [1.94 to 3.70].

PROGNOSTIC MODELS
Prognostic models aim to classify patients into risk groups for overall survival and could be used as decision aids in treatment decisions (see Table 4). These models are developed using clinical data from group of patients (the development cohort) but need to be tested in an independent set of patients to confirm their validity.

Culine et al (2002)
Culine et al (2002) developed a prognostic model to classify patients with CUP into high and low risk groups for death from any cause, using two prognostic factors: performance status and serum LDH. In the group of patients used to develop the model the median survival in high and low risk groups was 4 months and 12 months respectively . In an independent set of patients used to validate the model the median survival in high and low

risk groups was 7 and 12 months respectively. The model of Culine et al was validated by Van de Wouw et al (2004) who reported median survival of 1 month and 6.5 months median survival for the high and low risk groups in their cohort. Similarly Yonemori et al (2006) reported median survivals of 10 and 21 months for the high and low risk groups using the Culine model (P=0.003). Munoz et al (2008), however, failed to demonstrate a significant difference in the overall survival of the three risk groups in their cohort of patients with CUP.

Van der Gaast et al (1995)

Van der Gaast et al (1995) developed a model for patients with undifferentiated cancer of unknown primary using two prognostic factors: performance status and serum alkaline phosphatase. The median survival of high and intermediate risk groups was 4 and 10 months respectively. Median survival was not reached in the low risk group. Yonemori et al (2006) validated the model of Van der Gast, reporting median survival in the high, intermediate and low risk groups of 20, 12 and 7 months respectively (P not reported).

Ponce Lorenzo (2007)

Ponce Lorenzo (2007) developed a prognostic model to classify patients into three risk groups on the basis of performance status and presence of liver metastases. Munoz et al (2008) challenged this model, after testing it in their CUP cohort, claiming that it failed to discriminate between low and intermediate risk groups well enough. Unsuprisingly the model of Munoz et al (2008), using serum albumin and performance status, performed better in their own cohort (probably because it was developed using the same patients).

Seve et al (2006a)

Seve et al (2006a) reported a prognostic model to divide patients with CUP into high and low risk groups for death from any cause using serum albumin and the presence of liver metastases. The model was validated by the authors in an independent set of patients, with median survival of 3 months and 13 months in the high and low risk groups respectively (P<0.0001). Seve et al (2006a) suggested that the model of Culine et al (2002) was less powerful than their own, in this validation set: using Culine's model median survival in the high and low risk groups was 4 and 13 months respectively (P=0.07).

Trivanovic et al (2009)

Trivanovic et al (2009) reported a prognostic model to classify patients into three risk groups using the following adverse prognostic factors: elevated LDH, QTc prolongation, liver mets, PS 2 or more, anaemia, age 63 years or more. The model has not been validated.

Hess et al (1999)

Hess et al (1999) used classification and regression tree (CART) analysis to put patients into one of ten risk groups. Their CART model incorporates: presence of liver, bone, adrenal, lymph node and pleural metastases, neuroendocrine histology, age, number of metastatic sites and adenocarcinoma histology. The authors note that validation studies are particularly important for CART models as their structure is highly dependent on the development cohort. No validation studies were found for this model.

CHANGE IN MANAGEMENT AND AVOIDANCE OF INAPPROPRIATE TREATMENT

None of the studies reported change in management or avoidance of inappropriate treatment on the basis of prognostic factors

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Table 14.1 Prognostic factors investigated using multivariate analysis

Study	Liver mets	Low serum albumin	Elevated LDH	Elevated alkaline phosphatase	Male sex	Adenocarcinoma histology	Good PS	Fewer sites	Lymph node mets	Peritoneal involvement	Younger age	PDC
Abbruzzese 1994	-				-	-		+	++	+	NS	
Alberts 1989	-				-	NS	+	NS	+	NS	NS	
Assersohn 2003	NS	-	NS	NS	NS		NS		NS	NS	NS	
Culine 2002	-		--	NS	NS	NS	++	NS	NS	NS	NS	NS
Munoz 2004	NS	--	NS	NS			++	NS	NS			
Piga 2005	NS			--				NS				
Ponce Lorenzo 2007	-		NS	-	NS	NS	+	NS	NS		NS	NS
Seve 2006a	--	--	-	NS	NS		+	NS	NS	NS		NS
Trivanovic 2009	-		--	NS	NS	NS	+	NS			NS	
Van de Wouw 2004	--		--		NS		++	NS	NS		++	
Van der Gaast 1995	NS		NS	--	NS		++	NS	NS		NS	
Yonemori 2006	NS		-	NS	NS	NS	+	+			NS	
Summary	**adverse in 7/12 studies**	**adverse in 3/3 studies**	**adverse in 5/9 studies**	**adverse in 3/9 studies**	**adverse in 2/10 studies**	**adverse in 1/6 studies**	**favourable in 9/10 studies**	favourable in 2/11 studies	**favourable in 2/9 studies**	**favourable in 1/5 studies**	**favourable 1/9 studies**	**No effect**

+ favourable prognostic factor: hazard of death significantly decreased (HR between 1 and 0.50)
++ favourable prognostic factor: hazard of death greatly decreased (HR 0.50 or less)
- adverse prognostic factor: hazard of death significantly increased (HR between 1 and 2)
-- adverse prognostic factor: hazard of death greatly increased (HR 2 or more)
NS, not statistically significant (at the 0.05 level);
Abbreviations: LDH, lactate dehydrogenase; PS, performance status;

Table 14.2 Prognostic factors for overall survival, hazard ratio and 95% confidence interval

	Adverse prognostic factors	Favourable prognostic factors
Univariate analysis	Elevated serum LDH, HR = 1.64 [1.41 to 1.92] Liver metastases, HR =1.51 [1.36 to 1.67] Adenocarcinoma histology, HR = 1.32 [1.18 to 1.47] Lung metastases, HR = 1.26 [1.09 to 1.44] Male sex, HR = 1.23 [1.10 to 1.37]	Good performance status, HR = 0.50 [0.43 to 0.59] Lymph node involvement,HR=0.70 [0.61 to 0.81] Fewer metastatic sites, HR = 0.75 [0.68 to 0.83] Poorly differentiated adenocarcinoma or PDC, HR = 0.78 [0.67 to 0.91] Younger age group, HR = 0.79 [0.69 to 0.90]
Multivariate analysis*	Elevated serum LDH, HR = 1.94 [1.54 to 2.44] Liver metastases, HR=1.40 [1.24 to 1.57] Male sex, HR = 1.35 [1.16 to 1.57]	Lymph node involvement, HR = 0.46 [0.40 to 0.55] Good performance status,HR = 0.62 [0.53 to 0.73] Fewer metastatic sites, HR = 0.82 [0.73 to 0.92]

Hazard ratios greater than 1 indicate an increased hazard of death.
*Most studies included only statistically significant prognostic factors from their multivariate analyses so pooled estimates are likely to overestimate the effect of the factor.
Abbreviations: HR, hazard ratio; LDH, ; PDC, poorly differentiated carcinoma;

Table 14.3 Predictive factors for treatment response, risk ratio and 95% confidence interval

	Adverse predictive factors	Favourable predictive factors
Univariate analysis	Liver metastases, RR = 0.56 [0.45 to 0.69] Male sex, RR = 0.69 [0.53 to 0.91] Lung metastases, RR = 0.70 [0.53 to 0.93] Adenocarcinoma histology, RR=0.71 [0.59 to 0.86]	Lymph node involvement, RR = 2.68 [1.94 to 3.70] Good performance status, RR = 1.60 [1.09 to 2.35] Fewer metastatic sites, RR = 1.64 [1.18 to 2.29] Poorly differentiated adenocarcinoma or PDC, RR = 1.44 [1.16 to 1.78]

Risk ratios greater than 1 indicate increased probability of response to treatment.
Abbreviations: RR, risk ratio ; PDC, poorly differentiated carcinoma;

Table 14.4 Multivariate prognostic models for overall survival

Study	Low risk group	Intermediate risk group	High risk group	Validation
Culine 2002	PS 0 or 1 and normal serum LDH		PS > 1 or elevated serum LDH	Validated in an independent set of patients by the study authors. Also validated by Yonemori (2006), Seve (2006a) and Van de Wouw (2004). Not supported by Munoz (2008)
Ponce Lorenzo 2007	PS 0 or 1 and no liver mets	Either PS ≥2 or liver mets	PS ≥2 and liver mets	Not supported by Munoz (2008)
Van der Gaast 1995	PS 0 and normal alkaline phosphatase	Either PS > 0 or elevated alkaline phosphatase	PS > 0 and elevated alkaline phosphatase	Validated by Yonemori et al (2006)
Seve 2006a	Normal serum albumin and no liver mets		Low serum albumin or liver mets	Validated in an independent set of patients by the study authors.
Munoz 2008	PS 0 or 1 and normal serum albumin	Either PS ≥2 or low serum albumin	PS ≥2 and low serum albumin	None reported
Trivanovic 2009	None or one of the following adverse factors: elevated LDH, QTc prolongation, liver mets, PS 2 or more, anaemia, age 63 years or more	Two of the following adverse factors: elevated LDH, QTc prolongation, liver mets, PS 2 or more, anaemia, age 63 years or more	3 or more of the following adverse factors: elevated LDH, QTc prolongation, liver mets, PS 2 or more, anaemia, age 63 years or more	None reported

Abbreviations: QTc, heart rate-corrected QT interval; LDH, lactate dehydrogenase; PS, performance status;

Figure 14.1 Well or moderately well differentiated adenocarcinoma versus other histology, univariate analysis of treatment response.

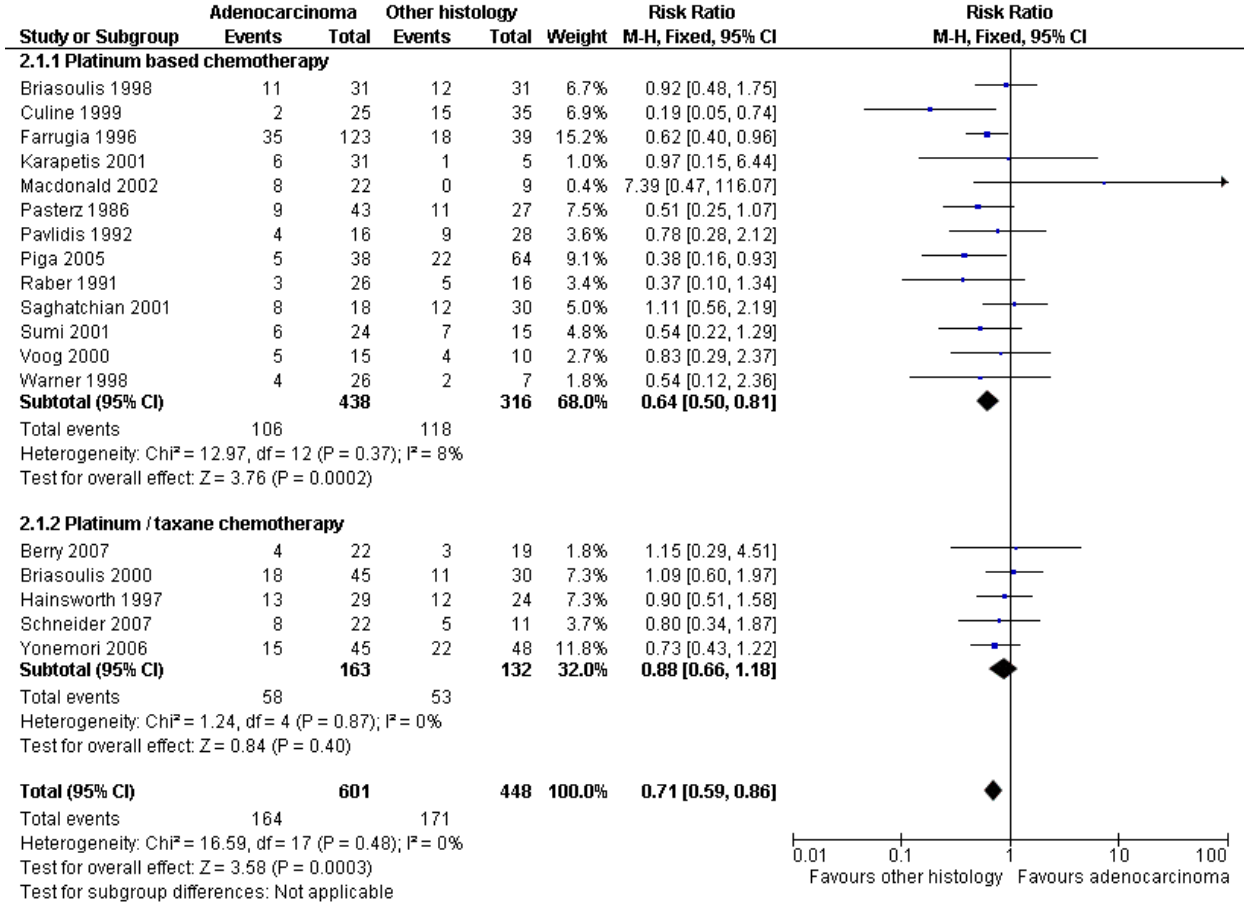


Figure 14.2 Well or moderately well differentiated adenocarcinoma versus other histology, univariate analysis of overall survival

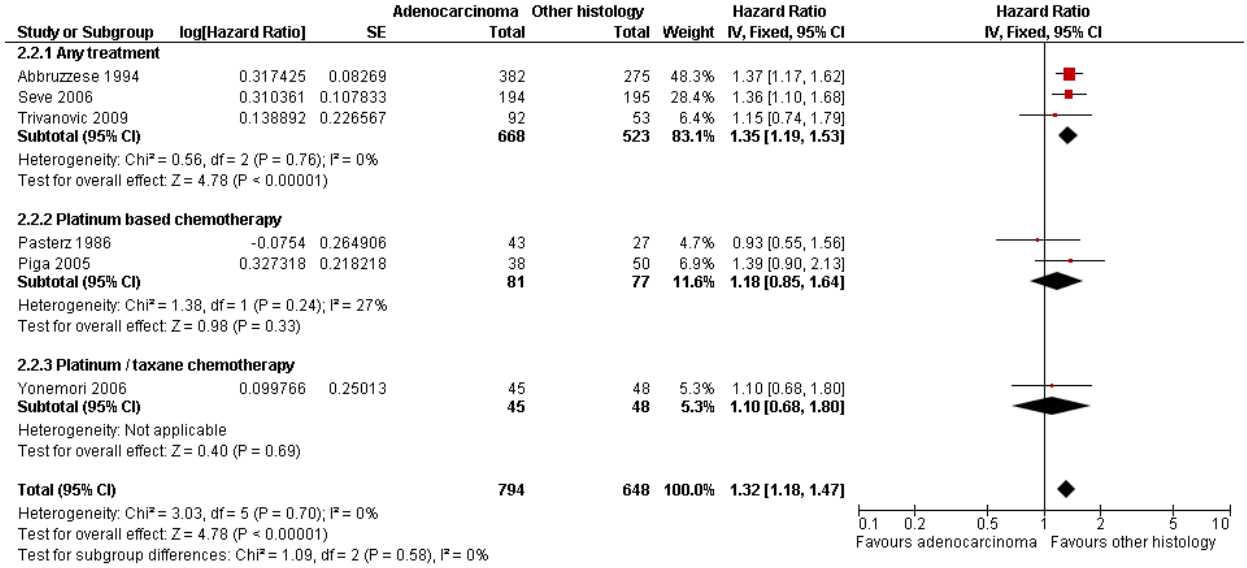


Figure 14.3 Poorly differentiated adenocarcinoma or carcinoma versus other histology, univariate analysis of treatment response

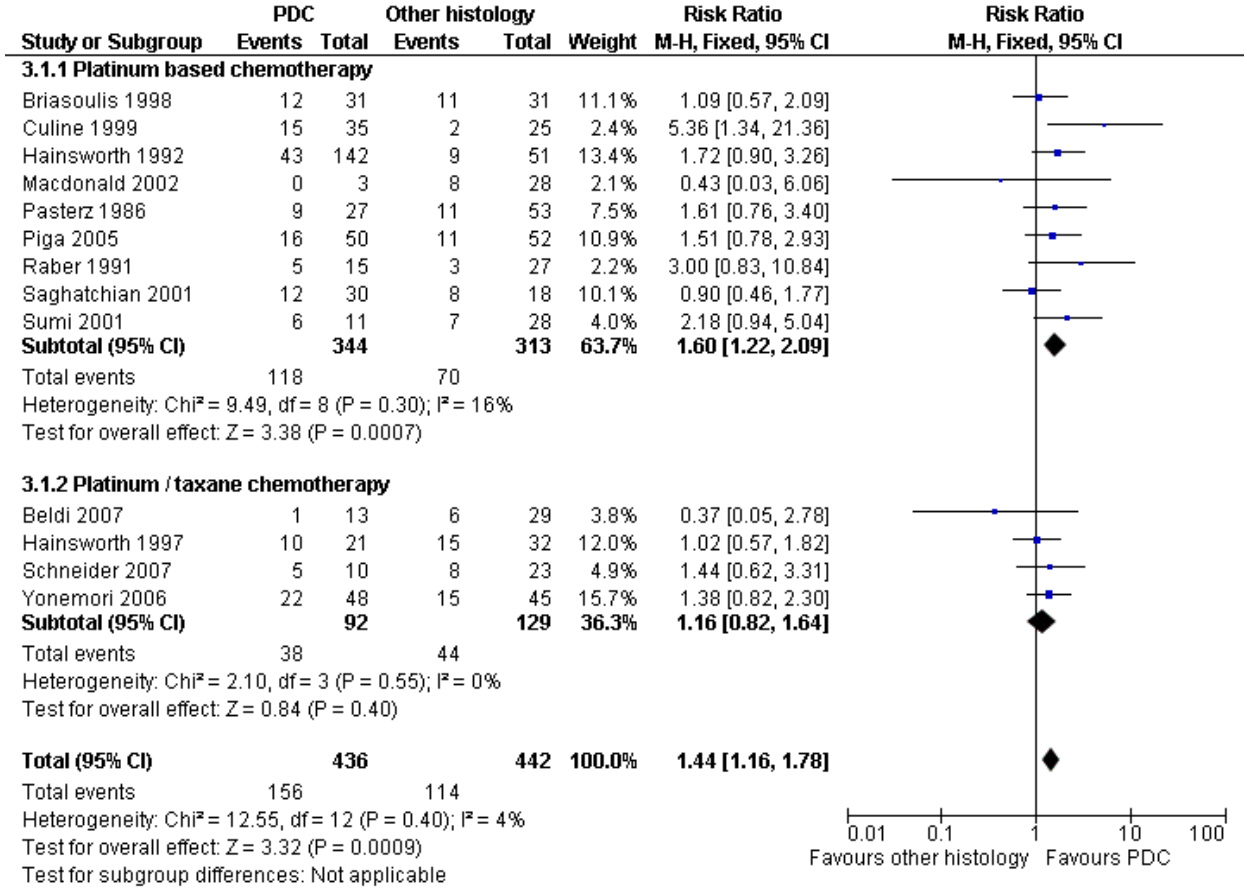


Figure 14.4 Poorly differentiated adenocarcinoma or carcinoma versus other histology, univariate analysis of overall survival

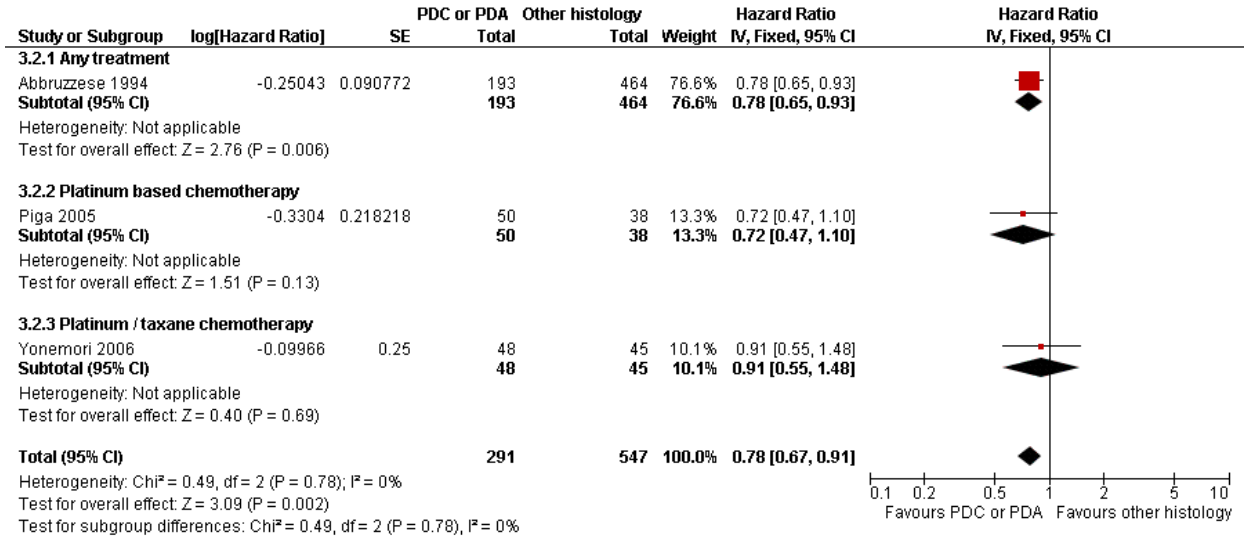


Figure 14.5 Undifferentiated carcinoma, univariate analysis of treatment response

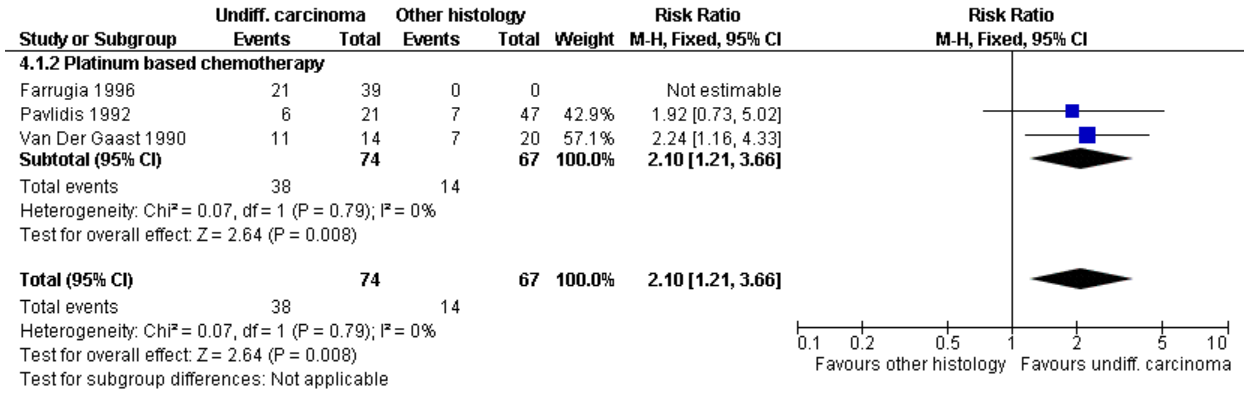


Figure 14.6 Male versus female, univariate analysis of treatment response

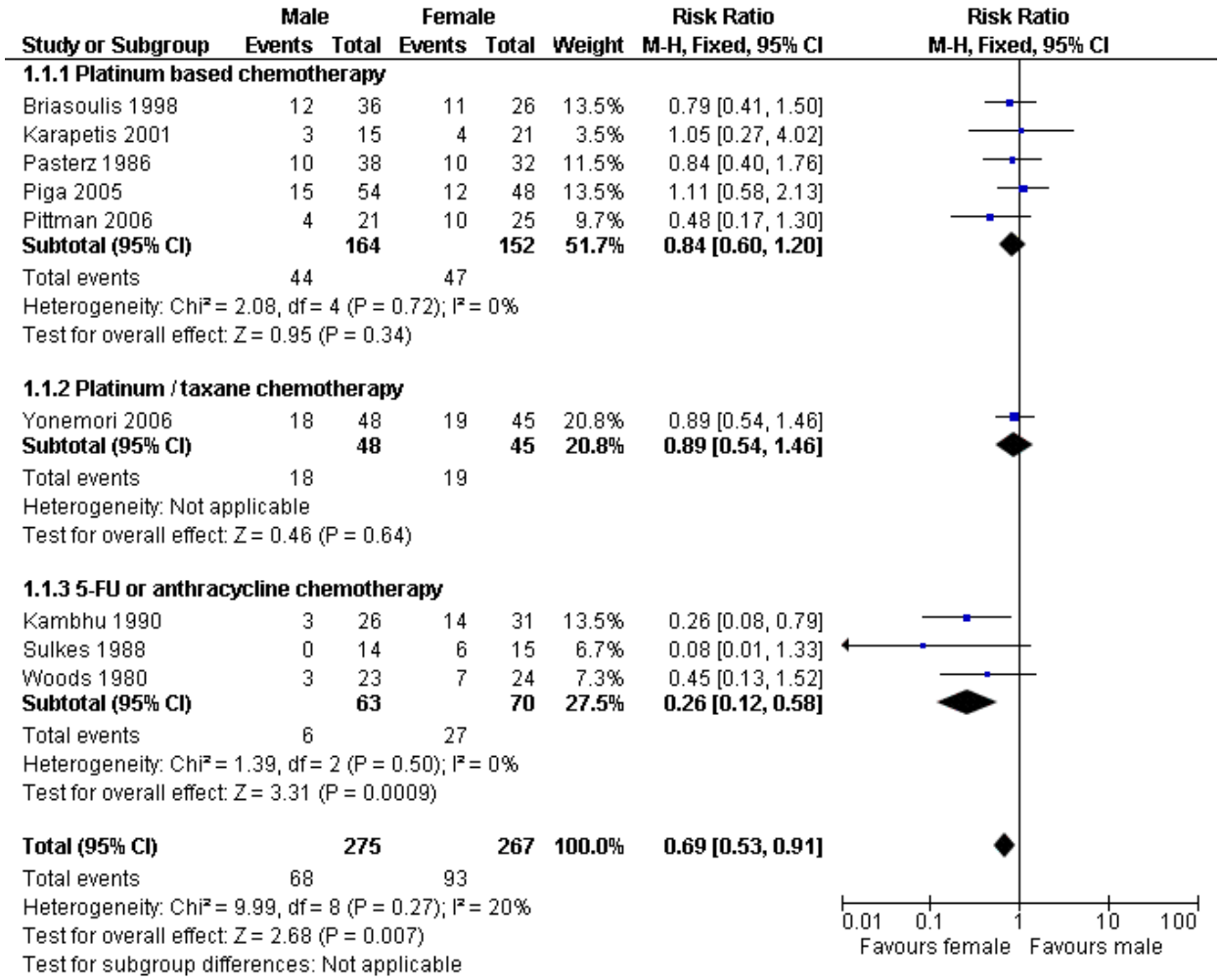


Figure 14.7 Male versus female, univariate analysis of overall survival

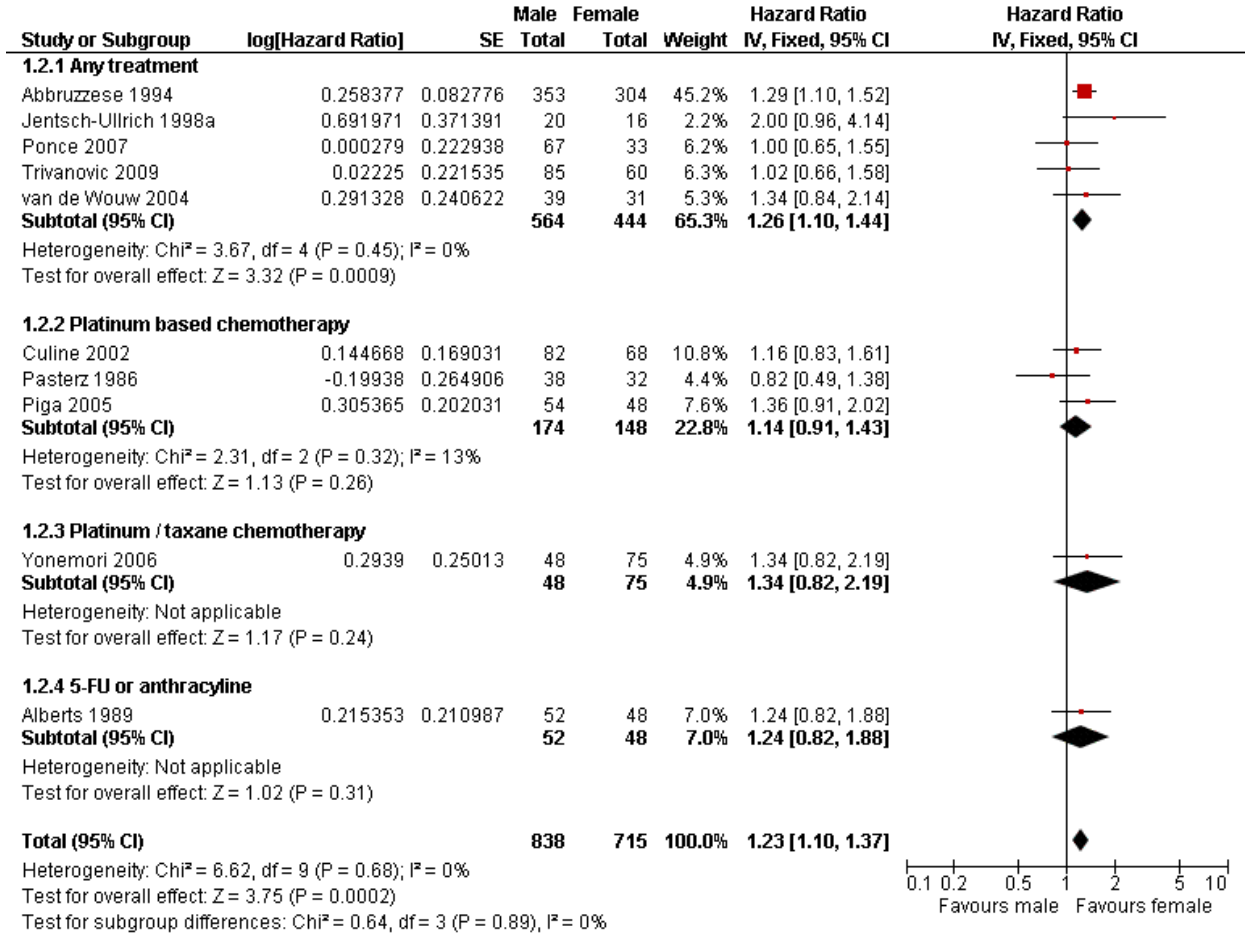


Figure 14.8 Male versus female, multivariate analysis of overall survival

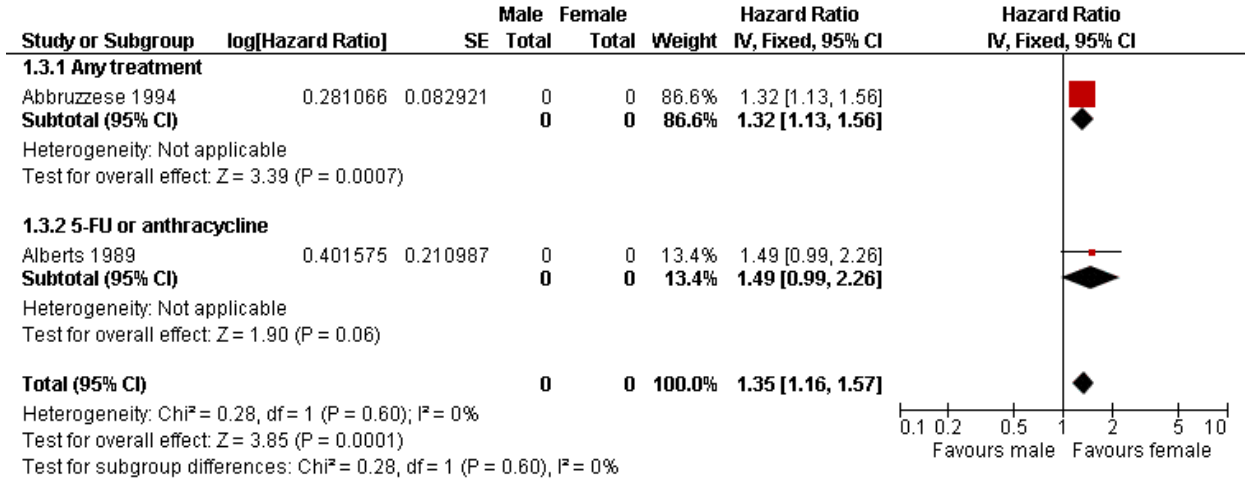


Figure 14.9 Liver involvement, univariate analysis of treatment response

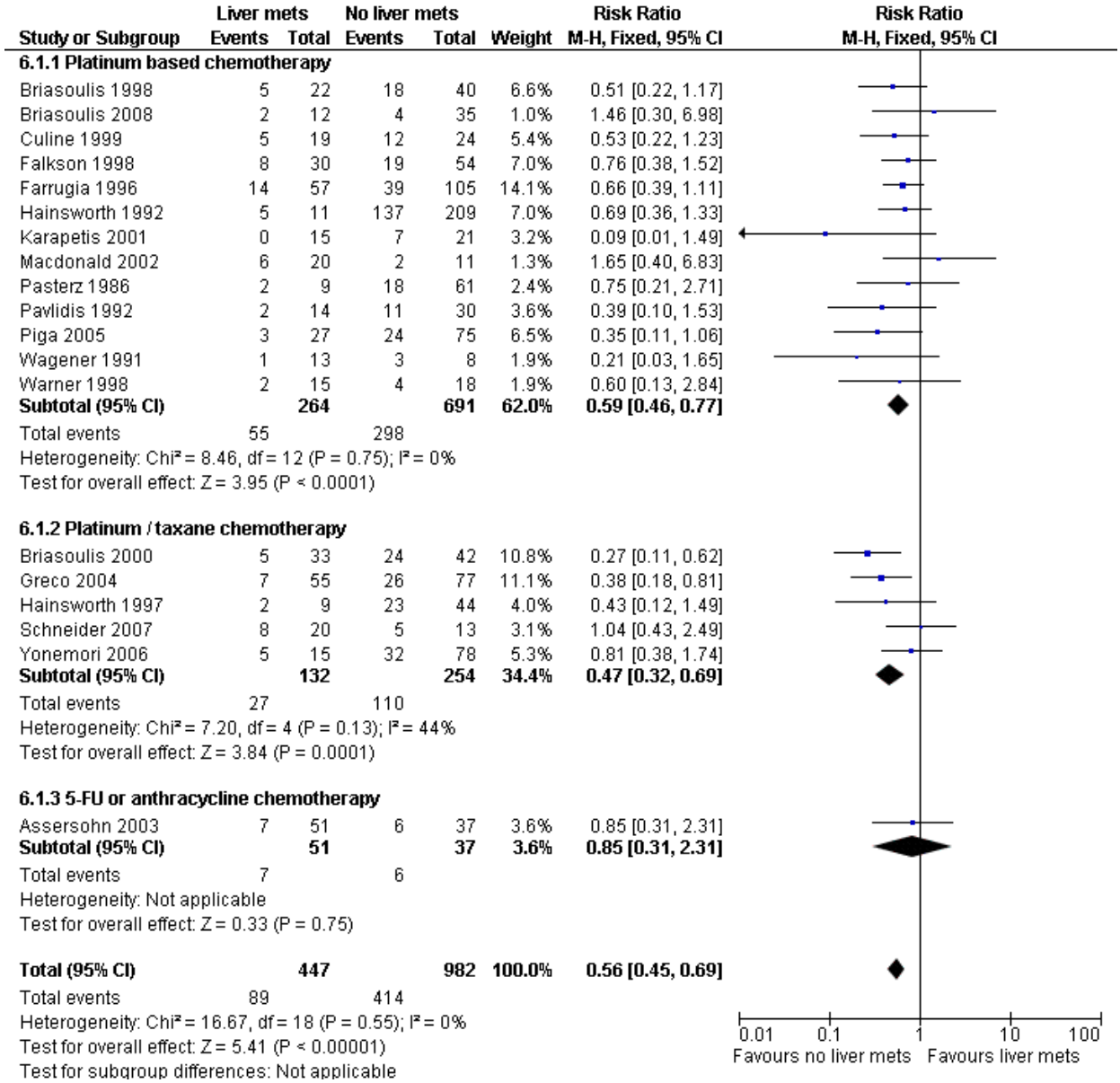


Figure 14.10 Liver involvement, univariate analysis of overall survival

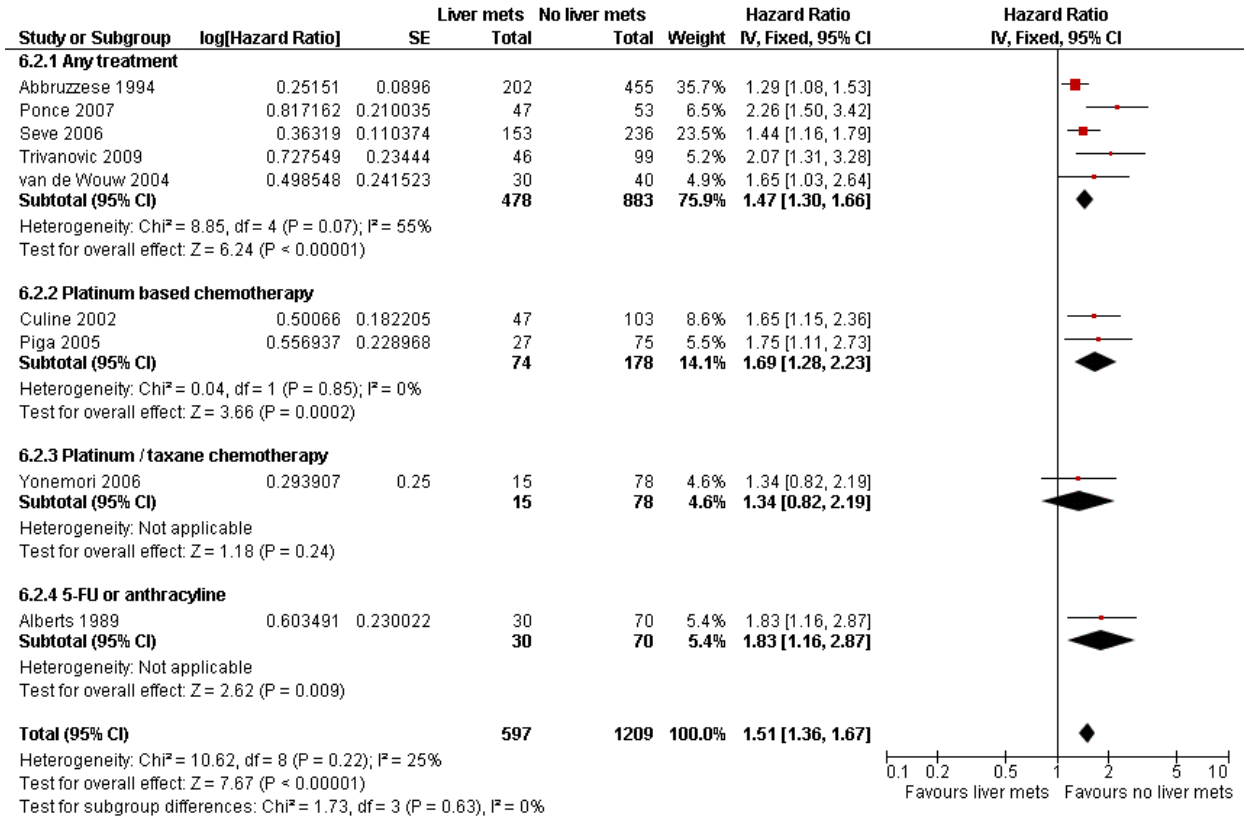


Figure 14.11 Liver involvement, multivariate analysis of overall survival

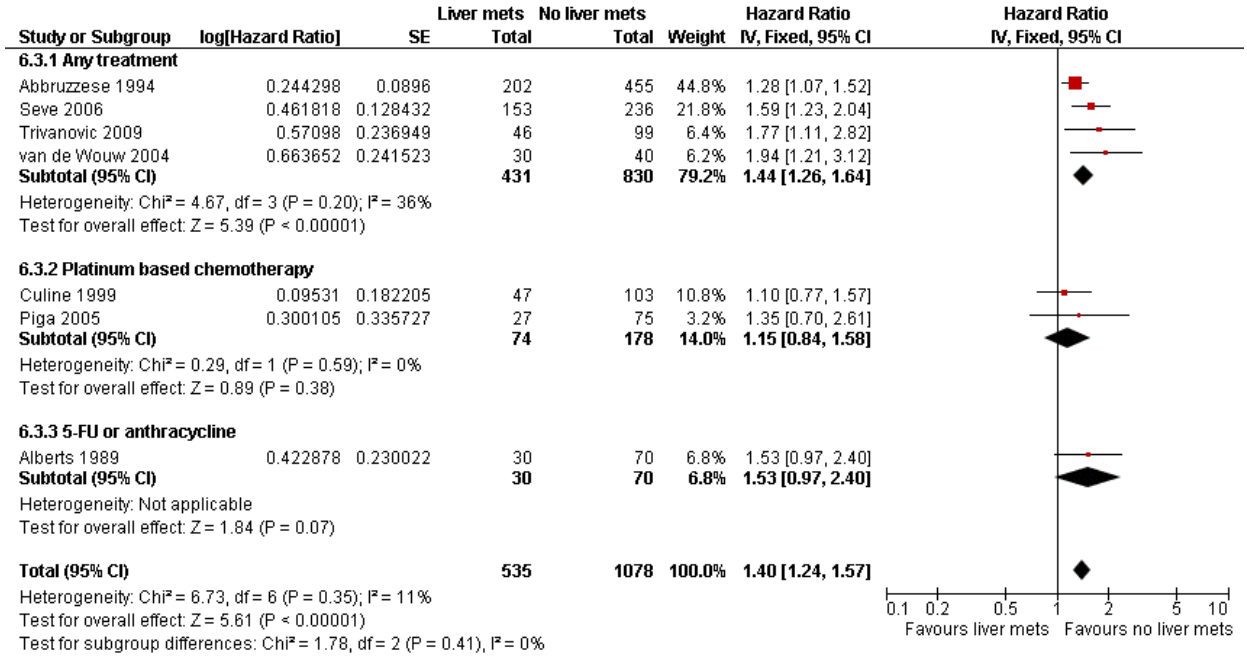


Figure 14.12 Lymph node involvement, univariate analysis of treatment response

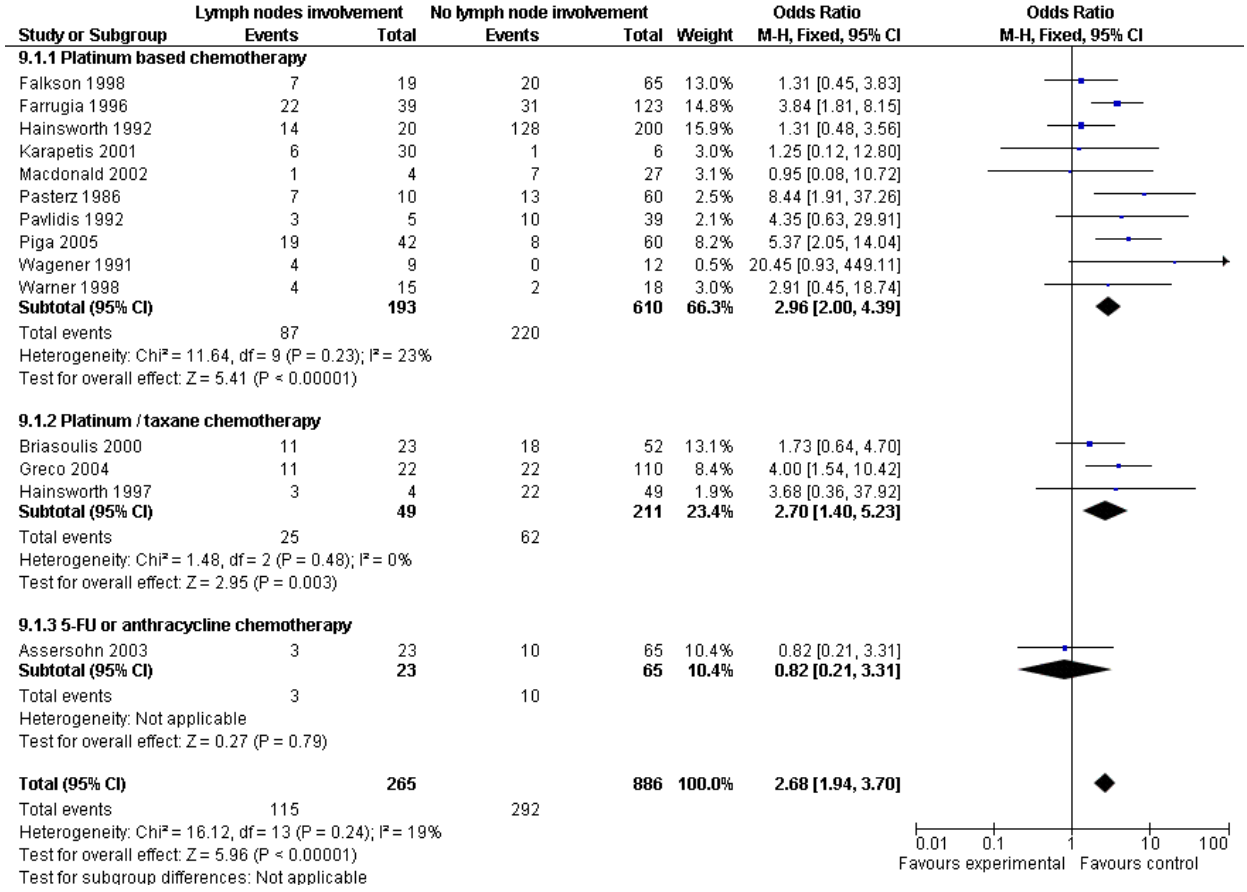


Figure 14.13 Lymph node involvement, univariate analysis of overall survival

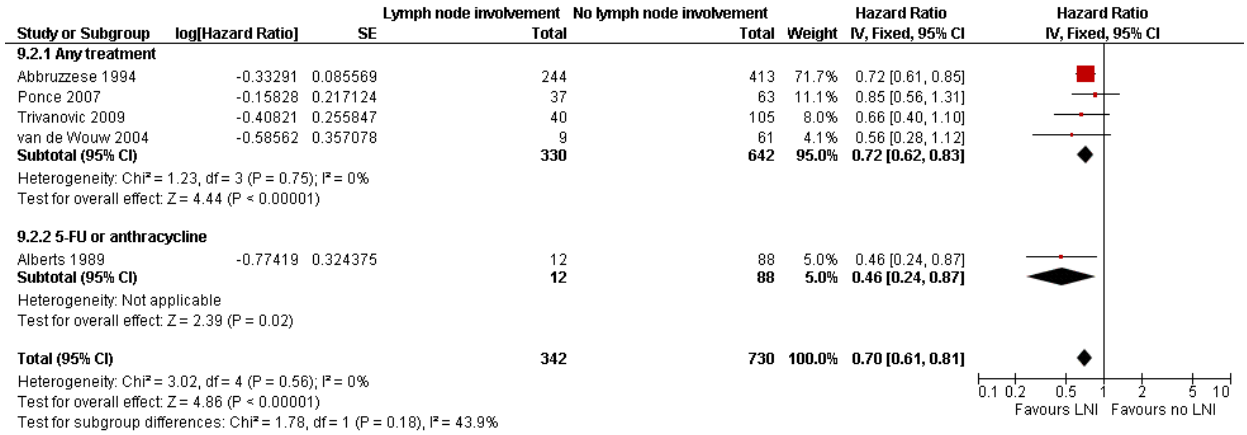


Figure 14.14 Lymph node involvement, multivariate analysis of overall survival

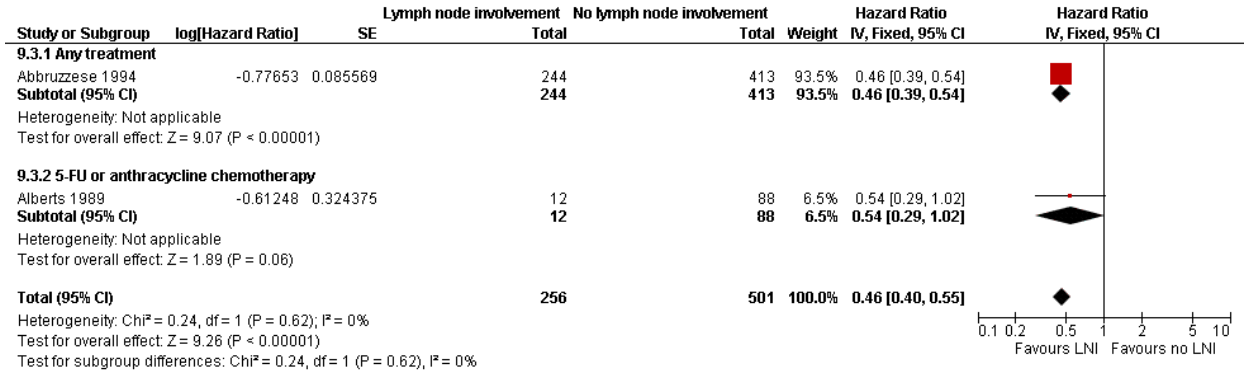


Figure 14.15 Lung metastases, univariate analysis of treatment response

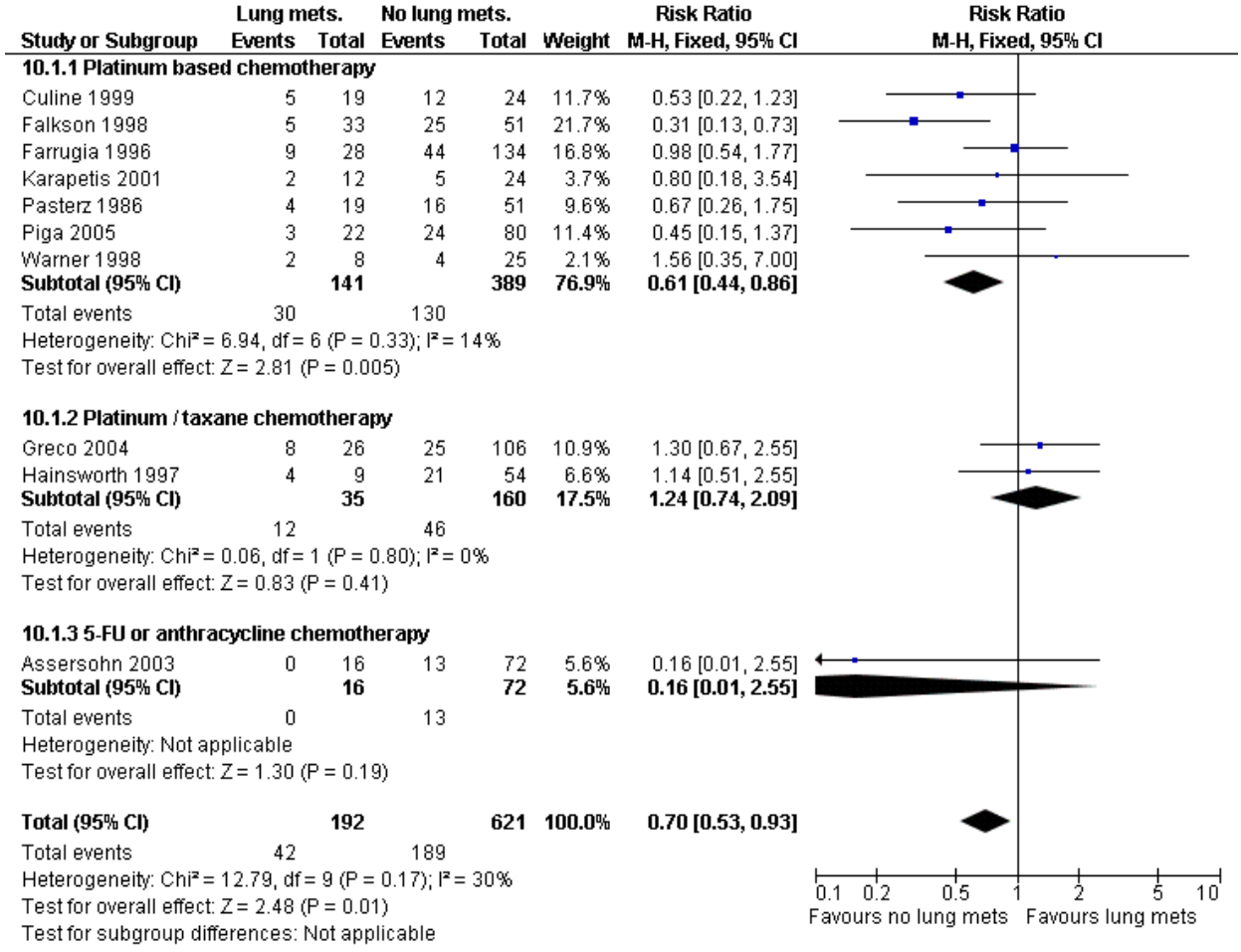


Figure 14.16 Lung metastases, univariate analysis of overall survival

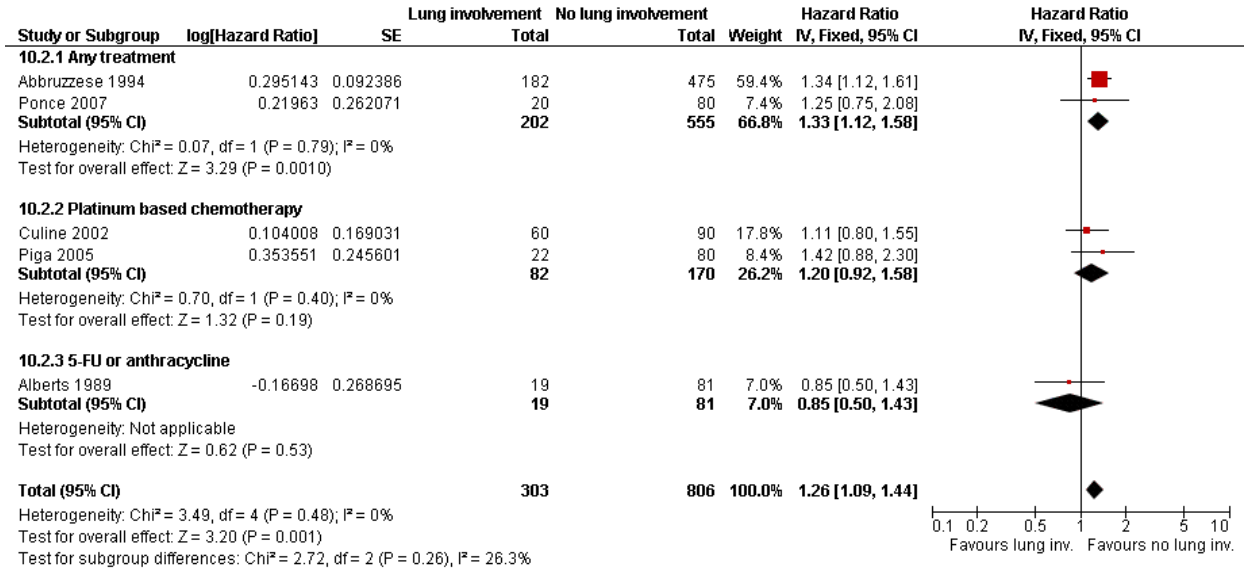


Figure 14.17 Elevated serum LDH, univariate analysis of treatment response

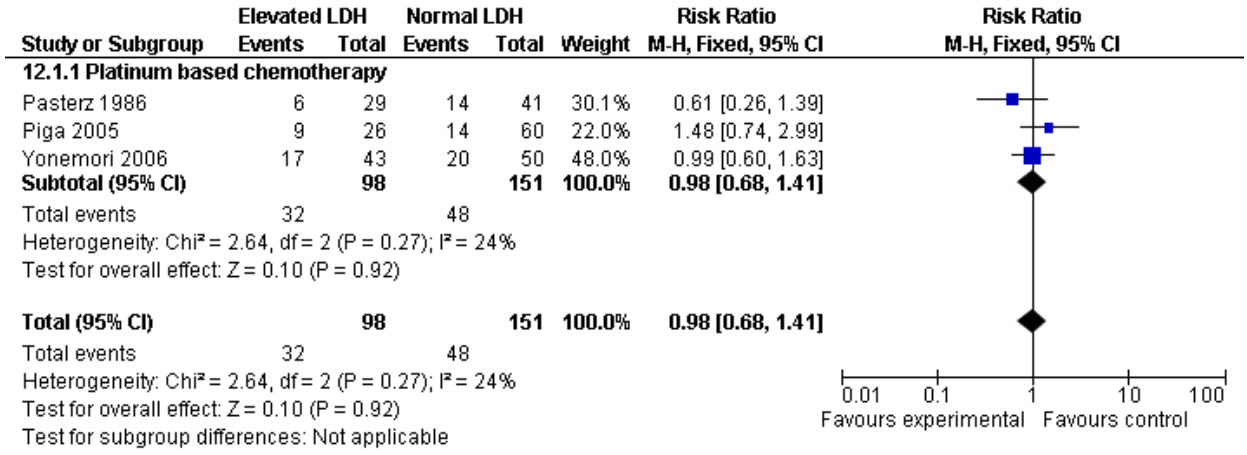


Figure 14.18 Elevated serum LDH, univariate analysis of overall survival

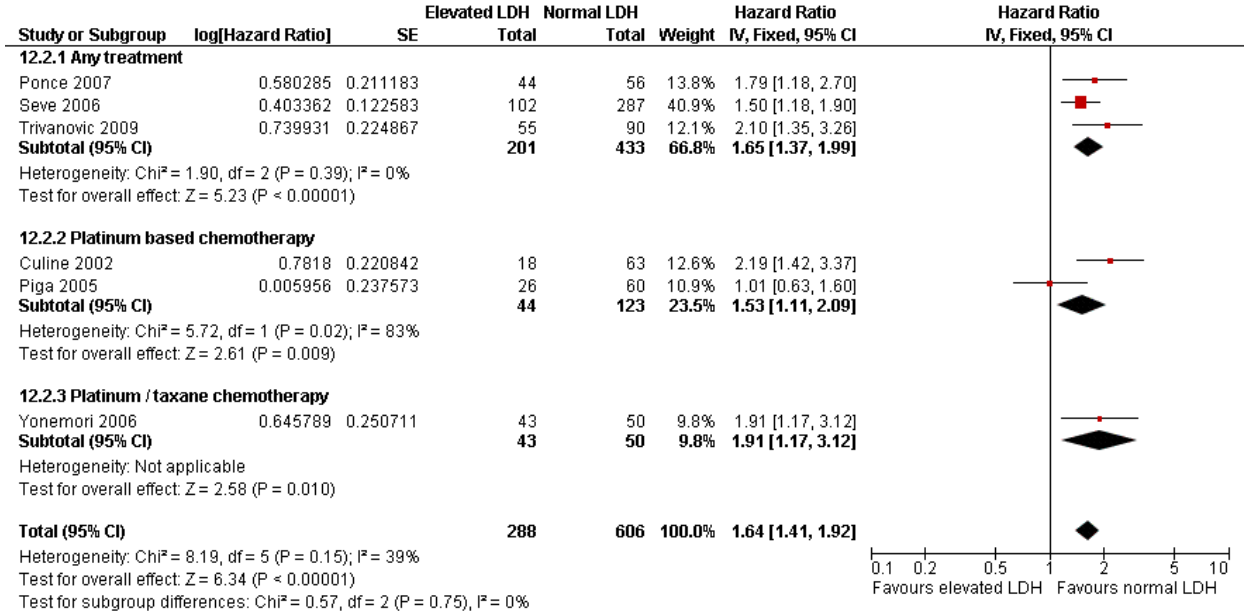


Figure 14.19 Elevated serum LDH, multivariate analysis of overall survival

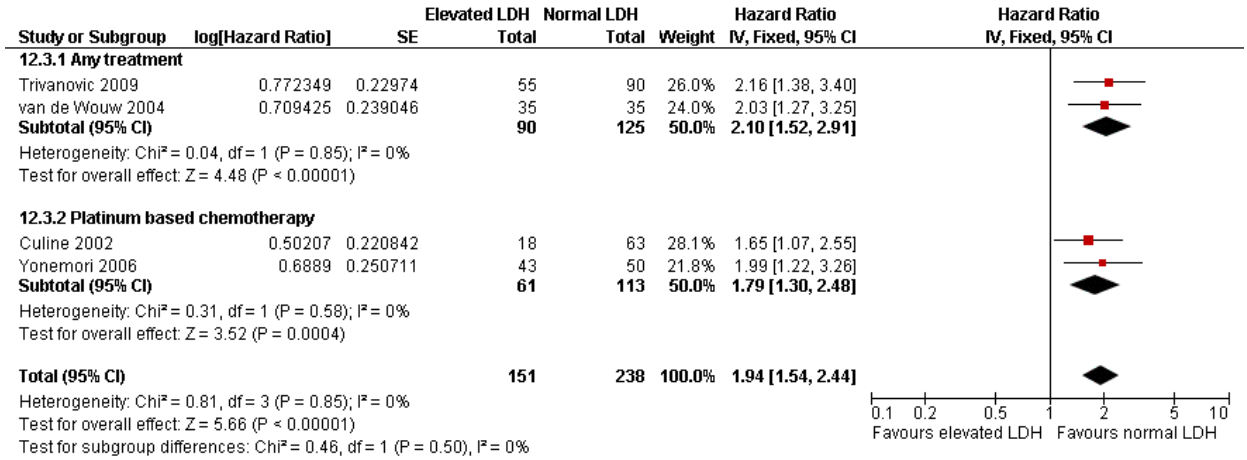


Figure 14.20 Performance status, univariate analysis of treatment response

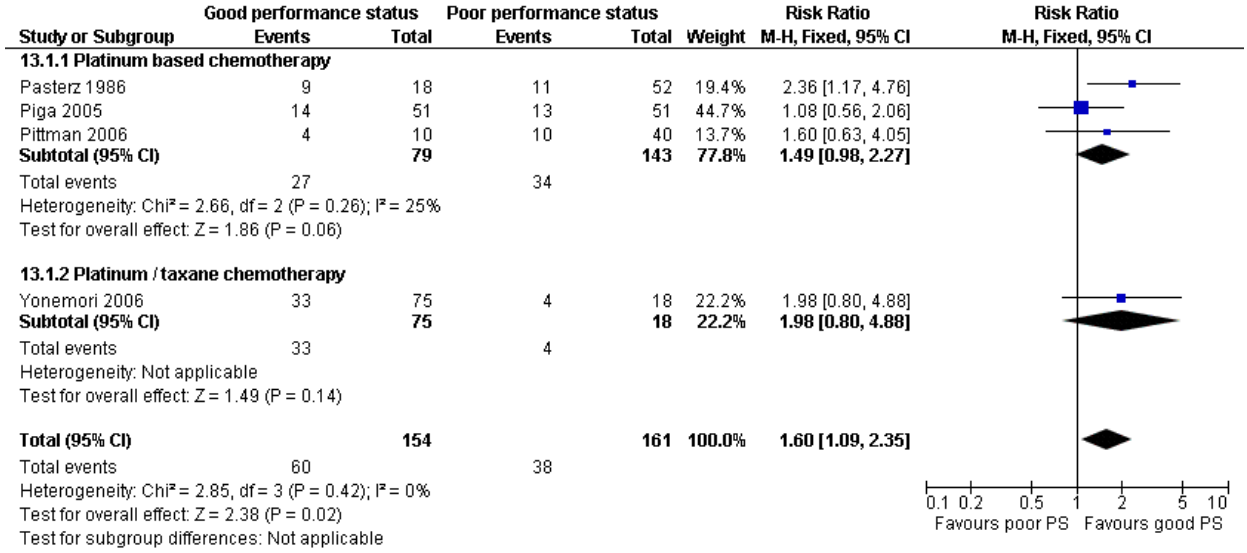


Figure 14.21 Performance status, univariate analysis of overall survival

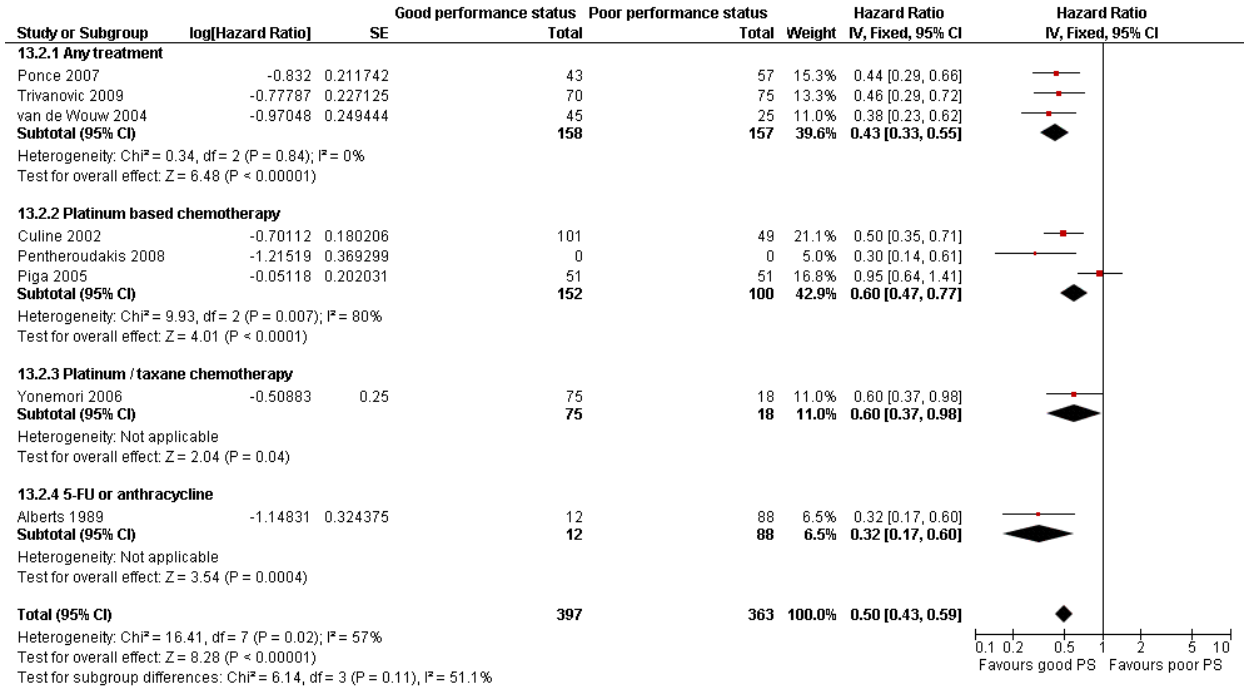


Figure 14.22 Performance status, multivariate analysis of overall survival

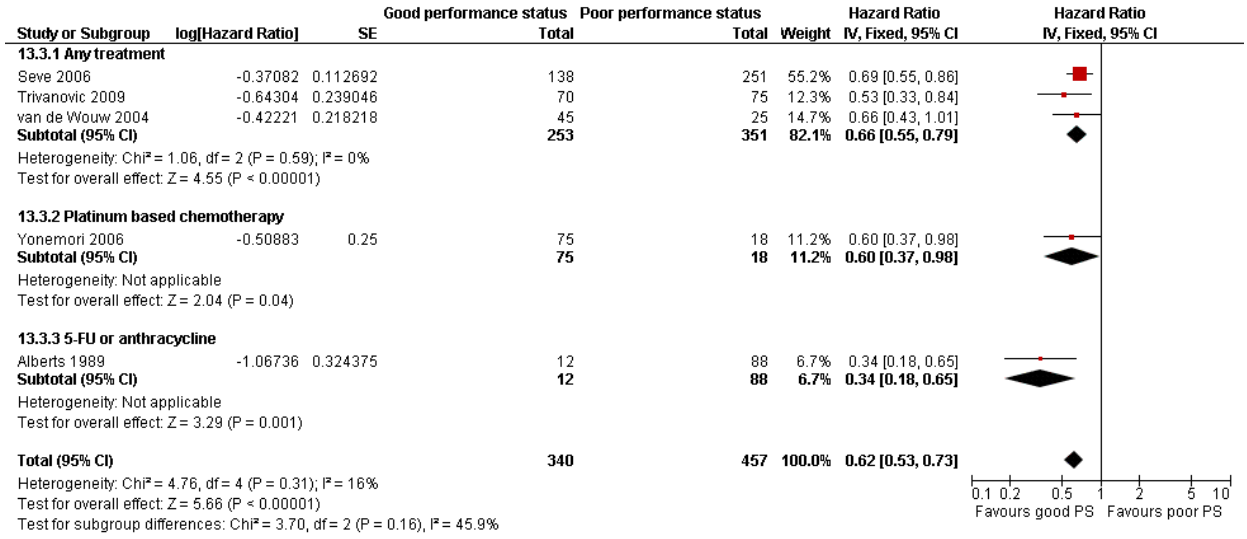


Figure 14.23 Age, univariate analysis of treatment response

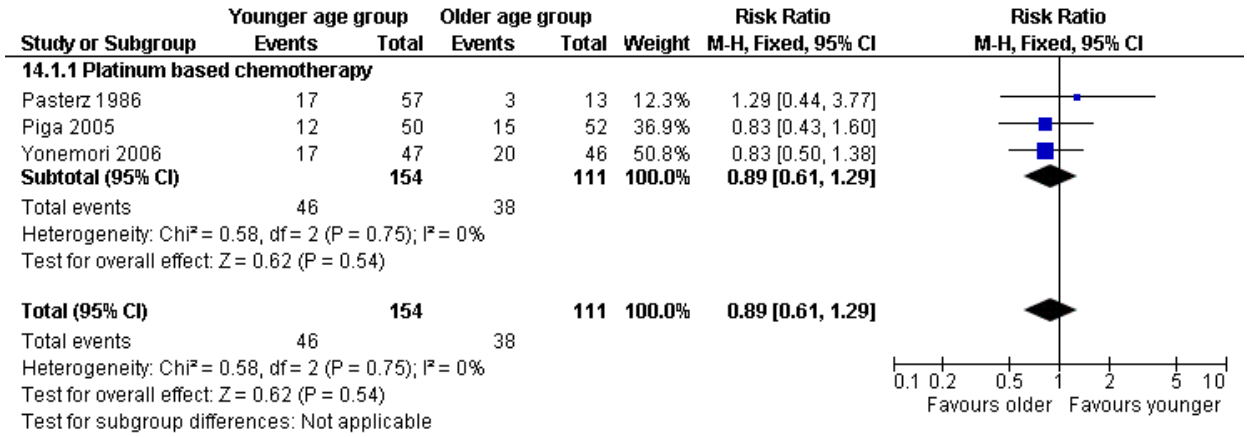


Figure 14.24 Age, univariate analysis of overall survival

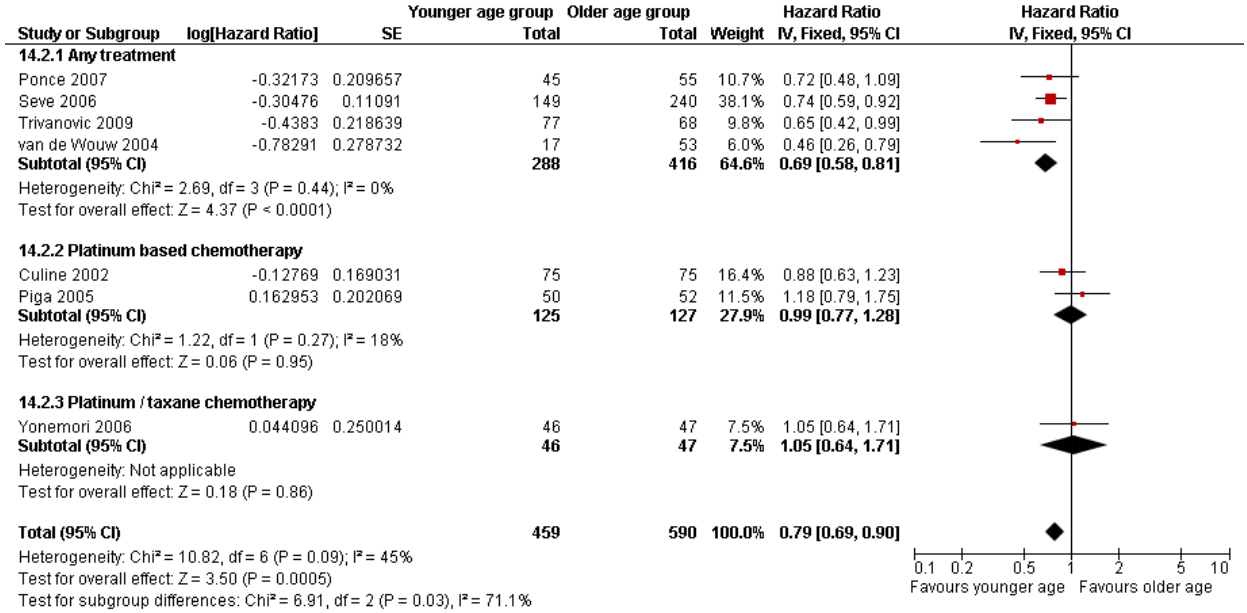


Figure 14.25 Age, multivariate analysis of overall survival

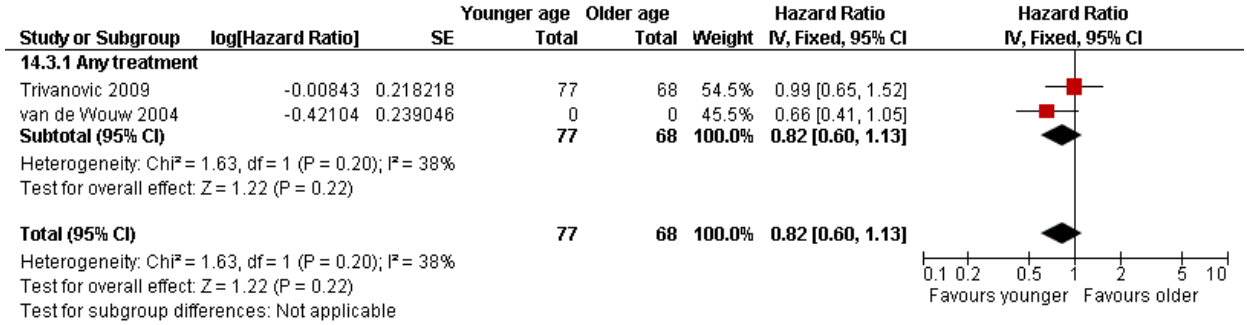


Figure 14.26 Number of metastatic sites, univariate analysis of treatment response

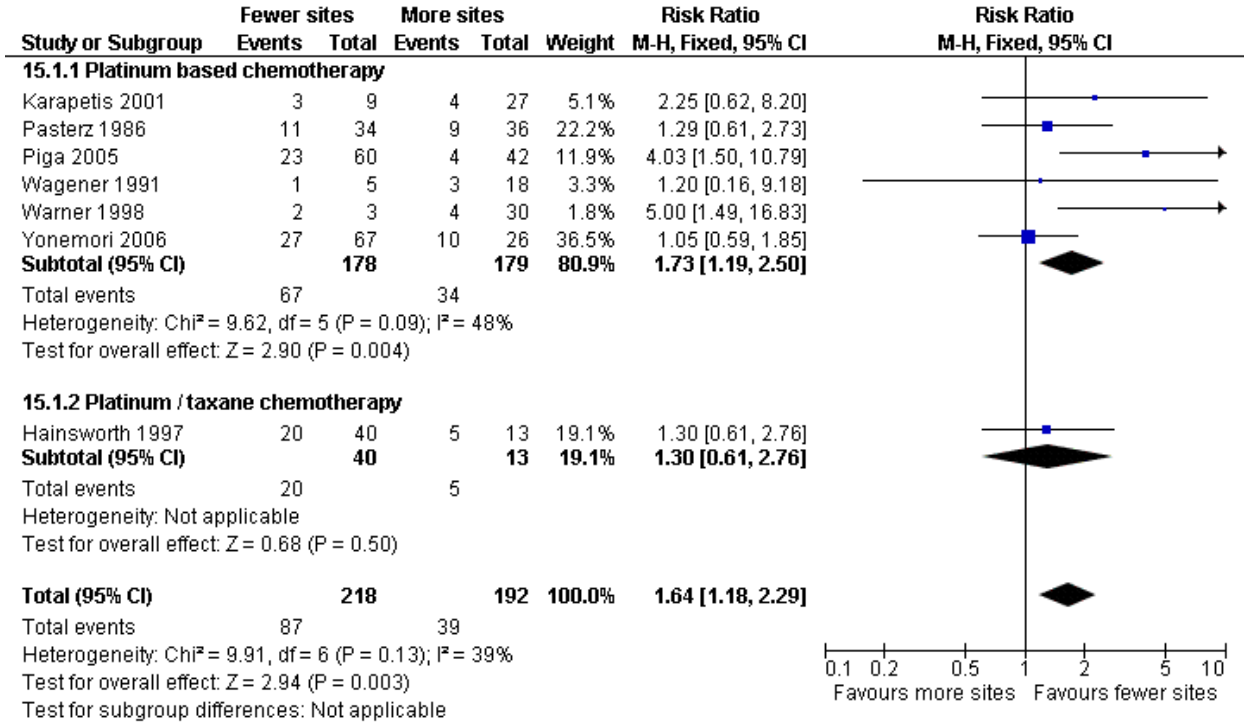


Figure 14.27 Number of metastatic sites, univariate analysis of overall survival

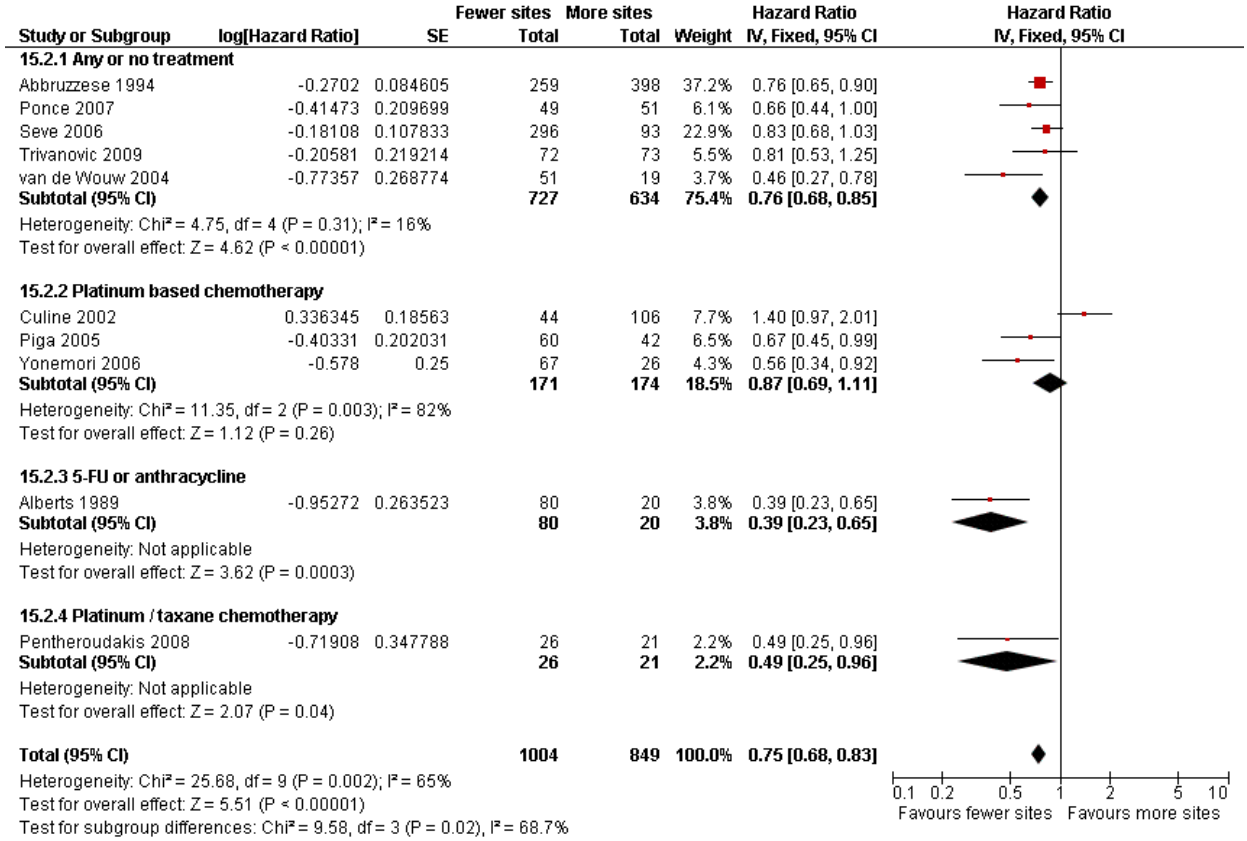


Figure 14.28 Number of metastatic sites, multivariate analysis of overall survival

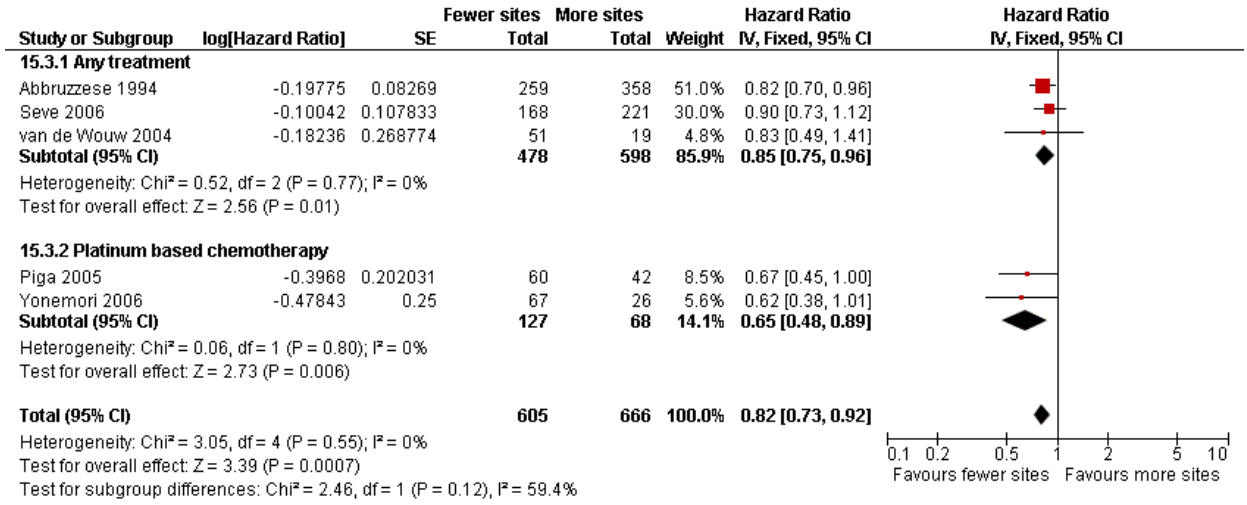


Figure 14.29 Peritoneal involvement, univariate analysis of treatment response

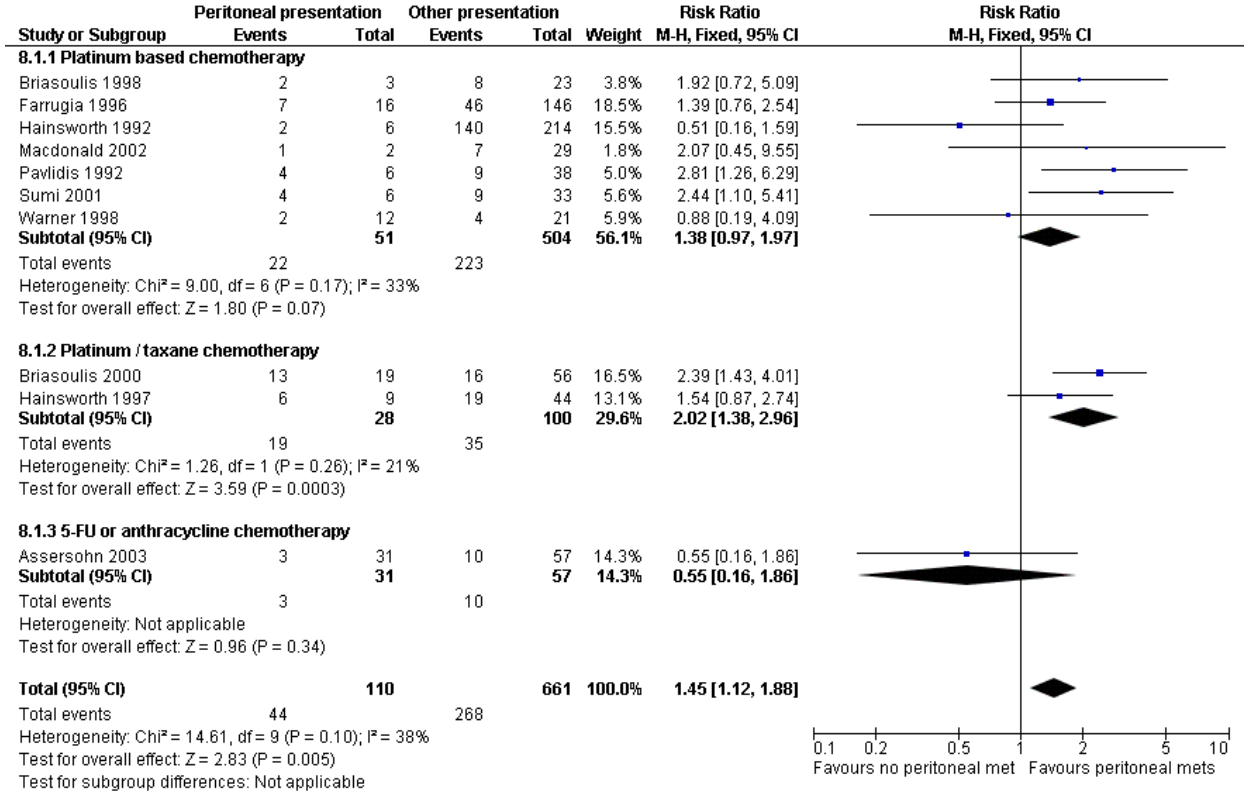


Figure 14.30 Peritoneal involvement, univariate analysis of overall survival

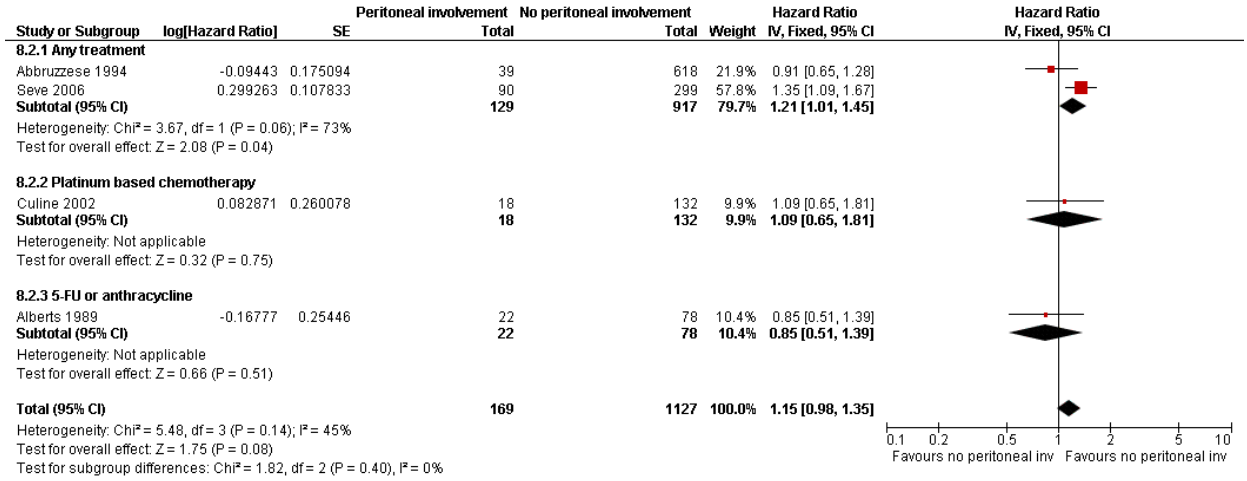
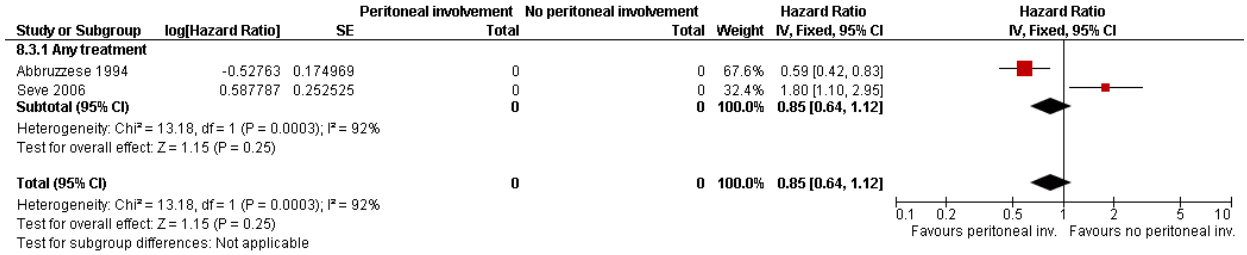


Figure 14.31 Peritoneal involvement, multivariate analysis of overall survival



14. Prognostic and predictive factors in CUP

Last updated: 30 / 10 / 2009.

Characteristics of included studies

Abbruzzese-1994

Methods	Retrospective case series
Participants and Country	657 patients with unknown primary cancer. (excluding SCC of upper/mid neck nodes)
Interventions	There was no uniform treatment
Outcomes	Overall survival
Prognostic factors (univariate)	Age, sex, race, number of sites, anatomical site, histology (adenocarcinoma, carcinoma, SCC or neuroendocrine carcinoma)
Prognostic factors (multivariate)	Reported only significant prognostic factors: sex, number of sites, anatomical site, histology (adenocarcinoma or neuroendocrine carcinoma)
Notes	

Al-Kubaisy-2003

Methods	Case series
Participants and Country	30 patients with CUP.
Interventions	Vinorelbine, gemcitabine and methotrexate.
Outcomes	Treatment response rate,
Prognostic factors (univariate)	
Prognostic factors (multivariate)	
Notes	

Alberts-1989

Methods	Retrospective case series
Participants and Country	100 patients with CUP
Interventions	80 patients received mitomycin-C chemotherapy
Outcomes	Overall survival
Prognostic factors (univariate)	PS, presentation, sex, histology, age, number of sites of metastases
Prognostic factors (multivariate)	PS, sex, lymph node metastases, liver metastases
Notes	

Assersohn-2003

Methods	Randomised controlled trial
Participants and Country	88 patients with CUP. UK. PS 2 or less, life expectancy at least 3 months. Unclear whether patients with treatable subsets were excluded.
Interventions	Protracted venous infusion of 5-fluorouracil with or without mitomycin-C.
Outcomes	Treatment response, failure free survival, overall survival, symptom relief and toxicity.
Prognostic factors (univariate)	Metastatic site, treatment centre, PS, treatment response, CA 19-9, CEA, beta-HCG, AFP, serum albumin,
Prognostic factors (multivariate)	ALT, bilirubin, serum albumin,
Notes	

Berry-2007

Methods	Phase II trial, non randomised
Participants and Country	42 patients with CUP, excluding treatable subsets or SCC. USA
Interventions	Weekly paclitaxel plus carboplatin
Outcomes	Overall survival, treatment response and toxicity.
Prognostic factors (univariate)	Histology
Prognostic factors (multivariate)	Not reported
Notes	

Briasoulis-1998

Methods	Phase II non randomised study
Participants and Country	62 patients with CUP, life expectancy at least 3 months, PS less than 3. Greece
Interventions	Carboplatin, epirubicin and etoposide
Outcomes	Treatment response, toxicity and overall survival.
Prognostic factors (univariate)	Sex, histology, metastatic site
Prognostic factors (multivariate)	None reported
Notes	

Briasoulis-2000

Methods	Phase II trial, non randomised
Participants and Country	77 patients with CUP any presentation excluding women with axillary node adenocarcinoma. Greece
Interventions	Carboplatin and paclitaxel (plus G-CSF).
Outcomes	Treatment response, toxicity and overall survival.
Prognostic factors (univariate)	Histology, anatomic site of metastasis

Prognostic factors (multivariate)	Not reported
Notes	

Briasoulis-2008

Methods	Phase II trial, non randomised
Participants and Country	47 patients with poor prognosis CUP (liver, bone or multiple visceral metastases). Greece.
Interventions	Irinotecan and oxaliplatin
Outcomes	Treatment response, toxicity and overall survival
Prognostic factors (univariate)	Liver metastasis
Prognostic factors (multivariate)	Not reported
Notes	

Culine-1999

Methods	Prospective case series
Participants and Country	60 patients with CUP - excluding treatable subtypes. Group A included only poorly differentiated carcinoma or poorly differentiated adenocarcinoma, group B included also included adenocarcinoma.
Interventions	Group A: alternate cycles of cyclophosphamide + doxorubicin and etoposide + carboplatin, with G-CSF and blood progenitor. Group B: alternate cycles of cyclophosphamide + doxorubicin and etoposide + cisplatin, with G-CSF.
Outcomes	Treatment response, overall survival and toxicity
Prognostic factors (univariate)	
Prognostic factors (multivariate)	
Notes	

Culine-2002

Methods	Retrospective case series.
Participants and Country	150 patients with CUP, excluding those subgroups with well defined treatments.
Interventions	Most (77%) had platinum based chemotherapy, 19/150 had non platinum chemotherapy and 15/150 had no chemotherapy.
Outcomes	Overall survival.
Prognostic factors (univariate)	Age, sex, PS, histology, anatomic location of metastases, number of metastatic sites, alkaline phosphatase, CEA, CA 19-9, CA-125, CA 15-3, LDH
Prognostic factors (multivariate)	PS, LDH, liver metastases
Notes	

Falkson-1998

Methods	Randomised trial
Participants and Country	84 patients with CUP, adenocarcinoma or undifferentiated carcinoma, excluding patients with cerivcal adenopathy and women with axillary adenopathy. South Africa
Interventions	Patients received either mitomycin-C, epirubicin and cisplatin or mitomycin-C alone.
Outcomes	Toxicity, treatment response,
Prognostic factors (univariate)	Sex, histology, metastatic site
Prognostic factors (multivariate)	None reported
Notes	

Farrugia-1996

Methods	Retrospective case series
Participants and Country	101 patients with CUP. Adenocarcinoma or undifferentiate carcinoma. UK
Interventions	Platinum based chemotherapy or single agent 5-fluorouracil.
Outcomes	Treatment response, overall survival, toxicity, symptom relief.
Prognostic factors (univariate)	Metastatic site, number of metastatic sites
Prognostic factors (multivariate)	None reported
Notes	

Greco-2004

Methods	Phase II study, non comparative
Participants and Country	132 patients with CUP excluding treatable subsets. USA
Interventions	Sequential chemotherapy: paclitaxel, carboplatin and oral etoposide, followed by gemcitabine and irinotecan.
Outcomes	Treatment response, progression free survival, overall survival, toxicity.
Prognostic factors (univariate)	Predominantly lymph node metastases, liver metastases
Prognostic factors (multivariate)	None reported
Notes	

Hainsworth-1992

Methods	Retrospective case series
Participants and Country	220 patients with poorly differentiated CUP. USA
Interventions	Cisplatin based chemotherapy: either cisplatin, vinblastine and bleomycin ± doxorubicin or cisplatin and etoposide ± doxorubicin.
Outcomes	Treatment response, overall survival

Prognostic factors (univariate)	
Prognostic factors (multivariate)	
Notes	Possible overlap with Greco 1997-2008 studies

Hainsworth-1997

Methods	Phase II study
Participants and Country	55 patients with CUP, excluding the treatable subsets.
Interventions	Carboplatin, paclitaxel and etoposide.
Outcomes	Treatment response
Prognostic factors (univariate)	histological type, metastatic location
Prognostic factors (multivariate)	None reported
Notes	

Hess-1999

Methods	Retrospecive observational study
Participants and Country	1000 patients with CUP
Interventions	Treatment varied according to the patient's presentation.
Outcomes	Overall survival
Prognostic factors (univariate)	None reported
Prognostic factors (multivariate)	Classification and regression tree (CART) analysis was used. The following were incorporated: anatomic site of the metastases, histology, number of metastases, age
Notes	

Jentsch-Ullrich-1998a

Methods	Retrospective case series
Participants and Country	36 patients with CUP any presentation or histology (excluding SCC in neck nodes who were treated as head/ neck cancer).
Interventions	No uniform treatment, some had chemotherapy but numbers are not reported.
Outcomes	Overall survival
Prognostic factors (univariate)	age, sex, histopathology, number of involved sites
Prognostic factors (multivariate)	Not reported
Notes	

Kambhu-1990

Methods	Phase II trial, non randomised
Participants and Country	57 patients with CUP. USA
Interventions	mitomycin-C, vindesine and adriamycin (MVA).
Outcomes	Treatment response, toxicity, and overall survival
Prognostic factors (univariate)	
Prognostic factors (multivariate)	
Notes	

Karapetis-2001

Methods	Retrospective case series, non randomised
Participants and Country	36 patients with CUP. UK
Interventions	Epirubicin, cisplatin and continuous infusional 5-fluorouracil (ECF). Standard (N=13) or modified (N=23) ECF regimen was used.
Outcomes	Treatment response rate, overall survival and toxicity.
Prognostic factors (univariate)	Sex, histology, disease site
Prognostic factors (multivariate)	Not reported
Notes	

Macdonald-2002

Methods	Phase II trial, non randomised
Participants and Country	31 patients with CUP, excluding treatable subsets. UK
Interventions	mitomycin-C, cisplatin and 5-fluorouracil
Outcomes	Toxicity, treatment response and overall survival
Prognostic factors (univariate)	histology, liver metastases
Prognostic factors (multivariate)	None reported
Notes	

Munoz-2004

Methods	
Participants and Country	48 patients with CUP
Interventions	Paclitaxel, carboplatin and etoposide
Outcomes	Overall survival
Prognostic factors (univariate)	PS, number of metastases, anatomic location of metastases, LDH, serum albumin level, haemoglobin,

Prognostic factors (multivariate)	PS and serum albumin
Notes	Cannot estimate number of deaths. Spanish language paper

Munoz-2008

Methods	Retrospective case series
Participants and Country	48 patients with CUP
Interventions	Carboplatin, paclitaxel and etoposide
Outcomes	Overall survival
Prognostic factors (univariate)	PS, number of metastatic sites, liver mets, lymph node metastases, LDH, alkaline phosphatase, low serum albumin, glutamic-pyruvic transaminase
Prognostic factors (multivariate)	low serum albumin and performance status
Notes	Letter in response to Ponce Lorenzo (2007), reporting the validity of the Culine and Van der Gaast models in their patient cohort (Munoz, 2004).

Pasterz-1986

Methods	Retrospective case series
Participants and Country	70 patients with CUP,
Interventions	Combination chemotherapy
Outcomes	Treatment response, overall survival
Prognostic factors (univariate)	sex, duration of symptoms, performance status, number of metastatic sites, histology, LDH, CEA, suspected site of primary, tumour bulk
Prognostic factors (multivariate)	None reported
Notes	

Pentheroudakis-2008

Methods	Phase II study, prospective.
Participants and Country	47 patients with CUP: adenocarcinoma or PDC. 23/47 had favourable risk (predominantly nodal disease or peritoneal carcinomatosis).
Interventions	Docetaxel and carboplatin combination therapy
Outcomes	Overall survival, time to progression, treatment response and toxicity
Prognostic factors (univariate)	Age, performance status, serum tumour markers, number of sites, liver metastases, chemotherapy dose intensity and CUP risk group (only significant factors were reported).
Prognostic factors (multivariate)	Not reported
Notes	

Piga-2005

Methods	Prospective phase II trial
Participants and Country	102 patients with CUP, carcinoma, adenocarcinoma or undifferentiated tumour. Patients with mid or upper neck node presentation were excluded.
Interventions	Platinum based combination chemotherapy.
Outcomes	Response to treatment, overall survival
Prognostic factors (univariate)	Age, sex, ECOG PS, pain, histology, number of metastases, number of sites of metastases, anatomical site of metastases, LDH, ALP, CEA, CA 125, CA19-9, epithelial markers, drug dose reduction, carboplatin AUC 6 or less, grade 3 to 4 toxicity.
Prognostic factors (multivariate)	CEA, ALP, pain,Epithelial tumour markers, number of metastases, number of sites of disease, liver involvement, bone/ visceral involvement, histology and response to chemotherapy.
Notes	

Pittman-2006

Methods	Phase II trial, non randomised
Participants and Country	50 patients with CUP, PS less than 3, life expectancy at least 3 month, histology adenocarcinoma, large cell carcinoma or undifferentiated carcinoma Australia
Interventions	Gemcitabine and carboplatin.
Outcomes	Treatment response and toxicity
Prognostic factors (univariate)	Sex, PS and age
Prognostic factors (multivariate)	None reported
Notes	

Ponce-2007

Methods	Retrospective case series
Participants and Country	100 patients with CUP, excluding any from subgroups with defined treatments.
Interventions	
Outcomes	Overall survival
Prognostic factors (univariate)	age, sex, performance status, histology, weight loss, location of metastasis, number of metastatic sites, alkaline phosphatase, LDH
Prognostic factors (multivariate)	PS and liver mets
Notes	

Saghatchian-2001

Methods	Prospective non comparative study

Participants and Country	48 patients with CUP: PDC or PDA (N=30) or well to moderately well differentiated adenocarcinoma (N=18), not belonging to a treatable subgroup
Interventions	Combination of cisplatin and etoposide. Patients with stable disease and good performance status received additional bleomycin, and ifosfamide combined with mesna plus G-CSF.
Outcomes	Treatment response, overall survival and toxicity.
Prognostic factors (univariate)	PDA/PDC versus well to moderately well differentiated adenocarcinoma
Prognostic factors (multivariate)	None reported
Notes	

Schneider-2007

Methods	Phase II trial, non randomised and non comparative
Participants and Country	33 patients with CUP, not belonging to treatable subset. USA
Interventions	Carboplatin, gemcitabine and capecitabine
Outcomes	Treatment response rate, progression free and overall survival, toxicity.
Prognostic factors (univariate)	PDC or UDC, liver metastases
Prognostic factors (multivariate)	None reported
Notes	

Seve-2006

Methods	Retrospective cohort study
Participants and Country	389 patients with CUP and epithelial histology. Favourable subsets were excluded.
Interventions	88/389 chemotherapy, 61/389 radiotherapy, 37/389 other treatment, 215/389 no treatment
Outcomes	Overall survival
Prognostic factors (univariate)	PS, comorbidity,location of metastases, LDH, number of metastatic sites, age, adenocarcinoma, histology
Prognostic factors (multivariate)	PS, comorbidity,liver metastases, peritoneal metastases, LDH, number of metastatic sites
Notes	

Seve-2006a

Methods	Retrospective case series
Participants and Country	patients with CUP not belonging to a treatable subgroup.
Interventions	Not reported
Outcomes	Overall survival
Prognostic factors (univariate)	age, sex, comorbidity, histology, PS, anatomic site of metastasis, number of metastatic sites, alkaline phosphatase, LDH, albumin level, haemoglobin level, platelet level, lymphocyte count

Prognostic factors (multivariate)	comorbidity score, no. of sites, liver mets, peritoneal mets, PS, LDH, alkaline phosphatase, lymphocyte count, haemoglobin level, platelet level, lymphocyte count
Notes	

Sulkes-1988

Methods	Comparitive study (non randomised)
Participants and Country	28 patients with adenocarcinoma of unknown primary
Interventions	Chemotherapy FAM or AVM
Outcomes	Overall survival, treatment response, toxicity.
Prognostic factors (univariate)	
Prognostic factors (multivariate)	
Notes	

Sumi-2001

Methods	Non-randomised comparative study
Participants and Country	50 patients with CUP
Interventions	Platinum based, non-platinum based or new agent chemotherapy. Chemotherapy versus no chemotherapy
Outcomes	Treatment response, overall survival
Prognostic factors (univariate)	
Prognostic factors (multivariate)	
Notes	Bias likely. Patients given palliative care only were most likely unfit for chemotherapy.

Trivanovic-2009

Methods	Prospective case series.
Participants and Country	145 patients with CUP not belonging to subgroups with defined treatment.
Interventions	Treatment is not described
Outcomes	Overall survival
Prognostic factors (univariate)	Age, sex, PS, smoking, histology, number of involved organs, liver mets, diabetes mellitus, white blood cell counts, anaemia, LDH, ALP, positive tumour markers (any), QTc interval, chemotherapy
Prognostic factors (multivariate)	LDH, Qtc interval, liver mets, ECOG PS, WBC, anaemia, ags
Notes	

van-de-Wouw-2004

Methods	Retrospective case series

Participants and Country	70 patients with CUP adenocarcinoma
Interventions	33/70 patients received treatment and 37/70 had no treatment
Outcomes	Overall survival
Prognostic factors (univariate)	Age, sex, PS, liver mets, lymph node mets, primary tumour found, treatment, M1B1, p-53, VEGF, CD34, CD44v6, Her2neu
Prognostic factors (multivariate)	Age, PS, number of involved organ sites, liver metastases, LDH
Notes	

Van-Der-Gaast-1995

Methods	Phase II chemotherapy trials
Participants and Country	77 patients with poorly differentiated adenocarcinoma or undifferentiated carcinoma of unknown primary. Most patients had one or more of the following clinical features: age less than 50 years, tumour located predominantly in a midline distribution, multiple pulmonary nodules or lymphadenopathy and clinical evidence of rapid tumour growth.
Interventions	Patients were entered into one of two platinum based chemotherapy trials: cisplatin plus etoposide (18/77) or cisplatin plus etoposide plus bleomycin (59/77)
Outcomes	Overall survival
Prognostic factors (univariate)	Histology, sex, age, PS, chemotherapy type, anatomic site of metastasis, number of metastatic sites, LDH, alkaline phosphatase, AST
Prognostic factors (multivariate)	PS and alkaline phosphatase
Notes	

Voog-2000

Methods	Phase II trial, non randomised non comparative study
Participants and Country	25 patients with CUP. France
Interventions	Cisplatin and Etoposide
Outcomes	Treatment response, overall survival, toxicity.
Prognostic factors (univariate)	Adenocarcinoma histology
Prognostic factors (multivariate)	Not reported
Notes	

Wagener-1991

Methods	Non comparative phase II trial
Participants and Country	21 patients with CUP, adenocarcinoma histology, PS 0 to 2, normal serum acid phosphatase, alpha-fetoprotein and beta-chorionic gonadotopin.
Interventions	Cisplatin
Outcomes	Overall survival, treatment response, response duration, toxicity.

Prognostic factors (univariate)	Site and number of metastases
Prognostic factors (multivariate)	Not reported
Notes	

Warner-1998

Methods	Phase II study, non comparative
Participants and Country	33 patients with CUP not belonging to a treatable sub-group. PS 2 or less. 30/33 adenocarcinoma, 3/33 undifferentiated carcinoma
Interventions	Combined carboplatin and etoposide
Outcomes	Treatment response
Prognostic factors (univariate)	Age, sex, performance status, histology, site of disease
Prognostic factors (multivariate)	Not reported
Notes	

Woods-1980

Methods	Randomised controlled trial
Participants and Country	47 patients with adenocarcinoma or undifferentiated carcinoma of unknown primary.
Interventions	CMF or DM. Patients switched treatment arms after 12 weeks if there was no response.
Outcomes	Overall survival, treatment response (complete or partial).
Prognostic factors (univariate)	Sex
Prognostic factors (multivariate)	Not reported
Notes	

Yonemori-2006

Methods	Retrospective case series
Participants and Country	93 patients with CUP, excluding the subgroups with defined treatments and SCC or neuroendocrine carcinoma.
Interventions	37 patients had paclitaxel plus carboplatin, 36 patients docetaxel plus cisplatin, and 20 patients irinotecan plus carboplatin.
Outcomes	Overall survival, treatment response
Prognostic factors (univariate)	Sex, age, PS, smoking, histology, number of involved organs, liver metastases, ALP, LDH, CRP, 5 or more elevated tumour markers (any), AFP, beta-HCG, PIVKA-II, CEA, SLX, Cyfra, CA 19-9, CA15-3, Erastase, STN, ST-439, NSE, ProGRP
Prognostic factors (multivariate)	PS, number of metastatic sites, LDH
Notes	Large number of prognostic factors investigated, given the sample size. Validates Culine and Van der Gaast models.

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15. Decision aids for people with cancer of unknown primary

Last updated: 30/ 10/ 2009.

Short summary

Decision aids are designed to help people understand options, consider the personal importance of harms and benefits and to take part in the decision making process (O'Connor et al 2009).

There was an absence of published decision aids for people with cancer of unknown primary.

There is good evidence, from randomised trials, that decision aids are useful when patients need to make diagnostic or treatment decisions in cancer. When compared with usual care, decision aids improved people's knowledge of their options and reduced difficulty with decision making.

Rationale

Rationale for asking this question needs to be written, including the key decisions faced by patients with CUP.

Methods

Study types

There was no restriction on study design.

Participants

People with confirmed cancer of unknown primary.

Interventions

Decision aids, such as pamphlets and videos, that describe treatment or diagnostic options. The comparison is usual care, with no decision aids. According to O'Connor et al (2009) decision aids are designed to help people make specific and deliberative choices among options (including the status quo) by providing (at the minimum) information on the options and outcomes relevant to a person's health status.

Outcomes

Patient satisfaction with decision making, decisional conflict, knowledge acquisition and anxiety.

Search results

Description of included studies

The literature search found no studies of decision aids for people with confirmed cancer of unknown primary. Several studies developed prognostic models for patients with CUP (Seve et al 2006; Trivanovic et al 2009; Culine et al 2002; Penel et al, 2009) . These could form the basis of a decision aid for treatment decisions, but they have not yet been evaluated as such.

A high level search of MEDLINE for systematic reviews of decision aids in patients with cancer identified one recent systematic review (O'Brien et al 2009) and a Cochrane review of decision aids for people facing health treatment or screening decisions (O'Connor et al 2009).

These reviews included no studies in patients with cancer of unknown primary, but many of the trials addressed similar decisions to those faced by patients with cancer of unknown primary. There were 22 randomised trials of screening for cancer, where people decided whether to proceed with a diagnostic test after considering the potential harms and benefits of diagnosis. Similarly there were also trials of decision aids for treatment options, when there was no obvious best treatment choice and patients had to consider the personal importance of the various harms and benefits when choosing.

Study quality

Both the included systematic reviews were of high quality.

Evidence summary

Knowledge Acquisition

Both reviews (O'Brien et al 2009 and O'Connor et al 2009) found that decision aids significantly improved people's knowledge of their options when compared with usual care. O'Connor et al estimated the magnitude of this improvement as approximately 15% (95% CI 12% to 19%; where knowledge was rated on a scale of 0 to 100%).

Decisional conflict

Decisional conflict is a composite measure that includes the patient's comfort with decisional making in terms of

how well informed they feel, the clarity of their values, how supported they feel in the decision making process, and their level of uncertainty (O'Brien et al 2009).

Both reviews (O'Brien et al 2009 and O'Connor et al 2009) found that decision aids reduced people's decisional conflict when compared with usual care. O'Connor et al estimated the magnitude of this reduction as approximately 8% (95% CI 5% to 12%; where decisional conflict was rated on a scale of 0 to 100%).

Satisfaction and Anxiety

Neither review found an effect of decision aids on patients satisfaction with their decision or on their levels of anxiety. It is plausible that information about treatment outcomes and harms could increase anxiety in some cases.

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15. Decision aids for people with cancer of unknown primary

Last updated: 30 / 10 / 2009.

Characteristics of included studies

O-Brien-2009

Methods	A systematic review of randomised trials of decision aids (DA) for patients with cancer or at increased risk of cancer.
Participants and Country	34 trials were included, 22 were in screening, five in high risk prevention,and seven in treatment. Most of the trials involved decisions regarding breast and prostate cancer. Three trials focused on colorectal cancer screening, two on cervical cancer screening, and one on ovarian cancer prevention.
Interventions	A decision aid was defined as "an intervention designed primarily to help patients or patients and clinicians together, with making cancer-related health care decisions, when options are available for screening, prevention, and treatment. At a minimum, it should target some component of decision making (for example, information exchange, involvement in the decision process)." Twenty four trials involved the comparison of DA versus usual practice; six trials of DA versus DA; and four trials of DA versus DA versus usual practice.
Outcomes	**Knowledge acquisition** Decision aids significantly improved knowledge about screening options when compared to usual practice (weighted average effect size, 0.50; 95% CI, 0.27 to 0.73; P=0 .0001). Similarly decision aids improved knowledge about preventive/treatment options (weighted average effect size, 0.50; 95% CI, 0.31 to 0.70; P=0 .0001). **Satisfaction with decisions** This outcome was not reported separately. **Decisional conflict** Decisional conflict is an outcome that is supposed to reflect the patient's comfort with decisional making in terms of how well informed they feel, the clarity of their values, how supported they feel in the decision making process, and their level of uncertainty. Decision aids reduced decisional conflict overall when compared with usual practice (when screening and treatment trials were combined the weighted average effect size was -0.11; 95% CI, -0.20 to -0.01). When screening and preventive/treatment studies were analysed separately, however, the effect was not statistically significant. **Anxiety** There was no clear overall effect of decision aids on anxiety levels. The authors comment that a decision aid would not necessarily reduce anxiety as realistic information about the outcomes and side effects of treatment choices could increase anxiety.
Notes	

O-Connor-2009

Methods	Systematic review of randomised trials comparing decision aids to no intervention, usual care, alternative interventions, or a combination.
Participants and Country	Included studies involving people who were making decisions about screening or treatment options for themselves, for a child, or for an incapacitated significant other. Excluded studies in which participants were making hypothetical choices. 55 RCTs were included, evaluating 51 separate decision aids for screening or treatment decisions in a range of health conditions.
Interventions	Decision aids were defined as "interventions designed to help people make specific and deliberative choices among options by providing information on the options and outcomes relevant to a person's health status and implicit methods to clarify values."
Outcomes	The review considered: decisional conflict., patient-practitioner communication, participation in decision making, satisfaction, adherence to chosen option, health status and quality of life, anxiety, depression, emotional distress, regret and confidence. **Knowledge acquisition** 18 studies measured knowledge acquisition (on a scale of 0 to 100). Decision aids improved knowledge acquisition when compared with usual care, mean difference was 15.18; 96% CI 11.66 to 18.69; P < 0.00001. **Satisfaction with decisions** 11 studies measured satisfaction, either with the decision itself or the process of decision making. Six of these studies found improvements in satisfaction but five did not and there was no overall effect of decision aids on satisfaction. **Decisional conflict** Ten studies measured decisional conflict (on a scale of 0 to 100). Decision aids reduced decisional conflict when compared with usual care, mean difference was -6.12; 96% CI -8.62 to -3.63; P < 0.00001. **Anxiety** Eleven studies measured state anxiety using the State Anxiety Inventory in trials of decision aids versus usual care. None of these studies reported a significant effect of decision aids on anxiety.
Notes	

References for included studies

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16. Post operative treatment for squamous carcinoma in upper or mid neck lymph nodes of unknown primary

Last updated: 30/ 10/ 2009.

Short summary

There was a lack of studies designed to evaluate post operative treatment. Evidence was limited to observational studies, with little data about patients treated with surgery alone.

Case series suggest that five year post-operative overall survival of between 22% and 60% in patients treated with adjuvant radiotherapy. In two small series of patients treated with surgery alone, five year overall survival ranged from 65% to 66%.

Treatment related morbidity was common after radiotherapy: including mucositis and xerostomia. There was no direct evidence about treatment toxicity in patients who did not have adjuvant therapy, but is reasonable to assume that this group would be spared some morbidity.

Rationale

A small minority of CUP patients present with squamous carcinoma in upper / mid neck lymph nodes from a presumed but unidentified head and neck primary. Furthermore, the pattern of nodal involvement is very similar to that seen with head and neck primary. Experience suggests that these groups may justifiably be treated with localized treatment with potentially curative intent. They may be considered to have a primary cancer which might fall under one or more of the following categories:

1. It might be treated with curative intent should it become apparent.

2. It might be eradicated by treatment directed at its likely anatomical site, either specifically or coincidentally from treatment directed principally against the metastatic disease.

3. It might never become apparent despite having no treatment directed against it.

Radical neck dissection, with or without subsequent radiotherapy, has been used as a treatment for this group of patients. However the effectiveness and cost-effectiveness of this management strategy has not been established. Certainly any treatment given with curative intent is likely to cause substantial morbidity hence investigation of the validity of this treatment approach is required.

Methods

Study types
Any study design.

Participants
People with metastatic squamous carcinoma in the mid/ upper neck nodes, without an identified primary, after specific head and neck investigations. Patients presenting with malignant supraclavicular nodes are excluded, as this presentation is often associated with primary malignancy outside the head or neck.

Interventions
Attempted curative surgery (node block dissection) alone compared with curative surgery plus post operative treatment. Post operative treatment is radiotherapy and or chemotherapy.

Outcomes
Treatment outcomes including: overall survival, disease specific survival, and treatment complications

Study selection
The information specialist (SA) screened the literature searches for relevant studies, on the basis of their title and abstract. One reviewer (KF) checked this list and ordered relevant articles. Additional studies were identified from references in the included papers.

Data extraction and synthesis
One reviewer (KF) appraised the studies and extracted data.

Quality assessment
All studies were retrospective and observational and considered at equally high risk of bias.

Heterogeneity assessment

There was no statistical assessment of heterogeneity (differences between studies) although potential sources of differences in results (such as patient and treatment characteristics) were noted in the evidence tables.

Search results

The literature search identified 152 potentially relevant papers. Nineteen were ordered for appraisal and seventeen included as evidence.

The majority of patients in the included studies received radical neck dissection with post operative radiotherapy. The post operative radiotherapy dose ranged from 50 Gy to 70 Gy, usually delivered in 2 Gy fractions. Radiotherapy was delivered to both sides of the neck and to mucosal regions in most cases, although Grau et al (2000) and Reddy et al (1997) contained a minority of patients treated with radiotherapy to the ipsilateral neck only.

Some patients had surgery without postoperative radiotherapy, but their results were only analysed separately in four studies (Coster et al 1992; Mistry et al 2008; Grau et al 1990; Wang et al 1990). Two studies reported combined treatment with surgery, chemotherapy and radiotherapy (Shehadeh et al 2006; Agiris et al 2003)

Description of included studies

Study quality

The included papers were retrospective observational studies, and at high risk of bias. The decision whether or not to give postoperative radiotherapy was probably influenced by patient and disease characteristics. Thus the patients receiving adjuvant treatment could have had a poorer prognosis to start with.

Evidence summary

Treatment outcomes are summarised in Table 16.1. Table 16.2 contains data from studies reporting outcomes separately for surgery and surgery plus adjuvant therapy groups.

Overall survival

Five year overall survival ranged from 65% to 66% in patients treated with radical neck dissection only (Coster et al 1992; Grau et al 2000). In nine studies of patients treated with surgery plus post operative radiotherapy overall survival ranged from 22% to 60%. Two studies of surgery plus chemoradiotherapy reported five year overall survival of 75% (Agiris et al, 2003) and 89% (Shehadeh et al, 2006).

Grau et al (2000) compared five year overall survival in patients treated with surgery alone (N=23) or surgery plus RT (N=26). Overall survival for the two groups was 65% and 28% respectively, but it is unclear whether their baseline characteristics were comparable. Mistry et al (2008) reported that the addition of postoperative radiotherapy did not significantly affect overall survival in their study, but only ten of the 89 patients were treated with surgery alone.

Disease specific survival

Five year disease specific survival ranged from 74% to 86% in those treated with surgery only. In studies of patients treated with post operative radiotherapy the range was 49% to 74%.

Two studies compared overall survival in patients treated with surgery with and without radiotherapy. Wang et al (1990) five year disease specific survival for those treated with surgery and surgery plus radiotherapy was 86% and 63% respectively. In Grau et al (2000) the corresponding figures were 76% and 49%.

Treatment complications

Most patients treated with radiotherapy experienced mucositis to some degree, and severe mucositis was reported in between 7% and 48% of patients. Late complications of head/neck radiotherapy were also reported: most experienced xerostomia to some degree and between 19% and 39% of patients had late neck fibrosis in three studies.

There was no evidence about complications in patients treated with surgery alone, although it is reasonable to assume that such patients would not experience morbidities commonly associated with head and neck radiotherapy like mucositis and xerostomia.

The rate of death from treatment toxicity ranged from 0% to <1% in patients treated with surgery plus RT. This compares with a rate of 4% in one study of surgery plus chemoradiotherapy (Agiris et al 2003).

Although evidence was limited to two studies (Shehadeh et al, 2006; Agiris et al, 2003), treatment with surgery plus chemoradiotherapy generally had higher rates of treatment toxicity than those treated with surgery plus radiotherapy. Some patients treated with chemoradiotherapy experienced neutropenia or renal toxicity.

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Table 16.1 Outcomes by treatment group

	Surgery alone	Surgery plus bilateral neck / mucosal RT	Surgery plus Chemotherapy plus RT
Overall survival at 5 years post op.	66% (Coster-1992) 65% (Grau-2000)	60% (Boscolo-Rizzo-2007) 60% (Colletier-1998) 45% (Davidson-1994) 22% (Fernandez-1998) 28% (Grau-2000) 43% (Issing-2003) 55% (Mistry-2008) 56% (Patel-2007) 52% (Strojan 1998)	75% (Argiris 2003) 89% (Shehadeh 2006)
Disease specific survival at 5 years post op.	74% (Coster-1992) 76% (Grau-2000) 86% (Wang-1990)	63% (Boscolo-Rizzo-2007) 74% (Colletier-1998) 60% (Davidson-1994) 49% (Grau-2000) 63% (McMahon-2000) 62% (Patel-2007) 66% (Strojan 1998) 63% (Wang-1990)	NR
Recurrence free survival at 5 years post op	NR	61% (Reddy-1997)	85% (Shehadeh 2006) 87% (Argiris 2003)
Local control in the neck at 5 years post op.	70% (Coster-1992) 58% (Grau-2000)	69% (Boscolo-Rizzo-2007) 100% (Colletier-1998, no ECE) 84% (Colletier-1998, ECE) 86% (Davidson-1994, no ECE) 57% (Davidson-1994,ECE) 62% (Grau-2000) 80% (Iganej-2002) 74% (Issing-2003) 84% (Patel-2007)	95% (Shehadeh 2006)
Death due to treatment toxicity	NR	0% (Boscolo-Rizzo-2007) <1% (Colletier-1998) <1% (Iganej-2002) 0% (Patel-2007)	4% (Argiris 2003)
Feeding tube required*	NR	7% (Colletier-1998)	24% (Shehadeh 2006) 56% (Argiris 2003)
Hospitalization for toxicity*	NR	NR	19% (Shehadeh 2006)
Mucositis*	NR	7% (Boscolo-Rizzo-2007) 43% (Iganej-2002) Varying degrees in all cases (Patel-2007) 48% (Strojan 1998)	46% (Shehadeh 2006) 68% (Argiris 2003)
Neutropenia*	NR	NR	11% (Shehadeh 2006) 28% (Argiris 2003)
Renal toxicity*	NR	NR	5% (Shehadeh 2006)
Xerostomia*	NR	varying degrees in most cases (Colletier-1998) varying degrees in all cases (Patel-2007) 21% (Reddy-1997) 63% (persistent xerostomia, Strojan 1998)	30% (Shehadeh 2006) 44% (Argiris 2003)
Oesophageal stricture*	NR	<1% (Colletier-1998)	8% (Shehadeh 2006)
Late neck fibrosis*	NR	27% (Iganej-2002) 19% (Reddy-1997) 39% (Strojan 1998)	NR

*Grade III or IV toxicity, unless otherwise stated.
Abbreviations: ECE, extracapsular extension; NR, not reported.

Table 16.2 Studies comparing surgery alone with surgery plus radiotherapy

Study	Surgery only	Surgery plus RT	Overall survival (surgery vs. surgery plus RT)	Disease specific survival (surgery vs. surgery plus RT)	Complications
Mistry-2008	N=10	N=79	No statistically significant difference in overall survival.	Comparison not reported	Comparison not reported
Wang-1990	N=57	N=41	Comparison not reported	86% vs 63% at 5 years	Comparison not reported
Grau-2000	N=23	N=26	65% vs 28% at 5 years	76% vs. 49% at 5 years	Comparison not reported

16. Post operative treatment for squamous carcinoma in upper or mid neck lymph nodes of unknown primary

Last updated: 30 / 10 / 2009.

Characteristics of included studies

Argiris-2003

Methods	Retrospective observational study
Participants and Country	25 patients. Nodal stage N2a (20%), N2b (52%), N2c (4%) and N3 (24%). 3/25 patients (12%) had supraclavicular node involvement. **Country:** USA
Interventions	**Neck dissection:** before chemoradiotherapy (56%), after induction chemotherapy (12%), after chemoradiotherapy (20%) or no surgery (12%). **Radiotherapy:** median dose 60 Gy (range 55.5 to 75 Gy) to bilateral neck and potential mucosal primary sites. **Chemotherapy:** all regimens included concomitant 5-FU and hydroxyurea with either once-daily or twice daily radiation therapy (FHX regimen). Some patients had induction chemotherapy (16%), and some had either paclitaxel (8%) or cisplatin (36%) in addition to the FHX regimen.
Outcomes	Overall survival, treatment response, treatment complications
inclusion exclusion criteria	**Inclusion criteria:** N2 or N3 squamous cell carcinoma of the head and neck lymph nodes, from an unknown primary. Treatment in one of five phase II trials of chemoradiotherapy. **Exclusion criteria:** none reported
Results	**5 year overall survival**, 75% **5 year progression free survival**, 87% **Death due to treatment toxicity** 1/25 (4%) **Grade 3 or 4 complication rates:** Acute mucositis 68%, acute dermatitis 40%, diarrhoea 8%, neutropenia 28%, infection 8%, neuropathy 4%, gastrostomy tube placement 56%, gastrostomy tube > 1 year 16%, and chronic xerostomia 44%.
Follow-up	Median follow up of surviving patients was 3.9 years (range 2.2 to 11.1 years).
Notes	

Boscolo-Rizzo-2007

Methods	Retrospective observational study.
Participants and Country	N=90 including 70 males. Median age: 62.5 years (range: 27 to 90 years). Levels of nodal metastases were: I = 17, II = 26, III = 24, IV = 17, V = 6. Nodal staging was: N1 = 12, N2a = 19, N2b = 21, N2c = 7, N3 = 31, extracapsular extension (ECE) = 48.

	Country: Italy
Interventions	All patients received radical neck dissection (and in 7 cases, type III modified radical neck dissection). Seven patients received bilateral surgery. After a median interval of 34 days (range: 27 to 43 days) patients were bilaterally irradiated in the supine position. Areas irradiated included oropharynx, larynx, hypopharynx, nasopharynx (n=13 patients) and oral cavity (n=17). Dosage ranged from 30Gy to 52Gy (median: 50Gy) at 2Gy daily fractions delivered five times weekly.
Outcomes	Overall survival (OS) disease-specific survival (DSS) regional (neck) control, mucosal control and distant failure. Adverse events.
inclusion exclusion criteria	**Inclusion criteria:** Patients with cervical lymph node metastasis, no primary site detected by clinical, instrumental or surgical investigation and treated with curative intent. **Exclusion criteria:** None stated
Results	**Overall survival:** 2 year OS rate: 71.7% (95%CI: 62.2-81.1%) 5 year OS rate: 59.9% (95%CI: 49.1-70.5%) **Disease-specific survival:** 2 year DSS rate: 73.6% (95%CI: 64.3-82.9%) 5 year DSS rate: 62.8% (95%CI: 51.9-73.7%) Prognostic factors: By univariate analysis, nodal level involvement, presence of ECE and nodal stage significantly affected the rate of DSS. Multivariate analysis showed that involvement of levels IV and V (P=0.001) and the presence of ECE (P=0.001) were negatively associated with DSS. Irradiation dose was not associated with DSS. **Neck control:** Neck control: 80% 5 year rate of neck control: 68.8% (95%CI: 58.9-78.7%) Prognostic factors: By univariate analysis, age, nodal level involvement, presence of macroscopic ECE and nodal stage significantly affected the rate of neck control. By multivariate analysis, the neck control rate was negatively associated with involvement of levels IV and V (P=0.006) but radiotherapy (RT) dose and regional control were not associated. **Mucosal control:** Primary tumours were detected in 13 patients between 3 and 75 months after treatment: upper aerodigestive tract (n=8) lung (n=4) and oesophagus (n=1). **Distant failure:** 5 year distant failure rate: 19.1% (95%CI: 9.4-28.9%) Prognostic factors: By univariate analysis, involvement of nodal levels IV and V (P<0.001) presence of ECE (P=0.007) and tumour stages 3 and 4 (P=0.002) significantly affected the rate of distant failure. Multivariate analysis showed that involvement of nodal levels IV and V (P=0.010) and the presence of ECE (P=0.013) were positively associated with distant failure. Irradiation dose was not associated with distant failure. **Adverse events:** No patients experienced severe post-operative complications. Following irradiation, 5 patients had grade 3 mucositis and 4 patients had dermatitis. One patient had grade 4 mucositis. Late side effects included ? grade 2 xerostomia (n=47) and subcutaneous fibrosis (n=39).
Follow-up	Patients received loco-regional examination at 2 month intervals during the 1st year, at 3 month intervals during the 2nd year, 4 month intervals between the 3rd and 5th years every 6 months thereafter. Median follow-up was 72 months (range: 15-149 months). At the time of analyses, 50/90 patients were alive (hence median values for survival outcomes were not achieved). Thirty-two patients (35.6%) had died from their primary disease

Notes	This study describes a non-comparative, retrospective case file review of 90 patients treated for cervical lymph node metastases between 1990 and 2002 at one Italian regional hospital. Thirteen patients were subsequently shown to have upper aerodigestive tract (n=8) lung (n=4) or oesophagus (n=1) primaries. Data were analysed by the Kaplan Meier method, log rank test, univariate and multivariate (Cox's proportional hazard ratio). Prognostic factors affecting the treatment outcomes were examined e.g. age, gender, nodal stage and level, presence of ECE

Colletier-1998

Methods	Retrospective observational study
Participants and Country	N=136 including 103 males. Median age: 59 years (range: 25 to 83 years). Patients had single nodal involvement (n=102) or multiple nodes (n=34). Nodal staging was: Nx = 10, N1 = 31, N2a = 49, N2b = 25, N2c = 3, N3 = 18, ECE = 87. **Country:** United States of America
Interventions	Radiotherapy (RT) was given a median period of 30 days (range: 13-188 days) after excisional biopsy (n=39), modified neck dissection (n=64) or radical dissection (n=33). Dosage ranged from 34Gy to 70Gy (median: 63Gy) at 2Gy daily fractions delivered five times weekly. Areas irradiated included nasopharynx, (n=91) nasopharynx and oropharynx only (n=21) oropharynx and hypopharynx (n=3) oropharynx only (n=1) oral cavity and oropharynx (n=2) and oral cavity only (n=2). In all patients both sides of the neck were irradiated, including supraclavicular nodes and mucosal.
Outcomes	Overall survival (OS) disease-specific survival (DSS) regional (neckl) control, mucosal control and distant failure. Adverse events
inclusion exclusion criteria	**Inclusion criteria:** Patients with squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary source. **Exclusion criteria:** Patients with disease limited to the supraclavicular fossae.
Results	**Overall survival:** 2 year OS rate: 75% (no 95%CI given) 5 year OS rate: 60% (no 95%CI given) 10 year OS rate: 41% (no 95%CI given) **Disease-specific survival:** 2 year DSS rate: 82% (no 95%CI given) 5 year DSS rate: 74% (no 95%CI given) 10 year DSS rate: 68% (no 95%CI given) 5 year DSS rate for patients with a single node: 58% (no 95%CI given) 5 year DSS rate for patients with multiple nodes: 85% (no 95%CI given) 5 year DSS rate for patients who had radical neck dissection: 61% (no 95%CI given) Prognostic factors: By univariate analysis, number of nodes (single vs multiple) nodal stage, type of surgery, presence of ECE and level of the most inferior node (low jugular vs the rest) were tested as potential prognostic factors. Multivariate analysis showed that disease-specific survival was negatively associated with having multiple nodes (P<0.001). **Neck control:** Neck control: 91% 5 year rate of neck control for patients with ECE: 84% (no 95%CI given) 5 year rate of neck control for patients without ECE: 100% (no 95%CI given) 5 year rate of neck control for patients with a single node: 96% (no 95%CI given)

	5 year rate of neck control for patients with multiple nodes: 86% (no 95%CI given) Prognostic factors: There was no clear association between nodal location and regional failure. Disease recurrence occurred in 6/33 patients who had received a radical neck dissection. Radiation dose, duration of RT and time intervals between surgery and RT were not associated with regional recurrence. The type of surgery in patients with ECE was not associated with neck failure but the rate of relapse was significantly higher for patients with multiple nodes and ECE than those patients with a single node and ECE (22% vs 9% P=0.02) **Mucosal control:** 5 year mucosal failure rate: 8% (no 95%CI given) 10 year mucosal failure rate: 14% (no 95%CI given) Primary tumours were detected in 14 patients, 5 of them occurring within 2 years of follow-up, 4 patients between years 2 and 5 and 5 patients after more than 5 years after treatment: oral cavity (n=6) hypopharynx (n=3) nasopharynx (n=2) oropharynx (n=1) and both nasopharynx and oropharynx together (n=1). **Distant failure:** 2 year distant failure rate: 12% (no 95%CI given) 5 year distant failure rate: 15% (no 95%CI given) 5 year distant failure rate for patients who had radical neck dissection: 19% (no 95%CI given) Prognostic factors: By univariate analysis, number of nodes (single vs multiple) nodal stage, type of surgery, presence of ECE and level of the most inferior node (low jugular vs the rest) were tested as potential prognostic factors. Multivariate analysis showed that the number of nodes was associated with a high distant failure rate. **Adverse events:** The majority of patients (no number given) who had been irradiated to the pharynx, experienced xerostomia. Ten patients had mild to moderate arytenoid oedema, 9 reported persistent dysphagia and 4 patients (3 having had radical neck dissection) developed aspiration problems from which 1 subsequently died. Three patients required HRT for hypothyroidism.
Follow-up	Median follow-up was 58 months (range: 3-267 months). At the time of last contact, 58/136 patients were alive and had a median duration of follow-up of 8.7 years. Thirty-two patients (35.6%) had died from their primary disease
Notes	This study describes a non-comparative, retrospective case file review of 103 patients treated for cervical lymph node metastases between July 1968 and December 1992 at one American cancer centre. Although some patients received radical neck dissection, not all outcomes are separately reported for this sub-group. Data were analysed by the Kaplan Meier method, log rank test, univariate and multivariate (Cox's proportional hazard ratio). Prognostic factors affecting the treatment outcomes were examined e.g. N stage, and level, presence of ECE etc

Coster-1992

Methods	Retrospective case series
Participants and Country	24 patients. Pathological lymph node stage: N1 58%, N2 38%, N3 4%, . Extracapsular extension, 25%; **Country:** USA
Interventions	Surgery: curative resection of all gross disease by neck dissection (N=23) or excisional biopsy (N=1).
Outcomes	Overall survival, disease specific survival, disease control in the neck, emergence of primary tumour
inclusion exclusion criteria	**Inclusion criteria:** patients entered in the Mayo Clinic tumour registry between 1965 and 1987, metastatic SCC involving cervical lymph nodes from unknown primary, unilateral disease, treatment with curative-intent surgery alone, **Exclusion criteria:** supraclavicular adenopathy, treatment with radiotherapy
Results	**5 year overall survival:** 66% **5 year disease specific survival:** 74%

	5 year disease control in the neck: 70% (read from graph) **Complications:** not reported
Follow-up	All patients were follow up until death or for a median of 8.5 years in the surviving patients.
Notes	

Davidson-1994

Methods	Retrospective observational study.
Participants and Country	N=115 including 103 males. Median age: 60 years (range: 27 to 82 years). Of 115 patients, 73 had a histological diagnosis of squamous cell carcinoma for which data is presented. Sixteen patients had a history of prior malignancy. Nodal staging was: N1 = 21, N2a = 18, N2b = 9, N2c = 3, N3 = 22. **Country:** United States of America
Interventions	After exploratory investigations, 65/73 patients received surgery. 11 patients had no further treatment after surgery: supraomohyoid neck dissection (n=2) radical neck dissection (n=8) extended neck dissection (n=1). 5 patients had pre-operative RT: radical neck dissection (n=4) extended neck dissection (n=1). 49 patients had post-operative RT: excision (n=3) parotidectomy (n=1) modified neck dissection (n=7) radical neck dissection (n=27) extended neck dissection (n=11). The post-operative RT group received a mean total dose of 5,969cGy.
Outcomes	Overall survival (OS) disease-specific survival (DSS) regional (neck) control, mucosal control and distant failure.
inclusion exclusion criteria	**Inclusion criteria:** Patients who had a neck dissection or excisional node biopsy for metastatic carcinoma of occult origin (primary unknown at the time of surgery). **Exclusion criteria:** Patients with lymphoma.
Results	**Overall survival:** 5 year OS rate: 45% (no 95%CI given) **Disease-specific survival:** 5 year DSS rate: 60% (no 95%CI given) Prognostic factors: Cumulative survival was significantly lower for patients with N3 disease (P=0.011) compared with other stages. Multivariate analyses showed that complete resection of the neck was the one factor that correlated with both overall and disease-specific survival. For these patients, significant predictors of poorer survival were higher clinical N status, treatment failure, development of a primary and the presence of multiple nodes (? N2b). **Neck control:** Neck control: 54/73 patients 74% 5 year rate of neck control for patients with N1 disease: 82% (no 95%CI given) 5 year rate of neck control for patients with N2 disease: 70% (no 95%CI given) 5 year rate of neck control for patients with N3 disease: 58% (no 95%CI given) Prognostic factors: In multivariate analyses, the only significant prognostic predictor of failure in the control of neck disease was the presence of ECE (P=0.032). Of the remainder of patients with local disease recurrence, 14/73 developed a primary lesion, disease in the contralateral neck or distant metastases. For these people, disease control was poor.

	Mucosal control: Primary tumours were detected in 9 patients, occurring between 2 and 77months after treatment., 6 presenting within 2 years, 8 within 5 years: base of tongue (n=4) pyriform sinus (n=2) supraglottic larynx (n=1) nasopharynx (n=1) and lung (n=1). Primary tumours were apparent in 4/11 patients who had not received RT compared with 5/54 who had. **Distant failure:** Distant failure rate in patients with controlled neck disease: 17% (no 95%CI given). Distant failure rate in patients without neck failure: 32% (no 95%CI given)
Follow-up	No specific details given but assumed to be ~5 years.
Notes	This study describes a non-comparative, retrospective review of 115 patients treated for cervical lymph node metastases at a single American cancer centre using data from operative records from 1977 to 1983 and records from a service database between 1984 and 1990. Not all patients in this series had radical neck dissection (n=39) and of those who did, 4 had RT before surgery. The population of interest is, therefore, 8 patients who had surgery only and 27 patients who had post-operative surgery but data is not separately presented for this sub-group. Data were analysed by the Kaplan Meier method, log rank test, univariate and multivariate (Cox's proportional hazard ratio). Prognostic factors affecting the treatment outcomes were examined e.g. patient age, gender and history, N status, affected node level, single vs multimodal disease and presence or otherwise of ECE and all outcome variables. The authors noted the comparatively higher proportion of patients who, having received surgery only, developed a primary cancer compared with patients who had received combined therapy but that the latter did not necessarily result in improved survival.

Fernandez-1998

Methods	Retrospective observational study
Participants and Country	N=67 including 66 males. Median age: 58 years (range: 36 to 81 years). Almost all patients were heavy smokers and had a history of alcohol abuse. Nodal staging was: N1 = 67%, N2 = 49%, N3 = 37%. Eighteen patient had unilateral multiple affected nodes, 45 patients had unilateral single nodes and 4 had bilateral nodal involvement. **Country:** Spain
Interventions	Of 67 patients, 3 received no surgery but the majority (77.6%) of the remainder had RT following surgery: classical radical neck dissection (77.9%) or functional neck dissection (22.1%). RT was delivered to the upper part of the neck to include the nasopharynx, oropharynx and hypopharynx. The minimum dose was 50Gy in 2Gy fractions.
Outcomes	Overall survival (OS) regional (neck) control, mucosal control and distant failure. Prognostic predictors of post-treatment survival.
inclusion exclusion criteria	**Inclusion criteria:** Patients with squamous cell carcinoma of the neck lymph nodes from an unknown primary lesion. **Exclusion criteria:** Patients who had a clinical history of prior malignancy or in whom a primary lesion was discovered on initial examination or within a six month period after surgery.
Results	**Overall survival:** 5 year OS rate: 22% (no 95%CI given) 5 year OS rate for N1 disease: 59% (no 95%CI given) 5 year OS rate for N2 disease: 35% (no 95%CI given) 5 year OS rate for N3 disease: 4% (no 95%CI given) 5 year OS rate for patients in whom a primary tumour appeared: 13% (no 95%CI given) 5 year OS rate for patients in whom a primary tumour did not appear: 31% (no 95%CI given) 10 year OS rate: 20% (no 95%CI given)

	There was a significant difference in survival rate between N stages of disease (P=0.0004). Multivariate analyses showed that neck stage was the most important, significant prognostic factor of survival (P=0.0001) but neither the appearance of a primary lesion, metastases or degree of differentiation were significant. **Neck control:** Neck control: 66% Disease recurrence occurred within a mean period of 5 months (range: 2 to 68 months) and 91% of cases were ipsilateral. **Mucosal control:** Primary tumours were detected in 19 patients, two primaries were found in 1 patient within 1 month. Other cases comprised: oropharynx (21%) lung (32%) skin and larynx (16%) and in 5% each in nasopharynx, hypopharynx and parotid. Mean time for appearance of a primary tumour was 21 months. **Distant failure:** Distant failure rate: 22% (no 95%CI given) The lung, brain, bone and then digestive tract were the most common sites of disease and distant metastases developed after a mean time of 17 months (range: 6 to 26 months).
Follow-up	Mean follow-up was for 49 months (range: 7 to 176 months). At the time of last examination, 22 patients remained alive with no evidence of disease, 21 patients had died of neck disease recurrence, 5 had died from a primary cancer, 15 from distant metastases and 4 patients had died from unrelated causes.
Notes	This study describes a non-comparative, retrospective case file review of 67 patients treated for cervical lymph node metastases between 1976 and 1996 at one Spanish hospital. The main purpose of the study was to determine prognostic predictors of post-treatment survival for which multivariate (Cox's proportional hazard ratio) was used. Authors identified presenting neck stage as the most significant predictor of survival but observe that in this patient group, the appearance of a primary lesion did not statistically significantly affect survival rates

Grau-2000

Methods	Retrospective observational study
Participants and Country	277 patients. Nodal stage was N1, N2 and N3 in 17%, 48% and 34% of cases respectively. **Country:** Denmark
Interventions	Surgery alone (radical neck dissection, N=23), RT alone (N=213) or RT plus surgery (either radical neck dissection or lymph node excision, N=26). RT to neck only: median dose 59 Gy (range 28 to 93 Gy). RT to neck and mucosa: median dose 66 Gy (range 20 to 70 Gy). 2 Gy per fraction and 5 fractions per week.
Outcomes	Overall survival, disease specific survival, neck control, mucosal control in the head and neck region, loco-regional tumour control and emergence of the primary tumour.
inclusion exclusion criteria	**Inclusion criteria:** Metastatic squamous cell or undifferentiated carcinoma in cervical lymph nodes from an unknown primary tumour, seen between 1975 and 1995 at any of five institutions, entered into a common database. **Exclusion criteria:** None reported.
Results	5 year overall survival: 65% vs 37% vs 28% (surgery alone vs. RT alone vs. surgery plus RT; P=0.04) 5 year disease specific survival: 76% vs 45% vs 49% (surgery alone vs. RT alone vs. surgery plus RT; P=0.0025) 5 year neck control: 58% vs 50% vs 49% (surgery alone vs. RT alone vs. surgery plus RT; P>0.05)
Follow-up	At least 5 years.
Notes	The "surgery only" group contained a greater proportion of N1 patients (39%) than the other treatment groups (<20%). 15 patients with isolated supraclavicular lymph node metastases were included.

Iganej-2002

Methods	Retrospective observational study
Participants and Country	N=106 including 82 males. Median age: 58 years (mean: 57.3 years). 93% of patients had a smoking history. Nodal staging was: N1 = 14, N2a = 27, N2b = 39, N2c = 2, N3 = 24. **Country:** United States of America
Interventions	This group received various treatment regimens: Excisional biopsy only (n=12), Excisional biopsy then RT (n=15), Radical neck dissection (n=29), RT alone (n=24), Radical neck dissection then RT (n=26) Patients treated with excisional biopsy alone had generally refused further treatment or were too unwell to receive aggressive therapy and patients receiving RT alone usually had inoperable disease. The median dose of RT was 66Gy (range: 48 to 70Gy) for those patients who had no further treatment and 60Gy (range: 50 to 70Gy) for those who had received prior surgery. Treatment areas encompassed the nasopharynx, oropharynx, larynx and hypopharynx.
Outcomes	Overall survival (OS) disease specific survival (DSS) regional (neck) control, mucosal control and distant failure. Prognostic predictors of post-treatment survival.
inclusion exclusion criteria	**Inclusion criteria:** Patients presenting with ipsilateral (n=104) or bilateral adenopathy with a diagnosis of cancer of unknown primary. **Exclusion criteria:** Patients with distant metastases at time of diagnosis, primary site discovered during work-up, non-squamous histology, inadequate documentation, requirement for palliation only or comorbidity.
Results	**Overall survival:** 5 year OS rate: 53% (no 95%CI given) **Disease-specific survival:** 5 year DSS rate: no data given but, from graph, appears to be ~64% Prognostic factors: Neck stage at presentation (N1 or N2a vs ?N2b) (P=0.0009) and the presence or absence of ECE (P=0.017). The appearance of a primary tumour did not significantly affect either outcome. **Neck control:** Neck control in all patients: 66% Neck control in patients receiving any single treatment regimen only: 59% Neck control in patients receiving combined treatment: 80% (P = 0.02) Prognostic factors: No statistically significant prognostic factors were identified. Tumour control above the clavicle was better for patients having received a combined treatment modality than for those on any single therapy but the difference was non-significant once the sub-group of patients treated with RT only were removed from the analysis. The volume of RT was not a prognostic factor of local control. **Mucosal control:** Primary tumours were detected in 19 patients: tonsil (n=6) base of tongue (n=4) pyriform sinus (n=4) supraglottis (n=3) and nasopharynx (n=2). All lesions were ipsilateral to initial presentation. Patients who received RT (including 39 patients who did not have radical neck dissection) had a significantly lower rate of primary lesion appearance (9%) compared with patients who did not receive RT as a component of their therapy (32%) (P=0.006). **Distant failure:** Distant metastases were identified in 10 patients after a median time after treatment of 4 months. The most common sites of metastasis were in the lung, followed by bone. All but one patient had initially presented with nodal stage ?N2b. **Adverse events:**

	All patients who had been irradiated experienced varying degrees of acute mucositis (43% grade 3/4 by RTOG criteria) and xerostomia (61% grade 1/2 by RTOG criteria). More patients having receiving combined therapy (radical neck dissection then RT) experienced severe late neck fibrosis (27%) compared with patients having received a single treatment modality (4%) (P<0.05).
Follow-up	Two patients were lost to follow-up after 36 and 40 months but neither had signs of disease. Minimum follow-up for the remainder of patients was 5 years or until patients had died. Median follow-up for surviving patients was 82 months and for all patients, 56 months. Authors reported that 57 patients had disease recurrence, most commonly in the ipsilateral neck, with a median interval of 7 months. Median time to a potential primary lesion was 20 months
Notes	This study describes a comparative, retrospective case file review of 106 patients treated for cervical lymph node metastases between January 1969 and December 1994 by one American medical group. Not all patients in this series had radical neck dissection and the population of interest, therefore, comprises 55 patients but data is not separately presented for this sub-group. Data were analysed by the Kaplan Meier method, univariate and multivariate (Cox's proportional hazard ratio). Prognostic factors affecting the treatment outcomes were examined but not always reported. There are few comparative statistics given in this paper. Authors commented that despite the fact that the rate of neck and mucosal failure was lower in patients receiving surgery and RT, no advantage in overall survival was demonstrated and that in those presenting with stage N1 and N2a disease, the associated morbidity of the combined modality may not be matched by a survival advantage

Issing-2003

Methods	Retrospective observational study.
Participants and Country	**Country:** Germany
Interventions	This group received various treatment regimens including: Radical neck dissection only (n=64) Radical neck dissection with bilateral tonsillectomy (n=26) Radical neck dissection with parotidectomy (n=10) Functional supraomohyoidal neck dissection (n=16) Radical modified neck dissection (n=1) Other treatments (radiotherapy, chemotherapy or both) (n=44) No treatment documented (n=6) For the purpose of survival data analyses, patients were divided into groups based on their entire treatment plan: Plan 1: neck dissection followed by radiotherapy (n=92) Plan 2: neck dissection and tonsillectomy followed by radiotherapy (n=26) Plan 3: radiotherapy only (n=28) Radiotherapy was given four to eight times per week with a single dose of between 2Gy to 3Gy with a total effective dose of between 54Gy to 70Gy. Both sides of the neck were treated and also the parotid region, if indicated.
Outcomes	Overall survival (OS) regional (neck) control and mucosal control. Prognostic predictors of post-treatment survival
inclusion exclusion criteria	**Inclusion criteria:** Patients with cervical metastases of unknown origin and in whom a primary tumour had not been identified after diagnostic work-up. **Exclusion criteria:** None stated
Results	**Overall survival:**

	3 year OS rate for all (n=167) patients: 49.2% (no 95%CI given) 5 year OS rate for all (n=167) patients: 42.7% (no 95%CI given) 10 year OS rate for all (n=167) patients: 30.6% (no 95%CI given) 3 year OS rate for N1 disease: 60.6% (no 95%CI given) 5 year OS rate for N1 disease: 47.7% (no 95%CI given) 3 year OS rate for N2 disease: 27.2% (no 95%CI given) 5 year OS rate for N2 disease: 20% (no 95%CI given) 3 year OS rate for N3 disease: 20% (no 95%CI given) 5 year OS rate for N3 disease: 15% (no 95%CI given) Prognostic factors: overall survival was significantly lower in patients who developed a known primary site compared with patients whose primary did not become apparent (P=0.004). There was no significant difference in survival rates of males compared with females. The level of nodal metastases was a significant predictor of a higher overall survival rate (II or II vs IV) (P=0.005). Nodal stage was a significant predictor of higher 3yr and 5yr survival rates (N1 vs N2 or N3) (P<0.05). There was no significant difference in survival rates between patients who experienced neck recurrence and those who did not. Patients treated by Plan 1 did not have a significantly better survival rate than those on Plan 3 but there were significant differences in survival rates between Plan 1 and Plan 2 (P=0.005) and between Plan 2 and Plan 3 (P=0.045). The authors concluded from their data that patients having been treated with a neck dissection with tonsillectomy and then RT (Plan 2) had better outcomes than patients having a neck dissection and RT or patients having RT only. **Neck control:** Neck control in all patients during 10 years of follow-up: 73.6%% **Mucosal control:** Primary tumours were detected in 36 patients between 6 to 32 months after treatment: floor of mouth (n=1) nasopharynx (n=4) oropharynx (n=13) hypopharynx (n=8) larynx (n=4) parotid gland (n=2) ear (n=1) and lung (n=2). A second primary was diagnosed in 8 patients, all occurring in different sites and having different histology from the first primary and from cervical metastases.
Follow-up	Patients were followed up for a maximum period of 10 years and examinations were performed monthly for the 1st year, two-monthly for the 2nd year, three-monthly for the 3rd year and every six months thereafter. It would appear that no patients were lost to follow-up.
Notes	This study describes a comparative retrospective case file review of 167 patients treated for cervical lymph node metastases between 1979 and 1998 by one German otorhinolaryngology clinic. Data were analysed by the Kaplan Meier method, univariate and multivariate (Cox's proportional hazard ratio). Prognostic factors affecting the treatment outcomes were reported. The authors advocated the use of radical neck dissection and a 'diagnostic' bilateral tonsillectomy followed by post-operative RT.

McMahon-2000

Methods	Retrospective observational study
Participants and Country	N=38 including 28 males. Median age: 67 years (range: 45 to 84 years, mean: 55.1 years). Levels of nodal metastases were: I = 8, II = 32, III = 22, IV = 6, V = 1. Nodal staging was: N1 = 6, N2a = 10, N2b = 6, N2c = 3, N3 = 13. **Country:** Australia
Interventions	Patients fell into three treatment groups: Neck dissection then RT (n=32) Neck dissection only (n=3). In 2 people, RT was inappropriate, 1 patient failed to attend.

	Pre-operative RT then radical neck dissection (n=2) Not treated with curative intent (n=1) The RT dose varied throughout the program being initially 50Gy in 25 fractions and then, more recently, 54Gy to 60Gy
Outcomes	Overall survival (OS) disease specific survival (DSS) regional (ipsilateral & contralateral neck) control and mucosal control. Prognostic predictors of post-treatment survival.
inclusion exclusion criteria	**Inclusion criteria:** Patients with metastatic squamous cell carcinoma from an occult primary site. **Exclusion criteria:** None stated
Results	**Overall survival:** 4 year OS rate: 49% (no 95%CI given) **Disease specific survival:** 4 year DSS rate: 63% (no 95%CI given) Prognostic factors: Nodal stage was a significant predictor of survival rates where N3 had a poorer prognosis (N3 vs N1 + N2) (P=0.02) although neither N3 vs N1 nor N3 vs N2 were statistically significant. **Mucosal control:** Primary tumours were detected in 5 patients between 6 to 18 months after treatment: supraglottic larynx & contralateral neck (n=2) anterior tonsillar pillar (n=1) tongue base & contralateral neck (n=1), tongue base (n=1). At last follow-up, 2 patients had died of their disease, 1 was alive with disease and 2 had no evidence of disease. The initial treatment of these patients had been surgery and comprehensive (n=1) or hemi-neck (n=4) RT. **Neck control with or without distant metastases:** Four patients experienced disease recurrence in the ipsilateral neck and 6 patients in the contralateral neck. In addition, 4/10 of these patients had distant metastases. At last follow-up, 4 patients had died form their disease, 3 were alive with disease and 3 patients had no evidence of disease. The initial treatment of this group had been surgery (radical neck dissection (n=9) or extended radical neck dissection (n=1)) and comprehensive (n=1) or hemi-neck (n=7) RT. The most significant predictor of treatment failure was the finding of a positive resection margin. **Distant failure:** Two patients died of distant metastases of which there were no further details.
Follow-up	**Follow-up:** Median follow-up for patients alive at last contact was 2.7 years (range: 0.9 to 6.7 years)
Notes	This study describes a retrospective case file review of 38 patients treated for cervical lymph node metastases between 1987 and 1998 by one Australian head and neck surgical department. Data were analysed by the Kaplan Meier method, univariate and multivariate (Cox's proportional hazard ratio). Prognostic factors affecting the treatment outcomes were reported. The authors do not advocate a particular treatment regimen from their results but offer their opinion that initial treatment directed at the involved neck alone may give a comparable outcome to using irradiation of the contralateral neck and all mucosal sites, allowing for the possibility of increased acute and late onset associated morbidity.

Mistry-2008

Methods	Retrospective observational study.
Participants and Country	N=89 including 78 males. Median age: 55 years (range: 28 to 84 years). Levels of nodal metastases were: I = 9, II = 67, III = 46, IV = 12, V = 1. Nodal staging was: N1 = 10, N2a = 25, N2b = 20, N2c = 31, Nx = 3 **Country:** India

Interventions	All patients underwent neck dissection and were advised to have a course of RT which 10 patients refused and 9 patients failed to complete. Therefore, for these patients the dose of RT ranged between 0Gy to 40Gy. The remaining patients received ?40Gy.
Outcomes	Overall survival (OS) disease specific survival (DSS) regional (ipsilateral & contralateral neck) control and mucosal control.
inclusion exclusion criteria	**Inclusion criteria:** Patients with metastatic squamous cell carcinoma from an occult primary site. **Exclusion criteria:** Patients who had received palliative RT because of advanced or comorbid disease. Those with histology other than squamous cell carcinoma or those with metastatic disease at presentation
Results	**Overall survival:** 5 year OS rate for all patients: 55% (no 95%CI given) 8 year OS rate for all patients: 51% (no 95%CI given) Median OS: 98 months Prognostic factors: extra nodal spread and neck stage at presentation were not significant predictors of survival. Postoperative RT, prior open biopsy of the neck or involvement of nodes at multiple nodes similarly had no impact on survival. **Neck control and/or distant metastases:** 29/89 patients experienced disease relapse, 19 with disease in the neck, 9 patients with distant metastases and 1 patient with both. Of those who had received RT ?40Gy, 15/60 patients experienced neck relapse compared with 4/19 patients who had received <40Gy but the difference between these groups was not significant. **Mucosal control:** A primary lesion was detected in 13 patients of which, 11 had received RT ?40Gy. Mean time to detection was 24 months. Primary lesions were located in: oropharynx (n=6) pyriform sinus (n=2) larynx (n=2) lung (n=2) or oral cavity (n=1). All but 3 of these patients died of their disease.
Follow-up	At the time of last review, 51 patients were alive. Ten patients had died from disease recurrence, 10 died from a primary lesion and 9 from metastatic disease. In 8 patients, cause of death was unknown.
Notes	This study describes a retrospective case file review of 89 patients treated for cervical lymph node metastases between 1989 and 1994 by one Indian hospital. Data were analysed by the Kaplan Meier method and compared with log rank testing although data reporting was limited. The authors offered the opinion that, with combined surgery and RT, these patients have survival comparable with patients with known primary lesions.

Patel-2007

Methods	Retrospective observational study
Participants and Country	N=70 including 57 males. Median age: 62 years (range: 38 to 86 years). Levels of nodal metastases were: I = 25%, II = 53%, III = 36%, IV = 26%, V = 16%. Nodal staging was: N1 = 5, N2a = 13, N2b = 30, N2c = 4, N3 = 18, ECE = 37%. **Country:** Australia
Interventions	Patients fell into three treatment groups: Unilateral neck dissection (n=64), Bilateral synchronous neck dissection (n=6) All patients then received RT: Irradiation to the dissected neck only (n=49), Comprehensive irradiation to both sides of the neck and potential mucosal sites (n=11), No irradiation (n=10). RT not recommended for 2 patients, declined by 4 patients, 2 patients died before commencement and 2 patients had incomplete records. Early in the study, patients received RT at the dose of 50GY in 2.5Gy fractions but later the total doses were between 54Gy and 60Gy
Outcomes	Overall survival (OS) disease specific survival (DSS) regional (ipsilateral & contralateral neck) control, mucosal control and distant metastases. Adverse events.

inclusion exclusion criteria	**Inclusion criteria:** Patients with metastatic squamous cell carcinoma from an occult primary site. **Exclusion criteria:** None stated
Results	**Overall survival:** 5 year OS rate for all patients: 56% (no 95%CI given) **Disease-specific survival:** 5 year DSS rate for all patients: 62% (no 95%CI given) **Neck control:** 5 year DSS rate for patients with ipsilateral recurrence: 84% (no 95%CI given) 5 year DSS rate for patients with contralateral recurrence: 93% (no 95%CI given) Local recurrence was experienced by 14 patients in a median time after treatment of 9 months (range: 2 to 63 months). All but one of these patients had demonstrated extracapsular spread (ECS). Ipsilateral failure occurred in 9 patients and contralateral failure in the remaining 5 patients. Risk of neck failure with N2 or N3 disease and ECS was 35%. This group had all received post-operative RT. Having N2 or N3 nodal disease and/or ECS was a significant predictor of poorer survival (P<0.001). **Mucosal control:** A primary lesion was detected in 8 patients after a median interval of 18 months (range: 5 to 36 months). Two of these patients had refused RT. Sites of recurrence were: base of tongue (n=4) larynx (n=2) oral tongue (n=2). In this group, 3 patients have died of their disease at a median of 44 months (range: 25 to 75 months) after salvage treatment. **Distant failure:** Recurrence at distant sites was experienced by 5 patients within a median time after treatment of 9 months (range: 3 to 12 months). Four of these patients subsequently died **Adverse events:** Treatment complications were experienced by 12/70 patients: RT caused varying grades of acute mucositis and xerostomia in all patients and 1 patient had laryngeal necrosis requiring total laryngectomy 47 months after RT. No patients died from RT complications.
Follow-up	The median follow-up for those patients alive at the end of the study was 45 months (range: 2 to 158 months) with reviews at 6-week intervals.
Notes	This study describes a retrospective case file review of 70 patients treated for cervical lymph node metastases between 1987 and 2006 by one Australian head and neck cancer institute. Data were analysed by the Kaplan Meier method, univariate and multivariate (Cox's proportional hazard ratio). Prognostic factors affecting the treatment outcomes were reported. Treatment failure, including all sites, was 27/70 patients (39%) of which 5 patients remained disease-free following salvage treatment. The authors conclude that comprehensive RT was not supported by their data since contralateral neck failure rates were low. The maintained, however, that more aggressive therapy should be offered to those patients with N2 or N3 disease and, in particular, those with ECS.

Reddy-1997

Methods	Retrospective observational study
Participants and Country	**Country:** USA
Interventions	Bilateral neck and mucosa RT (N=36), 20 of these patients had lymph node dissection Ipsiplateral neck RT (N=16) with an electron beam: The dose to the ipsilateral neck ranged from 60 to 76 Gy; the dose to the contralateral neck was 46 to 50 Gy.

Outcomes	Control of ipsilateral and contralateral neck metastases, emergence of the occult primary, overall survival, disease free survival, weight loss and complications, distant metastases and secondary cancer.
inclusion exclusion criteria	**Inclusion criteria:** Patients with metastatic SCC to the cervical lymph nodes of unknown primary treated with RT between 1974 and 1989 at a single institution. **Exclusion criteria:** supraclavicular metastases only, incurable disease, death during treatment from non-cancer causes, non SCC histology.
Results	5 year overall survival, for all patients, was 40% 5 year disease free survival, for all patients, was 51% 5 year disease free survival, for patients who received lymph node dissection plus RT, was 61%. Acute complications: All patients in the bilateral RT group had mucositis and dry desquamation of the skin. 56% of patients in the unilateral RT group had ipsilateral mucositis and moist desquamation of the skin. Late complications: severe xerostomia 31% in the bilateral RT group, none in the unilateral group. severe neck fibrosis 19% in the bilateral RT group, 3% in the unilateral group.
Follow-up	
Notes	

Shehadeh-2006

Methods	Retrospective observational study
Participants and Country	37 patients. **Country:** USA
Interventions	Most patients had modified comprehensive neck dissection and 7 had a radical neck dissection. Bilateral dissection 5/37, right 22/37 and left 9/37. Chemotherapy was cisplatin ar 100 mg/m2 I.V. given concurrently with radiotherapy every three weeks to a total of 3 cycles. Some patients were switched to carboplatin following renal dysfunction. Radiotherapy was 60 to 64 Gy, treatment volume encompassed potential primary sites and the neck. Given in 2 Gy fractions in 5 fractions per week.
Outcomes	Overall survival, recurrence-free survival, regional recurrence-free survival, and distant recurrence free survival. Treatment toxicity (grade III or IV.
inclusion exclusion criteria	**Inclusion criteria:** Squamous cell CUP of the cervical lymph nodes, diagnosed between 1995 and 2002. **Exclusion criteria:** Less than 12 months of follow up
Results	See Table 1 of evidence summary
Follow-up	The median follow up of surviving patients was 3.9 years.
Notes	

Spiro-1983

Methods	Retrospective observational study
Participants and Country	N=79 including 50 males. Median age: 61 years (range: 20 to 84 years). Levels of nodal metastases were: I = 11, II = 42, III = 22, IV = 14, V = 6. Nodal staging was: N1 = 21, N2a = 24, N2b = 14, N2c = 8, N3a = 8, N3b = 6 not known = 6. Multiple affected nodules were presented in 26 patients and single nodules in the remaining 53 patients.

	Country: United States of America
Interventions	Patients fell into four treatment groups: Pre-operative RT then radical neck dissection (n=11) Radical neck dissection only (n=48). Radical neck dissection and then RT (n=3) Other treatments: chemotherapy, RT only or both combined (n=17) Where given RT was given pre-operatively at between 20Gy to 30Gy. From the authors' discussion, the normal post-operative RT dose was ~50Gy.
Outcomes	Overall survival (OS) regional (ipsilateral & contralateral neck) control, mucosal control and distant metastases. Adverse events.
inclusion exclusion criteria	**Inclusion criteria:** Patients with metastatic squamous cell carcinoma from an occult primary site. **Exclusion criteria:** None stated.
Results	**Overall survival:** 5 year OS rate for all patients: 50% (no 95%CI given) 5 year OS rate for patients initially staged as N1: 74% (no 95%CI given) 5 year OS rate for patients initially staged as N2 or N3: 41% (no 95%CI given) Prognostic factors: There was a statistically significant difference in survival rate between patients initially diagnosed with N1 disease compared with either N2 or N3 disease (P<0.002) **Neck control:** With adequate follow-up information, 37/74 patients (50%) experienced ipsilateral neck disease recurrence: 16% patients staged as N1, 39% patients staged as N2 and 86% patients staged as N3. Extension beyond the node (ECE) was recorded for 15% of N1 patients, 43% of N2 patients and 86% N3 patients. **Mucosal control:** A primary tumour was subsequently identified in 12 patients (15%) within 14 to 67 months after treatment. Lesions occurred in the hypopharynx (n=4) oesophagus (n=3) nasopharynx (n=2) lung (n=2) and tonsil (n=1). Disease was uncontrolled in 7/12 of these patients. **Distant metastases:** Distant metastases were recorded for 19 patients, stated by authors to be commonly found in lung and bone (no further details were given). **Adverse events:** Post-surgical complications were experienced by 10 patients who had wound infection (n=4) carotid haemorrhage (n=3) significant pulmonary sepsis (n=2) and post-operative MI (n=1).
Follow-up	Twelve patients were either lost to follow-up or died free of disease (or died after surgery as above). Of the remainder, 19/66 were alive and disease-free after 5 years
Notes	This study describes a retrospective case file review of 79 patients treated for cervical lymph node metastases between 1965 and 1976 by one American cancer centre. Data were analysed by the Kaplan Meier method. Data reporting was minimal and did not differentiate between patients receiving different treatment modalities. Nevertheless, the authors advocated the use of radical neck dissection followed by RT for patients with SCC with N2 and N3 disease or N1 disease and multiple node involvement or ECE.

Strojan-1998

Methods	Retrospective observational study
Participants and Country	N=56 including 50 males. Median age: 56 years (range: 33 to 81 years). Levels of nodal metastases were: I = 14, II = 39, III = 19, IV = 8, V = 9. Nodal staging was: N1 = 6, N2 = 37 and N3 = 13. **Country:** Slovenia
Interventions	All patients underwent surgery and post-operative RT. Neck dissection was performed in 48 patients and extended to neighbouring structures (parotid gland, mandible and external carotid artery) in 6 patients. The surgery was classified as: · Radical neck dissection (n=29) · Modified radical neck dissection only (n=7) · Selective neck dissection (n=6) · Extended neck dissection (n=6) These procedures were assessed to have been complete in 45 cases but, in 11 patients, residual tumour was detected in histological samples. Post-operative RT was given to 48 patients at a dose of 18 to 62Gy (median 50Gy) in 1.8 to 2Gy daily fractions applied five times weekly, although 6 patients received a lower dose of <50Gy. Five patients refused treatment and 1 patient died before receiving RT. The field of treatment depended on the level of nodal involvement and patient lifestyle i.e. history of smoking and/or drinking.
Outcomes	Overall survival (OS) disease specific survival (DSS) regional (ipsilateral & contralateral neck) control, mucosal control and distant metastases. Adverse events
inclusion exclusion criteria	**Inclusion criteria:** Patients with metastatic squamous cell carcinoma of cervical lymph nodes from an unknown primary tumour. **Exclusion criteria:** None stated.
Results	**Overall survival:** 5 year OS rate for all patients: 52% (95%CI: 38-65%) 10 year OS rate for all patients: 22% (95%CI: 5-38%) **Disease-specific survival:** 5 year DSS rate for all patients: 66% (95%CI: 52-79%) 10 year DSS rate for all patients: 52% (95%CI: 31-72%) Prognostic factors: extracapsular spread (ECS, +ve vs ?ve) and the extent of the irradiation field (unilateral neck vs neck and potential primary tumour sites) were significant predictors of a poorer 5 year DSS (P = 0.01 and P = 0.04 respectively). **Neck control:** Neck failure occurred in 10 patients, 9 of whom failed a median of 4 months after treatment (38 months for 1 patient). All but one of the patients experienced failure in the RT field, at the site of pre-existent nodal disease (n=7) and/or outside of it (n=2). Prognostic factors: neck failure was correlated significantly with the extent of the RT field (P = 0.03) since when the neck alone received RT the failure rate was 50% compared with RT of potential primary sites (12%). **Mucosal control:** A primary lesion was detected in 5 patients after a median interval of 21 months (range: 16 to 98 months). None of the primary tumours occurred below the clavicles: oropharynx (n=2) maxillary sinus (n=1) nasopharynx (n=1) larynx (n=1). After further surgical or RT treatment, these patients survived between 29 and 108 months. One patient died of unrelated causes, 3 died of disease and 1 patient had no evidence of disease at last follow-up. **Distant failure:**

	Recurrence at distant sites was experienced by 6 patients within a median time after treatment of 7 months (range: 2 to 39 months). Metastases occurred in: liver (n=3) bone (n=2) lung (n=3) and other lymph nodes (n=1). All patients had ECS and were of stages N2 (n=4) or N3 (n=2). There Prognostic factors: there were no prognostic factors for this outcome. **Adverse events:** Thirty-three patients, all of whom had received radical, or extended radical, neck dissection experienced surgical morbidity to some extent, including pain and reduced mobility. In patients irradiated by a large field technique, 27 patients reported mucositis (grade 3 in 23 patients and grade 4 in 4 patients) and 3 patients had grade 3 dermatitis. Late adverse effects included xerostomia (n=35) subcutaneous and/or muscular fibrosis (n=22) and trismus (n=2).
Follow-up	**Follow-up:** The median follow-up time was 8.6 years (range: 1.6 to 17.8 years) and 79% of patients were followed for a minimum of 5 years.
Notes	This study describes a retrospective case file review of 56 patients treated for cervical lymph node metastases with surgery and post-operative RT between 1975 and 1994 at one Slovenian university oncology institute. Data were analysed by the Kaplan Meier method, univariate and multivariate (Cox's proportional hazard ratio). Prognostic factors affecting the treatment outcomes were reported but multivariate analysis was not performed due to the low patient number. The authors concluded that the combined therapy resulted in acceptable toxicity, good local disease control and favourable survival results but that patients with a poorer prognosis may benefit from a more aggressive approach, perhaps employing the use of chemotherapy.

Wang-1990

Methods	Retrospective case series
Participants and Country	N=328. Mean age 60.5 years. **Country:** USA
Interventions	Surgery alone 36%, surgery + preoperative RT 7%, surgery + postop RT 19%, RT alone 36% and other treatment 2%
Outcomes	5 yr overall survival.
inclusion exclusion criteria	**Inclusion criteria:** Patients listed at a single institution between 1953 and 1988, with metastatic SCC to the neck and unknown primary tumour. **Exclusion criteria:** treatment elsewhere, lack of pathological confirmation, lack of follow up or primary tumour found.
Results	See table 1 of evidence summary.
Follow-up	Median follow up was 3.9 years (range <1 year to 28 years)
Notes	Probably differences in baseline characteristicsThe surgery only group contained fewer patients with N3 disease and more patients with NX disease than the other treatment groups.

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17. Optimal management for patients with confirmed CUP who present with adenocarcinoma involving axillary nodes

Last updated: 29/ 10/ 2009.

Short summary

There is no direct evidence regarding the optimal management of patients presenting with adenocarcinoma involving axillary nodes but unknown primary tumour. The best available evidence was from a small number of retrospective case series studies (Ellerbroek 1990; Kemeny 1986; Knapper 1991;Jackson 1995; Medino-Franco 2002; Merson 1992; Rosen 1990; van Ooijen 1993; Varadarajan 2007; Whillis 1990).

Much of the available evidence is based on small numbers of patients with little consistency in treatment. There was little agreement across the studies in relation to how patients presenting with adenocarcinoma in the axillary nodes but no obvious primary tumour should be treated.

Rationale

A small minority of confirmed CUP patients present with metastatic adenocarcinoma in axillary nodes - from a presumed but unidentified breast primary. The pattern of nodal involvement is very similar to that seen with primary breast cancer with locoregional spread, and these patients are often treated with localized treatment with curative intent. They may be considered to have a primary cancer which might fall under one or more of the following categories:

1. It might be treated with curative intent should it become apparent.

2. It might be eradicated by treatment directed at its likely anatomical site, either specifically or coincidentally from treatment directed principally against the metastatic disease.

3. It might never become apparent despite having no treatment directed against it.

Axillary dissection, mastectomy or breast radiotherapy ± nodal radiotherapy, ± systemic therapy has been used as treatment in this population but its effectiveness and cost-effectiveness has not been established. Certainly any treatment given with curative intent is likely to cause substantial morbidity hence investigation of the validity of this treatment approach is required.

Methods

Study types

All study types were considered for inclusion, as well as any studies which reported potentially relevant or indirect information to answer the question.

Participants

People with metastatic adenocarcinoma in axillary nodes, without an identified primary, after specific breast investigations

Interventions

Attempted curative surgery and/or radiotherapy ± cytotoxic chemotherapy/hormonal treatment. Comparison is lesser treatment.

Outcomes

Treatment outcomes including: overall survival, local control and complications.

Study selection

The information specialist (SA) selected a list of relevant studies from the literature searches. The reviewer (SOC) selected studies from this for appraisal.

Data extraction and synthesis

One reviewer (SOC) appraised each study, extracting any relevant data. Only published studies were included and study authors were not contacted.

Quality assessment

Studies quality was assessed using NICE quality checklists.

Heterogeneity assessment

There was no statistical analysis of heterogeneity.

Search results

29 possibly relevant papers were identified in literature searches, based on their title and abstract. 18 of these

were ordered for appraisal and ten of these were included as evidence.

Description of included studies

The general characteristics and conclusions of the studies are summarised in table 1. The majority of the included studies had very small numbers which meant that any meaningful statistical analysis was difficult to conduct and although survival data was reported in many cases, it is difficult to attribute the outcome directly to any specific treatment regimen.

The PICO listed attempted curative surgery and/or radiotherapy +/- cytotoxic chemotherapy/hormonal treatment to be the interventions of choice compared with lesser treatment, many of the papers reviewed however appear to be concerned with evaluating whether less treatment can be used to effectively treat patients with occult breast carcinoma and axillary node metastases (i.e. can a patient have axillary dissection followed by radiotherapy and/or chemotherapy/ hormonal therapy rather than radical surgery following axillary biopsy and/or dissection). When discussing treatment regimens, the majority of the papers do not provide details regarding the details of radiotherapy and/ or chemotherapy given to patients and it is therefore not possible to make a judgement on the most effective regimens from the information provided.

Study quality

There is very little, poor quality evidence available to address this question. All of the evidence is drawn from retrospective case series in which the numbers of cases available to be reviewed is small and often drawn from a over a long period of time and with little detail provided with regards to factors such as inclusion/exclusion criteria.

Evidence summary

There is a lack of good quality evidence available on which to base recommendations for the optimal management of patients presenting with adenocarcinoma involving axillary nodes but no obvious primary tumour. This is most likely due the rarity of this presentation as few as 0.3% of all breast cancer patients present with no obvious primary tumour (Knapper et al, 1991) and this number may be even lower as imaging techniques have improved enabling more primary tumours to be found through imaging. Indeed the rarity of this presentation is evident from the small numbers in each of the studies included in the evidence review and the protracted period of time over which researchers were required to draw their cases for inclusion. For the purposes of this evidence review, it was not possible to combine data as it was presented in any of the included studies due to inconsistencies and differences in study aims.

The use of adjuvant treatment was not associated with improvement in survival or local control (Ellerbroek *et al* 1990, Knapper *et al* 1995, Merson *et al* 1992) but studies were probably too small to draw conclusions about the use of adjvant therapy in this patient group.

There was some evidence that patients presenting with adenocarcinoma involving axillary nodes could be treated in the same way as patients with stage II patients presenting with palpable breast tumours. From one study (Rosen *et al* 1990), there was evidence of a lower frequency of recurrence and death due to disease among patients presenting with axillary metastases and occult primary tumour but a measurable invasive carcinoma demonstrated at mastectomy when compared to a matched series of stage II patients with equivalent disease extent and presenting with palpable breast tumours. Patients with occult tumours showed a more favourable prognosis overall, including when stratified by tumour size and nodal status, though the differences were not statistically significant and the authors felt that the results may reflect the fact that the majority of stage II patients with clinically occult breast carcinoma normally have a grossly measurable invasive tumour detected pathologically and as a result the actual pathological stage, which takes tumour size into consideration, determines prognosis rather than apparent clinical stage described when the patient is first examined.

From the available evidence there appears to be an association between number of nodes and nodal size and survival and local control (Ellerbroek *et al* 1990, Whillis *et al* 1990).

Appearance of Breast Primary

Ellerbroek *et al* (1990) reported a non-significant difference (p=0.06) in actuarial 5 and 10 year freedom from appearance of breast primary was 43% in patients that did not receive radiotherapy whereas in patients receiving radiotherapy 5 and 10 year actuarial freedom from appearance of breast primary was 83% and 69% respectively.

Overall survival

Ellerbroek *et al* (1990) reported 2 year, 5 year and 10 year actuarial survival for the whole group under investigation as being 85.7%, 71.8% and 65% respectively. Five year actuarial survival for patients with N1 disease was 76.8% and for N2 disease was 53.6%. Five year survival was reportedly significantly better for patients receiving axillary dissection compared with those not receiving axillary dissection (88.9% and 46.7% respectively; P=0.03) and also for patients no residual tumour compared with those with evidence of residual disease (79.9% and 20% respectively; P=0.02). There was no significant difference in 5 year survival for patients receiving chemotherapy and those not receiving chemotherapy.

Kemeny *et al* (1986) reported no significant difference in survival for patients treated with or without mastectomy (P=0.6).

In a study by Jackson *et al* (1995) all patients died with disease and the mean survival was 42 months.

Knapper *et al* (1991) reported a 5 year actuarial survival of 75% and 10 year actuarial survival of 55% overall. There was no significant difference in survival for patients in the breast preservation group or for whether breast cancer was found in the breast specimen or not. Patients with a negative oestrogen receptor had a decreased 5 and 10 year survival when compared to patients with positive receptors. Five year survival was similar whether patients were treated with chemotherapy and/or hormonal therapy or not and Kaplan Meier curves showed that 5 and 10 year survival rates were not significantly different for patients with occult breast cancer and those with a known breast primary and N1 disease. No details on the numbers of patients in each of these categories nor any p values were given for any of the survival data however.

Merson *et al* (1992) reported overall 5 and 10 year survival rates of 76.6% and 58.3% respectively. There was no statistical difference in survival times for patients treated with immediate breast surgery or radiation and patients not treated to the breast but just followed up (P=0.06). The number of metastatic nodes appeared to be related to prognosis, with better prognosis for patients with 1-3 positive nodes, but this difference was not significant (P=0.3). There was no significant difference in survival times for patients treated with or without systemic treatment (P=0.2).

Rosen *et al* (1990) reported that overall 60% (N=29) of patients remained alive and disease free when last seen or contacted. Deaths due to causes other than breast carcinoma occurred in 4% of cases and the status was unknown in 4% of cases. No significant difference in survival was observed for patients with 1-3 positive nodes when compared to patients with 4 or more positive nodes. Separate follow-up for patients that did not under go mastectomy (N=9) found that 4 patients were still alive and disease free after a median follow up period of 44 months (range: 16 to 74 months). Patients with a measurable invasive carcinoma at mastectomy (N=22) were matched with women treated for breast carcinoma on the basis of tumour size, total number of involved nodes, tumour type and age at diagnosis. Follow up revealed a lower frequency of death due to disease in patients presenting with axillary metastases and an occult primary tumour. Patients with occult lesions showed a more favourable prognosis overall, including when stratified by tumour size and nodal status though this difference was not statistically significant.

Whillis *et al* (1990) reported an 5 year actuarial of 66%, similar to that of a group of stage II breast cancer patients treated in the same department and markedly different from another group of patients treated in the same department for metastatic adenocarcinoma from unknown primary presenting with lymph node metastases.

Local Control

Ellerbroek *et al* (1990) and Whillis *et al* (1990) reported local control for the patients and both observed that clinical N stage was related to local control. Ellerbroek *et al* (1990) reported that in patients with N1 disease was 72% at 5 years and in patients with N2 disease it was only 43%. Whillis *et al* (1990) reported that overall, 85% of patients achieved local control and that of the patients with N1 disease (N=16) all achieved local control while only a single patient with N2 disease achieved local control. In this study, nodal size also appeared to be associated with local control as in the single N2 patient achieving local control the node was quite small compared the other N2 patients had disease measuring 8cm or more in diameter. Ellerbroek *et al* (1990) noted that the presence of gross residual disease prior to radiotherapy was associated with a 53% 5-year freedom from local relapse compared to 72% for those with no evidence of disease. This study also found that the use of adjuvant chemotherapy was not associated with significant improvement in local control.

Complications

Only one study (Ellerbroek *et al* (1990)) reported on complications associated with treating patients with adenocarcinoma involving the axillary nodes with unknown primary. In this study 1/25 patients receiving radiotherapy had severe arm oedema following radiotherapy and axillary dissection. Two patients had symptomatic pneumonitis, one with rib fracture and three with moderate arm oedema, one with junctional fibrosis. A single patient, treated with a protracted technique, had pericarditis and a rib fracture as well as a decreased range of motion around the shoulder joint. In patients that did not receive radiotherapy, two patients had moderate breast oedema, one had recurring operative site infections over a ten year period and one had moderately sever operative site infection after radical mastectomy

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Medina-Franco H, Urist MM. *Occult breast carcinoma presenting with axillary lymph node metastases.* Revista de Investigacion Clinica 2002; 54: (3) 204-8

Merson M, Andreola S, Galimberti V. *Breast carcinoma presenting as axillary metastases without evidence of a primary tumor.* Cancer 1992; 70: (2) 504-8

Rosen PP, Kimmel M. *Occult breast carcinoma presenting with axillary lymph node metastases: a follow-up study of 48 patients.* Human Pathology 1990; 21: (5) 518-23

van Ooijen B, Bontenbal M, Henzen-Logmans SC, Koper PC. *Axillary nodal metastases from an occult primary consistent with breast carcinoma.* British Journal of Surgery 1993; 80: (10) 1299-300

Varadarajan R, Edge SB, Yu J, Watroba N, Janarthanan BR. *Prognosis of occult breast carcinoma presenting as isolated axillary nodal metastasis.* Oncology 2006; 71: (5-6) 456-9

Whillis D, Brown PW, Rodger A. *Adenocarcinoma from an unknown primary presenting in women with an axillary mass.* Clinical Oncology (Royal College of Radiologists) 1990; 2: (4) 189-92

Table 17.1 Study information

Study	N	Aim	Authors conclusions
Ellerbroek *et al* (1990)	42	To determine whether patients with axillary metastases should be treated similarly to patients with similar nodal stages and proven breast primary tumours	A treatment approach with a combination of modalities identical to those used for similarly advanced breast carcinoma (according to N stage) is appropriate. Favourable survival rates were not compromised by a conservative surgical approach provided the intact breast was irradiated.
Kemeny *et al* (1986)	20	To analyse patients presenting with adenocarcinoma in an axillary nodes and no obvious primary tumour for their presenting characteristics, treatment and length of survival.	Extensive radiographic and imaging searches for extra-mammary primary tumours are costly and ineffective in women, though may be justified in men. It appears that mastectomy offers no advantage over segmentectomy and radiotherapy for T1 and T2 breast cancers and therefore patients presenting with axillary metastases and negative mammograms need not undergo mastectomy as axillary dissection and radiotherapy appear to be as effective.
Knapper *et al* (1991)	35	To determine whether recent advances in mammographic techniques and steroid receptor analysis of specimens have aided in the diagnosis of occult stage II breast cancer and to evaluate the role of breast preservation and possible survival benefit of irradiation and/or systemic chemotherapy	When histological examination of an axillary node reveals adenocarcinoma compatible with breast primary, and there is no other obvious primary, mastectomy and/or limited resection plus removal of the remaining axillary nodes are indicated.
Jackson *et al* (1995)	10	To report the outcomes of patients with probably breast cancer in whom definitive treatment of the primary tumour was deferred	Careful workup including chest x-ray and bone scan should be done before considering definitive therapy. Ipsilateral modified radical mastectomy is recommended in the absence of other evidence of metastatic disease and if the patients chooses not to proceed with mastectomy then external beam radiation or watchful waiting with careful follow-up are options though watchful waiting appears to be associated with poor overall survival.
Medino-Franco *et al* (2002)	10	To review the experience with the presentation of occult breast cancer in patients seen at the University of Alabama at Birmingham from 1985 to 1998	Axillary dissection should be done in order to provide prognostic indicators including number of involved nodes and hormone receptor status.
Merson *et al* (1992)	56	To provide a detailed analysis of the histological characteristics and the long term follow-up according to various forms of treatment in patients with axillary presentation	The prognosis for patients with occult breast carcinoma was somewhat better than in Stage II cases of breast carcinoma. It is believed that aggressive surgical treatment is not necessary when signs of primary tumour are absent. Treatment with radiation or follow-up after axillary dissection are sufficient and if the tumour should become evident during strict clinical and mammographic follow-up then it may be removed with a quadrantectomy and, if required, the breast should be irradiated.
Rosen *et al* (1990)	48	To evaluate a series patients presenting with axillary mass which proved to be metastatic adenocarcinoma consistent with mammary origin when examined histologically	Treatment should be predicted on the assumption that there is an invasive carcinoma in the ipsilateral breast, and that other ipsilateral axillary lymph nodes contain metastatic carcinoma. Complete axillary dissection is recommended over radiation in the majority of cases as it allows accurate staging of the number of involved nodes and reduces the risk of axillary recurrence. Data regarding the number of involved nodes and hormone receptors are important factors for planning systemic adjuvant therapy.
van Ooijen *et al* (1993)	15	To examine the prognosis for patients presenting with metastatic enlargement of axillary lymph nodes when the breast is left untreated	The availability of modern mammographic equipment allows the option for withholding definitive local therapy until clinical or radiographic appearance of the primary tumour.
Varadarajan *et al* (2007)	10	To examine the outcome for women with an axillary lymph node adenocarcinoma with occult primary tumour who did not undergo mastectomy	A customised approach to occult breast cancer is the preferred option. Axillary lymph node dissection should be done to provide locoregional control and to provide staging and prognostic information. Mastectomy is unnecessary with breast conservation being feasible and preferred.
Whillis *et al* (1990)	20	To measure survival and locoregional control in patients presenting with adenocarcinoma confined to one group of axillary lymph nodes treated conservatively	The favourable survival, together with the good disease control achieved in both axilla and breast by radical irradiation, leads us recommend radical radiotherapy to the breast and peripheral lymphatics.

18. Treatment of patients with CUP who present with squamous cell carcinoma metastases to the inguinal lymph nodes

Last updated: 30/ 10/ 2009.

Short summary

There was sparse evidence about people with metastatic squamous cell carcinoma of unknown primary who present with inguinal lymphadenopathy.

Some patients with inguinal lymph node metastases from unknown primary had surgery with curative intent. Mean overall survival of 7.7 years was reported. It was unclear, however, whether lesser treatment would have been as effective.There was a relatively high rate of isolated lymph node metastasis in patients undergoing surgery: 8/9 patients (89%) in two series.

Evidence about complications came from one study (Guarishi et al 1987). Lymph node dissection was associated with lymphoedema. Severe acute toxicity was seen in 6% of those treated with radiotherapy. 31% of women older than 50 developed hip fracture in the radiotherapy treatment field. There were no treatment related deaths.

Rationale

A small minority of confirmed CUP patients present with metastatic disease in inguinal nodes as their only manifestation of malignancy. The pattern of nodal involvement is very similar to that seen with an anal or external genitalia primary tumour and experience suggests these groups may justifiably be treated with localized treatment with potentially curative intent. They may be considered to have a primary cancer which might fall under one or more of the following categories:

1. It might be treated with curative intent should it become apparent.

2. It might be eradicated by treatment directed at its likely anatomical site, either specifically or coincidentally from treatment directed principally against the metastatic disease.

3. It might never become apparent despite having no treatment directed against it.

Groin node dissection with or without subsequent chemoradiotherapy has been used to treat patients with metastatic squamous carcinoma in lymph nodes in the inguinal region from a presumed but unidentified primary in the external genitalia or anus. However the effectiveness and cost-effectiveness of a potentially curative management strategy for selected patients presenting with inguinal lymphadenopathy not been established. Treatment given with curative intent is likely to cause substantial morbidity hence investigation of the validity of this treatment approach is required.

Methods

Study types

All study designs were considered for inclusion.

Participants

People with metastatic squamous carcinoma in inguinal nodes, without an identified primary, after specific investigations to reveal anal or external genitalia primary.

Interventions

Attempted curative surgery (node block dissection), curative surgery plus radiotherapy or radiotherapy alone. Cytotoxic chemotherapy could be added to any of these interventions.

Outcomes

Treatment outcomes including overall survival. Complications of treatment.

Study selection

The information specialist (SA) selected a list of relevant studies from the literature searches. All studies were ordered for appraisal.

Data extraction and synthesis

One reviewer appraised each study and extracted any relevant data. Only published studies were included and study authors were not contacted.

Quality assessment

Studies quality was assessed using NICE quality checklists.

Heterogeneity assessment

There was no formal assessment of heterogeneity. Differences between studies that could bias results, such as the pathological classification of metastases, were noted.

Search results

Description of included studies

The literature search identified four papers, of which two were included. Another paper (Zaren and Copeland, 1978) was identified from reference lists of the included studies.

Studies were not restricted to patients with squamous cell carcinoma (SCC) histology. For Guarishi et al (1987) and Zaren and Copeland (1978) it was not possible to separate the data about SCC from the other histological diagnoses: the combined data from these studies contain a minority of patients with SCC (22%).

The histology diagnoses reported in patients with inguinal node CUP did not match those in series with inguinal nodes and known primary tumour. In those with known primary the most common histological type was melanoma (Zaren and Copeland, 1978) whereas in patients with CUP there was a predominance of unclassified / anaplastic carcinoma (Zaren and Copeland, 1978; Guarishi, 1987).

Study quality

All the studies were retrospective case series, and therefore at high risk of bias.

Evidence summary

Primary tumours associated with inguinal lymph node metastases

Zaren and Copeland (1978) reported a retrospective series of 2232 patients with inguinal node metastases (22 with unknown primary). The most common pathological diagnoses were melanoma (32%), squamous cell carcinoma (28%), adenocarcinoma (12%), unclassified carcinoma (5%), papillary serous carcinoma (5%) and transitional cell carcinoma (3%). The most common primary tumour locations were: skin of the lower extremities (18%), cervix of the uterus (10%), vulva (7%), skin of the trunk (6%), rectum or anus (5%), ovary (5%) and glans or foreskin of the penis (4%), although there were many other primary tumour sites.

Treatment outcomes

There was no evidence directly comparing different treatments for patients with metastatic squamous cell carcinoma of the inguinal lymph nodes from an unknown primary. Treatment outcomes are summarised in Table 18.1.

In the series reported by Zaren and Copeland (1978) none of the seven patients who received surgery with curative intent died from cancer. Their mean survival was 7.7 years compared with a median survival of less than two years in fifteen patients who did not receive such surgery. This was a non-randomised study and it is possible that patients selected for surgery had a better prognosis: only one had more than one lymph node involved with cancer. The mean value for overall survival may have been skewed by one patient who survived for 18 years, but Zaren and Copeland do not report median survival for the patients treated with surgery.

In the Zaren and Copeland series, five of 11 patients treated by excisional biopsy alone remained disease free for at least two years. The authors attribute this to a solitary lymph node metastasis combined with the involution of the primary tumour.

Wallack and Reynolds (1981) reported the cases of two patients with metastatic squamous cell carcinoma of the inguinal nodes and unknown primary. One was treated with superficial groin dissection and the other with radical groin dissection, both received post operative chemotherapy. In both cases the pathological examination of the surgical specimen found no further positive lymph nodes. Both patients remained disease free at the last follow-up visit (5 years post-operative in one case and 6 months in the other).

Guarishi et al (1987) reported a series of 56 patients with inguinal node CUP. A minority (14%) received surgery with curative intent, the remainder received radiotherapy (63%), chemotherapy (7%) or no further treatment (16%). Overall survival at five years for all patients was 27%. Outcomes for the various treatment groups are summarised in table 18.1 below. Median overall survival ranged from 1.5 years in patients treated with excisional biopsy only, to 2.25 years in those treated with radical radiotherapy.

Treatment morbidity

Evidence about complications came from one study (Guarishi et al 1987): treatment morbidity was not reported in any of the other studies.. Superficial inguinal lymph node dissection was associated with mild leg swelling in all seven cases. The single patient treated with radical ilioinguinal node dissection developed symptomatic lymphoedema. Two patients treated with surgery developed skin necrosis and seroma. Severe acute toxicity was seen in two patients with radiotherapy: one case each of moist desquamation and severe diarrhoea. 31% of women older than 50 developed hip fracture in the radiotherapy treatment field. No major complications were seen in the four patients who received chemotherapy. There were no treatment related deaths.

References

Guarischi A, Keane TJ, Elhakim T. *Metastatic inguinal nodes from an unknown primary neoplasm. A review of 56 cases.* Cancer 1987; 59: (3) 572-7

Wallack MK, Reynolds B. *Cancer to the inguinal nodes from an unknown primary site.* Journal of Surgical Oncology 1981; 17: (1) 39-43

Zaren HA, Copeland EM 3rd. *Inguinal node metastases.* Cancer 1978; 41: (3) 919-23

Table 18.1 Treatment outcomes

Outcome	Lymph node dissection	Local excision only	Local excision plus chemo therapy or RT
3 year overall survival	12.5% (Guarishi 1987)	33% (Guarishi 1987)	Chemotherapy: 50% (Guarishi 1987) Radical radiotherapy: 47% (Guarishi 1987) Palliative radiotherapy: 22% (Guarishi 1987)
5 year overall survival	12.5% (Guarishi 1987)	33% (Guarishi 1987)	Chemotherapy: 25% (Guarishi 1987) Radical radiotherapy: 35% (Guarishi 1987) Palliative radiotherapy: 16% (Guarishi 1987)
Median overall survival	Mean 7.7 years (Zaren 1978) Median 1.7 years (Guarishi 1987)	Median 1.5 years (Guarishi 1987)	Median < 2 years (Zaren 1978) Chemotherapy: median 2.1 years (Guarishi 1987) Radical radiotherapy: median 2.25 years (Guarishi 1987) Palliative radiotherapy: median 2.1 years (Guarishi 1987)
Solitary lymph node metastasis (%)	86% (Zaren 1978) 100% (Wallack 1981)	Not reported	33%* (Zaren 1978)
Deaths due to treatment toxicity	None (Guarishi 1987)	None (Guarishi 1987)	None (Guarishi 1987)
Complications	Minor leg swelling in all treated with superficial lymph node dissection (Guarishi, 1987) Lymphoedema in the single patient treated with radical lymph node ilioinguinal node dissection (Guarishi, 1987) Skin necrosis and seroma occurred in 2/9 patients (Guarishi, 1987).	Not reported	Radiotherapy: severe acute complications in 2/35 patients (Guarishi 1987), hip fracture in 4/13 women over 50 years of age treated with RT (Guarishi 1987). Chemotherapy: no major complications reported (Guarishi 1987)

* authors assumption, not confirmed with histopathology

Treatment of patients with CUP who present with squamous cell carcinoma metastases to the inguinal lymph nodes

Last updated: 27 / 4 / 2009.

Characteristics of included studies

Guarischi-1987

Methods	Retrospective case series.
Participants and Country	56 patients with inguinal node metastases from unknown primary. 24 patients had local disease (confined to the inguinal nodes only), 16 had locoregional disease (confined to the ipsilateral ilioinguinal nodes) and 16 systemic disease (any lymphatic disease beyond the ipsilateral iliac lymph nodes or distant metastases)
Interventions	Initial treatment following excisional biopsy was **Inguinal lymph node dissection**(N=8) : 7/8 patients had superficial lymph node dissection and one had radical ilioinguinal lymph node dissection. **Chemotherapy** (N=4): the choice of drugs was guided by the histologic subtype. **Radical radiotherapy** (N=18): dose was at least 35 Gy in 15 fractions. **Palliative radiotherapy** (N=17): dose < 35 Gy. About half these patients received hypofractionation schedules. Of the 35 patients treated with radiotherapy, 26 had radiation to the ilioinguinal region alone, seven had radiation to the whole pelvis and inguinal nodes. In two patients the whole abdomen and inguinal nodes were treated. **No further treatment** after excisional biopsy (N=9).
Outcomes	Overall survival, treatment related death, complications.
Histology	Pathologic subtypes were: anaplastic, 24; squamous, 11; adenocarcinoma, nine; melanoma, nine; and three others (malignant histiocytic fibroma, hemangiopericytoma and adenoidcystic carcinoma).
Notes	

Wallack-1981

Methods	Case report
Participants and Country	Two patients with metastatic squamous cell carcinoma to the inguinal nodes and no detectable primary site.
Interventions	Superficial groin dissection (N=1), radical groin dissection (N=1) plus chemotherapy
Outcomes	Disease free survival, overall survival
Histology	Squamous cell carcinoma. One patient with melanoma is excluded from this evidence review.
Notes	

Zaren-1978

Methods	Retrospective case series.
Participants and Country	Patients with metastases of the inguinal lymph nodes, identified from the records of a single institution between 1944 and 1975. 2232 patients (22 with cancer of unknown primary). USA
Interventions	Superficial inguinal node dissection with no adjuvant therapy (N=7), excisional biopsy only (N=11), excisional biopsy plus chemotherapy (N=2) plus radiotherapy (N=1) or plus chemoradiotherapy (N=1). Radiotherapy was 12.5 to 25 Gy given in fractions of 2 to 2.5 Gy. Chemotherapy was thioPETA, 5-FU and methotrexate.
Outcomes	Overall survival, disease free survival.
Histology	Unclassified carcinoma 64%, squamous cell carcinoma 27% and adenocarcinoma 9%
Notes	

References for included studies

GUARISCHI 1987
Guarischi A, Keane TJ, Elhakim T. Metastatic inguinal nodes from an unknown primary neoplasm. A review of 56 cases. Cancer 1987; 59 (3) 572-7

WALLACK 1981
Wallack MK, Reynolds B. Cancer to the inguinal nodes from an unknown primary site. Journal of Surgical Oncology 1981; 17 (1) 39-43

ZAREN 1978
Zaren HA, Copeland EM 3rd. Inguinal node metastases. Cancer 1978; 41 (3) 919-23

19. Radical local treatment for isolated brain metastasis of unknown primary

Last updated: 30/ 10/ 2009.

Short summary

There were no comparative studies comparing localised therapy for isolated brain metastases of unknown primary. Overall survival was better in patients treated with localised therapy that those receiving only palliative radiotherapy. It is likely, however, that patients treated with surgery had better pretreatment prognosis than those who received palliative radiotherapy only.

There was inconsistent evidence from randomised trials about the effect of surgery for brain metastases on overall survival in patients with known primary tumours. Evidence suggested surgery could improve functional independent survival and reduce the risk of death from neurological causes compared with whole brain radiotherapy alone. There was insufficient evidence to say which of the treatment options had the lowest complication rate.

Rationale

There is a distinct subset of confirmed CUP patients who present with an isolated deposit of metastatic disease at a single site. The usual sites of isolated confirmed CUP metastasis are brain, bone, liver, skin and lung. In some instances, relatively radical treatment of this disease can be associated with a long period before further metastatic disease or a primary tumour become evident. In rare cases, no further manifestations of the cancer ever emerge.

There are four priorities when faced with an apparently isolated metastasis from an unknown primary site.

Firstly, an unusual primary tumour masquerading as a metastasis must be excluded (examples include plasmacytoma, primary bone tumour, primary skin appendage tumour, hepatocellular carcinoma).

Secondly, the investigations to define the nature of the lesion must not confound subsequent radical therapy; for instance inappropriate biopsy of a primary bone tumour may lead to a requirement for more aggressive surgery than usual, and percutaneous biopsy of a liver metastasis may disseminate the tumour rendering cure impossible.

Thirdly, while the aim for most patients will remain palliative, using treatment of limited toxicity, more aggressive therapy (e.g. high dose radiotherapy, surgical resection) will be appropriate in some circumstances and these opportunities should be identified, with decisions based on sound prognostic factors where possible.

Fourthly, for patients suitable for more aggressive therapy, choice of the optimal intervention should be based on sound evidence.

Several interventions are possible for selected patients presenting with isolated metastatic cancer. Surgical excision is an option for many sites (e.g. liver, lung, brain, skin). High dose radiotherapy is applicable in the case of isolated bone lesions, and stereo-tactic “radio-surgery” can sometimes lead to prolonged control of brain metastases. Visceral metastases can be treated with a variety of interventions including radiofrequency ablation, embolization, or cryosurgery.

For patients with confirmed CUP who present with an isolated deposit of tumour, it is necessary to define optimal therapy for the subgroups who may gain the greatest benefit from relatively radical treatment.

Methods

Study types

There was no restriction on study design

Participants

People with a solitary brain metastasis of unknown primary

Interventions

Radical treatment (surgery, radiotherapy, or other local therapy) aiming to achieve total control of local disease. The comparator is lesser treatment such as symptom control or palliative radiotherapy.

Outcomes

Overall survival, treatment complications and symptom control.

Study selection

An initial list of studies was selected by SA. NB then selected potentially relevant studies from this list on the basis of their title and abstract. These studies were

ordered and each paper was checked against the inclusion criteria.

Data extraction and synthesis

One reviewer (NB) extracted data. Only published data were included and authors were not contacted.

Quality assessment

Heterogeneity assessment

Search results

The literature search identified 48 studies, 11 of which were included. An additional systematic review (Hart et al, 2007) was identified by a MEDLINE search for randomised trials of localised therapy for brain metastases of known primary.

Description of included studies

All the CUP studies were retrospective case series. Seven studies reported surgery, two studies radiosurgery and two studies whole brain radiotherapy (WBRT) alone. The systematic review included three randomised trials comparing

Study quality

Evidence summary

Overall survival

Overall survival according to treatment is summarised in table 19.1. In patients with isolated brain metastasis of unknown primary treated with gross total resection of their metastasis plus whole brain radiotherapy (WBRT) median survival ranged from 10 to 21 months. Median survival ranged from 6 to 15 months in those treated with radiosurgery plus WBRT. This compares with 5 to 10 months in patients treated with WBRT alone.These studies were retrospective case series, however, and the patients selected for surgery or radiosurgery could have had better initial prognosis than those treated with WBRT only.

A systematic review (Hart et al, 2007) identified three randomised trials comparing surgery plus WBRT with WBRT alone in patients with solitary brain metastases of known primary. There was uncertainty over the effect of surgery on overall survival as results of the three trials were heterogeneous: two showed better overall survival with surgery plus WBRT whereas one suggested better survival with WBRT only.

Across the studies there was a consistent (but not statistically significant) reduction in the risk of neurological death with surgery : HR = 0.68 (95% C.I. 0.43 to 1.09).

Symptom control

One of the trials included in the Hart et al (2007) systematic review measured functionally independent survival and found it better in patients treated with surgery plus WBRT than in those treated with WBRT only: HR = 0.42 (95% C.I. 0.22 to 0.82).

Adverse events

Petrovich et al (2002) reported toxicity associated with radiosurgery in a series of 458 patients (3% of whom had CUP). Acute toxicity included: seizures in 3% of patients, mild to moderate nausea in 4% of patients and mild to moderate fatigue in most cases. Late toxicity, consisting of peritumoural oedema occurred in 20% of patients. This peritumoural oedema required corticosteroid treatment in 35% of cases and surgery in 22% of cases.

Salvati et al (1995) report a perioperative death rate of 6/100 (6%) in patients treated with surgery for isolated brain metastasis of unknown primary.

In their systematic review of surgery for isolated brain metastases in patients with known primary, Hart el al (2007) reported an adverse event rate ranging from 8% to 41% in patients treated with surgery plus WBRT. This compares with a range of 17% to 29% in patients treated with WBRT only. There was no statistically significant difference in the adverse event rates of the two treatment strategies. For surgery plus WBRT versus WBRT alone the relative risk of an adverse event was 1.27 (95%C.I. 0.77 to 2.09). Confidence intervals were wide, however, and it is possible that either of the treatments could have a higher risk of adverse events than the other.

References

Bartelt S, Lutterbach J. *Brain metastases in patients with cancer of unknown primary.* Journal of Neuro-Oncology 2003; 64: (3) 249-53

Debevec M. *Management of a patient with solitary brain metastasis of unknown origin.* Radiology and Oncology 1992; 26: (1) 56-9

Hart MG, Grant R, Walker M, Dickinson HO. *Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases.* Cochrane Database of Systematic Reviews 2007; (2)

Khansur T, Routh A, Hickman B. *Brain metastases from unknown primary site.* Journal of the Mississippi State Medical Association 1997; 38: (7) 238-42

Maesawa S, Kondziolka D, Thompson TP, Flickinger JC, Dade L. *Brain metastases in patients with no known primary tumor.* Cancer 2000; 89: (5) 1095-101

Maiuri F. *Brain metastases: A survey of the surgical treatment of 240 patients.* Cancer Journal 1998; 11: (2) 76-81

Merchut MP. *Brain metastases from undiagnosed systemic neoplasms*. Archives of Internal Medicine 1989; 149: (5) 1076-80

Nguyen LN, Maor MH, Oswald MJ. *Brain metastases as the only manifestation of an undetected primary tumor*. Cancer 1998; 83: (10) 2181-4

Petrovich Z, Yu C, Giannotta SL, O'Day S, Apuzzo ML. *Survival and pattern of failure in brain metastasis treated with stereotactic gamma knife radiosurgery*. Journal of Neurosurgery 2002; 97: (5 Suppl) 499-506

Ruda R, Borgognone M, Benech F, Vasario E, Soffietti R. *Brain metastases from unknown primary tumour: a prospective study*. Journal of Neurology 2001; 248: (5) 394-8

Salvati M, Cervoni L, Raco A. *Single brain metastases from unknown primary malignancies in CT-era*. Journal of Neuro-Oncology 1995; 23: (1) 75-80

Yardeni D, Reichenthal E, Zucker G, Rubeinstein A, Cohen M, Israeli V, et al. *Neurosurgical management of single brain metastasis*. Surgical Neurology 1984; 21: (4) 377-84

Table 19.1 Median overall survival according to treatment in patients with solitary brain metastasis of unknown primary

	Gross total resection* N (N with solitary mets)	Gross total resection* Median survival (months)	Partial resection* N (N with solitary mets)	Partial resection* Median survival (months)	Brain biopsy* N (N with solitary mets)	Brain biopsy* Median survival (months)	Radiosurgery* N (N with solitary mets)	Radiosurgery* Median survival (months)	WBRT only N (N with solitary mets)	WBRT only Median survival (months)
Bartelt (2003)	15 (11)	9.5	-	-	-	-	-	-	-	-
Debevec (1990)	22 (21)	9.5	7 (6)	2	6 (4)	2	-	-	-	-
Khansur (1997)	-	-	-	-	-	-	-	-	14 (14)	5
Maesawa (2000)	-	-	-	-	-	-	15 (9)	15	-	-
Maiuri (1998)	27(27)**	16.6								
Nguyen (1998)	24(N.R.)†	21	8 (N.R.)	-	-	-	-	-	7(N.R.)	10
Petrovich (2002)	-	-	-	-	-	-	14 (N.R.)	6	-	-
Ruda (2001)	21 (21)	13	-	-	-	-	-	-	-	-
Salvati (1995)	100 (100)	10.8	-	-	-	-	-	-	-	-
Yardeni (1984)	26 (26)	11	-	-	-	-	-	-	-	-

* patients treated with surgery or radiosurgery usually also received WBRT
†the majority of these patients had a single metastasis but the exact number is not reported
* *figures for gross and partial resection were combined in Mairui et al (1998)
Abbreviations: N.R., not reported; WBRT, whole brain radiotherapy

Table 19.2 Overall survival at two years after treatment

	Gross total resection* N (N with solitary mets)	Gross total resection* 2 year survival	Partial resection* N (N with solitary mets)	Partial resection* 2 year survival	Brain biopsy* N (N with solitary mets)	Brain biopsy* 2 year survival	Radiosurgery* N (N with solitary mets)	Radiosurgery* 2 year survival	WBRT only N (N with solitary mets)	WBRT only 2 year survival
Bartelt (2003)	15 (11)	22%	-	-	-	-	-	-	-	-
Debevec (1990)	22 (21)	N.R. (1 year survival was 41%)	7 (6)	N.R. (1 year survival was 29%)	6 (4)	0%	-	-	-	-
Khansur (1997)	-	-	-	-	-	-	-	-	14 (14)	7%
Maesawa (2000)	-	-	-	-	-	-	15 (9)	53%	-	-
Maiuri (1998)	27(27)**	N.R.	-	-	-	-	-	-	-	-
Nguyen (1998)	24(N.R.)†	40%	8 (N.R.)	N.R.	-	-	-	-	7(N.R.)	<10%

	Gross total resection* N (N with solitary mets)	Gross total resection* 2 year survival	Partial resection* N (N with solitary mets)	Partial resection* 2 year survival	Brain biopsy* N (N with solitary mets)	Brain biopsy* 2 year survival	Radiosurgery* N (N with solitary mets)	Radiosurgery* 2 year survival	WBRT only N (N with solitary mets)	WBRT only 2 year survival
Petrovich (2002)	-		-	-	-	-	14 (N.R.)	N.R.	-	-
Ruda (2001)	21 (21)	15%	-	-	-	-	-	-	-	-
Salvati (1995)	100 (100)	11% (primary tumour identified) 19% (primary tumour unknown)	-	-	-	-	-	-	-	-
Yardeni (1984)	26 (26)	12%	-	-	-	-	-	-	-	-

Table 19.3 Overall survival at five years after treatment

	Gross total resection* N (N with solitary mets)	Gross total resection* 5 year survival	Partial resection* N (N with solitary mets)	Partial resection* 5 year survival	Brain biopsy* N (N with solitary mets)	Brain biopsy* 5 year survival	Radiosurgery* N (N with solitary mets)	Radiosurgery* 5 year survival	WBRT only N (N with solitary mets)	WBRT only 5 year survival
Bartelt (2003)	15 (11)	N.R. (insufficient follow-up)	-	-	-	-	-	-	-	-
Debevec (1990)	22 (21)	N.R. (insufficient follow-up)	7 (6)	0%	6 (4)	0%	-	-	-	-
Khansur (1997)	-		-	-	-	-	-	-	14 (14)	0%
Maesawa (2000)	-		-	-	-	-	15 (9)	N.R. (insufficient follow-up)	-	-
Maiuri (1998)	27(27)**	N.R.								
Nguyen (1998)	24(N.R.)†	30%	8 (N.R.)	N.R.	-	-	-	-	7(N.R.)	0%
Petrovich (2002)	-		-	-	-	-	14 (N.R.)	N.R.	-	-
Ruda (2001)	21 (21)	0%	-	-	-	-	-	-	-	-
Salvati (1995)	100 (100)	N.R.	-	-	-	-	-	-	-	-
Yardeni (1984)	26 (26)	N.R.	-	-	-	-	-	-	-	-

19. Radical local treatment for isolated brain metastasis of unknown primary

Last updated: 30 / 10 / 2009.

Characteristics of included studies

Bartelt-2003

Methods	Retrospective case series of patients with brain metastases from an unknown primary treated with WBRT at a single institution between 1985 and 2000.
Participants and Country	47 patients in total, 16 with solitary metastasis and 31 with multiple brain metastases.
Interventions	WBRT in all cases, 15 patients had gross total resection of their metastases and 12 stereotactic biopsy.
Outcomes	**Overall survival** Median overall survival for patients with solitary brain metastases was 7.3 months. For patients receiving gross total resection median survival was 9.5 months, 11/15 of these patients had a solitary metastasis.
Notes	

Debevec-1992

Methods	Retrospective case series of patients treated for brain metastases of unknown primary at a single institution between 1973 and 1987.
Participants and Country	75 patients: 32 with solitary metastasis.
Interventions	All patients received WBRT. Some also had surgical resection: gross total resection in 22 patients, partial resection in 7 and biopsy in 6. 40 patients did not have surgery.
Outcomes	**Median overall survival** Gross total resection: 9.5 months (22 patients, 21 with solitary metastasis) Partial resection: 2 months (7 patients, 6 with solitary metastasis) Biopsy: 2 months (6 patients, 4 with solitary metastasis) WBRT only: 4 months (40 patients, 1 with solitary metastasis) **1 year overall survival** Gross total resection: 41% months (22 patients, 21 with solitary metastasis) Partial resection: 29% months (7 patients, 6 with solitary metastasis) Biopsy: 0% months (6 patients, 4 with solitary metastasis) WBRT only: 1% months (40 patients, 1 with solitary metastasis)
Notes	

Hart-2007

Methods	Systematic review
Participants and Country	Studies of patients with systemic cancer (primary site confirmed by histology) and a suspected single brain metastasis (on imaging and clinical findings) were included; the brain metastasis did not have to be histologically proven. Three RCTs were included in the review.
Interventions	Surgical resection and WBRT versus WBRT alone. Radiosurgery was not included.
Outcomes	**Overall survival** There was no statistically significant difference in overall survival between the two treatment groups (HR = 0.72, 95% CI 0.34 to 1.53, P = 0.40). There was significant heterogeneity between the trials (I2 = 82%); two of the trials reported better survival in those undergoing surgery and WBRT while one reported better survival in patients receiving only WBRT. **Functionally independent survival** Data about functionally independent survival could only be extracted from one trial. This trial found that those treated by surgery and WBRT maintained functional independence for longer than those treated by WBRT alone (HR = 0.42, 95% CI 0.22 to 0.82, P = 0.01). **Neurological death** Patients treated with surgery were less likely to die from neurological causes (RR = 0.68 95% CI 0.43 to 1.09, P = 0.11), but this result was not statistically significant. Results were reasonably consistent between trials, with no significant heterogeneity. **Adverse events** Adverse events were not well reported, and it was unclear whether patients had experienced multiple adverse events. Allowing for this there was no significant difference in the adverse event rates of the two treatments (RR = 1.27 95% CI = 0.77 to 2.09 P =0.35). However the confidence interval is wide, and it is possible that either of the treatments could cause significantly more adverse events than the other
Notes	

Khansur-1997

Methods	Retrospective case series of patients treated for brain metastases of unknown primary at a single institution between 1982 and 1989.
Participants and Country	32 patients, 14 had a solitary brain metastasis.
Interventions	All received WBRT in dose ranging from 30 Gy in 10 fractions to 54 Gy in 15 fractions. Two patients also received chemotherapy.
Outcomes	**Median overall survival** 5 months in patients with solitary brain metastasis
Notes	

Maesawa-2000

Methods	Retrospective case series of patients with brain metastases from an unknown primary tumour treated with radiosurgery between 1988 and 1998 at a single institution.
Participants and Country	15 patients: 9 patients had a single brain metastasis, 6 patients had 2 or more brain metastases. 4 had extra cranial metastases
Interventions	Stereotactic radiosurgery: mean marginal dose was 16.2 Gy (range 12 to 20 Gy). 14/15 patients also had WBRT (before radiosurgery in 12 patients and after radiosurgery in 2 patients). Three patients received adjuvant chemotherapy.
Outcomes	**Overall survival**

	For patients with a single brain metastasis median overall survival was 15 months.
Notes	

Maiuri-1998

Methods	Retrospective case series including patients treated with surgery for solitary brain metastasis at a single institution between 1976 and 1993.
Participants and Country	240 patients with solitary brain metastases, 27 with unknown primary.
Interventions	Patients received surgical resection (either complete or incomplete). Most (180/240) patients also received WBRT.
Outcomes	**Overall survival** Mean survival for patients with CUP was 17 months and median survival 16.5 months
Notes	

Merchut-1989

Methods	Retrospective case series of patients with brain metastases from an undiagnosed primary tumour treated at a single institution between 1977 and 1987.
Participants and Country	56 patients: 32/56 (57%) with a solitary brain metastasis and 24/56 (43%) with multiple brain metastases.
Interventions	WBRT was performed in 88% of patients. 43% of patients received craniotomy and 23% of patients received systemic chemotherapy.
Outcomes	**Overall survival for patients with isolated metastasis** 6 month overall survival was 66%, 1 year overall survival was 23%
Notes	Survival was not reported according to the treatment received. A primary tumour was eventually diagnosed in 47/56 (84%) of patients.

Nguyen-1998

Methods	Retrospective series of patients treated for brain metastasis of unknown primary (and no extra-cranial metastases) at a single institution between 1977 and 1996.
Participants and Country	39 patients. 19 patients had single metastasis and 20 patients
Interventions	24 patients had gross total resection (the majority had single metastasis but the exact number is not given), 8 patients had partial resection or biopsy only for diagnosis, and 7 patients had no surgery. All patients had WBRT.
Outcomes	**Overall survival** Median survival for patients who had gross total resection plus WBRT was 21 months. For patients who had WBRT but not gross total resection median survival was 10 months.
Notes	

Petrovich-2002

Methods	Retrospective case series of patients treated with gamma knife radiosurgery for brain metastasis at a single institution between 1994 and 2002.

Participants and Country	458 patients in total, 14 with unknown primary. The mean number of brain metastases per patient with CUP was 2.4.
Interventions	Gamma knife radiosurgery (median dose 18 Gy), the radiation dose depended on tumour histology, tumour volume, tumour location and prior radiotherapy. 114/458 patients also received WBRT.
Outcomes	**Overall survival** Median survival was 6 months for patients with CUP.
Notes	

Ruda-2001

Methods	Retrospective case series of patients with brain metastases of unknown primary treated at a single institution between 1987 and 1993
Participants and Country	33 patients with CUP and brain metastases: 21 patients with solitary brain metastasis, 12 patients with multiple metastasis..
Interventions	WBRT in all cases, gross total resection in 21 patients with single metastasis and in 5 patients with multiple metastases.
Outcomes	**In the 21 patients with solitary metastasis treated with gross total resection and WBRT:** **Overall survival** median 13 months **Neurological improvement** 18/21 (85%) **Neurological progression** 11/21 (52%) **System progression** 10/21 (48%)
Notes	

Salvati-1995

Methods	Retrospective series of patients treated with surgery for a single brain metastasis as the first sign of malignancy (metastasis of undiagnosed primary) to a single institution between 1975 and 1988.
Participants and Country	100 patients.
Interventions	All patients received surgery. Gross total resection in 93 cases and partial resection in the remaining 7 cases. 81 patients received WBRT
Outcomes	**Diagnosis of the primary tumour** 83/100 patients had a primary tumour diagnosed during their lifetime. A further 14/100 patients had a primary tumour diagnosed at autopsy. **Overall survival for patients treated with surgery plus WBRT** Overall survival at one year was 30% and at two years was 11%. Median survival was 10.8 months. **Overall survival for patients treated with surgery only** Overall survival at one year was 30% and at two years was 11%. Median survival was 10.7 months. **Overall survival excluding those with undifferentiated or small cell carcinoma histology** Median survival 16.8 months. **Perioperative mortality** Six patients (6%) died in the immediate perioperative period.

	WBRT toxicity Overall 5/81(6%) patients experienced late radiotherapy dementia. In the patients surviving more than three years this figure is 5/19 (26%).
Notes	

Yardeni-1984

Methods	Retrospective series of patients with single brain metastases treated at a single institution between 1975 and 1981
Participants and Country	74 patients in total, 26 with an unknown primary tumour.
Interventions	Gross total resection of the brain metastasis and WBRT.
Outcomes	**Median overall survival** Median overall survival was 3.5 months for patients with CUP and single brain metastasis **One year overall survival** One year overall survival was 19.2% for patients with CUP and single brain metastasis was 3.5 months **Two year overall survival** Two year overall survival was 11.5% for patients with CUP and single brain metastasis was 3.5 months **Operative mortality** Operative mortality was 23% for patients with CUP and single brain metastasis
Notes	

References for included studies

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Bartelt S, Lutterbach J. Brain metastases in patients with cancer of unknown primary. Journal of Neuro-Oncology 2003; 64 (3) 249-53

DEBEVEC 1992
Debevec M. Management of a patient with solitary brain metastasis of unknown origin. Radiology and Oncology 1992; 26 (1) 56-9

HART 2007
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KHANSUR 1997
Khansur T, Routh A, Hickman B. Brain metastases from unknown primary site. Journal of the Mississippi State Medical Association 1997; 38 (7) 238-42

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Maesawa S, Kondziolka D, Thompson TP, Flickinger JC, Dade L. Brain metastases in patients with no known primary tumor. Cancer 2000; 89 (5) 1095-101

MAIURI 1998
Maiuri F. Brain metastases: A survey of the surgical treatment of 240 patients. Cancer Journal 1998; 11 (2) 76-81

MERCHUT 1989
Merchut MP. Brain metastases from undiagnosed systemic neoplasms. Archives of Internal Medicine 1989; 149 (5) 1076-80

NGUYEN 1998
Nguyen LN, Maor MH, Oswald MJ. Brain metastases as the only manifestation of an undetected primary tumor. Cancer 1998; 83 (10) 2181-4

PETROVICH 2002
Petrovich Z, Yu C, Giannotta SL, O'Day S, Apuzzo ML. Survival and pattern of failure in brain metastasis treated with stereotactic gamma knife radiosurgery. Journal of Neurosurgery 2002; 97 (5 Suppl) 499-506

RUDA 2001
Ruda R, Borgognone M, Benech F, Vasario E, Soffietti R. Brain metastases from unknown primary tumour: a prospective study. Journal of Neurology 2001; 248 (5) 394-8

SALVATI 1995
Salvati M, Cervoni L, Raco A. Single brain metastases from unknown primary malignancies in CT-era. Journal of Neuro-Oncology 1995; 23 (1) 75-80

YARDENI 1984
Yardeni D, Reichenthal E, Zucker G, Rubeinstein A, Cohen M, Israeli V, et al. Neurosurgical management of single brain metastasis. Surgical Neurology 1984; 21 (4) 377-84

20. Radical local treatment for isolated liver metastasis of unknown primary

Last updated: 30/ 10/ 2009.

Short summary

There was sparse evidence about local therapy for isolated liver metastases of unknown primary. Less than 10% of patients presenting with CUP and liver metastases had surgery.

It was unclear what effect localised therapy for isolated liver metastases has on outcomes. It is clear from retrospective series that patients who had surgery for liver metastases of unknown primary had better overall survival than patients with CUP and liver metastases who did not have surgery. Median survival was 30 months for patients treated with surgery (Adams et al, 2006) compared with 4 to 10 months for patients with CUP and liver metastases in general (Lazaridis et al, 2008). However patients selected for surgery probably had a more favourable preoperative prognosis than those not selected.

Rationale

See rationale for radical local treatment for isolated brain metastasis of unknown primary.

Methods

Study types

Any study design was considered for inclusion.

Participants

People with confirmed Cancer of Unknown Primary presenting with a single metastasis involving the liver.

Interventions

Radical treatment (surgery, radiotherapy, or other local therapy) aiming to achieve total control of local disease. The comparison was lesser treatment with the aim of symptom control.

Outcomes

Overall survival, treatment complications and symptom control.

Study selection

An initial list of studies was selected by SA. NB then selected potentially relevant studies from this list on the basis of their title and abstract. These studies were ordered and each paper was checked against the inclusion criteria.

Data extraction and synthesis

One reviewer (NB) extracted data. Only published data were included and authors were not contacted.

Search results

The literature search identified ten studies, eight of which were included.

Description of included studies

Five studies were retrospective case series of liver metastases of unknown primary. One of these studies (Hawksworth et al, 2004) reported outcomes for patients treated with surgery or radiofrequency ablation for their liver metastases. One study (Adam et al, 2006) was a multi-centre series of patients treated with hepatic resection for noncolorectal nonendocrine liver metastases, which reported results for a sub-group of patients with unknown primary tumours.

Evidence summary

Overall survival

Surgery for liver metastases from unknown primary was relatively uncommon. In the largest CUP liver series (Ayoub et al, 1998) only 8% of patients received surgery, and their outcomes were not reported separately. The proportion of patients receiving surgery ranged from 2 to 5% to from in the other included CUP-liver series (Hogan et al, 2002; Lazaridis et al, 2008; Pouessel et al, 2005).

Hawksworth et al (2004) reported outcomes in a group of seven patients treated with local therapy (radio frequency ablation or surgery). Although follow-up was limited some patients had good survival outcomes. For those treated with radiofrequency ablation: at last follow up two patients had died of their disease at 3 and 6 months respectively, one patient was alive with no evidence of disease at 4 years post treatment, another was alive with disease at 2.25 years after treatment. For

those treated with surgery: at last follow up all three patients were alive with disease at 5, 9 and 12 months post-op respectively

Adam et al (2006) reported a large multi centre series of patients with liver metastases from non-colorectal non-endocrine primary tumours. In this study the 29 patients with unknown primary tumours had a median survival of 30 months and 5 year overall survival probability of 38%. It is unclear how many of the patients with unknown primary tumours had single liver metastases, but the patients in this study represented a highly selected group. Adam et al (2006) estimated that less than ten percent of patients with non-colorectal non-endocrine liver metastases were candidates for liver resection.

SYMPTOM CONTROL

None of the studies reported this outcome.

TREATMENT COMPLICATIONS

Hawksworth et al (2004) reported no treatment related complications in their series of seven patients treated with either surgery or radiofrequency ablation.

References

Adam R, Chiche L, Aloia T, Elias D, Salmon R, Rivoire M, Jaeck D, Saric J, Le Treut YP, Belghiti J, Mantion G, Mentha G. *Hepatic Resection for Noncolorectal Nonendocrine Liver Metastases*. Annals of Surgery 2006; 244: (4) 524-535

Ayoub J-P. *Unknown primary tumors metastatic to liver*. Journal of Clinical Oncology 1998; 16: (6) 2105-12

Hawksworth J, Geisinger K, Zagoria R, Kavanagh P, Howerton R, Levine EA, et al. *Surgical and ablative treatment for metastatic adenocarcinoma to the liver from unknown primary tumor*. American Surgeon 2004; 70: (6) 512-7

Hogan BA. *Hepatic metastases from an unknown primary neoplasm (UPN): Survival, prognostic indicators and value of extensive investigations*. Clinical Radiology 2002; 57: (12) 1073-7

Lazaridis G, Pentheroudakis G, Fountzilas G, Pavilidis N. *Liver metastases from cancer of unknown primary (CUPL): A retrospective analysis of presentation, management and prognosis in 49 patients and systematic review of the literature.*. Cancer Treatment Reviews 2008; 34:693-700

Pouessel D. *Hepatic metastases from carcinomas of unknown primary site: Experience of the montpellier cancer center*. Gastroenterologie Clinique et Biologique 2005; 29: (12) 1224-32

20. Radical local treatment for isolated liver metastasis of unknown primary

Last updated: 30 / 10 / 2009.

Characteristics of included studies

Adam-2006

Methods	Meta-analysis of retrospective case series of patients with non-colorectal liver metastases treated with hepatic resection. 41 institutions contributed data from patients treated between 1983 and 2004.
Participants and Country	1452 patients: 56% had a solitary liver metastasis and 83% had less than four liver metastases. 29 patients had an unknown primary tumour.
Interventions	All patients had surgical resection of liver metastases. 42% of patients had chemotherapy before surgery: chemotherapy made previously unresectable lesions resectable in 8% of patients. Primary tumours had been surgically resected in 90% of patients, and primary tumours were treated with preoperative and postoperative chemotherapy in 13% and 42% of patients respectively.
Outcomes	**Median overall survival** Breast primary tumours (N=460) 45 months G.I. primary tumours (N=230) 26 months Urologic primary tumours (N=206) 51 months Melanoma primary tumours (N=148) 20 months Gynaecologic primary tumours (N=126) ranged from 32 months for uterine primary tumours to 98 months for ovarian primary Pancreaticobiliary primary tumours (N=84) ranged from 20 months for exocrine pancreatic primary tumours to 38 months for ampullary primary Head & neck and pulmonary primary tumours (N=50) 18 and 16 months respectively Unknown primary tumours (N=29) 30 months **5 year overall survival** Breast primary tumours (N=460) 41% G.I. primary tumours (N=230) 31% Urologic primary tumours (N=206) 48% Melanoma primary tumours (N=148) 21% Gynaecologic primary tumours (N=126) 48% Pancreaticobiliary primary tumours (N=84) 27% Head, neck and pulmonary primary tumours (N=50) 15% Unknown primary tumours (N=29) 38% **Prognostic model**

	The authors developed a multivariate prognostic model to predict survival after hepatectomy. The model included the following risk factors: extrahepatic metastases, major hepatectomy, R2 resection, patient age, interval between primary tumour treatment and metastasis, tumour site and tumour histology.
Notes	

Ayoub-1998

Methods	Retrospective case series of patients with liver metastases of unknown primary referred to a single institution between 1987 and 1995
Participants and Country	365 patients with liver metastases.
Interventions	Therapy was: chemotherapy 216/365 (59%), surgery 29/365 (8%), radiotherapy 41/365 (11%) and supportive care only 144/365 (39%). Some patients received more than one type of treatment.
Outcomes	**Overall survival** The survival data for patients with isolated metastases or those treated with surgery or radiotherapy was not reported separately.
Notes	

Hawksworth-2004

Methods	Retrospective case series of patients treated with surgery or radiofrequency ablation for adenocarcinoma liver metastases of unknown primary. All patients were treated at a single institution between 1999 and 2003.
Participants and Country	Seven patients: 2 with 2 liver lesions and 5 with a single liver metastasis.
Interventions	4/7 patients received radiofrequency ablation (percutaneous CT-guided), one received wedge resection and the other two hepatectomy. 5/7 patients received chemotherapy (not specified).
Outcomes	**Overall survival in those treated with RFA** At last follow up two patients had died of their disease at 3 and 6 months respectively, one patient was alive with no evidence of disease at 4 years post treatment, another was alive with disease at 2.25 years after treatment. **Overall survival in those treated with surgery** At last follow up all three patients were alive with disease at 5, 9 and 12 months post-op respectively. **Treatment complications of surgery or radiofrequency ablation** The authors reported that there were no complications
Notes	

Hogan-2002

Methods	Retrospecive case series of patients with adenocarcinoma liver metastases of unknown primary
Participants and Country	62 patients. 7 patients had a single liver metastasis and 55 had multiple metastases.
Interventions	46/62 patients received palliative care only. 16/62 received active treatment: chemotherapy alone 11/16, chemotherapy plus radiotherapy 2/16, surgery alone 1/16, surgery plus chemotherapy 1/16, surgery plus chemotherapy plus radiotherapy 1/16.
Outcomes	**Overall survival**

	Median survival for the seven patients with a single liver metastasis was 77 days compared with 44 days for the 55 patients with multiple metastases. Median overall survival for patients receiving active treatment was 52 days compared with 49 days for those who received palliative care only. The survival of the three patients treated with surgery was not reported separately.
Notes	

Lazaridis-2008

Methods	Retrospective case series of patients with liver metastases from cancer of unknown primary, referred to any of the Hellenic Cooperative Oncology Group Centres between 1999 and 2007.
Participants and Country	49 patients: the number of liver metastases was not reported.
Interventions	47 patients received first line chemotherapy, 2 had surgery and 4 had radiotherapy.
Outcomes	The outcomes for patients receiving surgery or radiotherapy were not reported separately. **Median overall survival** for the group as a whole was ten months. On multivariate analysis the following favourable prognostic factors were identified: age less than 55 years and metastases confined to the liver. **Treatment toxicities.** The most common haematologic toxicities were neutropenia and anaemia associated with chemotherapy. The most frequent non-haematologic toxicities were gastrointestinal.
Notes	

Pouessel-2005

Methods	Retrospective case series of patients with liver metastases of unknown primary treated at a single institution between 1993 and 2002.
Participants and Country	118 patients, 20 with single liver metastasis and 98 with multiple liver metastases.
Interventions	107/118 (91%) patients received chemotherapy. 3/118 (2.5%) patients were treated with surgery
Outcomes	Outcomes for patients treated with surgery or radiotherapy were not reported separately **Overall survival** 6 month overall survival was 65% for patients with isolated liver metastasis compared with 49% for those with multiple metastases (P=0.180).
Notes	

References for included studies

ADAM 2006
Adam R, Chiche L, Aloia T, Elias D, Salmon R, Rivoire M, Jaeck D, Saric J, Le Treut YP, Belghiti J, Mantion G, Mentha G. Hepatic Resection for Noncolorectal Nonendocrine Liver Metastases. Annals of Surgery 2006; 244 (4) 524-535

AYOUB 1998
Ayoub J-P. Unknown primary tumors metastatic to liver. Journal of Clinical Oncology 1998; 16 (6) 2105-12

HAWKSWORTH 2004
Hawksworth J, Geisinger K, Zagoria R, Kavanagh P, Howerton R, Levine EA, et al. Surgical and ablative treatment for metastatic adenocarcinoma to the liver from unknown primary tumor. American Surgeon 2004; 70 (6) 512-7

HOGAN 2002
Hogan BA. Hepatic metastases from an unknown primary neoplasm (UPN): Survival, prognostic indicators and value of extensive investigations. Clinical Radiology 2002; 57 (12) 1073-7

LAZARIDIS 2008
Lazaridis G, Pentheroudakis G, Fountzilas G, Pavilidis N. Liver metastases from cancer of unknown primary (CUPL): A retrospective analysis of presentation, management and prognosis in 49 patients and systematic review of the literature.. Cancer Treatment Reviews 2008; 34 () 693-700

POUESSEL 2005
Pouessel D. Hepatic metastases from carcinomas of unknown primary site: Experience of the montpellier cancer center. Gastroenterologie Clinique et Biologique 2005; 29 (12) 1224-32

Cancer of Unknown Primary clinical guideline

Radical local treatment for isolated bone, lung or skin metastasis of unknown primary

Last updated: 24/ 7/ 2009.

Short summary

There was no direct evidence about the radical local treatment of isolated bone, lung or skin metastases from unknown primary.

Rationale

See rationale for radical local treatment for isolated brain metastasis of unknown primary.

Methods

STUDY TYPES
There was no restriction on study design.

PARTICIPANTS
People with confirmed cancer of unknown primary presenting with a single metastasis involving bone, lung or skin.

INTERVENTIONS
Radical treatment (surgery, radiotherapy, or other local therapy) aiming to achieve total control of local disease. The comparison was lesser treatment, such as palliative radiotherapy with aim of symptom control.

OUTCOMES
Overall survival, treatment complications and symptom control.

STUDY SELECTION
An initial list of studies was selected by the information specialist (SA). One reviewer (NB) then selected potentially relevant studies from this list on the basis of their title and abstract. These studies were ordered and checked against the inclusion criteria.

DATA EXTRACTION AND SYNTHESIS
One reviewer (NB) extracted data.

Search results

The literature search for isolated bone metastasis studies identified eight papers, but none were included. For lung metastases the literature search found eight papers but again none were included (although two papers were included from other sources). For skin metastases one paper was included from the 15 studies found in the search.

DESCRIPTION OF INCLUDED STUDIES
For pulmonary metastectomy there were three studies: one expert review (Seve, 2008), one retrospective case series of patients with known primary (Pastorino et al, 1997) and a lung cancer guideline which considered the treatment of isolated pulmonary metastasis (ACCP, 2007). One case report and literature review (Carroll et al, 2002) about isolated skin metastasis was also included.

Evidence summary

BONE METASTASES
Searches identified no studies about the treatment of solitary bone metastases of unknown primary. A number of studies discussed diagnostic strategies but none reported the outcomes of radical local treatment.

LUNG METASTASES
No directly relevant papers were identified. One expert review (Seve, 2008) suggested that single peripheral lung nodules of unknown primary are traditionally treated as primary lung cancer, but it provided no supporting evidence.

Pastorino et al (1997) analysed overall survival following pulmonary metastectomy in a multicentre series of 5026 patients. These patients had previously received curative treatment for their primary tumour. Multivariate analysis showed a better overall survival for patients with germ cell tumours and single metastases. For example, five year survival was 68% for patients with germ cell tumours compared with 37% for those with epithelial tumours. It is unclear, however, the extent to which metastectomy affected outcomes and whether equivalent outcomes could be expected in patients with unknown primary tumours.

Using such evidence from retrospective case series, the American College of Chest Physicians guidelines (ACCP, 2007) recommended that, in surgical candidates with a solitary pulmonary metastasis, pulmonary metastasectomy should be performed when there is no

evidence of extrapulmonary malignancy and there is no better available treatment.

SKIN METASTASES

Carroll et al (2002) reported the case of a woman with an isolated cutaneous metastasis of unknown origin. Their search of the literature did not find a standardised approach for the management of CUP presenting in this way. The patient was treated with wide local excision of the skin metastasis and was disease free at the last follow up visit one year after treatment.

References

ACCP. *Diagnosis and management of lung cancer: ACCP guidelines (2nd edition).. Chest* 2007; 132:1S-422S

Carroll MC, Fleming M, Chitambar CR, Neurberg M. *Diagnosis, workup and prognosis of cutaneous metastases of unknown primary origin. Dermatologic Surgery* 2002; 28: (6) 533-5

Pastorino U, Buyse M, Friedel G, Ginsberg RJ, Girard P, Goldstraw P, Johnston M, McCormack P, Pass H, Putnam JB. *Long term results of lung metastectomy: prognostic analyses based on 5026 cases. The Journal of Thoracic and Cardiovascular Surgery* 1997; 113: (1) 37-49

Seve P. *Clinical presentations of metastatic carcinomas of unknown origin. Metastatic carcinomas of unknown origin* 2008; 1-26

22. Systemic treatment guided by the supposed primary site for patients with brain metastases of unknown primary

Last updated: 30/ 10/ 2009.

Short summary

Evidence from case series, suggests chemotherapy is rarely used in the treatment of people with brain metastases of unknown primary. In 18 studies including over 350 patients it was only possible to extract data for three patients treated with chemotherapy (Maesawa et al 2000).

There is insufficient published evidence to reach a conclusion about the effectiveness of chemotherapy guided by the putative primary site in this group.

Randomised trials have investigated the addition of chemotherapy to WBRT for the treatment of brain metastases of known primary, typically in patients with non-small cell lung cancer. A systematic review of three such trials (Tsao et al, 2005) concluded that the use of chemotherapy in this group remains experimental, with insufficient evidence to judge its effectiveness.

Rationale

Patients with confirmed Cancer of Unknown Primary involving the brain, in addition to other sites, pose particular problems because of the generally bad prognosis associated with this presentation. The therapeutic nihilism which surrounds the management of this group of patients has led to an approach which involves providing symptomatic care (with some use of palliative cranial irradiation) rather than considering a more active approach combining brain radiotherapy and systemic therapy to try and control the disease. Factors such as the poor median survival of confirmed CUP patients with brain involvement, the belief that chemotherapy has limited efficacy in brain metastases because of the "blood-brain barrier", and the limited impact of chemotherapy in confirmed CUP have all led to the adoption of this cautious approach.

If evidence emerged that active treatment of confirmed CUP with brain metastases could result in favourable outcomes in a reasonable proportion of cases, or in defined subsets, then current management approaches would alter leading to more widespread use of chemotherapy in this group.

Methods

Study types

The ideal study design was a randomised controlled trial, but in the absence of such studies data from observational studies were included.

Participants

People with confirmed cancer of unknown primary with multiple brain metastases.

Interventions

Palliative cranial irradiation plus best supportive care with or without systemic treatment guided by the putative primary tumour.

Outcomes

Overall survival, treatment complications, symptom control and quality of life.

Study selection

An initial list of studies was selected by SA. NB then selected potentially relevant studies from this list on the basis of their title and abstract. These studies were ordered and checked against the inclusion criteria.

Data extraction and synthesis

One reviewer (NB) extracted data. Only published data were included and authors were not contacted.

Quality assessment

Study quality was assessed by one reviewer (NB) using the NICE checklists for intervention studies.

Heterogeneity assessment

There was no statistical assessment of heterogeneity.

Search results

The literature search found 52 studies of which 20 were included. Studies identified in the chemotherapy search (topics 27 and 28) were also checked for sub-group analyses of patients with brain metastases, but none

were found. A second search, for high quality evidence about WBRT and systemic therapy in people with brain metastases in general, identified one systematic review (Tsao et al, 2004).

DESCRIPTION OF INCLUDED STUDIES

18 case series of patients with brain metastases of unknown primary were included. All but one (Ruda et al 2001) were retrospective. Systemic chemotherapy was rarely used in these studies. The combined series included more than 356 patients but chemotherapy was only reported in seven cases. Outcome data for chemotherapy were only available for three patients in one study (Maesawa et al 2000), and the regimen was not reported.

Eight series reported outcomes after palliative WBRT plus supportive care, nine series included patients treated with surgery before WBRT

Due to the lack of relevant chemotherapy studies in CUP, studies in patients with known primary tumour were included as indirect evidence. A systematic review (Tsao et al, 2004) summarised three randomised trials of chemotherapy for brain metastases in patients with known primary (mostly lung cancer). Two studies compared combined chemotherapy and WBRT to WBRT alone (Ushio et al 1991; Antonadou et al 2002). One study compared early with delayed WBRT in addition to chemotherapy (Robinet et al, 2001). The chemotherapy used in Ushio et al (1991) and Antonadou et al (2002) (chloroethylnitrosourea and temozolomide respectively) was directed at the brain metastases rather than the primary tumour itself. Robinet et al (2001) used cisplatin and vinorelbine which could be considered appropriate for non-small cell lung cancer.

STUDY QUALITY

No studies attempted to evaluate systemic therapy for patients with CUP and brain metastases. The evidence from observational studies was sparse and of low quality. The only randomised studies were in patients with known tumours and had limited applicability to the review question.

Evidence summary

OVERALL SURVIVAL

Patients with CUP

There was very little data about survival after chemotherapy plus WBRT in this population. One series (Maesawa et al, 2000) included individual patient data and it was possible to construct a Kaplan Meier plot comparing survival in patients treated with chemotherapy, radiosurgery and WBRT to those treated with radiosurgery and WBRT only (see Figure 1). There was no statistically significant difference in survival between the two groups but it is inappropriate to draw any conclusions about the effectiveness of chemotherapy based on a non-randomised study of 3 patients treated with an unknown regimen.

Data about median overall survival in patients treated with WBRT plus supportive care are presented in Table 22.1. Overall survival data for those treated with surgery (or radiosurgery) plus WBRT are presented in Table 22.2. Median survival ranged from two to 10.5 months. Series of patients treated with surgery or radiosurgery before WBRT tended to have better median overall survival, ranging from six to 21 months, possibly due to careful case selection for surgery.

Patients with known primary tumours

In their systematic review Tsao et al (2005) concluded that the use of chemotherapy as primary or adjuvant therapy for brain metastases remains experimental. The chemotherapy trials included in the Tsao et al (2005) review were probably underpowered to detect differences in overall survival. Guerrieri et al RCT (2004) calculated that at least 300 patients would be required in their trial of the addition of chemotherapy to WBRT for the treatment of brain metastases. Guerrieri et al (2004) failed to recruit this number, stopping their trial with inconclusive results after recruiting only 44 patients.

Nussbaum et al (1996) reported a large series of patients with brain metastases, some of whom received chemotherapy. Multivariate analysis showed a statistically significant benefit for chemotherapy on survival, but no hazard ratio was reported so it is unclear whether this effect was clinically significant.

TREATMENT COMPLICATIONS

Patients with CUP

No data about complications due to combined WBRT and chemotherapy were available. Some studies reported treatment toxicity following surgery and/or WBRT. Ruda et al (2001) reported late radiation dementia in 1/33 patients treated with surgery plus WBRT. Rades et al (2007) reported acute toxicity rates of 3% and 5% in patients receving long and short course WBRT respectively.

Treatment toxicities associated with chemotherapy for CUP are summarised in the evidence review for topic 27.

Patients with known primary tumours

In their systematic review Tsao et al (2004) comment that the addition of chemotherapy to WBRT increases toxicity. In one of the studies, examining the timing of WBRT and chemotherapy, the rate of death due to treatment toxicity was 8% (Robinet et al 2001). Ushio el al (1991) reported a toxic death rate of 3%. The third trial. Antonadu et al (2002) was published in abstract form only and did not report toxicity.

Guerrieri et al (2004) report that the addition of chemotherapy to WBRT did not lead to significant

increase in gastrointestinal or haematological toxicity in their randomised trial. Their trial was stopped early, however, and underpowered to detect moderate differences in toxicity.

Tsao et al (2004) also summarised the acute toxicity associated with WBRT alone in patients with known primary tumours, using data from five trials of WBRT dose. The rate of acute toxicity associated with WBRT (30 Gy in ten fractions) ranged from 8% to 35%. Acute toxicities included: nausea, vomiting, headache and increased neurological symptoms.

SYMPTOM RELIEF

Patients with CUP

Symptom relief was poorly reported and there were no comparative data about the relative effectiveness of systemic therapy plus WBRT versus other treatments for the relief of symptoms.

Kirschberger et al (1983) reported symptom relief in 7/9 CUP patients treated with WBRT. Chee (1991) reported that neurological symptoms improved in 15/19 patients after surgery for brain metastases of unknown primary.

Patients with known primary tumours

Guerrieri et al (2007) reported symptom relief in 6/21 (29%) patients treated with WBRT plus chemotherapy compared with 8/21(38%) of those treated with WBRT alone in a randomised trial in patients with brain metastases from non-small cell lung cancer.

Petrovich et al (2002) reported that good to excellent palliation was achieved in 79% of patients with neurology symptoms treated with radiosurgery for brain metastases. Tsao et al (2004) found no data relating symptom relief to the use of systemic therapy, in their systematic review of trials in patients with brain metastases of known primary.

QUALITY OF LIFE

None of the CUP series reported quality of life and the review Tsao et al (2004) found no data about quality of life in patients with known primary tumours and brain metastases.

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Table 22.1 Palliative radiotherapy series of patients with brain metastases of unknown primary

Study	Population	N (WBRT)	WBRT details	Median OS (mths) WBRT	N (WBRT + chemo)	WBRT plus systemic therapy details	Median OS (mths) systemic therapy	Statistical comparison
Bartelt 2003	Patients with brain metastases of unknown primary	32	WBRT	3.6	None	-	-	-
Debevec 1990	Patients with brain metastases of unknown primary	40	WBRT	4	not reported	not reported	not reported	not reported
Hamann 1993	Patients with brain metastases of unknown primary	33	Not reported	5.1**	not reported	not reported	not reported	not reported
Khansur 1997	Patients with brain metastases of unknown primary	32	WBRT	4.5	2	not reported	not reported	not reported
Kirschberger 1983	Patients with brain metastases of unknown primary	8	WBRT	2.2	not reported	not reported	not reported	not reported
Kurtz 1981	Patients with brain metastases of unknown primary (subgroup of a larger trial)	12	WBRT 30 or 50 Gy in 2 or 4 weeks respectively	10.5	not reported	not reported	not reported	not reported
Nguyen 1998	Patients with brain metastases as the only manifestation of an unknown primary	15	WBRT	<12	none	-	-	-
Rades	Patients with brain metastases of unknown primary	101	WBRT plus corticosteroids	4	not reported	not reported	not reported	not reported
Shaw 2007	Patients with brain metastases of unknown primary	21	Cranial radiotherapy alone or supportive care	2.0	none	-	-	-

* from metastasis to death.
** combined results from 33 patients with CUP and 46 with known primary.
Abbreviations: OS, overall survival; WBRT, whole brain radiotherapy;

Table 22.2 Surgical series of patients with brain metastases from unknown primary tumour

Study	Population	N (Surgery+WBRT)	Surgery + WBRT details	Median OS (mths) Surgery +WBRT	N (Surgery, WBRT + chemo)	Chemotherapy details	Median OS (mths) Surgery, WBRT + chemo	Statistical comparison
Chee 1990	Patients with brain metastases of unknown primary	not reported	No WBRT reported, patients had surgery and/or corticosteroids.		1	not reported	not reported	not reported
D'Ambrosio 2007	Patients with brain metastases of unknown primary and favourable prognosis	32	WBRT plus surgery or radiosurgery	13.7	not reported	not reported	not reported	not reported
Debevec 1990	Patients with brain metastases of unknown primary	29	All had WBRT, 22 had complete resection and 7 partial resection	9.5 and 2 for complete and partial resection respectively	not reported	not reported	not reported	not reported

Study	Population	N (Surgery+WBRT)	Surgery + WBRT details	Median OS (mths) Surgery +WBRT	N (Surgery, WBRT + chemo)	Chemotherapy details	Median OS (mths) Surgery, WBRT + chemo	Statistical comparison
Eapen 1988	Patients with brain metastases of unknown primary and no extra-cranial metastases	39	39 had WBRT, 29 had surgical resection.	6 (for the entire group)	1	Cyclophosphamide and lomustine.	not reported	not reported
Maesawa 2000	Patients with brain metastases of unknown primary	11	WBRT and radiosurgery	21	3	WBRT, radiosurgery and chemotherapy (not specified)	4	Log-rank statistic= 1.26, P=0.24 (calculated from individual patient data)
Mairui 1998	Patients with brain metastases of unknown primary (subgroup of a larger series)	not reported	All had surgical resection and 75% had WBRT	16.5	not reported	not reported	not reported	not reported
Petrovich 2002	Patients with brain metastases of unknown primary (subgroup of a larger trial)	14	Radiosurgery (plus WBRT in some cases).	6	not reported	not reported	not reported	not reported
Ruda 2001	Patients with brain metastases of unknown primary	33	All had WBRT, 21/33 had surgery	10	None	-	-	-
Shaw 2007	Patients with brain metastases of unknown primary	5	Surgery plus WBRT	13.5 (mean)	None	-	-	-

Abbreviations: OS, overall survival; WBRT, whole brain radiotherapy;

Table 22.3 Outcomes after WBRT with or without systemic therapy in people with brain metastases of known primary

Study	Population	N (WBRT)	WBRT details	Median OS (mths) WBRT	N (WBRT + chemo)	WBRT + chemotherapy details	Median OS (mths) chemotherapy	Statistical comparison
Guerrieri 2004	Patients with non-small cell lung cancer and brain metastases	21	WBRT plus corticosteroids at the discretion of the treating doctor	4.4 [95% C.I. 2.0 to 5.1]	21	WBRT plus carboplatin before every radiation dose plus corticosteroids at the discretion of the treating doctor.	3.7 [95% C.I. 3.0 to 4.8]	No statistically significant difference (HR not reported, P=0.64)
Nussbaum 1996	Patients with brain metastases (5% of unknown primary)	not reported	WBR plus corticosteroids	not reported	140	WBRT, chemotherapy (not specified) plus corticosteroids	not reported	On multivariate analysis chemotherapy was associated with improved survival (HR=not reported;P=0.03)
Kurtz 1981	Patients with brain metastases (6% of unknown primary)	240	WBRT	4.3	15	WBRT plus unspecified chemotherapy	5	Not reported
Ushio 1991*	Patients with brain metastases from lung primary	31	WBRT	6.8	69	WBRT plus nitrosurea (N=36), WBRT plus nitrosurea plus tegafur (N=33)	7.3 and 6.0 with and without tegafur respectively	No statistically significant difference (HR not reported)

Study	Population	N (WBRT)	WBRT details	Median OS (mths) WBRT	N (WBRT + chemo)	WBRT + chemotherapy details	Median OS (mths) chemotherapy	Statistical comparison
Robinet 2001*	Patients with brain metastases from non-small cell lung primary	None	-	-	171	Early (N=85) or delayed WBRT (N=86) with cisplatin and vinorelbine	5.3 and 6.0 for early and delayed WBRT respectively	No statistically significant difference (HR not reported; P=0.83)
Antonadu 2002*	Patients with brain metastases (82% from lung primaries)	N.R.	WBRT	6.3	N.R.	WBRT and temozolomide	8.3	No statistically significant difference (HR not reported; P=0.179)

* From the Tsao et al (2005) systematic review.

Figure 22.1 Survival functions derived from individual patient data in Maesawa et al (2000).

22. Systemic treatment guided by the supposed primary site for patients with brain metastases of unknown primary

Last updated: 30 / 10 / 2009.

Characteristics of included studies

Bartelt-2003

Methods	Retrospective case series of patients treated with WBRT at a single institution between 1985 and 2000
Participants and Country	Patients with cancer of unknown primary. Germany
Interventions	WBRT
Outcomes	Overall survival
WBRT fractionation	50 or 30 Gy in fractions of 2 or 3 Gy respectively
Notes	

Chee-1990

Methods	Retrospective case series of patients with brain metastases from unknown primary presenting to a department of Neurosurgery between 1973 to 1984.
Participants and Country	33 patients. UK
Interventions	Surgery (N=19), adjuvant chemotherapy (N=1), steroids and anticonvulsants (N=10), not specified (N=4).
Outcomes	Neurological outcome (quality of life), one-month mortality, overall survival.
WBRT fractionation	Not reported
Notes	19/33 (56%) lost to follow up

D-Ambrosio-2007

Methods	Retrospective case series of patients with CT diagnosed brain metastases at a single institution between 1983 and 1998.
Participants and Country	122 patients with brain metastases of unknown primary. Switzerland (220 patients with known primary tumours were included for comparison).
Interventions	Surgery plus WBRT (46/122, 38%), radiosurgery plus WBRT (4/122, 3%), WBRT only (45/122, 37%), or corticosteroids (27/122, 22%).
Outcomes	Not reported
WBRT fractionation	Overall survival
Notes	

Debevec-1990

Methods	Retrospective case series of patients treated at a single institution between 1973 and 1987.
Participants and Country	75 patients with brain metastases of unknown origin. Yugoslavia
Interventions	WBRT in all cases, surgery in 35/75 patients.
Outcomes	Overall survival
WBRT fractionation	30 Gy in ten fractions
Notes	

Eapen-1988

Methods	Retrospective case series of patients with brain metastases of unknown primary (and no other sites of metastases) presenting to a single institution between 1970 and 1983.
Participants and Country	43 patients. Canada.
Interventions	WBRT (39/43), surgical resection (29/43) and biopsy (5/43). One patient had chemotherapy (cyclophosphamide and CCNU)
Outcomes	Overall survival, detection of primary tumour
WBRT fractionation	Most received 30 to 40 Gy in 10 to 20 fractions.
Notes	

Guerrieri-2004

Methods	Randomised controlled trial
Participants and Country	42 patients with non-small cell carcinoma of the lung. Australia
Interventions	WBRT alone or WBRT plus carboplatin (70 mg/m^2 IV for 5 days)
Outcomes	Overall survival, objective response, symptom control and toxicity
WBRT fractionation	20 Gy in 5 fractions
Notes	Trial planned to enroll 300 patients but was stopped early due to poor accrual.

Hamann-1993

Methods	Retrospective case series comparing patients with brain metastases of known and unknown primary
Participants and Country	122 patients with CUP and 121 patients with known primary.
Interventions	Therapy groups were: none (n=24), cortisone (n=117), cortisone plus surgery (n=15), cortisone plus radiotherapy (n=69). 28 patients received various forms of chemotherapy.
Outcomes	Overall survival
WBRT fractionation	Not reported
Notes	Survival by treatment group is not reported separately for patients with CUP.

Khansur-1997

Methods	Retrospective case series of patients with brain metastases of unknown primary
Participants and Country	32 patients. USA
Interventions	WBRT plus dexamethasone (N=32). Chemotherapy (N=2).
Outcomes	Overall survival, recurrence, diagnosis of primary tumour
WBRT fractionation	30 Gy to 54 Gy in 10 to 30 fractions
Notes	

Kirschberger-1983

Methods	Retrospective case series of patients with brain metastases of unknown primary presenting to a single institution between 1981 and 1983
Participants and Country	35 patients. Germany
Interventions	WBRT
Outcomes	Overall survival
WBRT fractionation	Total dose of 30 to 40 Gy, using 5 X 2 Gy or 4 X 2.5 Gy per week fractions.
Notes	German language

Kurtz-1981

Methods	RCT
Participants and Country	255 patients with brain metastases. 12/255 (5%) had unknown primary tumours. USA
Interventions	WBRT (30 Gy vs 50 Gy)
Outcomes	Overall survival, symptom relief, neurologic function
WBRT fractionation	30 or 50 Gy in 2 or 4 weeks respectively
Notes	

Maesawa-2000

Methods	Retrospective case series of patients with brain metastases of unknown primary treated with radiosurgery at a single institution between 1988 and 1998.
Participants and Country	15 patients. USA
Interventions	Stereotactic radiosurgery in all cases, WBRT (14 patients), Chemotherapy (3 patients)
Outcomes	Overall survival, control of brain metastases
WBRT fractionation	30 to 50 Gy (mean 37 Gy)
Notes	

Maiuri-1998

Methods	Retrospective case series of patients with brain metastases treated with surgery at a single institution between 1976 and 1993
Participants and Country	240 patients (27 with CUP). Italy
Interventions	Surgery in all cases (175/240 complete resection, 65/240 partial resection. 180/240 WBRT
Outcomes	Overall survival
WBRT fractionation	36 Gy in 18 fractions
Notes	

Nguyen-1998

Methods	Retrospective case series of patients treated for brain metastasis of unknown primary tumour at a single institution between 1977 and 1996, with no extracranial metastases.
Participants and Country	39 patients. USA
Interventions	WBRT in all cases. Surgical resection in some cases (24/39).
Outcomes	Overall survival (from the first day of radiotherapy), intracranial disease free survival.
WBRT fractionation	30 Gy in ten fractions
Notes	

Nussbaum-1996

Methods	Retrospective case series of patients treated for brain metastases at a single institution between 1973 and 1993.
Participants and Country	729 patients. 33/729 (5%) had unknown primary tumour. USA
Interventions	Surgery, radiotherapy and chemotherapy, depending on performance status and life expectancy.
Outcomes	Overall survival
WBRT fractionation	30 Gy in 10 fractions
Notes	

Petrovich-2002

Methods	Retrospective case series of patients treated with radiosurgery for brain metastases at a single institution 1994 and 2002.
Participants and Country	458 patients. 14/458 had unknown primary tumour. USA
Interventions	Gamma knife radiosurgery. 114/458 received WBRT
Outcomes	Overal survival, tumour control, treatment toxicity
WBRT fractionation	Not reported, most received WBRT in another institution
Notes	

Rades-2007

Methods	Retrospective case series of CUP patients who received either short course or long-course WBRT for brain metastases
Participants and Country	101 patients with CUP.
Interventions	Short course WBRT (n=34) long-course WBRT (n=67)
Outcomes	Overall survival, intracerebral control
WBRT fractionation	Short-course RT was 20 Gy in 5 fractions (5 x 4 Gy) given over 5 days. Long course WBRT was 10 x 3 Gy given over 2 weeks or 20 x 2 Gy given over 4 weeks.
Notes	Paper not in file

Ruda-2001

Methods	Retrospective case series of patients with biopsy proven brain metastasis and unknown primary tumour treated in a single institution between 1987 and 1996.
Participants and Country	33 patients. Italy
Interventions	WBRT in all cases. Surgery in 22/33 cases
Outcomes	Overall survival
WBRT fractionation	30 to 50 Gy in 2 or 3 Gy fractions
Notes	

Shaw-2007

Methods	Retrospective case series of patients diagnosed with CUP in a single cancer centre during 2003.
Participants and Country	166 patients in total. 26 patients had CUP with brain metastases (16%). UK
Interventions	17 had WBRT, five patients underwent craniotomy, none had chemotherapy
Outcomes	Overall survival
WBRT fractionation	Not reported
Notes	

Tsao-2005

Methods	Systematic review of randomised controlled trials.
Participants and Country	Patients with brain metastases. Five trials were included with a total of 601 patients.
Interventions	WBRT and chemotherapy. Each trial examined a different drug: chloroethylnitro-soureas, tegafur, teniposide, fotemustine and temozolomide.
Outcomes	Median survival, response rate, control of brain tumour.
WBRT fractionation	
Notes	

Yuile-2002

Methods	Retrospective case series of patients undergoing palliative cranial radiation for intracranial metastases in the years 1993-1998.
Participants and Country	378 patients. Australia
Interventions	WBRT
Outcomes	Overall survival
WBRT fractionation	
Notes	Full paper not in file

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23. Chemotherapy for people with Cancer of Unknown Primary not belonging to a recognised syndrome

Last updated: 30/ 10/ 2009.

Short summary

Evidence about chemotherapy for CUP comes from small phase II trials. There was no strong evidence of the optimal chemotherapy regimen for the treatment of people with CUP not belonging to a recognised subgroup.

No studies have been designed to compare chemotherapy with supportive care alone in patients with CUP. Observational studies report poorer overall survival in patients treated with supportive care only than in those treated with chemotherapy. However, evidence suggests that fitter patients tend to receive chemotherapy and this could explain the differences in survival.

Evidence from phase II trials suggested slightly better median survival and treatment response rates with platinum or platinum/taxane based regimens than with fluorouracil / anthracycline regimens, at the cost of greater treatment toxicity.

Rationale

In common with patients who have metastatic cancer from a known primary, confirmed CUP patients are often candidates for systemic therapy (chemotherapy or hormonal therapy) given with the aim of eradicating as much cancer as possible, to achieve a symptomatic and survival benefit.

For patients with confirmed Cancer of Unknown Primary, the evidence for justifying chemotherapy treatment (on the basis of demonstrated benefit over supportive care alone), and for selecting particular regimens (on the basis of a satisfactory balance of efficacy and toxicity) is far more limited than for the common solid tumours. To date, studies to define optimal chemotherapy have almost exclusively been either small phase II trials of various regimens, without control arms, or retrospective analyses of treatment policies aiming to identify favourable outcomes based on treatment and patient factors.

The paucity of high quality data about treatment benefits, combined with the generally low levels of health gain seen, have led some authorities to question the value of the general use of chemotherapy in confirmed CUP.

Methods

Study types

Any study comparing chemotherapy with supportive care. Prospective clinical trials of chemotherapy and retrospective case series were also included. Studies published before 1980 or with less than ten patients were excluded.

Participants

People with cancer of unknown primary who did not belong to a subgroup with well defined treatment. This meant the exclusion of those with predominantly midline (nodal) disease, female patients with predominantly peritoneal disease or unilateral axillary lymphadenopathy, those with isolated or predominantly cervical (neck) lymphadenopathy and those with metastatic carcinoma with neuroendocrine differentiation.

Interventions

First line cytotoxic chemotherapy (using any regimen) or supportive care.

Outcomes

Overall survival treatment response rate, treatment toxicity and quality of life.

Study selection

An initial list of studies was selected by the information specialist (SA). One reviewer (NB) then selected potentially relevant papers from this list on the basis of their title and abstract. These studies were ordered and the reviewer checked each paper against the inclusion criteria.

Data extraction and synthesis

One reviewer extracted outcome data from the papers.

QUALITY ASSESSMENT

Study quality (risk of bias) was assessed using the NICE checklists for critical appraisal.

HETEROGENEITY ASSESSMENT

Differences in the study populations and the chemotherapy regimens were noted in tables (see below). Studies were organised into three sub groups: 5-fluorouracil / anthracycline based regimens, platinum based regimens and platinum-taxane based regimens.

Search results

The literature search identified 185 studies published between 1981 and 2008, of which 79 were included.

DESCRIPTION OF INCLUDED STUDIES

Randomised studies

Ten trials were included, all phase II studies exploring efficacy and toxicity in small numbers of patients.

Non-randomised prospective studies

54 phase II studies were included.

Retrospective studies

Thirteen observational studies reported chemotherapy case series or cancer registry data.

Six of these studies compared outcomes in sub groups of patients who did or did not receive chemotherapy. Five were retrospective case series and one was a Canadian population based study (Seve et al, 2006). Two French studies were limited to patients with liver metastases (Pouessel et al 2005; Mousseau et al 1991), one study was limited to poorly differentiated carcinoma or adenocarcinoma (Lenzi et al 1997) and the remaining three included any patient with CUP (Sumi et al 2001; Seve et al 2006 and Shaw et al 2007).

Chemotherapy regimens used

The studies investigated a variety of combination chemotherapy regimens over the period 1980 to 2008 (see Table 23.7 and Figure 23.1). The earliest trials used 5-fluorouracil, doxorubicin plus mitomycin-C (FAM) or cisplatin (FAP). In the 1990s platinum based chemotherapy (cisplatin and carboplatin) was investigated more widely. From the year 2000 studies began to use taxanes (paclitaxel and docetaxel) and from 2003 onwards trials investigated the addition of irinotecan, capecitabine and gemcitabine to combination chemotherapy. Greco et al (2008) examined the biological agents erlotinib and bevacizumab in combination with taxane/platinum chemotherapy.

STUDY QUALITY

Selection and allocation bias

Trial inclusion criteria often stated a minimum life expectancy and performance status: it is possible that patients selected for trials were not representative of the true CUP population.

Observational studies comparing chemotherapy with supportive care had a high risk of allocation bias, because patients were not randomised to receive treatment. The decision to offer chemotherapy involved consideration of the patient's performance status, comorbidity and life expectancy. In a multivariate analysis, Seve et al (2006) reported that young age, no or mild comorbidity, lymph node and pleural involvement and a good performance status were all independently associated with the likelihood of a CUP patient receiving chemotherapy. For these reasons it is likely that patients offered chemotherapy had a better prognosis than patients who received supportive care only.

Some of the studies attempted to control for the differences between chemotherapy and non-chemotherapy groups.

Changing definitions of CUP

During the late 1980s the notion of treatable CUP syndromes emerged. This means that earlier studies contained a significant proportion of patients with treatable syndromes whereas the later studies, of platinum/taxane regimens, tended to include only patients not belonging to a subgroup with well defined treatment. This would tend to enhance the apparent effectiveness of the treatments used in the earlier trials.

Differences in the diagnostic criteria for CUP could lead to bias. Due to lead time bias, the sooner CUP is diagnosed and treated the longer overall survival (if survival is measured from the initiation of treatment).

Evidence summary

Chemotherapy versus no chemotherapy

Median survival ranged from 4 to 16 months in patients treated with chemotherapy compared with 0.6 to 13 months in patients receiving supportive care only (see Table 23.1). In studies reporting unadjusted comparisons, median survival tended to be much lower in the supportive care group than in chemotherapy group (Lofts et al 1999; Mousseau et al 1991; Shaw et al 2007; Sumi et al 2006). When studies adjusted for prognostic factors, however, the difference between groups in overall survival either disappeared (Seve et al 2006; Lenzi et al 1997) or was less marked (Pouessel et al, 2005).

There were no data about other outcomes. It would be reasonable to assume that patients treated with supportive care only would be spared the treatment toxicity associated with chemotherapy at the possible expense of symptomatic benefit.

Randomised comparisons of chemotherapy regimens

In general the randomised phase II trials did not find statistically significant differences in overall survival or treatment response between regimens (see Table 23.2). It is likely that these studies were underpowered to

detect such differences. Some authors reported significant differences in the toxicity profiles of the regimens under investigation (Miliken et al, 1987; Culine et al 2003; Eagan et al 1987).

Golfinopoulos et al (2009) used multiple comparisons meta-analysis to estimate the relative effectiveness of the regimens used in these randomised trials. Their analysis used five categories: platinum without taxane, taxane without platinum, platinum plus taxane, non-platinum non-taxane monotherapy and non-platinum non-taxane combination therapy. The resulting confidence intervals were too wide to draw any conclusions about the relative effectiveness of the regimens. This is not surprising as many of the trials were phase II studies with low statistical power.

Non randomised phase II trials and observational studies

The results of these trials were grouped according to regimen: fluorouracil/anthracycline based (see Table 23.3), platinum based (see Table 23.4) and platinum/ taxane based (see Table 23.5 Table 5).

Due to differences in patient populations, and chemotherapy regimens it was not appropriate to combine the results in statistical meta-analysis. The ranges of values for each outcome are given in Table 6 below. There appears to be slightly better median survival and treatment response rates with platinum or platinum/taxane based regimens than with fluorouracil / anthracycline regimens (see Figures Table 23.2 and Table 23.3), at the cost of greater treatment toxicity.

Andenis et al (2009) combined data from 29 phase II trials of 39 regimens in patients with CUP. The pooled objective response rate was 430/1380: 31% [95% C.I. 27% to 33%]. Nine methodological characteristics influenced response rate at least as much as the type of chemotherapy used. Thus the response rates reported in these studies are highly biased and it is inappropriate to use them to estimate the relative effectiveness of chemotherapy regimens for CUP.

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Table 23.1 Chemotherapy versus no chemotherapy

Study	Population	N (chemotherapy)	Median OS in months [95% CI] with chemotherapy	N (no chemo,)	Median OS in months [95% CI] with no chemotherapy	Statistical comparison
Lenzi 1997 non-cisplatin based chemotherapy	Patients with poorly differentiated carcinoma of unknown origin	23	16 [4 to -]	58	13 [8 to 32]	No significant difference
Lenzi 1997 cisplatin based chemotherapy	Patients with poorly differentiated carcinoma of unknown origin	59	13 [11 to 21]	58	13 [8 to 32]	No significant difference
Lenzi 1997 non-cisplatin based chemotherapy	Patients with poorly differentiated adenocarcinoma of unknown origin	31	8 [5 to 13]	99	8 [5 to 12]	No significant difference
Lenzi 1997 cisplatin based chemotherapy	Patients with poorly differentiated adenocarcinoma of unknown origin	67	12 [9 to 17]	99	8 [5 to 12]	No significant difference
Lofts 1999	Patients with adenocarcinoma of unknown origin	44	4 [1.4 to 6.5]	29	0.6 [CI not reported]	Not reported
Mousseau 1991	Patients with liver metastases of unknown origin.	73	4 [CI not reported]	18	1 [CI not reported	P = 0.005 (Mantel-Cox test)
Pouessel 2005	Patients with liver metastases of unknown origin.	107	7 [CI not reported]	11	1 [CI not reported]	Multivariate analysis showed a small but significant effect of chemotherapy on survival OR = 0.07 [95% CI 0.02 to 0.22] (P < 0.0001)
Seve 2006	Patients with CUP and good performance score (PS 0 or 1)	61	10.7 [CI not reported]	60	10.4 [CI not reported]	P=0.45
Shaw 2007	Patients with CUP of any type	37	13 [7 to 19]	129	2 [1 to 3]	Not reported but significant difference likely
Sumi 2006	Patients with CUP of any type	39	8 [CI not reported]	11	4.5 [CI not reported]	Not reported

Table 23.2 Randomised trials of chemotherapy

Study	Population	Phase	Number of patients	Treatment A	Treatment B	Median OS in months (A vs. B)	Respose rate (A vs. B)	Death due to treatment toxicity	Neutro-penia*	Thrombo-cytopenia*	Anemia*	Nausea and vomiting*	Mucositis*	Diarrhoea*	Renal*	Neuropathy*
Assersohn 2003	CUP	NR	A 45 B 43	5-fluorouracil	5-fluorouracil , mitomycin-C	7 vs. 5 (P=0.60)	12% vs. 20% (P=0.29)	0% vs 0% (P=1.00)	0% vs 5% (P=0.22)	4% vs 7% (P=0.68)	7% vs 0% (P=0.24)	0% vs 7% (P=0.10)	4% vs 9% (P=0.41)	2% vs 2% (P=1.00)	NR	NR

Study	Population	Phase	Number of patients	Treatment A	Treatment B	Median OS in months (A vs. B)	Respose rate (A vs. B)	Death due to treatment toxicity	Neutro-penia*	Thrombo-cytopenia*	Anemia*	Nausea and vomiting*	Mucositis*	Diarrhoea*	Renal*	Neuropathy*
Culine 2003	CUP, not belonging to a subgroup with well defined treatment	II	A 38 B 40	cisplatin, gemcitabine	cisplatin, irinotecan	8 vs 6 (P NR)	55% vs 38% (P NR)	0% vs 5% (P NR)	60% vs 55% (P>0.05)	74% vs 5% (P=0.0001)	63% vs 15% (P=0.02)	26% vs 35% (P>0.05)	3% vs 0% (P>0.05)	5% vs 15% (P>0.05)	0% vs 0%	
Dowell 2001	CUP, not belonging to a subgroup with well defined treatment	II	A 17 B 17	paclitaxel, leucovorin, 5-fluorouracil	etoposide, carboplatin	8 vs 6 (P=0.91)	19% vs 19%	0% vs 0%	42% vs 67% (P NR)	0% vs 42% (P NR)	NR	18% vs 18%	NR	NR	NR	0% vs 0%
Eagan 1987	CUP	NR	A 28 B 28	mitomycin-C, doxorubicin	cisplatin, mitomycin-C, doxorubicin	5.5 vs 4.6	14% vs 26% (P=0.14)	NR	NR	NR	NR	21% vs 56% (P=0.01)	NR	NR	NR	NR
Huebner 2005	CUP - adenocarcinoma or undifferentiated carcinoma	II	A 42 B 45	paclitaxel, carboplatin	gemcitabine, vinorelbine	11 vs 6.1	23.8% vs 20.0%	2% vs 4%	33.3% vs 55.6%	23.8% vs 31.1%	NR	52.4% vs 62.2%	NR	NR	NR	38.1% vs 44.4%
Miliken 1987	CUP - adenocarcinoma	NR	A 51 B 50	doxorubicin, mitomycin-C	cisplatin, vinblastine, bleomycin	4 vs 6 (P>0.05)	39% vs 30% (P>0.05)	NR	myelotoxicity 39% vs. 18% (P=0.015)	18% vs 2% (P=0.008)	NR	53% vs 80% (P=0.002)	12% vs 10% (P NR)	NR	NR	NR
Palmeri 2006	CUP	II	A 33 B 33	cisplatin, gemcitabine, vinorelbine	cisplatin, gemcitabine, paclitaxel	14 vs 10	46% vs 49%	NR	12% vs 18%	9% vs 12%	9% vs 9%	0% vs 3%	0% vs 3%	3% vs 0%	0% vs 0%	NR
Shildt 1983	CUP - adenocarcinoma	NR	A 20 B 16	5-fluorouracil	5-fluorouracil , doxorubicin, cyclophosphamide	3 vs 3	0% vs 0%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Van de Wouw 2005	CUP - adenocarcinoma	II**	A 23 B 23	carboplatin, etoposide, paclitaxel	5-fluorouracil , leucovorin	7 vs 6 (P=0.76)	39% vs 10% (P=0.036)	9% vs 0%	39% vs 4%	22% vs 0%	Incidence was similar	NR	NR	NR	NR	NR
Woods 1980	CUP - undifferentiated carcinoma or adenocarcinoma	NR	A 25 B 22	doxorubicin, mitomycin-C	cyclophosphamide, methotrexate, 5-fluorouracil	4 vs 2	36% vs 5% (P<0.01)	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: NR, not reported; OS, overall survival;
*Grade 3 or 4 toxicities (A vs. B). ** Study title describes the trial as phase III but patient numbers and other features suggest it is a phase II trial.

Table 23.3 Fluorouracil / anthracycline based chemotherapy

Study	Population	N	Regimen	5-FU infusion	Median OS in months [95% CI]	Treatment response [95% CI]	Death due to treatment toxicity	Neutro-penia*	Thrombo-cytopenia*	Anemia*	Nausea and vomiting*	Mucositis*	Diarrhoea*	Neuro-pathy*	Toxicity criteria
Al Idrissi 1990	CUP - liver metastases	29	5-fluorouracil, doxorubicin, mitomycin-C	NR (bolus?)	<3	10%	0%	21%	NR	NR	NR	NR	NR	NR	NR
Assersohn 2003	CUP	43	CI-5-fluorouracil, mitomycin-C	continuous	5 [3 to 7]	20% [9 to 36%]	0%	5%	7%	0%	7%	9%	2%	NR	
Assersohn 2003	CUP	45	CI-5-fluorouracil	continuous	7 [3 to 10]	12% [4 to 25%]	0%	0%	4%	7%	0%	4%	2%	NR	
Goldberg 1986	CUP - adenocarcinoma	45	5-fluorouracil, doxorubicin, mitomycin-C	NR (bolus?)	10	30%	7%	7%	11%	NR	NR	7%	NR	NR	ECOG
Kambu 1990	CUP - adenocarcinoma	57	doxorubicin, vindesine, mitomycin-C	NA	9 (no liver mets) 6 (liver mets)	30%	5%	NR	NR	NR	0%	NR	NR	9%	NR
Kelsen 1992	CUP - adenocarcinoma	21	5-fluorouracil, methotrexate, leucovorin, N-phosphonacetyl -L-aspartate	NR (bolus?)	2	5%	NR	NR	NR	NR	4%	0%	14%	NR	NR
Nole 1993	CUP - adenocarcinoma	17	5-fluorouracil, leucovorin	NR (bolus?)	5	0%	NR	0%	0%	NR	NR	0%	6%	NR	WHO
Romero 1990	CUP	28	etoposide, mitomycin-C	NA	NR	14%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Shildt 1983	CUP - adenocarcinoma	20	CI-5-fluorouracil	continuous	3	0%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Shildt 1983	CUP - adenocarcinoma	16	CI-5-fluorouracil, doxorubicin, cyclophosphamide	continuous	3	0%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sulkes 1988	CUP - adenocarcinoma	18	5-fluorouracil, doxorubicin, mitomycin-C	bolus	5	13%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sulkes 1988	CUP - undifferentiated carcinoma	14	doxorubicin, vinblastine, mitomycin-C	NA	9	29%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tichler 2003	CUP	26	5-fluorouracil plus cisplatin or carboplatin or mitomycin-C	infusion	7	4%	8%	NR	NR	NR	NR	19%	8%	NR	NR
Treat 1989	CUP - adenocarcinoma -	19	methotrexate, 5-fluorouracil, doxorubicin, mitomycin-C	bolus	15	37%	NR	5%	5%	NR	NR	NR	NR	NR	ECOG

Study	Population	N	Regimen	5-FU infusion	Median OS in months [95% CI]	Treatment response [95% CI]	Death due to treatment toxicity	Neutro-penia*	Thrombo-cytopenia*	Anemia*	Nausea and vomiting*	Mucositis*	Diarrhoea*	Neuro-pathy*	Toxicity criteria
	excluding serous effusions														
Van der Gaast 1988	CUP - adenocarcinoma	22	5-fluorouracil, doxorubicin, mitomycin-C	bolus	8	14%	NR	9%	9%	NR	NR	NR	NR	NR	NR
Van der Gaast 1993	CUP - well or moderately well differentiated carcinoma	25	etoposide	NA	NR	8%									WHO
Van der Wouw 2005	CUP - adenocarcinoma	23	CI-5-fluorouracil , leucovorin	continuous	6	10%	0%	4%	0%	NR	NR	NR	NR	NR	NR
Woods 1980	CUP - undifferentiated carcinoma or adenocarcinoma	25	doxorubicin, mitomycin-C	NA	4	36%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Woods 1980	CUP - undifferentiated carcinoma or adenocarcinoma	22	5-fluorouracil, cyclophosphamide, methotrexate,		2	5%	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: CI-5-fluorouracil, continuous infusion 5-5-fluorouracil

Table 23.4 Platinum based chemotherapy

Study	Population	N	Regimen	5-FU infusion**	Median OS in months [95% CI]	Treatment response [95% CI]	Death due to treatment toxicity	Neutro-penia*	Thrombo-cytopenia*	Anemia*	Nausea and vomiting*	Mucositis*	Diarrhoea*	Renal*	Neuropathy*	Toxicity criteria
Ando 2008	CUP, not belonging to a subgroup with well defined treatment	43	carboplatin, irinotecan	NA	11 [7 to 20]	40% [26 to 54%]	NR	33%	16%	22%	NR	NR	NR	NR	NR	NR
Balana 2003	CUP, not belonging to a subgroup with well defined treatment	30	cisplatin, gemcitabine, etoposide	NA	7.2 [2.6 to 11.8]	37% [20 to 56%]	0%	60%	33%	47%	23%	3%	16%	NR	0%	WHO

Study	Population	N	Regimen	5-FU infusion**	Median OS in months [95% CI]	Treatment response [95% CI]	Death due to treatment toxicity	Neutro-penia*	Thrombo-cytopenia*	Anemia*	Nausea and vomiting*	Mucositis*	Diarrhoea*	Renal*	Neuropathy*	Toxicity criteria
Briasoulis 1998	CUP	62	carboplatin, epirubicin, etoposide	NA	10	37% [25 to 49%]	NR	16%	7%	5%	0%	0%	NR	NR	NR	NCI
Briasoulis 2007	CUP, not belonging to a subgroup with well defined treatment	47	oxaliplatin, irinotecan	NA	10 [6 to 14]	13% [5 to 26%]	0%	10%	0%	0%	2%	NR	16%	NR	2%	WHO
Culine 1999, high dose	CUP, not belonging to a subgroup with well defined treatment	20	carboplatin, etoposide, doxorubicin, cyclophosphamide	NA	11	42% [22 to 62%]	0%	100%	NR	NR	25%	14%	10%	0%	NR	WHO
Culine 2002	CUP, not belonging to a subgroup with well defined treatment	82	doxorubicin, cyclophosphamide, cisplatin, etoposide	NA	10	39% [30 to 48%]	2%	49%	20%	29%	16%	4%	3%	NR	NR	WHO
Culine 2003	CUP, not belonging to a subgroup with well defined treatment	39	cisplatin, gemcitabine	NA	8	55% [34 to 66%	0%	60%	74%	63%	26%	3%	5%	0%	3%	NCI
Culine 2003	CUP, not belonging to a subgroup with well defined treatment	40	cisplatin, irinotecan	NA	6	38% [23 to 54%]	5%	55%	5%	15%	35%	0%	15%	0%	0%	NCI
Dowell 2001	CUP, not belonging to a subgroup with well defined treatment	17	carboplatin, etoposide	NA	8	19% [4 to 45%]	0%	42%	0%	NR	18%	NR	NR	NR	0%	NCI
Falkson 1998	CUP, not belonging to a subgroup with well defined treatment	41	cisplatin, mitomycin-C, epirubicin	NA	9	49%	2%	NR	NR	NR	0%	NR	NR	NR	0%	ECOG
Farrugia 1996	CUP	93	platinum based (including 5-FU in most cases)	39% bolus 50% continuous	8	37% [27 to 47%]	2%	46%	NR	NR	5%	3%	4%	NR	0%	WHO

Study	Population	N	Regimen	5-FU infusion**	Median OS in months [95% CI]	Treatment response [95% CI]	Death due to treatment toxicity	Neutro-penia*	Thrombo-cytopenia*	Anemia*	Nausea and vomiting*	Mucositis*	Diarrhoea*	Renal*	Neuropathy*	Toxicity criteria
				11% no 5-FU												
Gill 1991	CUP (excluding germ cell tumours)	16	cisplatin, etoposide	NA	7	19%	6%	50%	NR	44%	NR	NR	NR	6%	0%	ECOG
Gisselbrecht 1981	CUP adenocarcinoma	11	5-fluorouracil , doxorubicin, cisplatin	bolus	NR	9%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Guardiola 2001	CUP - adenocarcinoma	22	cisplatin, doxorubicin, cyclophosphamide	NA	11	50% [38 to 72%]	5%	64%	41%	55%	41%	9%	0%	5%	0%	NCI
Hainsworth 1992	CUP- poorly differentiated carcinoma or adenocarcinoma	220	cisplatin based	NA	12	52%	3%	NR	NR	NR	NR	NR	NR	NR	NR	-
Karapetis 2001	CUP	36	cyclophosphamide, etoposide, CI-5-fluorouracil	continuous	9	22% [8 to 36%]	0%	9%	3%	0%	19%	0%	3%	0%	0%	WHO
Kim 2008	CUP	33	irinotecan, cisplatin	NA	11.2 [9.7 to 12.7]	41%	0%	28%	NR	NR	NR	NR	NR	NR	NR	-
Khansur 1995	CUP - squamous cell carcinoma	15	cisplatin, CI-5-fluorouracil	continuous	11	53% [27 to 79%]	0%	27%	0%	7%	13%	7%	NR	0%	7%	NR
Kusaba 2007	CUP, not belonging to a subgroup with well defined treatment	11	cisplatin, CI-5-fluorouracil	continuous	10	55% [23 to 83%]	0%	18%	9%	9%	9%	18%	0%	0%	0%	NCI
Lofts 1999	CUP - adenocarcinoma	44	cisplatin, CI-5-fluorouracil, tamoxifen	continuous	4 [1.4 to 6.5]	27% [14 to 40%]	0%	5%	0%	0%	NR	5%	2%	NR	NR	WHO
Macdonald 2002	CUP, not belonging to a subgroup with well defined treatment	31	cisplatin, mitomycin-C, CI-5-fluorouracil	continuous	8 [6 to 10]	27% [11 to 42%]	0%	19%	16%	10%	13%	13%	0%	0%	NR	NCI
Piot 1984	CUP - liver metastases, adenocarcinoma	11	CI-5-fluorouracil, doxorubicin, cisplatin	continuous	10	27%	NR	0%	0%	0%	100%	NR	NR	NR	NR	NR

Study	Population	N	Regimen	5-FU infusion**	Median OS in months [95% CI]	Treatment response [95% CI]	Death due to treatment toxicity	Neutro-penia*	Thrombo-cytopenia*	Anemia*	Nausea and vomiting*	Mucositis*	Diarrhoea*	Renal*	Neuropathy*	Toxicity criteria
Palmeri 2006	CUP, not belonging to a subgroup with well defined treatment	33	cisplatin, gemcitabine, vinorelbine	NA	14 [7 to 12]	42%	NR	12%	9%	9%	0%	0%	3%	0%	0%	NCI
Parnis 2000	CUP, not belonging to a subgroup with well defined treatment	43	cisplatin, epirubicin, CI-5-fluorouracil	continuous	5	23%	2%	19%	2%	2%	0%	5%	5%	0%	0%	WHO
Pavlidis 1992	CUP - undifferentiated carcinoma, adenocarcinoma and epidermoid carcinoma	34	cisplatin based	NA	NR	24%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pavlidis 1992	CUP - undifferentiated carcinoma, adenocarcinoma and epidermoid carcinoma	14	carboplatin based	NA	NR	36%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Piga 2004	CUP - excluding neck nodes	102	carboplatin, etoposide, doxorubicin	NA	9	27%	1%	47%	28%	30%	NR	NR	NR	NR	NR	WHO
Pittman 2006	CUP - adenocarcinoma, large cell carcinoma, undifferentiated carcinoma or carcinoma not otherwise specified	50	carboplatin, gemcitabine	NA	8 [4 to 10]	31% [19 to 44%]	2%	14%	8%	10%	2%	NR	NR	NR	NR	WHO
Raats 2000	CUP (phase I dose ranging study)	12	cisplatin, ralitrexed	NA	NR	25%	17%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Raber 1991	CUP	36	cisplatin, etoposide, CI-5-fluorouracil	continuous	11	22%	NR	52%	NR	NR	NR	42%	NR	NR	NR	NR

Study	Population	N	Regimen	5-FU infusion**	Median OS in months [95% CI]	Treatment response [95% CI]	Death due to treatment toxicity	Neutro-penia*	Thrombo-cytopenia*	Anemia*	Nausea and vomiting*	Mucositis*	Diarrhoea*	Renal*	Neuropathy*	Toxicity criteria
Rigg 1997	CUP or inoperable pancreatic or upper GI adenocarcinoma	40	carboplatin, leucovorin, 5-fluorouracil	bolus	8	25%	5%	59%	13%	NR	NR	9%	6%	NR	NR	WHO
Sagatchian 2001	CUP	48	platinum based. Well differentiated carcinoma: cisplatin, 5-FU and alpha-interferon. Poorly differentiated carcinoma or adenocarcinoma: cisplatin and etoposide, then bleomycin, ifosfamide and G-CSF in some cases	continuous	13 [8 to 18]	43% [36 to 50%]	2%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sprenger 2008	CUP	51	capecitabine, oxaliplatin	continuous	7	12%	2%	0%	2%	4%	0%	2%	4%	0%	2%	NR
Voog 2000	CUP	25	cisplatin, etoposide	NA	8	32%	4%	40%	16%	NR	20%	NR	NR	NR	NR	WHO
Wagener 1991	CUP - adenocarcinoma	21	cisplatin	NA	5	19% [6 to 43%]	NR	0%	0%	0%	52%	0%	0%	0%	0%	WHO
Warner 1998	CUP, not belonging to a subgroup with well defined treatment	33	carboplatin, etoposide	NA	6	23%	9%	33%	30%	NR	6%	3%	NR	0%	3%	ECOG
Yonemori 2009	CUP, not belonging to a subgroup with well defined treatment	45	carboplatin, irinotecan	NA	12	42%	0%	33%	20%	25%	4%	NR	8%	NR	NR	NCI

*Reported toxicity rates are for grade 3 to 4 (severe or life threatening) toxicities only.
**Capecitabine (taken orally) was considered equivalent to continuous infusion 5-FU
Abbreviations; CI, confidence interval; CI-5-fluorouracil, continuous infusion 5-fluorouracil; NA, not applicable; NR, not reported.

Table 23.5 Platinum/Taxane based chemotherapy

Study	Population	N	Regimen	Median survival in months [95% CI]	Treatment response [95% CI]	Death due to treatment toxicity	Neutro-penia*	Thrombo-cytopenia*	Anemia*	Nausea and vomiting*	Mucositis*	Diarrhoea*	Neuro-pathy*	Toxicity criteria
Berry 2007	CUP, not belonging to a subgroup with well defined treatment	42	paclitaxel, carboplatin	9	17%	0%	19%	NR	NR	4%	2%	NR	4%	NCI
Briasoulis 2000	CUP - excluding probable breast cancer	77	paclitaxel, carboplatin	13	39% [28 to 50%]	4%	7%	3%	3%	NR	NR	3%	4%	WHO
Darby 2001	CUP - adenocarcinoma or poorly differentiated carcinoma	29	docetaxel	6	7%	N.R	55%	N.R	N.R	N.R	4%	N.R	N.R	NR
Dowell 2001	CUP, not belonging to a subgroup with well defined treatment	17	paclitaxel, 5-fluorouracil, leucovorin	6	19% [4 to 45%]	0%	67%	42%	NR	18%	NR	NR	0%	NCI
El Rayes 2005	CUP - adenocarcinoma not belonging to a subgroup with well defined treatment	22	paclitaxel, carboplatin	7 [6 to 10]	23% [11 to 40%]	0%	14%	5%	9%	5%	NR	NR	5%	WHO
Greco 2000	CUP - adenocarcinoma not belonging to a subgroup with well defined treatment	26	docetaxel, cisplatin	8	26%	0%	54%	2%	NR	35%	NR	NR	9%	WHO
Greco 2000	CUP - adenocarcinoma not belonging to a subgroup with well defined treatment	47	docetaxel, carboplatin	8	22%	4%	50%	4%	NR	9%	NR	NR	6%	WHO
Greco 2000a	CUP, not belonging to a subgroup with well defined treatment	71	paclitaxel, carboplatin, etoposide	11	48%	0%	63%	23%	NR	8%	NR	NR	7%	WHO
Greco 2004	CUP, not belonging to a subgroup with well defined treatment	132	paclitaxel, carboplatin, etoposide -- gemcitabine, irinotecan (sequential treatment)	9 [8 to 10]	30%	4%	71%	13%	11%	11%	NR	4%	2%	NCI
Greco 2008	CUP - adenocarcinoma or poorly differentiated carcinoma / squamous cell carcinoma	51	paclitaxel, carboplatin plus erlotinib, bevacizumab	11	48%	NR	19%	9%	NR	NR	NR	12%	NR	NR
Hainsworth 2006	Patients with advanced poorly differentiated neuroendocrine carcinoma	78 (48 CUP)	paclitaxel, carboplatin, etoposide	15	53%	4%	82%	31%	18%	10%	6%	5%	NR	NR
Mel 2006	CUP	63	docetaxel, carboplatin, gemcitabine	12 [9 to 12]	37% [25 to 48%]	8%	24%	38%	13%	16%	11%	18%	NR	NR

Study	Population	N	Regimen	Median survival in months [95% CI]	Treatment response [95% CI]	Death due to treatment toxicity	Neutro-penia*	Thrombo-cytopenia*	Anemia*	Nausea and vomiting*	Mucositis*	Diarrhoea*	Neuro-pathy*	Toxicity criteria
Moller 2009	CUP	87	paclitaxel, cisplatin and gemcitabine	9	47%	2%	NR	NR	NR	NR	NR	NR	NR	NR
Mukai 2003	CUP	45	docetaxel, cisplatin	12	64%	0%	36%	NR	NR	24%	NR	NR	NR	NR
Munoz 2004	CUP, not belonging to a subgroup with well defined treatment	48	paclitaxel, carboplatin, etoposide	7 [5 to 10]	31% [20 to 47%]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Palmeri 2006	CUP, not belonging to a subgroup with well defined treatment	33	paclitaxel, cisplatin, gemcitabine	10 [7 to 12]	49%	NR	81%	12%	9%	3%	3%	0%	0%	NCI
Park 2004	CUP, not belonging to a subgroup with well defined treatment	37	paclitaxel, cisplatin	11 [8 to 13]	42% [23 to 61%]	0%	41%	0%	0%	6%	NR	0%	0%	WHO
Pouessel 2004	CUP, not belonging to a subgroup with well defined treatment	35	docetaxel, gemcitabine	10	40% [28 to 52%]	3%	27%	3%	3%	NR	3%	6%	NR	NCI
Seve 2007	CUP, not belonging to a subgroup with well defined treatment	40	paclitaxel, cisplatin or carboplatin, etoposide	3	18%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Schneider 2007	CUP, not belonging to a subgroup with well defined treatment	33	paclitaxel, carboplatin, capecitabine	8 [6 to 14]	40% [23 to 58%]	6%	67%	48%	33%	18%	6%	3%	NR	NR
Van de Wouw 2005	CUP	23	paclitaxel, carboplatin, etoposide	7	39%	9%	40%	22%	NR	NR	NR	NR	NR	NR

*Reported toxicity rates are for grade 3 to 4 (severe or life threatening) toxicities only.
Abbreviations: A, doxorubicin; B, bleomycin; Be, bevacizumab; C, cyclophosphamide; Cb, carboplatin; CI, confidence interval; Dx, docetaxel; E, etoposide; Ep, epirubicin; Er, erlotinib; F, 5-fluorouracil; G, gemcitabine; Ir, irinotecan; P, cisplatin; Pl, paclitaxel; Ra, raltitrexed; L, leucovorin; Mi, mitomycin-C;

Table 23.6 Combined results. Ranges of overall survival, treatment response and toxicity .

Regimen	time period	median survival (months)	response rate	death due to toxicity	neutro-penia	thrombo-cytopenia	anaemia	nausea, vomiting	diarrhoea	mucositis	neurological toxicity
fluorouracil/ anthracycline based	1980 to 2005	2 to 15	0 to 37%	0 to7%	0 to 21%	0 to 11%	0 to 7%	0 to 7%	2 to 14%	0 to 9%	9%
platinum based	1981 to 2008	4 to 14	4 to 55%	0 to 17%	0 to 100%	0 to 74%	0 to 63%	0 to 100%	0 to 16%	0 to 19%	0 to 7%

Regimen	time period	median survival (months)	response rate	death due to toxicity	neutro-penia	thrombo-cytopenia	anaemia	nausea, vomiting	diarrhoea	mucositis	neurological toxicity
platinum/ taxane based	2000 to 2008	3 to 15	7 to 64%	0 to 9%	7 to 82%	0 to 48%	0 to 33%	3 to 35%	0 to 19%	2 to 11%	0 to 9%

Table 23.7 Timeline of chemotherapy studies

Year	5-FU based	Platinum based	Platinum / taxane based
1980	Woods 1980 (doxorubicin, mitomycin-C)		
	Woods 1980 (5-fluorouracil, cyclophosphamide, methotrexate,)		
1981		Gisselbrecht 1981 (5-fluorouracil , doxorubicin, cisplatin)	
1982			
1983	Shildt 1983 (CI-5-fluorouracil)		
	Shildt 1983 (CI-5-fluorouracil, doxorubicin, cyclophosphamide)		
1984		Piot 1984 (CI-5-fluorouracil, doxorubicin, cisplatin)	
1985			
1986	Goldberg 1986 (5-fluorouracil, doxorubicin, mitomycin-C)		
1987			
1988	Sulkes 1988 (5-fluorouracil, doxorubicin, mitomycin-C)		
	Sulkes 1988 (doxorubicin, vinblastine, mitomycin-C)		
	Van der Gaast 1988 (5-fluorouracil, doxorubicin, mitomycin-C)		
1989	Treat 1989 (methotrexate, 5-fluorouracil, doxorubicin, mitomycin-C)		
1990	Al Idrissi 1990 (5-fluorouracil, doxorubicin, mitomycin-C)		
	Kambu 1990 (doxorubicin, vindesine, mitomycin-C)		
	Romero 1990 (etoposide, mitomycin-C)		
1991		Gill 1991 (cisplatin, etoposide)	
		Raber 1991 (cisplatin, etoposide, CI-5-fluorouracil)	
		Wagener 1991 (cisplatin)	
1992	Kelsen 1992 (5-fluorouracil, methotrexate, leucovorin, N-phosphonacetyl -L-aspartate)	Hainsworth 1992 (cisplatin based)	
		Pavlidis 1992 (cisplatin or carboplatin based)	
1993	Nole 1993 (5-fluorouracil, folinic acid)		

Year	5-FU based	Platinum based	Platinum / taxane based
1994			
1995		Khansur 1995 (cisplatin, CI-5-fluorouracil)	
1996		Farrugia 1996 (platinum based (including 5-FU in most cases))	
1997		Rigg 1997 (carboplatin, leucovorin, 5-fluorouracil)	
1998		Briasoulis 1998 (carboplatin, epirubicin, etoposide)	
		Falkson 1998 (cisplatin, mitomycin-C, epirubicin)	
		Warner 1998 (carboplatin, etoposide)	
1999		Culine 1999 (carboplatin, etoposide, doxorubicin, cyclophosphamide)	
		Lofts 1999 (cisplatin, CI-5-fluorouracil, tamoxifen)	
2000		Parnis 2000 (cisplatin, epirubicin, CI-5-fluorouracil)	Briasoulis 2000 (paclitaxel, carboplatin)
		Raats 2000 (cisplatin, ralitrexed)	Greco 2000 (docetaxel, cisplatin)
		Voog 2000 (cisplatin, etoposide)	Greco 2000 (docetaxel, carboplatin)
			Greco 2000a (paclitaxel, carboplatin, etoposide)
2001		Guardiola 2001 (cisplatin, doxorubicin, cyclophosphamide)	Darby 2001 (docetaxel)
		Karapetis 2001 (cyclophosphamide, etoposide, CI-5-fluorouracil)	Dowell 2001 (paclitaxel, 5-fluorouracil, leucovorin)
		Sagatchian 2001 (platinum based)	
2002		Culine 2002 (doxorubicin, cyclophosphamide, cisplatin, etoposide)	
		Macdonald 2002 (cisplatin, mitomycin-C, CI-5-fluorouracil)	
2003		Balana 2003 (cisplatin, gemcitabine, etoposide)	Mukai 2003 (docetaxel, cisplatin)
		Culine 2003 (cisplatin, gemcitabine)	
		Culine 2003 (cisplatin, irinotecan)	
2004		Piga 2004 (carboplatin, etoposide, doxorubicin)	Greco 2004 (paclitaxel, carboplatin, etoposide -- gemcitabine, irinotecan)
			Munoz 2004 (paclitaxel, carboplatin, etoposide)
			Park 2004 (paclitaxel, cisplatin)
			Pouessel 2004 (docetaxel, gemcitabine)
2005			El Rayes 2005 (paclitaxel, carboplatin)
			Van de Wouw 2005 (paclitaxel, carboplatin, etoposide)
2006		Palmeri 2006 (cisplatin, gemcitabine, vinorelbine)	Hainsworth 2006 (paclitaxel, carboplatin, etoposide)

Year	5-FU based	Platinum based	Platinum / taxane based
		Pittman 2006 (carboplatin, gemcitabine)	Mel 2006 (docetaxel, carboplatin, gemcitabine)
			Palmeri 2006 (paclitaxel, cisplatin, gemcitabine)
2007		Briasoulis 2007 (oxaliplatin, irinotecan)	Berry 2007 (paclitaxel, carboplatin)
		Kusaba 2007 (cisplatin, CI-5-fluorouracil)	Seve 2007 (paclitaxel, cisplatin or carboplatin, etoposide)
			Schneider 2007 (paclitaxel, carboplatin, capecitabine)
2008		Ando 2008 (carboplatin, irinotecan)	Greco 2008 (paclitaxel, carboplatin plus erlotinib, bevacizumab)
		Sprenger 2008 (capecitabine, oxaliplatin)	
		Kim 2008 (cisplatin irinotecan)	
		Gross-Goupil (cisplatin, gemcitabine)	
		Alva 2008 (carboplatin, gemcitabine and capecitabine)	
2009		Yonemori 2009 (carboplatin, irinotecan)	Moller 2009 (paclitaxel, cisplatin and gemcitabine)

Figure 23.1 Cancer treatment drugs used in studies of Cancer of Unknown Primary, 1980 to 2008. The size of each point indicates the number of studies using each agent in a given year. Only drugs investigated in more than one study are included.

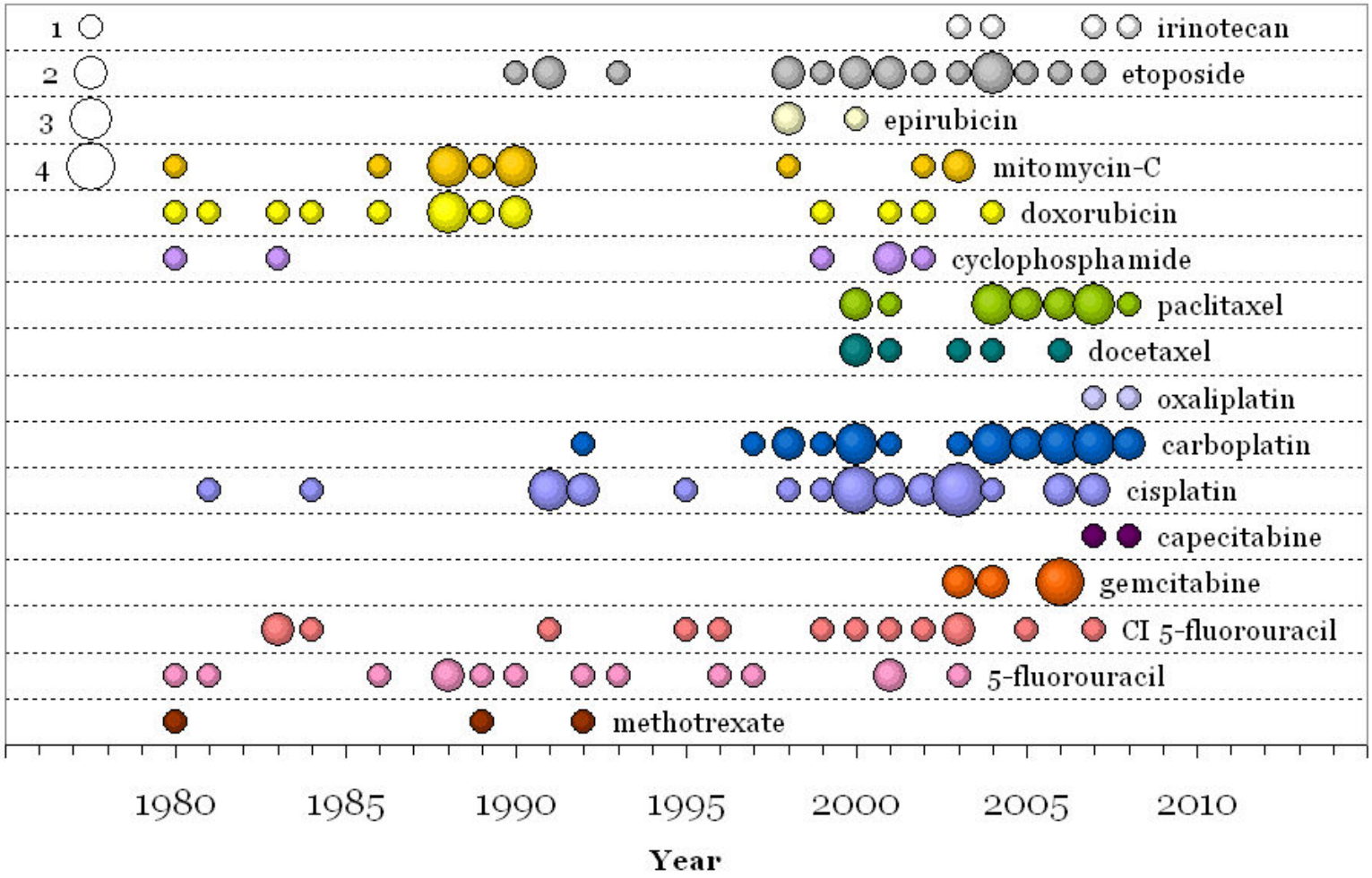


Figure 23.2 Median overall survival versus year of publication. Studies grouped according to chemotherapy regimen.

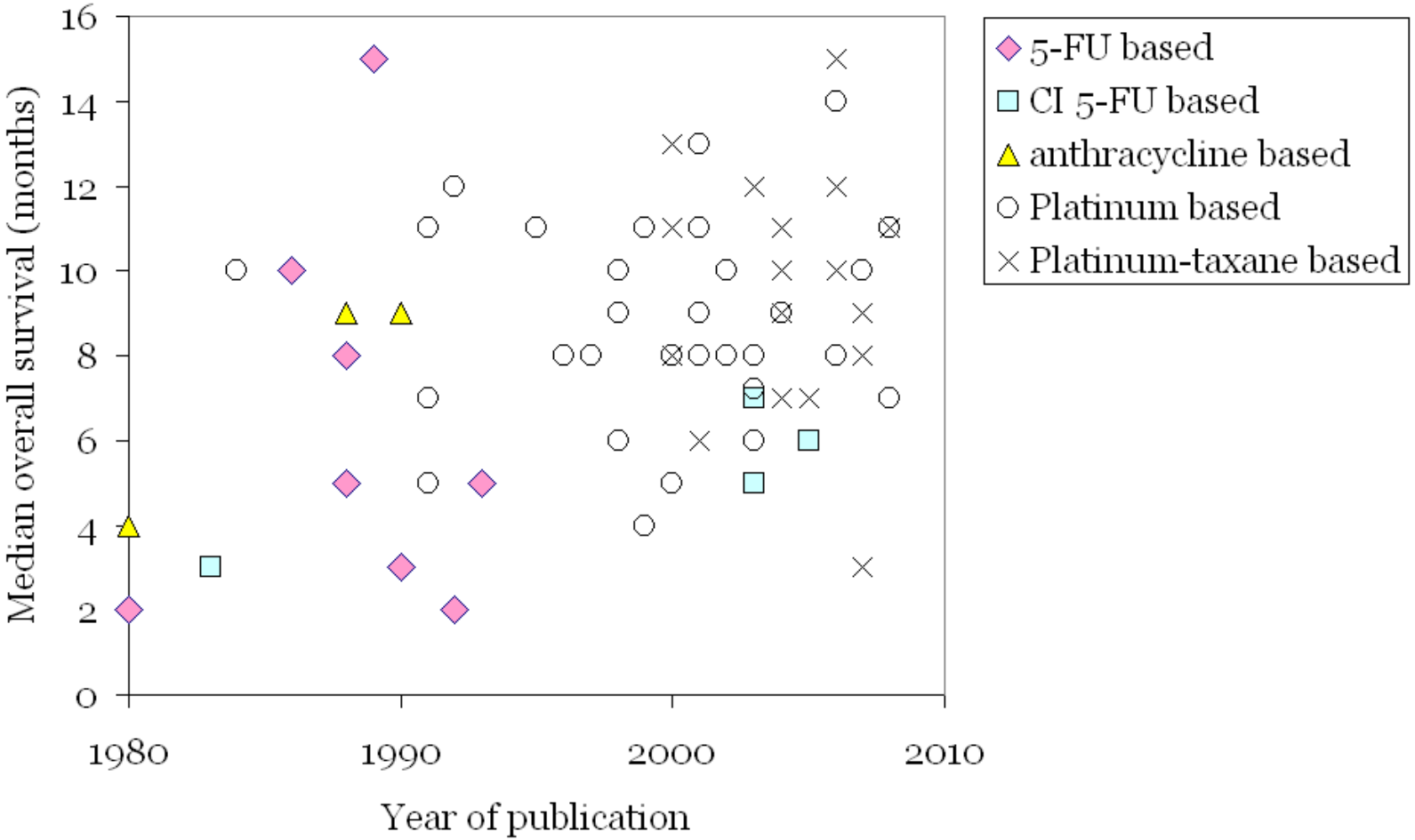


Figure 23.3 Treatment response rate versus year of publication. Studies grouped according to chemotherapy regimen.

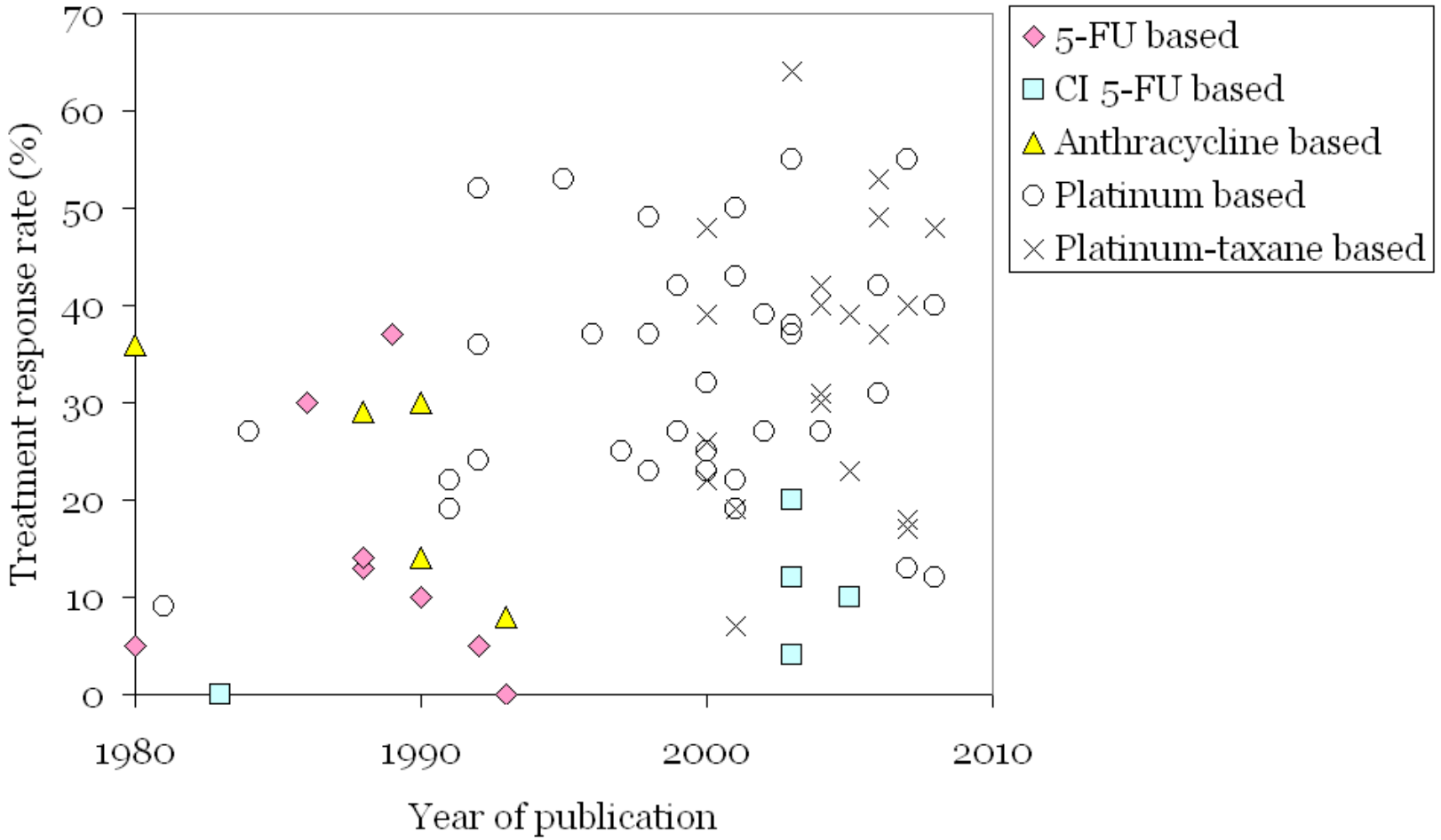


Figure 23.4 Median overall survival versus year of publication, for studies of regimens containing 5-fluorouracil or capecitabine. Studies grouped according to rate of 5-fluorouracil infusion.

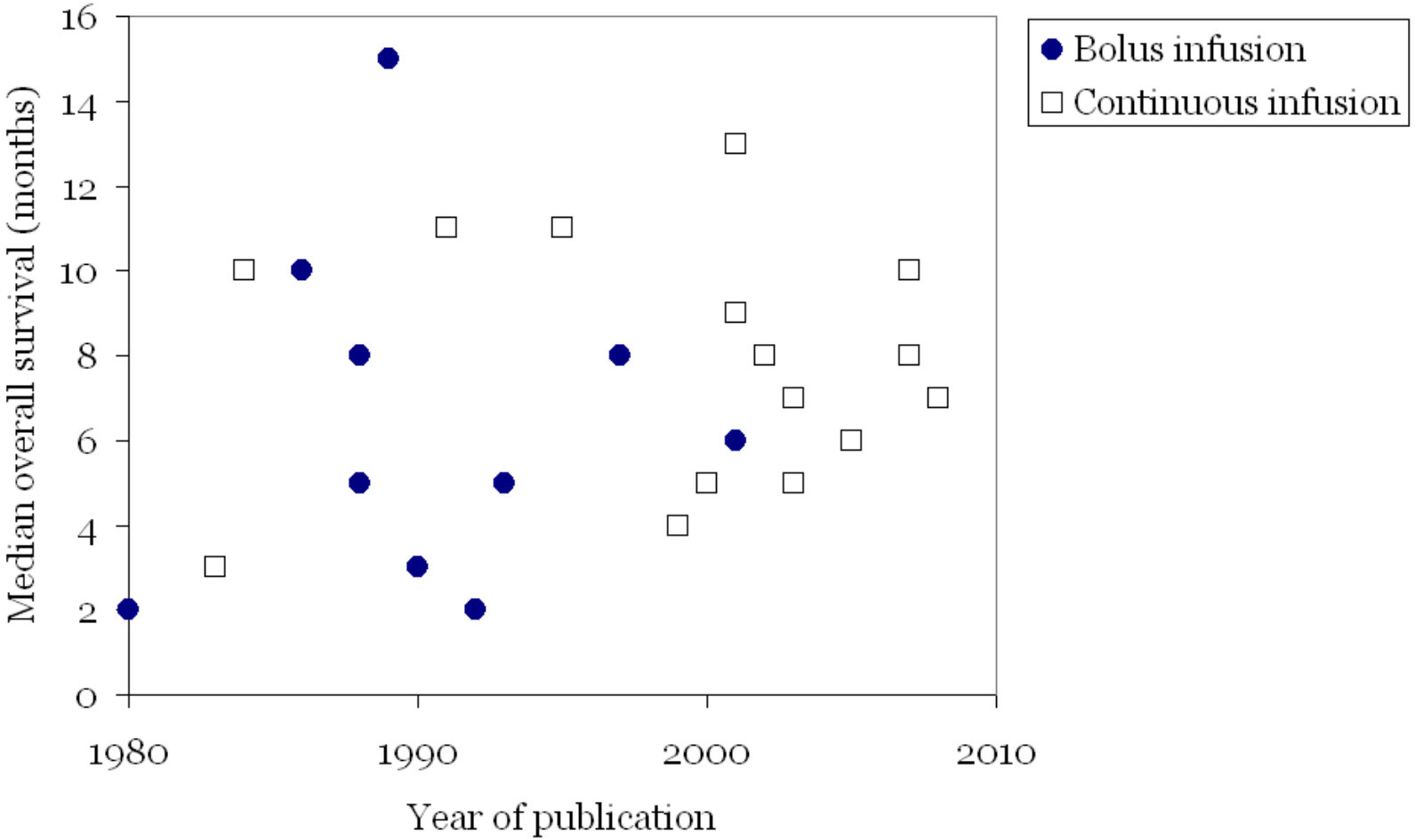
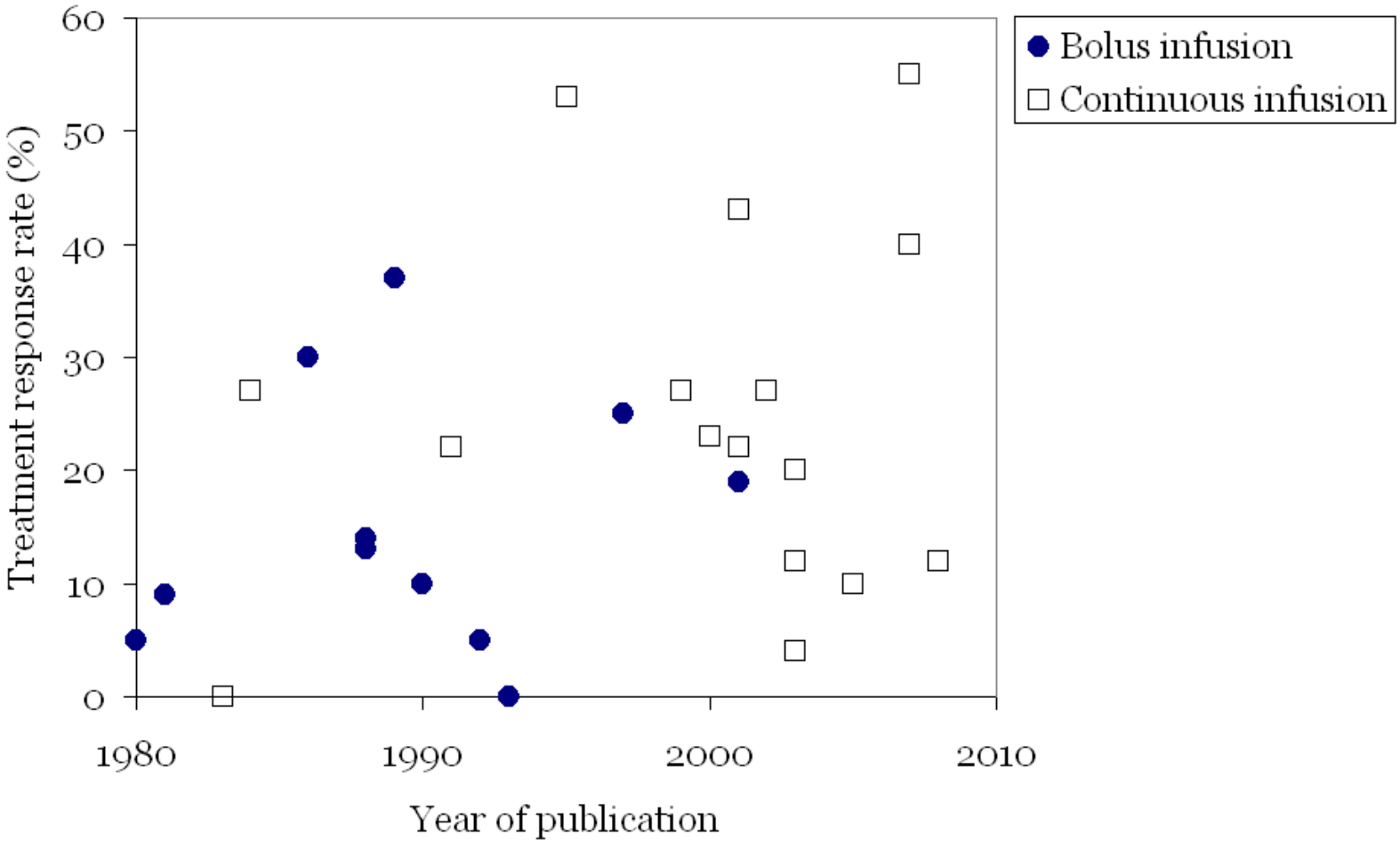


Figure 23.5 Treatment response versus year of publication, for studies of regimens containing 5-fluorouracil or capecitabine. Studies grouped according to rate of 5-fluorouracil infusion.



23. Chemotherapy for people with Cancer of Unknown Primary not belonging to a recognised syndrome

Last updated: 30 / 10 / 2009.

Characteristics of included studies

Adenis-2009

Methods	Meta-analysis of phase II trials in patients with carcinoma of unknown primary
Participants and Country	29 studies investigating 38 regimens in 1820 patients. studies were published between 1997 and 2008. Some studies explicitly excluded patients from treatable subgroups, others did
Interventions	38 different chemotherapy regimens were included. 34 were first line and 4 second line therapy.
Outcomes	**Treatment response to first line therapy** The pooled objective response rate was 430/1380: 31% [95% C.I. 27% to 33%] **Overall survival following first line therapy** The combined median overall survival was 8 months **Progression free survival following first line therapy** The combined median free survival was 4.2 months **Methodological factors associated with response rates** Nine factors had a statistically significant effect on response rate: reports published in highest impact factor journals single centre studies European studies exclusion of women with peritoneal carcinomatosis exclusion of patients with squamous cell carcinoma exclusion of patients with resectable metastases studies with central radiology review studies with sample size calculation based on statistical hypothesis studies with stratification **Treatment factors associated with response rates** Response rate for regimens including cisplatin was 204/508 (40%) compared with 226/872 (26%) for other regimens: OR=1.92 [1.52 to 2.42] Response rate for regimens including carboplatin was 189/692 (27%) compared with 241/688 (35%) for other regimens: OR=0.70 [0.55 to 0.88]

	In general confidence intervals were wide and included possible clinical benefits as well as possible ineffectiveness for other regimens.
Notes	Pooling used averages (no inverse variance etc.)

Al-Idrissi-1990

Methods	Phase I/II trial, non randomised
Participants and Country	29 patients with CUP and liver metastases. Saudi Arabia.
Interventions	5-fluorouracil, adriamycin and mitomycin-C (FAM).
Outcomes	Treatment response, overall survival, haematological toxicity
Notes	

Al-Kubaisy-2003

Methods	Case series
Participants and Country	30 patients with CUP.
Interventions	Vinorelbine, gemcitabine and methotrexate.
Outcomes	Treatment response rate,
Notes	

Ando-2008

Methods	Phase II study, non randomised
Participants and Country	43 patients with CUP
Interventions	Carboplatin and irinotecan.
Outcomes	Treatment response rate, progression free and overall survival, toxicity.
Notes	

Assersohn-2003

Methods	Randomised controlled trial
Participants and Country	88 patients with CUP. UK
Interventions	Protracted venous infusion of 5-fluorouracil with or without mitomycin-C.
Outcomes	Treatment response, failure free survival, overall survival, symptom relief and toxicity.
Notes	

Balana-2006

Methods	Phase II study
Participants and Country	30 patients with CUP (not belonging to a treatable syndrome). Spain
Interventions	Cisplatin, etoposide and gemcitabine

Outcomes	Overall survival, response rate and toxicity
Notes	

Berry-2007

Methods	Phase II trial, non randomised
Participants and Country	42 patients with CUP. USA
Interventions	Weekly paclitaxel plus carboplatin
Outcomes	Overall survival, treatment response and toxicity.
Notes	

Briasoulis-1998

Methods	Phase II non randomised study
Participants and Country	62 patients with CUP. Greece
Interventions	Carboplatin, epirubicin and etoposide
Outcomes	Treatment response, toxicity and overall survival.
Notes	

Briasoulis-2000

Methods	Phase II trial, non randomised
Participants and Country	77 patients with CUP. Greece
Interventions	Carboplatin and paclitaxel (plus G-CSF).
Outcomes	Treatment response, toxicity and overall survival.
Notes	

Briasoulis-2008

Methods	Phase II trial, non randomised
Participants and Country	47 patients with poor prognosis CUP (liver, bone or multiple visceral metastases). Greece.
Interventions	Irinotecan and oxaliplatin
Outcomes	Treatment response, toxicity and overall survival
Notes	

Culine-1998

Methods	Retrospective case series
Participants and Country	100 patients with CUP (59 had chemotherapy). France
Interventions	Chemotherapy (usually platinum based).
Outcomes	Treatment response

Notes	French language paper.

Culine-1999

Methods	Prospective case series
Participants and Country	60 patients with CUP - excluding treatable subtypes. Group A included only poorly differentiated carcinoma or poorly differentiated adenocarcinoma, group B included also included adenocarcinoma.
Interventions	Group A: alternate cycles of cyclophosphamide + doxorubicin and etoposide + carboplatin, with G-CSF and blood progenitor. Group B: alternate cycles of cyclophosphamide + doxorubicin and etoposide + cisplatin, with G-CSF.
Outcomes	Treatment response, overall survival and toxicity
Notes	

Culine-2002

Methods	Phase I/II, non comparative study
Participants and Country	82 patients with CUP
Interventions	Alternative bimonthly cycles of doxorubicin plus cyclophosphamide and etoposide plus cisplatin
Outcomes	Overall survival, treatment response and toxicity
Notes	

Culine-2003

Methods	Randomised phase II study
Participants and Country	89 patients with CUP. France
Interventions	Cisplatin in combination with either gemcitabine or irinotecan
Outcomes	Treatment response, toxicity and overall survival.
Notes	

Darby-2001

Methods	Phase II study, non randomised
Participants and Country	29 patients with CUP. UK
Interventions	Docetaxel
Outcomes	Treatment response, toxicity and overall survival
Notes	Abstract only

de-Campos-1994

Methods	Retrospective case series
Participants and Country	57 patients with initial diagnosis of CUP

Interventions	40 patients had 6 or 10 cycles of vincristine, doxorubicin and cyclophosphamide (VAC) 17 patients VAC alternating with cisplatin and etoposide (PE) for six cycles.
Outcomes	Response rate, overall survival.
Notes	After histologic review, six tumours were reclassified as non-Hodgkin's lymphoma (NHL), one as hepatocarcinoma, and one as adenocarcinoma. Lymphoma cases accounted for 6/11 treatment responders.

Dowell-2001

Methods	Randomised phase II trial
Participants and Country	34 patients with CUP
Interventions	Patients were randomised to receive either paclitaxel, leucovorin and 5-fluorouracil or carboplatin and etoposide.
Outcomes	Treatment response, overall survival and toxicity
Notes	

Eagan-1987

Methods	Randomised trial
Participants and Country	55 patients with CUP. USA
Interventions	Either mitomycin and doxorubicin (MA) or mitomycin, doxorubicin and cisplatin (MAP).
Outcomes	Treatment response, overall survival and toxicity.
Notes	

El-Rayes-2005

Methods	Phase II study, non randomised
Participants and Country	22 patients with CUP. USA
Interventions	Carboplatin and paclitaxel
Outcomes	Treatment response, toxicity and overall survival.
Notes	

Falkson-1998

Methods	Randomised trial
Participants and Country	84 patients with CUP. South Africa
Interventions	Patients received either mitomycin-C, epirubicin and cisplatin or mitomycin-C alone.
Outcomes	Toxicity, treatment response,
Notes	

Farrugia-1996

Methods	Retrospective case series

Participants and Country	101 patients with CUP. UK
Interventions	Platinum based chemotherapy or single agent 5-fluorouracil.
Outcomes	Treatment response, overall survival, toxicity, symptom relief.
Notes	

Gill-1991

Methods	Phase I study, non randomised.
Participants and Country	16 patients with CUP. USA
Interventions	Cisplatin and etoposide (high dose intensity)
Outcomes	Treatment response, toxicity.
Notes	

Gisselbrecht-1981

Methods	Phase II trial, non randomised
Participants and Country	11 patients with CUP. France
Interventions	5-fluorouracil, adriamycin and cisplatin (FAP)
Outcomes	Treatment response, toxicity and overall survival
Notes	Abstract only.

Goldberg-1986

Methods	Phase II study, non randomised
Participants and Country	45 patients with CUP.
Interventions	Combined 5-fluorouracil, adriamycin and mitomycin (FAM)
Outcomes	Treatment response, overall survival and toxicity.
Notes	

Golfinopoulos-2009

Methods	Systematic review and meta-analysis of randomised trials of chemotherapy regimens for cancer of unknown primary site
Participants and Country	Ten RCTs of chemotherapy for patients with CUP, not belonging to the favourable subsets: Woods 1980, Shildt 1983, Milliken 1987, Eagan 1987, Falkson 1998, Dowell 2001, Assersohn 2003, Culine 2003, Huebner 2005 / 2009, and Palmeri 2006 (see tables above and below for the individual study characteristics). There was variability between studies in the proportion of patients with performance status 2 or more, ranging from 12.8% to 38.9%.
Interventions	**Chemotherapy:** Platinum without taxane - 5 study arms (170 patients) Platinum plus taxane - 2 study arms (70 patients) Taxane without platinum - 1 study arm (17 patients)

	Non-platinum, non-taxane monotherapy (nPnTm) - 3 study arms (106 patients) Non-platinum, non taxane combination (nPnTc)- 5 study arms (180 patients) No trials compared chemotherapy to best supportive care. **Meta-analysis** Multiple treatment comparison using a hierarchical Bayesian model (using WinBUGS)
Outcomes	**Overall survival** A hazard ratio (HR) greater than one means that the risk of death is higher with the first rather than the second listed regimen nPnTc vs. nPnTm HR 1.01 (95% CI 0.59 to 1.72) Platinum vs. nPn.Tm HR 0.69 (95% CI 0.39 to 1.28) Taxane vs. nPnTm HR 0.66 (95% CI 0.22 to 2.08) Platinum plus taxane vs. nPnTm HR 0.81 (95% CI 0.34 to 1.89) Platinum vs. nPnTc HR 0.69 (95% CI 0.43 to 1.15) Taxane vs. nPnTc HR 0.66 (95% CI 0.23 to 2.00) Platinum plus taxane vs. nPnTc HR 0.80 (95% CI 0.39 to 1.67) Taxane vs. platinum HR 0.95 (95% CI 0.37 to 2.5) Platinum plus taxane vs. platinum HR 1.16 (95% CI 0.56 to 2.38) Platinum plus taxane vs. taxane HR 1.16 (95% CI 0.56 to 2.38) There was no statistically significant benefit for any one regimen over the others, confidence intervals were too large to make conclusions about the relative effectiveness of the regimens.
Notes	

Greco-2000

Methods	Phase II trials, non randomised
Participants and Country	26 (trial A) and 47 (trial B) patients with CUP. USA
Interventions	Docetaxel and cisplatin (study A), or docetaxel and carboplatin (study B).
Outcomes	Treatment response, overall survival and toxicity.
Notes	

Greco-2000a

Methods	Phase II, non comparative study
Participants and Country	71 patients with CUP. USA
Interventions	Combination of paclitaxel, carboplatin and oral etoposide
Outcomes	Overall survival, treatment response, toxicity.
Notes	

Greco-2004

Methods	Phase II study, non comparative

Participants and Country	132 patients with CUP and poor prognostic features. USA
Interventions	Sequential chemotherapy: paclitaxel, carboplatin and oral etoposide, followed by gemcitabine and irinotecan.
Outcomes	Treatment response, progression free survival, overall survival, toxicity.
Notes	

Greco-2004a

Methods	Phase II trials (results combined from 5 trials, 1995 to 2002)
Participants and Country	396 patients with CUP. USA
Interventions	Study 1 paclitaxel, carboplatin and oral etoposide (PCE). Study 2 docetaxel and cisplatin. Study 3 docetaxel and carboplatin. Study 4 gemcitabine, carboplatin and etoposdie. Study 5 sequential PCE with gemcitabine and irinotecan.
Outcomes	Overall survival, treatment response and toxicity.
Notes	

Greco-2008

Methods	Phase II trial, non randomised.
Participants and Country	51 patients with CUP. USA
Interventions	Paclitaxel and carboplatin plus bevacizumab and erlotinib
Outcomes	Overall and progression free survival, treatment response and toxicity
Notes	

Gross_x002d_Goupil-2008

Methods	Randomised Trial
Participants and Country	52 patients with CUP - without poor prognostic factors.
Interventions	Patients were randomised to receive cisplatin either with or without gemcitabine.
Outcomes	Overall survival, treatment response, toxicity.
Notes	Trial was stopped early due to poor accrual: the intended sample size was 192 patients.

Guardiola-2001

Methods	Phase II trial, non randomised non comparative
Participants and Country	22 patients with CUP. France
Interventions	Cisplatin, doxorubicin and cyclophosphamide
Outcomes	Treatment response, toxicity and overall survival
Notes	

Hainsworth-1992

Methods	Retrospective case series
Participants and Country	220 patients with poorly differentiated CUP. USA
Interventions	Cisplatin based chemotherapy: either cisplatin, vinblastine and bleomycin ± doxorubicin or cisplatin and etoposide ± doxorubicin.
Outcomes	Treatment response, overall survival
Notes	Possible overlap with Greco 1997-2008 studies

Holtan-2008

Methods	Phase II trial. non randomised
Participants and Country	31 patients with CUP
Interventions	Gemcitabine and irinotecan
Outcomes	Time to treatment failure, time to disease progression, treatment response rate, toxicity.
Notes	

Huebner-2005

Methods	Phase II trial, randomised
Participants and Country	92 patients with CUP. Germany
Interventions	Paclitaxel / carboplatin versus gemcitabine / vinorelbine.
Outcomes	Overall and progression free survival, practicability of the regimen, treatment toxicity.
Notes	

Kambhu-1990

Methods	Phase II trial, non randomised
Participants and Country	57 patients with CUP. USA
Interventions	mitomycin-C, vindesine and adriamycin (MVA).
Outcomes	Treatment response, toxicity, and overall survival
Notes	

Karapetis-2001

Methods	Retrospective case series, non randomised
Participants and Country	36 patients with CUP. UK
Interventions	Epirubicin, cisplatin and continuous infusional 5-fluorouracil (ECF). Standard (N=13) or modified (N=23) ECF regimen was used.
Outcomes	Treatment response rate, overall survival and toxicity.

Notes	

Kelsen-1992

Methods	Phase II trial, non comparative
Participants and Country	21 patients with CUP
Interventions	5-FU, with methotrexate, leucovorin and N-phosphonoacetyl-l-aspartate
Outcomes	Treatment response, toxicity
Notes	

Khansur-1995

Methods	Prospective trial, non randomised
Participants and Country	15 patients with metastatic squamous cell carcinoma of unknown primary.
Interventions	Cisplatin and 5-fluorouracil
Outcomes	Treatment response, overall survival and treatment toxicity
Notes	

Kim-2008

Methods	Case series of patients with histologically confirmed CUP, treated between 2001 and 2006.
Participants and Country	33 patients, Korea.
Interventions	Irinotecan (70 mg/m^3) followed by cisplatin (80 mg/m^2) on day 1 and the same dose of irinotecan on day 15. The chemotherapy was repeated every 4 weeks and the response evaluated every 2 cycles.
Outcomes	**Overall survival** Median overall survival was 11.2 months (95% CI 9,7 to 12.7 months) **Treatment response** Overall response rate was 41% **Treatment toxicity (grade 3 or 4)** Neutropenia 28% Anorexia 12.5% (grade not reported) Fatigue 12.5% (grade not reported) **Treatment related death** There were no treatment related deaths
Notes	

Kusaba-2007

Methods	Retrospective case series
Participants and Country	11 patients with CUP. Japan

Interventions	Cisplatin and 5-fluorouracil
Outcomes	Treatment response and toxicity. Overall survival.
Notes	

Lenzi-1997

Methods	Retrospective case series
Participants and Country	907 patients with CUP. USA
Interventions	No chemotherapy versus cisplatin-based chemotherapy versus non-cisplatin based chemotherapy
Outcomes	Overall survival
Notes	

Lofts-1999

Methods	Non comparative study
Participants and Country	44 patients with CUP
Interventions	Comination of 5-fluorouracil, cisplatin and tamoxifen (CFTam).
Outcomes	Treatment response, overall survival and toxicity.
Notes	

Macdonald-2002

Methods	Phase II trial, non randomised
Participants and Country	31 patients with CUP. UK
Interventions	mitomycin-C, cisplatin and 5-fluorouracil
Outcomes	Toxicity, treatment response and overall survival
Notes	

Mel-2006

Methods	Phase II study, non randomised
Participants and Country	63 patients with CUP. Spain
Interventions	Docetaxel, carboplatin and gemcitabine (plus G-CSF support).
Outcomes	Toxicity, treatment response, progression free and overall survival.
Notes	Abstract only

Milliken-1987

Methods	RCT
Participants and Country	95 patients with CUP.
Interventions	Combined doxorubicin and mitomycin-C (DM) or combined cisplatin, vinblastine and bleomycin (PVB)

Outcomes	Treatment response, overall survival and toxicity.
Notes	

Moller-2009

Methods	Prospective phase II study
Participants and Country	87 patients with CUP. PS 0-1, age 18 to 65.
Interventions	Cisplatin, gemcitabine and paclitaxel
Outcomes	Treatment response, overall survival, treatment toxicity.
Notes	Abstract only

Mousseau-1991

Methods	Retrospective case series
Participants and Country	91 patients with hepatic metastases from unknown primary. France
Interventions	Chemotherapy or no chemotherapy
Outcomes	Overall survival. Treatment response.
Notes	French language paper with English abstract

Mukai-2003a

Methods	Phase I trial, non comparative
Participants and Country	45 patients with CUP. Japan
Interventions	Docetaxel and cisplatin
Outcomes	Overall survival, treatment toxicity, treatment response.
Notes	Abstract only.

Munoz-2004

Methods	Phase II study, non randomised
Participants and Country	48 patients with CUP, not belonging to favourable syndrome. Spain
Interventions	Paclitaxel, carboplatin and etoposide.
Outcomes	Treatment response, overall survival
Notes	Spanish language with English abstract.

Nole-1993

Methods	Phase II trial, non randomised
Participants and Country	17 patients with CUP suggestive of a gastrointestinal primary (liver metastases, elevated CEA or CA 19.9). Italy
Interventions	5-fluorouracil plus folinic acid.
Outcomes	Treatment response, toxicity and overall survival.

Notes	

Palmeri-2006

Methods	Phase II study, randomised
Participants and Country	66 patients with CUP. Italy
Interventions	All patients received cisplatin and gemcitabine, and were randomised to receive either paclitaxel or vinorelbine.
Outcomes	Overall survival, treatment response and toxicity
Notes	

Park-2004

Methods	Phase I/II trial, non comparative
Participants and Country	37 patients with CUP. Korea
Interventions	Combination of paclitaxel and cisplatin
Outcomes	Treatment response, overall survival and toxicity.
Notes	

Parnis-2000

Methods	Phase II study
Participants and Country	43 patients with CUP. Australia
Interventions	Combination of epirubicin, cisplatin and 5-fluorouracil.
Outcomes	Treatment response, toxicity
Notes	

Pavlidis-1992

Methods	Retrospective case series, non comparative
Participants and Country	48 patients with CUP. Greece
Interventions	Combination chemotherapy containing cisplatin or carboplatin.
Outcomes	Response rate, toxicity
Notes	

Piga-2004

Methods	Phase II study, non randomised non comparative
Participants and Country	113 patients with CUP. Italy
Interventions	Carboplatin, doxorubicin and etoposide
Outcomes	Treatment response, toxicity and overall survival.
Notes	

Piot-1984

Methods	Non-comparative study
Participants and Country	11 patients with CUP and liver metastases
Interventions	5-FU, adriamycin, cisplatin
Outcomes	Overall survival, treatment response, toxicity
Notes	

Pittman-2006

Methods	Phase II trial, non randomised
Participants and Country	50 patients with CUP. Australia
Interventions	Gemcitabine and carboplatin.
Outcomes	Treatment response and toxicity
Notes	

Pouessel-2004

Methods	Phase II study, non randomised non comparative
Participants and Country	35 patients with CUP. France
Interventions	Gemcitabine and docetaxel
Outcomes	Treatment response, overall and progression free survival, toxicity.
Notes	

Pouessel-2005

Methods	Non randomised comparative study
Participants and Country	118 patients with CUP and liver metastases.
Interventions	Chemotherapy versus no chemotherapy
Outcomes	Median survival
Notes	High risk of bias - unadjusted comparison. Untreated patients were probably unfit for chemotherapy.

Raats-2000

Methods	Phase I trial
Participants and Country	12 patients with CUP
Interventions	Combination of cisplatin and ralitrexed
Outcomes	Treatment response, toxicity
Notes	

Raber-1991

Methods	Phase II trial,
Participants and Country	36 patients with CUP
Interventions	5-fluorouracil, cisplatin and etoposide
Outcomes	Treatment response, toxicity
Notes	

Rigg-1997

Methods	Phase I/II study
Participants and Country	40 patients with CUP or inoperable pancreatic or upper GI cancer.
Interventions	Combination of leucovorin, carboplatin and 5-fluorouracil (LCF).
Outcomes	Toxicity, treatment response, quality of life, overall survival
Notes	

Romero-1990

Methods	Non comparative prospective study
Participants and Country	45 patients with CUP
Interventions	VP16 plus mitomycin-C
Outcomes	Treatment response, disease progression, toxicity
Notes	

Saghatchian-2001

Methods	Prospective non comparative study
Participants and Country	48 patients with CUP: poorly differentiated (N=30) or well to moderately well differentiated (N=18)
Interventions	Combination of cisplatin and etoposide. Patients with stable disease and good performance status received additional bleomycin, and ifosfamide combined with mesna plus G-CSF.
Outcomes	Treatment response, overall survival and toxicity.
Notes	

Schneider-2007

Methods	Phase II trial, non randomised and non comparative
Participants and Country	33 patients with CUP. USA
Interventions	Carboplatin, gemcitabine and capecitabine
Outcomes	Treatment response rate, progression free and overall survival, toxicity.
Notes	

Seve-2006a

Methods	Cohort study
Participants and Country	389 patients with CUP. Canada
Interventions	Chemotherapy versus no chemotherapy
Outcomes	Overall survival
Notes	

Seve-2007

Methods	Retrospective observational study
Participants and Country	40 patients with CUP, identified from a cancer registry. Canada
Interventions	Paclitaxel based chemotherapy
Outcomes	Treatment response, overall survival.
Notes	

Shaw-2007

Methods	Retrospective case series
Participants and Country	166 patients with CUP. UK
Interventions	Chemotherapy versus no chemotherapy
Outcomes	Overall survival.
Notes	

Shildt-1983

Methods	Randomised trial, phase II
Participants and Country	36 patients with CUP
Interventions	5-FU or FAC
Outcomes	Overall survival, treatment response, toxicity.
Notes	

Sprenger-2008

Methods	Phase II trial, non randomised.
Participants and Country	51 patients with CUP
Interventions	Capecitabine and oxaliplatin (CAPOX)
Outcomes	Treatment response and toxicity. Progression free and overall survival
Notes	

Sulkes-1988

Methods	Comparitive study (non randomised)
Participants and Country	28 patients with adenocarcinoma of unknown primary
Interventions	Chemotherapy FAM or AVM
Outcomes	Overall survival, treatment response, toxicity.
Notes	

Sumi-2001

Methods	Non-randomised comparative study
Participants and Country	50 patients with CUP
Interventions	Platinum based, non-platinum based or new agent chemotherapy. Chemotherapy versus no chemotherapy
Outcomes	Treatment response, overall survival
Notes	Bias likely. Patients given palliative care only were most likely unfit for chemotherapy.

Tichler-2003

Methods	Retrospective case series
Participants and Country	26 patients with CUP. Israel
Interventions	Dose intense 5-fluorouracil based chemotherapy.
Outcomes	Overall survival, treatment response and toxicity.
Notes	Abstract only

Treat-1989

Methods	Phase II, non randomised trial
Participants and Country	19 patients with CUP
Interventions	Methotrexate, 5-fluorouracil, doxorubicin and mitomycin (M-FAM)
Outcomes	Response rate, overall survival and toxicity
Notes	

van-de-Wouw-2005

Methods	Randomised trial
Participants and Country	46 patients with CUP.
Interventions	Carboplatin, etoposide and paclitaxel (PCE) or 5-fluorouracil and folinic acid
Outcomes	Overall survival, progression free survival, toxicity and treatment response.
Notes	

van-der-Gaast-1988

Methods	Phase II study, non randomised
Participants and Country	23 patients with CUP
Interventions	Combined 5-fluorouracil, adriamycin and mitomycin-C (FAM)
Outcomes	Treatment response, overall survival and toxicity.
Notes	

van-der-Gaast-1993

Methods	Phase II non comparative study
Participants and Country	25 patients with CUP
Interventions	Etoposide
Outcomes	Treatment response, toxicity
Notes	

Voog-2000

Methods	Phase II trial, non randomised non comparative study
Participants and Country	25 patients with CUP. France
Interventions	Cisplatin and Etoposide
Outcomes	Treatment response, overall survival, toxicity.
Notes	

Wagener-1991

Methods	Non comparative phase II trial
Participants and Country	21 patients with CUP.
Interventions	Cisplatin
Outcomes	Overall survival, treatment response, response duration, toxicity.
Notes	

Warner-1998

Methods	Phase II study, non comparative
Participants and Country	35 patients with CUP.
Interventions	Combined carboplatin and etoposide
Outcomes	Treatment response, toxicity, overall survival.
Notes	

Woods-1980

Methods	Randomised controlled trial
Participants and Country	47 patients with adenocarcinoma of unknown primary.
Interventions	CMF or DM. Patients switched treatment arms after 12 weeks if there was no response.
Outcomes	Overall survival, treatment response (complete or partial).
Notes	

Yonemori-2009

Methods	Phase II clinical trial
Participants and Country	48 patients with CUP, not belonging to treatable subsets. Age > 20 years, no prior chemotherapy, life expectancy at least 3 months, PS 2 or less, and sufficiently fit to receive chemotherapy.
Interventions	Irinotecan and carboplatin
Outcomes	Treatment response, overall survival and treatment toxicity.
Notes	

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24. Chemotherapy selected according to the presumed organ of origin in patients with one of the CUP treatable syndromes.

Last updated: 30/ 10/ 2009.

Short summary

There was a lack of prospective studies comparing systemic treatment according to CUP syndrome with empirical chemotherapy. Patients with the so-called treatable syndromes are normally excluded from clinical trials of CUP chemotherapy.

Evidence from case series and phase II studies indicates response rates to chemotherapy amongst patients with the treatable syndromes are higher than in the rest of the CUP population.

The evidence also suggests that the outcomes of patients with treatable syndromes who receive site specific therapy are similar to those with advanced disease of that primary site.

Rationale

In common with patients who have metastatic cancer from a known primary, confirmed CUP patients are often candidates for systemic therapy (chemotherapy or hormonal therapy) given with the aim of eradicating as much cancer as possible, to achieve a symptomatic and survival benefit.

For patients with confirmed Cancer of Unknown Primary, the evidence for justifying chemotherapy treatment (on the basis of demonstrated benefit over supportive care alone), and for selecting particular regimens (on the basis of a satisfactory balance of efficacy and toxicity) is far more limited than for the common solid tumours. To date, studies to define optimal chemotherapy have almost exclusively been either small phase II trials of various regimens, without control arms, or retrospective analyses of treatment policies aiming to identify favourable outcomes based on treatment and patient factors.

The paucity of high quality data about treatment benefits, combined with the generally low levels of health gain seen, have led some authorities to question the value of the general use of chemotherapy in confirmed CUP. On the other hand, the recognition of certain confirmed CUP "syndromes" with consistent and considerable benefit from chemotherapy means that appropriate use of chemotherapy in some circumstances can certainly be justified in selected cases. The treatable syndromes are:

Patients with predominantly midline nodal disease. These patients may have extra-gonadal germ cell tumour, and may respond to chemotherapy used to treat these tumours, with a good prognosis in some cases.

Female patients with predominantly peritoneal adenocarcinoma. These patients tend to have a clinical course similar to women with ovarian / primary peritoneal carcinoma. Treatment with carboplatin or cisplatin-based chemotherapy often yields clinical benefit.

Female patients with unilateral axillary lymphadenopathy. Treatment as for breast cancer often yields clinical benefit.

Patients with cervical (neck) lymphadenopathy containing carcinoma. Treatment as for head and neck cancer often yields clinical benefit.

Patients with metastatic carcinoma with neuroendocrine differentiation. These patients are usually treated similarly to those with neuroendocrine tumours of known primary origin.

The validity of the "recognised" syndromes is however open to question, and requires confirmation. An objective analysis of the available data about systemic therapy in confirmed CUP is required to determine whether, in patients with confirmed CUP who fall into one of the recognised treatable syndromes, chemotherapy selected according to the presumed organ of origin more successful than generic treatment.

Methods

STUDY TYPES

There was no restriction on study design.

Participants

People with confirmed Cancer of Unknown Primary in whom systemic therapy is being considered, with clinical features fitting a recognised confirmed CUP syndrome. People with confirmed Cancer of Unknown Primary in whom systemic therapy is being considered, with clinical features fitting a recognised confirmed CUP syndrome. Treatable syndromes are defined as: patients with predominantly midline nodal disease, female patients with predominantly peritoneal adenocarcinoma, female patients with unilateral axillary lymphadenopathy, patients with cervical lymphadenopathy containing carcinoma and patients with metastatic carcinoma with neuroendocrine differentiation.

Interventions

Chemotherapy used in patients with an identified primary correlating with the CUP syndrome. The comparison is generic (empirical) chemotherapy

Outcomes

Overall survival, quality of life and treatment complications.

Study selection

An initial list of studies was selected by SA. NB then selected potentially relevant studies from this list on the basis of their title and abstract. These studies were ordered and each paper was checked against the inclusion criteria. The literature search results from other relevant questions in the guideline (management of axillary and cervical lymph node metastases of unknown primary) were also searched for studies.

Data extraction and synthesis

One reviewer (NB) extracted data. Only published data were included and authors were not contacted.

Heterogeneity assessment

There was no assessment of heterogeneity: results were not pooled in meta-analysis.

Search results

Description of included studies

Eleven studies were included. Two were expert reviews which summarised evidence from case series (Hainsworth and Fizazi, 2009; Spigel, Hainsworth and Greco, 2009) .Two were a prospective phase II trials (Hainsworth et al 2006; van der Gaast et al, 1990), two a prospective case series (Hainsworth et al 1992; Khansur et al 1995) and the remainder retrospective studies.

Study quality

There was a lack of prospective or randomised studies comparing systemic treatment according to CUP syndrome with empirical chemotherapy. Patients with these so-called treatable syndromes are normally excluded from clinical trials of CUP chemotherapy. It was clear that patients with treatable syndromes have better treatment response rates than the rest of the CUP population (e.g. Adenis et al 2009) but it was unclear whether they would achieve similar response rates with empirical chemotherapy.

Treatment response was always reported in the studies but overall survival was not as well reported. It does not necessarily follow that better treatment response will translate into improved survival.

Evidence summary

Poorly differentiated carcinoma with a midline distribution

Six case series included 203 patients with poorly differentiated carcinoma and features of extragonadal germ cell tumours. The largest series (Hainsworth et al, 1992) reported complete and overall response rates of 43% and 74% respectively to cisplatin based therapy. Response rates in the remaining studies tended to be lower. Median survival, reported in two of the studies, ranged from 10 to 15 months.

Women with predominantly peritoneal adenocarcinoma

Hainsworth and Fizazi (2009) summarised evidence from seven peritoneal carcinomatosis case series including 258 women with primary peritoneal carcinomatosis or unknown primary tumours. All received platinum-based or platinum/taxane chemotherapy. The complete response rate ranged from 10% to 40%, median survival ranged from 11 to 24 months and long term survival from 6% to 26%.

Evidence from five CUP case series, including 81 patients with peritoneal carcinomatosis, suggests complete response rates of around 33% and overall response rates of around 66% to platinum-based or platinum/taxane chemotherapy. Most patients survived at least a year.

Women with adenocarcinoma involving the axillary lymph nodes

Evidence about the management of patients with axillary lymph node metastases of unknown primary is reviewed in that section. The evidence suggests that women with adenocarcinoma involving the axillary lymph nodes who receive breast cancer specific therapy have similar outcomes to those with stage II breast cancer of known primary. There was insufficient evidence, however, to identify the most effective systemic therapy in this group of patients.

Squamous cell carcinoma of the cervical nodes

Evidence about the management of patients with cervical lymph node squamous cell lymph node metastases of unknown primary is reviewed in that section. In that review, two studies (Agiris et al 2003; Shehadeh et al 2006) used combined modality treatment with

concurrent chemotherapy and radiotherapy, in addition to neck dissection. Five year overall survival ranged from 75% to 83% but there was considerable treatment related toxicity.

Other evidence comes from small case series. Pavlidis (1992) reported complete response to platinum based chemotherapy in 2/5 patients with unknown primary SCC in cervical nodes. Khansur et al (1995) reported palliative chemotherapy (cisplatin and 5-FU) in a series of 15 patients SCC of unknown primary, most of whom had cervical node metastases. Treatment response rates were similar to those in patients with known head/neck primary.

POORLY DIFFERENTIATED NEUROENDOCRINE CARCINOMA

Two studies reported chemotherapy in 94 patients with poorly differentiated neuroendocrine carcinoma of unknown primary. Hainsworth et al (2006) conducted a prospective trial of paclitaxel, carboplatin and etoposide in this patient group. Complete response rate was 13% and median overall survival 14.1 months (95% C.I. 9.5 to 18.5 months). Two drug cisplatin-based regimens (Spiegel et al, 2009) were at least as effective with less toxicity.

References

Hainsworth JD, Johnson DH, Greco FA. *Cisplatin-Based Combination Chemotherapy in the Treatment of Poorly Differentiated Carcinoma and Poorly Differentiated Adenocarcinoma of Unknown Primary Site - Results of A 12-Year Experience.* Journal of Clinical Oncology 1992; 10: (6) 912-22

Hainsworth JD. *Phase II trial of paclitaxel, carboplatin, and etoposide in advanced poorly differentiated neuroendocrine carcinoma: A minnie pearl cancer research network study.* Journal of Clinical Oncology 2006; 24: (22) 3548-54

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Khansur T, Allred C, Little D, Anand V. *Cisplatin and 5-fluorouracil for metastatic squamous cell carcinoma from unknown primary.* Cancer investigation 1995; 13: (3) 263-6

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Pentheroudakis G, Briasoulis E, Karavassilis V, Fountzilas G, Xeros N, Samelis G, et al. *Chemotherapy for patients with two favourable subsets of unknown primary carcinoma: Active, but how effective?.* Acta Oncologica 2005; 44: (2) 155-60

Spigel DR, Hainsworth JD, Greco FA. *Neuroendocrine carcinoma of unknown primary site.* Seminars in oncology 2009; 36: (1) 52-9

Sumi H, Itoh K, Onozawa Y, Shigeoka Y, Kodama K, Ishizawa K, et al. *Treatable subsets in cancer of unknown primary origin.* Japanese Journal of Cancer Research 2001; 92: (6) 704-9

van der Gaast A, Verweij J, Henzen-Logmans SC, Rodenburg CJ, Stoter G. *Carcinoma of unknown primary: identification of a treatable subset?.* Annals of Oncology 1990; 1: (2) 119-22

Varadhachary GR, Raber MN, Matamoros A, Abbruzzese JL. *Carcinoma of unknown primary with a colon-cancer profile - changing paradigm and emerging definitions.* Lancet Oncology 2008; 9: (6) 596-9

Table 24.1 Treament outcomes for patients with CUP treatable syndromes

Syndrome	Study	N	Chemotherapy	Complete response rate	Overall response rate	Median survival
Women with peritoneal carcinomatosis	Pentheroudakis (2005)	47	Platinum with or without taxane	36%	53%	15 months
	Briasoulis (2000)*	19	Carboplatin and paclitaxel	47%	68%	13 months
	Pavlidis (1992)	6	Platinum based	33%	67%	N.R.
	Briasoulis (1998)*	3	Carboplatin, etoposide and epirubicin	0%	67%	16 months
	Sumi (2001)	6	Platinum based	17%	67%	Median N.R., 2 year survival was 33%
PDC midline distribution / or other features of germ cell tumours	Hainsworth (1992)	105	Cisplatin based	43%	74%	N.R.
	Pavlidis (1992)	11	Platinum based	27%	45%	N.R.
	Pentheroudakis (2005)	33	Platinum with or without taxane	9%	30%	10 months
	Sumi (2001)	6	Cisplatin and etoposide	50%	83%	Median N.R., 2 year survival was 33%
	Van-der-Gaast (1990)	34	Cisplatin, etoposide and bleomycin	12%	53%	N.R.
	Briasoulis (1998)*	14	Carboplatin, etoposide and epirubicin	21%	64%	15 months
Poorly differentiated carcinoma (regardless of metastatic site)	Lenzi (1997)	59	Cisplatin based	N.R.	N.R.	13 months
	Lenzi (1997)	23	non-platinum based	N.R.	N.R.	16 months
	Lenzi (1997)	58	no chemotherapy	N.A.	N.A.	13 months
	Sumi (2001)	11	Cisplatin and etoposide	27%	55%	N.R.
	Briasoulis (1998)*	31	Platinum based		39%	
	Culine (1999)*	35	Platinum based		43%	
	Hainsworth (1992)*	142	Platinum based		30%	
	Pasterz (1986)*	27	Platinum based		33%	
	Piga (2005)*	50	Carobplatin, doxorubicin and etoposide		32%	
	Raber (1991)*	15	Platinum based		33%	
	Sagahatchian (2001)*	30	Platinum based		55%	
	Yonemori (2006)	48	Platinum based		46%	
	Beldi (2007)	13	Platinum taxane		8%	
	Hainsworth (1997)	21	Platinum taxane		48%	
	Schnieder (2007)	10	Platinum taxane		50%	
SCC cervical lymph nodes	Pavlidis (1992)	5	Platinum based	40%	60%	N.R.

Syndrome	Study	N	Chemotherapy	Complete response rate	Overall response rate	Median survival
SCC any nodes	Khansur (1995) (any SCC)	15	Cisplatin and 5-FU continuous infusion (second line therapy)	7%	53%	4 months
Poorly differentiated neuroendocrine carcinoma	Hainsworth (2006)	48	Paclitaxel, carboplatin and etoposide	12.5%	54%	14.1 months
	Spigel (2009)	46	Cisplatin doublet therapy (N=38) or non-platinum (N=8)	28%	71%	N.R.

* Studies appraised in the prognostic/predictive factors section.
Abbreviations: PDA, poorly differentiated adenocarcinoma; PDC, poorly differentiated carcinoma; SCC, squamous cell carcinoma; UDC, undifferentiated carcinoma.

24. Chemotherapy selected according to the presumed organ of origin in patients with one of the CUP treatable syndromes.

Last updated: 30 / 10 / 2009.

Characteristics of included studies

Hainsworth-1992

Methods	Prospective case series of patients with poorly differentiated adenocarcinoma (PDA) or poorly differentiated carcinoma (PDC) of unknown primary.
Participants and Country	220 patients USA. 166 were male and 54 female. 105/220 (48%) of patients had a predominantly midline distribution of disease. Performance status was 0-1 in 85% and 2-3 in 15%.
Interventions	All were treated with cisplatin based chemotherapy. 209 patients received at least two courses of treatment and were included in the analysis.
Outcomes	**Treatment response** *for the entire group* Complete response rate 62/220 (28%) Partial response rate 80/220 (36%) Overall response rate 138/209 (66%) *for patients with mediastinal, peritoneal or peripheral node disease:* Complete response rate 45/105 (43%) Partial response rate 33/105 (31%) Overall response rate 78/105 (74%) *for patients without mediastinal, peritoneal or peripheral node disease:* Complete response rate 17/114 (15%) Partial response rate 47/104 (45%) Overall response rate 64/104 (62%) *for patients with features of extragonadal germ cell tumour* Criteria were males aged less than 45 years with predominantly mediastinal or peritoneal disease Complete response rate 17/34 (50%) Partial response rate 12/34 (35%) Overall response rate 29/34 (85%) **Overall survival** Median survival for the entire group was 12 months. There were long term survivors: 12 year survival was 16%

	Toxicity Not reported.
Notes	Patient group was heterogeneous and diagnosis was changed from PDA/PDC in a number of patients: 11% had neuroendocrine carcinoma, 4% melanoma, 3% lymphoma, 2% sarcoma, 2% squamous cell carcinoma and 2% other diagnoses.

Hainsworth-2006

Methods	Phase II prospective study in patients with advanced neuroendocrine tumour.
Participants and Country	78 patients, USA. 30/78 had known primary site and 48/78 had poorly differentiated neuroendocrine carcinoma of unknown primary tumour. 86% had good performance status (0 or 1), median age was 58 years.
Interventions	88% of patients had at least two courses of treatment with paclitaxel, carboplatin and etoposide. Paclitaxel 200 mg/m^2 administered by 1 hr IV infusion on day 1; carboplatin at an area under the concentration-time curve of 6.0 IV on day 1; and etoposide 50 mg alternating with 100 mg orally on days 1 to 10. Treatment courses were repeated at 21 day intervals.
Outcomes	**Treatment response** *In patients with CUP:* complete response rate 6/48 (12.5%), partial response rate 20/48 (42%), overall response rate 26/48 (54%). *In patients with known primary:* complete response rate 6/30 (20%), partial response rate 9/30 (30%), overall response rate 15/30 (50%). **Overall survival** *In patients with CUP:* median overall survival was 14.1 months (95% CI 9.5 to 18.5) *In patients with known primary:* median overall survival was 15.6 months (95% CI 7.1 to 24.5) **Treatment toxicity (grade 3 or 4)** *In the entire group:* neutropenia in 82% of patients, thrombocytopenia in 31%, nausea and vomiting in 10%, **Treatment related death** I*n the entire group:* 3/78 (4%) associated with neutropenic sepsis.
Notes	Authors argue that their previous results with platinum/etoposide were comparable to this regimen, and less toxic. They argue that patients with advanced PDNE should be treated with small cell lung cancer chemotherapy: preferably a platinum/ etoposide regimen of brief duration.

Hainsworth-2009

Methods	Expert review
Participants and Country	Review includes 58 studies reporting studies patients with CUP and favourable prognostic factors, or patients with similar characteristics but known primary tumours.
Interventions	Chemotherapy (other therapies are discussed, but are not included in this appraisal).
Outcomes	**Women with peritoneal carcinomatosis** Seven studies (including 258 women), published between 1989 and 1998, reported platinum based chemotherapy in this group. The complete response rate ranged from 10% to 40%. Median survival ranged from 11 to 24 months. 2 year survival ranged from 9% to 26%. **Women with axillary lymph node metastasis** The role of adjuvant systemic therapy has not the subject of clinical trials in this patient group, but the authors recommend adjuvant treatment according to stage II breast cancer guidelines. **Men with possible prostate cancer**

No studies were identified, but the authors recommend treatment according to guidelines for advanced prostate cancer.

Adencarcinoma presenting as a single lesion

Authors state that the role of adjuvant chemotherapy is undefined in this group, but adjuvant empiric chemotherapy might be considered especially in patients with poorly differentiated carcinoma.

Young men with features compatible with extragonadal germ cell tumour

Evidence from six case series was presented. One series reported a response rate of 9/12 (75%) to testicular cancer chemotherapy regimens, in young men with extragonadal germ cell tumour diagnosed using molecular genetics. There were several long term survivors.

In men with a clinical diagnosis of extragonadal germ cell tumour the authors suggest chemotherapy for poor-prognosis germ cell carcinoma, on the basis of results from case series. The proportion of men with highly responsive tumours was uncertain, however, but the authors argue that the major benefits seen in some patients warrant a treatment trial in patients with this presentation. The syndrome also occurs in women, but rarely.

Squamous cell carcinoma involving cervical lymph nodes or inguinal nodes

The authors report that evidence about combination treatment, with concurrent radiotherapy and chemotherapy, is limited in this group, although it's use is becoming more common in patients with locally advanced head and neck cancer and cancers of the anus, cervix and bladder.

Poorly differentiation carcinoma

Evidence from a case series (Hainsworth et al) suggests that some patients in this group have highly chemosensitive tumours. This group also contains young men with extragonadal germ cell tumours, and sometimes patients with poorly differentiated melanomas or neuroendocrine tumours who need to be identified and offered specific treatment. Authors argue that the remaining patients with PDC should be offered empiric combination chemotherapy.

Notes	

Khansur-1995

Methods	Prospective case series of patients with metastatic squamous cell carcinoma of unknown primary, following CT head/neck and chest, endoscopies of the nasopharynx, larynx, bronchus and oesophagus. All patients were treated between 1984 and 1992.
Participants and Country	15 patients. USA. Location of the metastasis was upper cervical nodes in 3 patients, lower cervical nodes in 5, inguinal nodes in 2, skin and subcutaneous tissue in 2 and lung/multiple nodules in 2. Histology was well differentiated
Interventions	The three patients with upper/mid neck node presentation had relapsed following surgery and radiotherapy. None of the other patients received localised therapy. Chemotherapy: cisplatin (100 mg/m^2) on day 1, 5-FU 1g/m^2/day administered as a continuous infusion in dextrose for 4 days. The regimen was repeated every 21 days.
Outcomes	**Treatment response** Complete response 1/15, Partial response 7/15, Overall response rate 8/15 (53%, 95% C.I. 27% to 79%) **Overall survival** Median survival was 48 weeks, range 29 to 85 weeks. **Grade 3 or 4 toxicity** Neutropenia 4/15 (27%) Anaemia 1/15 (7%) Mucositis 1/15 (7%)

	Nausea and vomiting 2/15 (13%) **Treatment related death** None reported
Notes	

Lenzi-1997

Methods	Retrospectiove case series of patients referred to an unknown primary tumours clinic between 1987 and 1994. All histological types were included.
Participants and Country	957 patients, USA. 140/957 had poorly differentiated carcinoma.
Interventions	Systemic therapy for patients with PDC, classed as cisplatin based (N=59), non-cisplatin based (N=23) and no chemotherapy (N=58).
Outcomes	**Overall survival in patients with PDC** *Cisplatin based chemotherapy*, median overall survival 13 months (96% CI 11 to 21 months) *Non-cisplatin based chemotherapy*, median overall survival 16 months (96% CI 4 to -- months) *No chemotherapy*, median overall survival 13 months (96% CI 8 to 32 months) **Treatment response** Not reported **Treatment toxicity** Not reported
Notes	

Pavlidis-1992

Methods	Retrospective case series of patients with biopsy proven CUP, following thorough diagnostic work-up. No primary sites were found during follow-up or post-mortem. Patients were treated with chemotherapy between 1986 and 1991.
Participants and Country	48 patients, Greece. 18 patients had predominantly midline distribution
Interventions	Cisplatin based chemotherapy in 34/48 patients (71%), mean dose 88 mg/m^2 (60 to 110 mg/m^2) Carboplatin-based in 14/48 (29%) , mean dose 270 mg/m^2 (200 to 400 mg/m^2). 5/48 (10%) received radiotherapy.
Outcomes	**Treatment response** *Peritoneal carcinomatosis* Complete response 2/6 (33%), partial response 2/6 (33%), overall response 4/6 (67%) *Midline distribution undifferentiated histology* Complete response 3/11 (27%), partial response 2/11 (18%), overall response 5/11 (45%) *Cervical nodes* Complete response 2/5 (40%), partial response 1/5 (20%), overall response 3/5 (60%) **Overall survival**

	for the entire group median survival was 4.3 months, the range was 1 to 67 months **Toxicity (grade was not reported)** *Cisplatin-based therapy related toxicity:* Anemia 23.5%, leukopenia 29%, thrombocytopenia 20.5%, alopecia 35%, nausea and vomiting 41%, neurotoxicity 9%, stomatitis 9% and nephrotoxicity 3% *Carboplatin-based therapy related toxicity:* Anemia 283.5%, leukopenia 43%, thrombocytopenia 36%, alopecia 7%, nausea and vomiting 28.5%, neurotoxicity 9%, stomatitis 9% and nephrotoxicity 3%
Notes	

Pentheroudakis-2005

Methods	Retrospective case series of patients with CUP. Patients belonged to one of two favourable risk sub-sets: those with midline lymph node metastases or women with peritoneal carcinomatosis.
Participants and Country	80 patients. Greece. 47 women in the peritoneal carcinomatosis group and 33 patients in the midline lymph node group (21 men and 12 women). Histology was poorly differentiated or undifferentiated carcinoma in most cases. Performance status was 0 to 1 in 54/80 (68%) and 2 to 3 in 25/80 (31%).
Interventions	Most patients received at least 6 cycles of platinum based chemotherapy, often combined with a taxane. Chemotherapy regimen was platinum-taxane in 48/80 patients (60%), platinum without taxane 20/80 (25%), taxane without platinum 6/80 (7.5%) or neither platinum or taxane 6/80(7.5%).
Outcomes	***Patients with peritoneal carcinomatosis (N=47)*** **Treatment response** Complete response 36%, Partial response 17%, Overall response rate 53% **Overall survival** Median survival was 15 months (95% CI 13 to 17 months), range 1 to 102 months. ***Patients with midline lymph node involvement (N=33)*** **Treatment response** Complete response 9%, Partial response 21%, Overall response rate 30% **Overall survival** Median survival was 10 months (95% CI 7 to 13 months), range 2 to 54+ months.
Notes	Authors note the high complete response rate in women with peritoneal carcinomatosis treated with platinum-taxane therapy, compared with historical rates of 10 to 20% in those treated with platinum alkylator regimes.

Spigel-2009

Methods	Expert review also presents data from a cases series of patients with poorly differentiated neuroendocrine tumour of unknown primary

Participants and Country	99 patients, USA.
Interventions	8 patients received cyclophosphamide, doxorubicin, vincristine with/without etoposide 38 patients received cisplatin doublet combinations 48 patients received carboplatin, paclitaxel and etoposide (Hainsworth et al, 2006 trial) 5 patients received surgery or radiotherapy only
Outcomes	**Treatment response** Complete response rate 19/99 (19%), partial response rate 40/99 (40%), overall response rate 59/99 (59%). **Overall survival** Median overall survival was 15 months.
Notes	Also presents evidence from studies of low grade neuroendocrine tumours of known primary: median survival in this group is over ten years. authors note that primary treatment is either localised (surgery, ablative therapy, arterial/chemoembolization or radiotherapy) or directed towards symptoms (using octreotide) as the low grade tumours are relatively unresponsive to chemotherapy.

Sumi-2001

Methods	Retrospective case series of patients with carcinoma of unknown primary site, following extensive diagnostic work up (H&P, CT chest-abdomen-pelvis, endoscopies, serum tumour markers and IHC analysis of metastases)
Participants and Country	50 patients, Japan. Histology was adenocarcinoma 68%, squamous cell carcinoma 10% and poorly differentiated carcinoma 22%.
Interventions	39 patients received chemotherapy. There were various regimens but the general rules were: Cisplatin and etoposide for patients with PDC involving midline structures Cyclophosphamide, doxorubicin and cisplatin or carboplatin and cyclophosphamide for women with elevated CA 125 Cyclophosphamide, doxorubicin with or without 5-FU for women with axillary lymph node metastases
Outcomes	**Treatment response** *for the entire group* complete 4/39 (10%), partial 9/39 (23%) and overall 13/39 (33%) *for women with peritoneal carcinomatosis* complete 1/6 (17%), partial 3/6 (50%) and overall 4/6 (67%) *for poorly differentiated carcinoma* complete 3/11 (27%), partial 3/11 (27%) and overall 6/11 (55%) *for possible extragonadal germ cell tumour (PDC and b-HCG > 10 mIU/ml)* complete 3/6 (50%), partial 2/6 (33%) and overall 5/6 (83%) **Overall survival** *for the group treated with chemotherapy* Median survival was 8 months, 2 year survival was 14%. *for the group treated with best supportive care* Median survival was 4.5 months, 2 year survival was 14%. *for females with peritoneal carcinomatosis*

	2 year overall survival was 33.3% *for possible extragonadal germ cell tumour (PDC and b-HCG > 10 mIU/ml)* 2 year overall survival was 33.3% **Treatment toxicity** not reported
Notes	

van-der-Gaast-1990

Methods	Phase II trial. Patients with undifferentiated or poorly differentiated adenocarcinoma of unknown primary, and at least one of the following characteristics: age <50 years, clinical evidence of rapid tumour growth, tumour located predominantly in a midline distribution, good response to radiotherapy.
Participants and Country	34 patients. The Netherlands. Performance status was 0-1 in 28/34 and 2 in 6/34. Median age was 51 years (range 21 to 63 years).
Interventions	8/34 patients had received radiotherapy. Chemotherapy: cisplatin, etoposide and bleomycin
Outcomes	**Treatment response** *Complete response rate:* entire group 4/34 (12%). In patients with midline disease 3/21 (14%). In patients with undifferentiated carcinoma 4/14 (29%). In patients with poorly differentiated carcinoma, 0/20 (0%). *Partial response rate:* entire group 14/34 (41%). In patients with midline disease 9/21 (43%). In patients with undifferentiated carcinoma 7/14 (50%). In patients with poorly differentiated carcinoma, 7/20 (35%). *Overall response rate:* entire group 18/34 (53%). In patients with midline disease 12/21 (57%). In patients with undifferentiated carcinoma 11/14 (79%). In patients with poorly differentiated adenocarcinoma, 7/20 (35%). **Overall survival** Median survival for complete responders was 12.5 months (range 4 to 20 months). Median survival for partial responders was 8 months (range 3 to 19 months). Median survival for those with stable disease was 4 months (range not reported) Median survival for those with progressive disease was 2 months (range 1 to 3 months) **Grade 3 or 4 toxicity** Leukopaenia 15/34 (44%) Thrombocytopaenia 7/34 (21%) Nausea and vomiting occurred in all patients, but the severity was not reported. **Treatment related death** 2/34 (6%), due to treatment related cerebral haemorrhage and bleomycin-induced pneumonitis.
Notes	Patients with an apparent diagnosis of extra-gonadal germ cell tumour were excluded from this analysis.

Varadhachary-2008

Methods	Case series of patients with CUP and histology/IHC suggesting a colon primary (e.g. CK20+, CK7-, CDX2+) or a gene profile pointing to a colon primary. In two of these patients a latent colon primary was later found.

Participants and Country	4 patients, ages were 40, 46, 56 and 72 years.
Interventions	Chemotherapy tailored to colon primary: FOLFOX (fluorouracil/leucovorin and oxaliplatin) or FOLFIRI (fluorouracil/ leucovorin and irinotecan), XELOX (capecitabine and oxaliplatin) either as first or second line therapy. 3 patients received both first and second line chemotherapy.
Outcomes	**Overall survival** All patients were still alive at last follow-up (36, 40, 24 and 20 months respectively).
Notes	

References for included studies

HAINSWORTH 1992
Hainsworth JD, Johnson DH, Greco FA. Cisplatin-Based Combination Chemotherapy in the Treatment of Poorly Differentiated Carcinoma and Poorly Differentiated Adenocarcinoma of Unknown Primary Site - Results of A 12-Year Experience. Journal of Clinical Oncology 1992; 10 (6) 912-22

HAINSWORTH 2006
Hainsworth JD. Phase II trial of paclitaxel, carboplatin, and etoposide in advanced poorly differentiated neuroendocrine carcinoma: A minnie pearl cancer research network study. Journal of Clinical Oncology 2006; 24 (22) 3548-54

HAINSWORTH 2009
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Khansur T, Allred C, Little D, Anand V. Cisplatin and 5-fluorouracil for metastatic squamous cell carcinoma from unknown primary. Cancer investigation 1995; 13 (3) 263-6

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VARADHACHARY 2008
Varadhachary GR, Raber MN, Matamoros A, Abbruzzese JL. Carcinoma of unknown primary with a colon-cancer profile - changing paradigm and emerging definitions. Lancet Oncology 2008; 9 (6) 596-9

Appendix A – Search Strategies

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: For patients with malignancy of undefined primary origin does evaluation by a specialist oncology team at an earlier time than is traditionally the case improve outcomes?

Question no: 5

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	210	8	29/04/09
Premedline	All	17	1	29/04/09
Embase	All	192	5	29/04/09
Cochrane Library	All	28	0	29/04/09
Cinahl	All	260	1	29/04/09
HMIC	All	5	0	29/04/09
Psychinfo	All	2	1	29/04/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	513	5	29/04/09
BIOSIS	All	289	3	29/04/09

Total References retrieved (after de-duplication): 10
(Also see update searches below)

Total References retrieved after Update Searching: 0

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. oncologist$.tw.

9. (nurs$ adj2 (special$ or expert$)).tw.

10. ((imaging or radiolog$) adj2 (special$ or expert$)).tw.

11. ((oncolog$ or cancer$) adj2 (special$ or expert$)).tw.

12. (oncologist$ or consultant$ or specialist$ or expert$).tw.

13. ((cancer or oncology) adj (unit$ or centre$ or center$ or service$ or team$)).tw.

14. (special$ adj (facilit$ or team$ or service$)).tw.

15. Specialism/

16. or/8-15

17. 7 and 16

2. Health Economics Literature search details – NOT REQUIRED

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSC & ISI ProceedingsI)		

3. Any further comments:

Sifting Criteria:

4. Update Searches

New references added:

Date	Database	No. of new refs

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	26	0	21/09/09
Premedline	2008-9	9	0	21/09/09
Embase	2008-9	31	0	21/09/09
Cochrane Library	2008-9	7	0	21/09/09
Cinahl	2008-9	30	0	06/10/09

Psychinfo	2008-9			
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	38	0	16/09/09
BIOSIS	2008-9	15	0	16/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: Is consistent support from an identified key worker, e.g. a specialist nurse, from the point a patient is diagnosed with an unknown or uncertain primary cancer, more effective than no support?

Question no: 6

5. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	1	0	29/07/08
Premedline	All	0	0	29/07/08
Embase	All	4	0	29/07/08
Cochrane Library	All	0	0	04/08/08
Cinahl	All	0	0	29/07/08
BNI	All	0	0	29/07/08
Psychinfo	All	0	0	29/08/08
HMIC	All	0	0	29/07/08
Web of Science (SCI & SSCI)	All	3	0	04/08/08

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2004-2008	231	24	06/08/08
Premedline	All	48	3	06/08/08
Embase	2004-2008	256	7	06/08/08
Cochrane Library	2004-2008	50	3	06/08/08
Cinahl	2004-2008	135	15	06/08/08
BNI	2004-2008	21	12	06/08/08
Psychinfo	2004-2008	44	1	06/08/08
HMIC	2004-2008	19	7	06/08/08
Web of Science (SCI & SSCI)	2004-2008	266	7	06/08/08

Total References retrieved (after de-duplication): 44

Total References after Update Searching: 2

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or

micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ origin$1 or unidentifi$ primar$) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. ((key adj work$) or keywork$).tw.
9. (key adj nurs$).tw.
10. ((care adj coordinator$) or (care adj co-ordinator$)).tw.
11. ((named adj nurs$) or (named adj work$)).tw.
12. (care adj manag$).tw.
13. or/8-12
14. 7 and 13

General Cancer search:
1. ((key adj2 work$) or keywork$).tw.
2. (key adj2 nurs$).tw.
3. ((care adj2 coordinator$) or (care adj2 co-ordinator$)).tw.
4. ((named adj2 nurs$) or (named adj2 work$)).tw.
5. (care adj1 manag$).tw.
6. or/1-5
7. exp neoplasms/
8. Cancer Care Facilities/
9. Oncology Service, Hospital/
10. (cancer$ or neoplas$ or tumo$ or carcinoma$ or hodgkin$ or adenocarcinoma$ or leukaemia$1 or leukemia$1 or metasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$).tw.
11. or/7-10
12. 6 and 11
13. limit 12 to yr="2004 - 2008"

6. Health Economics Literature search details - NOT REQUIRED

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		

NHSEED		
Cinahl		
BNI		
Psycinfo		
EconLit		
Web of Science (SCI & SSCI)		
SIGLE		

7. Any further comments:

No evidence found. General cancer search performed with a date limit of after 2004 (end date of service guidance searches when this general search was also performed)

8. Update Searches

New references added:

Date	Database	No. of new refs
10/12/08	**CINAHL**	**2**
13/05/09	**CINAHL**	**1**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	27	0	21/09/09
Premedline	2008-9	32	1	21/09/09
Embase	2008-9	27	0	21/09/09
Cochrane Library	2008-9	24	0	21/09/09
Cinahl	2008-9	8	0	06/10/09
Psychinfo	2008-9	0	0	21/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	55	2	21/09/09
HMIC	2008-9	38	1	21/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: For patients with undefined primary cancer undergoing screening investigations to identify a primary site, does management by a specialist CUP MDT result in greater benefits than the existing non-MDT management?

Question no: 10

9. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	19	10	14/07/08
Premedline	All	6	1	14/07/08
Embase	All	17	10	14/07/08
Cochrane Library	All	3	0	14/07/08
Cinahl	All	4	0	15/07/08
BNI	All	0	0	14/07/08
Psychinfo	All	0	0	14/07/08
HMIC	All	0	0	14/07/08
Web of Science (SCI & SSCI)	All	22	3	15/07/08

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2004-2008	1550	207	11/08/08
Premedline	All	136	17	11/08/08
Embase	2004-2008	660	75	12/08/08
Cochrane Library	2004-2008	68	2	12/08/08
Cinahl	2004-2008	245	42	12/08/08
BNI	200-2008	50	13	11/08/08
Psychinfo	2004-2008	62	7	12/08/08
HMIC	2004-2008	39	5	11/08/08
Web of Science (SCI & SSCI)	2004-2008	569	69	12/08/08

Total References retrieved (after de-duplication): 310
(Also see update searches below)

Total References retrieved after Update Searching: 44

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ origin$1 or unidentifi$ primar$) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. exp Interprofessional Relations/
9. ((multiprofession$ or multi-profession$ or multi profession$) adj2 team$).tw.
10. ((multidisciplinary or multi-disciplinary or multi disciplinary) adj2 team$).tw.
11. ((interprofession$ or inter-profession$ or inter profession$) adj2 team$).tw.

12. ((crossdisciplinary or cross-disciplinary or cross disciplinary) adj2 team$).tw.
13. MDT$1.tw.
14. exp Patient Care Team/
15. assessment$ team$.tw.
16. specialist$ team$.tw.
17. skill$ mix$.tw.
18. (skillmix$ or skill$-mix$).tw.
19. team meeting$.tw.
20. management plan$.tw.
21. Continuity of Patient Care/
22. (integrated adj2 care).tw.
23. teamwork$.tw.
24. (team-work$ or team work$).tw.
25. or/8-24
26. 7 and 25

10. Health Economics Literature search details – NOT REQUIRED

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
BNI		
Psycinfo		
EconLit		
Web of Science (SCI & SSCI)		
SIGLE		

11. Any further comments:

General cancer was searched due to lack of evidence for CUP.
Update searching covers general cancer only.

12. Update Searches

New references added:

Date	Database	No. of new refs
17/11/08	**Medline**	**4**
19/01/09	**Embase & Medline**	**2**
15/04/09	**Medline**	**2**

15/04/09	**CINAHL**	**1**
13/05/09	**Web of Science**	**2**
06/07/09	**Medline**	**1**
12/08/09	**Cinahl**	**6**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	618	13	23/09/09
Premedline	2008-9	84	2	23/09/09
Embase	2008-9	286	5	23/10/09
Cochrane Library	2008-9	76	1	23/09/09
Cinahl	2008-9	192	9	06/10/09
Psychinfo	2008-9	31	0	23/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	269	24	21/09/09
HMIC	2008-9	10	0	23/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: For patients with malignancy of undefined primary origin, is there an optimal initial diagnostic strategy?

Question no: 1

13. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	1431	62	06/07/09
Premedline	All	24	6	06/07/09
Embase	All	1258	28	08/07/09
Cochrane Library	All	121	1	07/07/09
Cinahl	All	747	5	08/07/09
Psychinfo	All	1	0	07/07/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	671	46	07/07/09
BIOSIS	All	646	31	07/07/09

Total References retrieved (after de-duplication): 128
(Also see update searches below)

Total References retrieved after Update Searching: 1

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. exp "Sensitivity and Specificity"/
9. sensitivity.tw.
10. specificity.tw.
11. ((pre-test or pretest) adj probability).tw.
12. post-test probability.tw.
13. predictive value$.tw.
14. likelihood ratio$.tw.
15. or/8-14
16. 7 and 15

14. Health Economics Literature search details - NOT REQUIRED

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSC & ISI ProceedingsI)		

15. Any further comments:

Sifting Criteria:

16. Update Searches

New references added:

Date	Database	No. of new refs
05/10/09	**Embase**	**1**
14/09/09	**Medline**	**1**
03/08/09	**Web of Science**	**1**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2009	32	1	14/09/09
Premedline	2009	5	1	14/09/09
Embase	2009	34	1	14/09/09
Cochrane Library	2009	14	0	14/09/09
Cinahl	2009	37	0	06/10/09
Psychinfo	2009	1	0	14/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2009	44	1	16/09/09
BIOSIS	2009	25	0	16/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: For patients with undefined primary cancer, is the application of a broad panel of tumour markers during the screening investigation phase effective in identifying the maximum number of possible primary cancers as rapidly as possible?

Question no: 3

17. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	1170	99	25/11/08
Premedline	All	27	0	01/12/08
Embase	All	887	82	01/12/08
Cochrane Library	All	28	0	08/12/08
Cinahl	All	38	1	08/12/08
Psychinfo	All	0	0	01/12/08
Web of Science (SCI & SSCI & ISI Conference Proceedings)	All	722	58	26/11/08
BIOSIS	All	573	46	08/12/08

Total References retrieved (after de-duplication): 219
(Also see update searches below)

Total References retrieved after Update Searching: 6

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ origin$1 or unidentifi$ primar$) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. exp Tumor Markers, Biological/
9. alpha-Fetoproteins/
10. (AFP or "alpha fetoprotein$").tw.
11. exp Chorionic Gonadotropin/
12. (HCG or "chorionic gonadotropin").tw.
13. Carcinoembryonic Antigen/
14. (CEA or "carcinoembryonic antigen$").tw.
15. "carbohydrate antigen$".tw.
16. ("CA 125" or CA125).tw.
17. ("CA 199" or CA199).tw.
18. Prostate-Specific Antigen/
19. (PSA or "prostate specific antigen$").tw.
20. ("CA 153" or CA153).tw.
21. Thyroglobulin.tw. or Thyroglobulin/
22. Calcitonin.tw. or Calcitonin/
23. Chromogranin$.tw. or Chromogranins/
24. Phosphopyruvate Hydratase/
25. (NSE or "neuron specific enolase").tw.
26. or/8-25
27. 7 and 26

18. Health Economics Literature search details – NOT SEARCHED FOR THIS QUESTION

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search

Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSCI & ISI Proceedings)		

19. Any further comments:

Sifting Criteria:
Excluded articles discussing diagnosis of occult metastases from existing primaries.

20. Update Searches

New references added:

Date	Database	No. of new refs
11/02/09	**Medline**	**3**
29/06/09	**Embase**	**1**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	102	5	15/09/09
Premedline	2008-9	14	0	15/09/09
Embase	2008-9	104	1	15/09/09
Cochrane Library	2008-9	3	0	15/09/09
Cinahl	208-09	10	0	06/10/09
Psychinfo	2008-9	1	0	15/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	88	1	16/09/09
BIOSIS	2008-9	46	1	16/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: For patients with primary malignancy of undefined primary origin, is the use of upper- and lower-GI endoscopy in asymptomatic patients effective in identifying the maximum number of possible primary cancers?

Question no: 4

21. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	345	28	06/01/09
Premedline	All	20	1	06/01/09
Embase	All	368	25	06/01/09
Cochrane Library	All	123	2	07/01/09
Cinahl	All	291	11	06/01/09
Psychinfo	All	0	0	06/01/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	229	14	05/01/09
BIOSIS	All	199	9	05/01/09

Total References retrieved (after de-duplication): 34
(Also see update searches below)

Total References retrieved after Update Searching: 2

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Endoscopy, Gastrointestinal/
2. (((gastrointestin$ or intestin$) adj endoscop$) or (gi adj endoscop$)).tw.
3. ((upper adj1 endoscop$) or (lower adj1 endoscop$)).tw.
4. gastroscop$.tw.
5. Esophagoscopy/
6. esophagoscop$.tw.
7. (oesophagogastroduodenoscop$ or esophagogastroduodenoscop$ or OGD).tw.
8. Colonoscopy/ or colonoscop$.tw.
9. or/1-8
10. Neoplasms, Unknown Primary/
11. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
12. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
13. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
14. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
15. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
16. or/10-15
17. 9 and 16

22. Health Economics Literature search details - Not Required

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSC & ISI ProceedingsI)		

23. Any further comments:

The majority of search results retrieved were about colorectal cancer screening and occult blood testing, which were excluded from sift.

24. Update Searches

New references added:

Date	Database	No. of new refs

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	44	0	15/09/09
Premedline	2008-9	14	0	15/09/09
Embase	2008-9	15	0	15/09/09
Cochrane Library	2008-9	11	0	15/09/09
Cinahl	208-09	23		06/10/09
Psychinfo	2008-9	5	0	15/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	34	2	16/09/09
BIOSIS	2008-9	24	1	16/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: For patients with malignancy of undefined primary origin, is there an optimal initial diagnostic strategy (for women undergoing mammography)

Question no: 1a

25. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	479	49	20/07/09
Premedline	All	4	0	21/07/09
Embase	All	436	34	21/07/09
Cochrane Library	All	15	0	21/07/09
Cinahl	All	117	2	21/07/09
Psychinfo	All	5	0	21/07/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	542	32	21/07/09
BIOSIS	All	340	22	21/07/09

Total References retrieved (after de-duplication): 76
(Also see update searches below)

Total References retrieved after Update Searching: 1

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

26. Health Economics Literature search details - NOT REQUIRED

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSC & ISI ProceedingsI)		

27. Any further comments:

Sifting Criteria:

28. Update Searches

New references added:

Date	Database	No. of new refs

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2009	6	0	14/09/09
Premedline	2009	5	1	14/09/09
Embase	2009	9	0	14/09/09
Cochrane Library	2009	2	0	14/09/09
Cinahl	2009	8		06/10/09
Psychinfo	2009	0	0	14/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2009	26	1	16/09/09
BIOSIS	2009	9	0	16/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: For patients with provisional Cancer of Unknown Primary with clinical features compatible with metastatic breast cancer, does contrast-enhanced breast MRI improve detection of occult primary breast cancer?

Question no: 11

29. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	182	59	06/10.08
Premedline	All	13	8	06/10/08
Embase	All	379	59	13/10/08
Cochrane Library	All	10	1	07/10/08
Cinahl	All	43	11	15/10/08
Psychinfo	All	1	1	13/10/08
Web of Science (SCI & SSCI)	All	137	70	14/10/08
BIOSIS	All	63	22	14/10/08
ISI Proceedings	All	19	6	14/10/08

Total References retrieved (after de-duplication): 137

Total References after Update Searching: 2

Medline search strategy *(This search strategy is adapted to each database.)*

. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

7. or/1-6

8. exp Magnetic Resonance Imaging/

9. magnet$ resonance.tw.

10. (MRI$1 or NMRI$1).tw.

11. ((MR or NMR) adj (imag$ or scan$)).tw.

12. (magnet$ adj (imag$ or scan$)).tw.

13. or/8-12

14. exp Breast Neoplasms/

15. exp "Neoplasms, Ductal, Lobular, and Medullary"/

16. Carcinoma, Intraductal, Noninfiltrating/

17. Carcinoma, Lobular/

18. Carcinoma, Medullary/

19. exp mammary neoplasms/

20. or/14-19

21. (breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw.

22. (mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw.

23. 21 or 22

24. 20 or 23

25. 24 and 7

26. 25 and 13

30. Health Economics Literature search details

(SIGN Health Economics filter added to above search)

[SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
BNI		
Psycinfo		
EconLit		
Web of Science (SCI & SSCI)		

31. Any further comments:

Sifting Criteria:

Excluded breast metastases from the search strategy as many articles did not mention if the breast tumour was mestastatic.

32. Update Searches

New references added:

Date	Database	No. of new refs
12/08/09	**Medline**	**1**
29/06/09	**Embase**	**1**
15/04/09	**Medline**	**1**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2009	26	2	22/09/09
Premedline	2009	4	0	22/09/09
Embase	2009	61	2	22/09/09
Cochrane Library	2009	1	0	22/09/09
Cinahl	2009	11	0	06/10/09
Psychinfo	2009	0	0	22/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2009	26	0	28/09/09
BIOSIS	2009	10	0	28/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: What is the diagnostic utility of PET-CT for the detection of the primary tumour site in people with metastatic cancer of unknown primary?

Question no: 13

33. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	468	140	04/02/08
Premedline	All	17	7	05/02/08
Embase	All	473	174	06/02/08
Cochrane Library	All	14	7	12/02/08
Cinahl	All	16	6	05/02/08
BNI	All	0	0	05/02/08
Psychinfo	All	3	1	12/02/08
Web of Science (SCI & SSCI)	All	451	133	13/02/08
BIOSIS	All	0	0	12/02/08

Total References retrieved (after de-duplication): 295

Total References after Update Searching: 9

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/
2. (Unknown primar$ and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Unknown origin and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. (Undetermined origin adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. (Undetermined primar$ adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. (Unidentifi$ origin adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
8. (Unidentifi$ primar$ adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
9. or/1-5
10. exp Tomography, Emission-Computed/
11. (positron adj3 tomograph$).tw.
12. PET.tw.
13. (gamma adj1 camera$).tw.
14. Gamma Cameras/
15. SPECT.tw.
16. or/10-15
17. 9 and 16

34. Health Economics Literature search details –

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline	6	01/07/08
Premedline	1	01/07/08
Embase	8	01/07/08
Cochrane Library (except NHSEED)	2	01/07/08
NHSEED	0	01/07/08
Cinahl	0	01/07/08
BNI	0	01/07/08
Psycinfo	0	01/07/08
EconLit	0	01/07/08
Web of Science (SCI & SSCI)	6	01/07/08

35. Any further comments:

Sifting Criteria:

36. Update Searches

New references added:

Date	Database	No. of new refs
02/09/09	**Medline**	**1**
29/06/09	**Web of Science**	**1**
15/06/09	**Medline**	**1**
03/06/09	**Medline**	**1**
06/05/09	**Medline**	**2**
15/04/09	**Medline**	**1**
02/02/09	**Embase**	**4**
19/01/09	**Embase**	**1**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	103	1	22/09/09
Premedline	2008-9	24	2	22/09/09
Embase	2008-9	128	4	22/09/09
Cochrane Library	2008-9	7	1	22/09/09
Cinahl	2008-9	7	0	06/10/09
Psychinfo	2008-9	0	0	22/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	159	2	28/09/09
BIOSIS	2008-9	43	1	28/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: For patients with malignancy of undefined primary origin, does immuno-histochemical analysis result in improved outcomes? (Adenocarcinoma only)

Question no: 8

37. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	390	71	11/02/09
Premedline	All	8	1	11/02/09
Embase	All	333	61	11/02/09
Cochrane Library	All	32	1	11/02/09
Cinahl	All	87	21	11/02/09
Psychinfo	All	10	0	11/02/09
Web of Science (SCI &	All	156	56	11/02/09

SSCI & ISI Proceedings))				
BIOSIS	All	121	20	11/02/09

Total References retrieved (after de-duplication): 167
(Also see update searches below)

Total References retrieved after Update Searching: 2

Medline search strategy *(This search strategy is adapted to each database.)*

1. exp Immunohistochemistry/
2. immunohisto$.tw.
3. immunocyto$.tw.
4. or/1-3
5. ((unknown primar$ or unknown origin$ or occult or undetermined origin$ or undetermined primar$ or unidentif$ origin$ or unidentif$ primar$) adj adeno$).tw.
6. ACUP.tw.
7. (metasta$ adj adenocarcinoma$).tw.
8. 6 or 7 or 5
9. 8 and 4

38. Health Economics Literature search details - NOT REQUIRED

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSC & ISI ProceedingsI)		

39. Any further comments:

Sifting Criteria:

40. Update Searches

New references added:

Date	Database	No. of new refs
24/06/09	**Embase**	**1**
08/06/09	**Web of Science**	**1**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	38	1	06/10/09
Premedline	2008-9	5	0	06/10/09
Embase	2008-9	34	1	06/10/09
Cochrane Library	2008-9	10	0	06/10/09
Cinahl	2008-9	20	0	06/10/09
Psychinfo	2008-9	0	0	06/10/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	44	1	21/09/09
BIOSIS	2008-9	17	0	21/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: For patients with provisional Cancer of Unknown Primary who present with intra-pulmonary nodules without evidence of endobronchial disease, does bronchoscopy result in improved outcomes?

Question no: 17

41. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	236	42	07/01/09
Premedline	All	8	1	07/01/09
Embase	All	212	45	13/01/09
Cochrane Library	All		0	13/01/09
Cinahl	All	59	2	14/01/09
Psychinfo	All	0	0	12/01/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	207	38	14/01/09
BIOSIS	All	172	25	14/01/08

Second Search:

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	408	21	21/01/09
Premedline	All	0	0	21/01/09
Embase	All	272	4	21/01/09
Cochrane Library	All	22	0	21/01/09

Cinahl	All			21/01/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	190	8	21/01/09
BIOSIS	All	113	1	21/01/09

Total References retrieved (after de-duplication): 94
(Also see update searches below)

Total References retrieved in second search (after de-duplication): 33
(Also see update searches below)

Total References retrieved after Update Searching: 0

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. Bronchoscopy/
9. Thoracoscopy/
10. Mediastinoscopy/
11. Bronchography/
12. (bronchoscop$ or thoracoscop$ or pleuroscop$ or mediastinoscop$ or bronchograph$).tw.
13. (endoscop$ adj3 pleur$).tw.
14. or/8-13
15. exp thoracic surgery, video-assisted/
16. (video adj5 thora$).tw.
17. (videothoracoscop$ adj2 surg$).tw.
18. VATS.tw.
19. ((thora$ or transbronchial or transthoracic or pleur$) adj3 (biops$ or needle or puncture or aspiration)).tw.
20. or/15-19
21. 14 or 20

22. 21 and 7

Second search strategy:

1. Bronchoscopy/
2. Thoracoscopy/
3. Mediastinoscopy/
4. Bronchography/
5. (bronchoscop$ or thoracoscop$ or pleuroscop$ or mediastinoscop$ or bronchograph$).tw.
6. (endoscop$ adj3 pleur$).tw.
7. or/1-6
8. exp thoracic surgery, video-assisted/
9. (video adj5 thora$).tw.
10. (videothoracoscop$ adj2 surg$).tw.
11. VATS.tw.
12. ((thora$ or endothora$ or endobronch$ or transbronchial or transthoracic) adj3 (biops$ or needle or puncture or aspiration)).tw.
13. or/8-12
14. 7 or 13
15. exp Neoplasm Metastasis/
16. Lung Neoplasms/
17. 15 and 16
18. (lung adj2 metasta$).tw.
19. ((pulmonary or endobronch$ or thora$ or mediastin$ or occult) adj metasta$).tw.
20. 18 or 19
21. 17 or 20
22. 14 and 21
23. exp diagnosis/ or diagnos$.tw.
24. 22 and 23
25. limit 24 to yr="2003 - 2009"

42. Health Economics Literature search details – Not Required

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search

Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSC & ISI ProceedingsI)		

43. Any further comments:

PICO includes a comparison with Video-assisted thoracic surgery and biopsy (VATS)

Poor evidence in first search, so a second search was performed leaving out the CUP set and replacing it with a lung metastases set, along with a date limit 2003-present

44. Update Searches

New references added:

Date	Database	No. of new refs

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	126	0	23/09/09
Premedline	2008-9	16	0	23/09/09
Embase	2008-9	170	0	23/09/09
Cochrane Library	2008-9	6	0	23/09/09
Cinahl	2008-9	5	0	06/10/09
Psychinfo	2008-9	0	0	23/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	93	0	28/09/09
BIOSIS	2008-9	46		28/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: Methods of initial investigation for patients who present predominately with malignant ascites: Is fluid cytology sufficient for establishing a diagnosis and eliminating primary sites or is a formal biopsy (image guided or laparoscopic) necessary?

Question no: 19

45. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	99	37	18/06/08
Premedline	All	1	1	18/06/08
Embase	All	80	19	23/06/08
Cochrane Library	All	15	1	24/06/08
Cinahl	All	3	2	24/06/08
Psychinfo	All	0	0	23/06/08
Web of Science (SCI & SSCI & ISI Proceedings))	All	95	11	24/06/08
BIOSIS	All	55	3	24/06/08

Total References retrieved (after de-duplication): 53
(Also see update searches below)

Total References retrieved after Update Searching: 0

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ origin$1 or unidentifi$ primar$) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. Ascites/
9. Ascitic Fluid/
10. ascit$.tw.
11. (peritone$ adj2 fluid$).tw.
12. hydroperitoneum.tw.
13. abdominal drops$.tw.
14. (fluid$ adj2 (collection or accumulation or retention)).tw.
15. or/8-14
16. exp Peritoneal Diseases/
17. (peritone$ adj2 disease$).tw.
18. peritonitis.tw.
19. (hemoperitoneum$ or haemoperitoneum$).tw.
20. ((mesenteric or peritoneal) adj1 lymphadeniti$).tw.
21. ((mesenteric or peritoneal) adj2 occlusion$).tw.
22. (((mesenteric or peritoneal) adj1 inflammation) or mesenteritis).tw.
23. ((mesenter$ or peritone$ or omental) adj1 (panniculitis or lipodystroph$)).tw.

24. (mesenter$ adj1 disease$).tw.
25. ((subphrenic or subdiaphragmatic) adj2 abscess$).tw.
26. pneumoperiton$.tw.
27. or/16-26
28. 15 or 27
29. 7 and 28
30. Cytology/
31. Cytodiagnosis/
32. cytolog$.tw.
33. aspiration.tw.
34. cytospin$.tw.
35. Cytological Techniques/
36. or/30-35
37. exp biopsy/
38. biops$.tw.
39. Laparoscopy/
40. laparoscop$.tw.
41. celioscop$.tw.
42. peritoneoscop$.tw.
43. excis$.tw.
44. or/37-43
45. 36 or 44
46. 29 and 45

46. Health Economics Literature search details – NOT REQURIED

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSCI)		

47. Any further comments:

Sifting Criteria:

48. Update Searches

New references added:

Date	Database	No. of new refs

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	7	0	23/09/09
Premedline	2008-9	1	0	23/09/09
Embase	2008-9	8	0	23/09/09
Cochrane Library	2008-9	1	0	23/09/09
Cinahl	2008-9	0	0	06/10/09
Psychinfo	2008-9	0	0	23/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	9	0	28/09/09
BIOSIS	2008-9	4	0	28/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: For patients with malignancy of undefined primary origin, is it beneficial for investigations to be undertaken to end uncertainty when there is little likelihood of clinical benefit?

Question no: 7

49. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	120	6	13/05/09
Premedline	All	3	0	13/05/09
Embase	All	189	4	20/05/09
Cochrane Library	All	16	0	13/05/09
Cinahl	All	64	4	26/05/09
Psychinfo	All	6	0	13/05/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	249	2	26/05/09
BIOSIS	All	243	0	26/05/09

Total References retrieved (after de-duplication): 14
(Also see update searches below)

Total References retrieved after Update Searching: 2

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/

2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

7. or/1-6

8. exp Adaptation, Psychological/

9. Stress, Psychological/

10. Depression/

11. exp Emotions/

12. uncertainty/

13. (depression or anxiety or anger or hopelessness or helplessness or stress or self-esteem or coping or distress).tw.

14. (psycholog$ adj support$).tw.

15. (social adj support$).tw.

16. (patient$ adj support$).tw.

17. or/8-16

18. Physician-Patient Relations/

19. exp Professional-Family Relations/

20. Truth Disclosure/

21. ((doctor$ or clinician$ or professional$ or physician$ or consultant$ or oncologist$) adj confidence).tw.

22. counsel$.tw.

23. or/18-22

24. Attitude to Death/

25. 17 or 23 or 24

26. 25 and 7

50. Health Economics Literature search details - NOT REQUIRED

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSC & ISI ProceedingsI)		

51. Any further comments:

Sifting Criteria:

52. Update Searches

New references added:

Date	Database	No. of new refs

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	65	1	21/09/09
Premedline	2008-9	5	0	21/09/09
Embase	2008-9	72	1	21/09/09
Cochrane Library	2008-9	9	0	21/09/09
Cinahl	2008-9	68	2	06/10/09
Psychinfo	2008-9	5	0	21/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	92	0	21/09/09
HMIC	2008-9	2	0	21/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: For patients with confirmed Cancer of Unknown Primary, in whom systemic treatment is being considered, are there prognostic factors that significantly influence outcome and which should be considered in treatment decisions?

Question no: 25

53. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	519	43	25/03/09
Premedline	All	26	5	25/03/09
Embase	All	496	37	35/04/09
Cochrane Library	All	15	0	25/03/09
Cinahl	All	126	19	25/03/09
Psychinfo	All	1	1	25/03/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	509	40	25/03/09
BIOSIS	All	402	22	25/03/09

Total References retrieved (after de-duplication): 76
(Also see update searches below)

Total References retrieved after Update Searching: 4

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. Biological Factors/
9. prediction.tw.
10. performance status.tw.
11. (prognostic adj1 (score$ or factor$ or indicator$ or index$)).tw.
12. (predictive adj1 (score$ or factor$ or indicator$ or index$)).tw.
13. or/8-12
14. 7 and 13

54. Health Economics Literature search details - NOT REQUIRED

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		

Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSC & ISI ProceedingsI)		

55. Any further comments:

Sifting Criteria:

56. Update Searches

New references added:

Date	Database	No. of new refs

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	57	4	05/10/09
Premedline	2008-9	25	2	05/10/09
Embase	2008-9	65	4	05/10/09
Cochrane Library	2008-9	3	0	05/10/09
Cinahl	2008-9	120	0	06/10/09
Psychinfo	2008-9	0	0	05/10/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	171	1	30/09/09
BIOSIS	2008-9	68	0	30/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: Decision aids for people with cancer of unknown primary

Question no: 29

57. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	172	12	02/06/09
Premedline	All	8	0	02/06/09
Embase	All	30	1	02/06/09
Cochrane Library	All	151	3	02/06/09
Cinahl	All	240	1	03/06/09
Psychinfo	All	2	0	02/06/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	185	13	03/06/09
BIOSIS	All	164	9	03/06/09

Total References retrieved (after de-duplication): 20
(Also see update searches below)

Total References retrieved after Update Searching: 0

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. choice behavior/
9. decision making/
10. exp decision support techniques/
11. ((patient$ or consumer$) adj3 (decision$ or choice or preference or participation)).tw.
12. ((personal or interpersonal or individual) adj3 (decision$ or choice or preference$ or participat$)).tw.
13. (decision$ adj3 (aid$ or support$)).tw.
14. exp Patient Participation/
15. Pamphlets/
16. exp Audiovisual Aids/
17. (video$ or dvd$).tw.
18. exp Internet/
19. exp Self-Help Groups/
20. (support$ adj2 (group$ or meet$)).tw.
21. exp Patient Education/mt
22. ((inform$ or support$) adj2 (tool$ or method$ or group$)).tw.
23. (nomogram$ or nomograph$).tw.
24. (alignment$ adj2 chart$).tw.
25. *"models, statistical"/
26. or/8-25
27. 7 and 26

58. Health Economics Literature search details

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSC & ISI ProceedingsI)		

59. Any further comments:

Sifting Criteria:

60. Update Searches

New references added:

Date	Database	No. of new refs

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	24	0	05/10/09
Premedline	2008-9	2	0	05/10/09
Embase	2008-9	20	0	05/10/09
Cochrane Library	2008-9	5	0	05/10/09
Cinahl	2008-9	54	0	06/10/09
Psychinfo	2008-9	0	0	05/10/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	83	0	30/09/09
BIOSIS	2008-9	43	0	30/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: Can gene-expression based profiling guide targeted investigations to identify primary tumours more frequently and more rapidly in patients with provisional cancer of unknown primary?

Question no: 26

61. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	70	30	17/02/09
Premedline	All	3	2	17/02/09
Embase	All	72	25	17/02/09
Cochrane Library	All	1	0	17/02/09
Cinahl	All	45	15	17/02/09
Psychinfo	All	0	0	17/02/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	85	34	17/02/09
BIOSIS	All	69	17	17/02/09

Total References retrieved (after de-duplication): 74
(Also see update searches below)

Total References retrieved after Update Searching: 5

Medline search strategy *(This search strategy is adapted to each database.)*

1. Gene Expression Profiling/
2. "gene expression" or "genetic profil$".tw.
3. (geno$ adj (identif$ OR classif$))
4. Microarray Analysis/
5. MicroRNAs/
6. analysis.tw.
7. 5 and 6
8. "RNA expression analysis".tw.
9. or/1-4
10. 9 or 7 or 8
11. Neoplasms, Unknown Primary/
12. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
13. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
14. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
15. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

16. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

17. or/11-16

18. 17 and 10

62. Health Economics Literature search details – NOT REQUIRED

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSC & ISI ProceedingsI)		

63. Any further comments:

Sifting Criteria:

64. Update Searches

New references added:

Date	Database	No. of new refs
02/09/09	**Medline**	**1**
12/08/09	**Cochrane**	**1**
27/07/09	**Web of Science**	**1**
24/06/09	**Web of Science**	**2**
24/06/09	**Medline**	**1**
08/06/09	**Web of Science**	**1**
03/06/09	**Medline**	**1**
13/05/09	**Web of Science**	**1**
15/04/09	**Medline**	**1**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	23	2	05/10/09
Premedline	2008-9	5	1	05/10/09
Embase	2008-9	23	3	05/10/09
Cochrane Library	2008-9	0	0	05/10/09

Cinahl	2008-9	12	1	05/10/09
Psychinfo	2008-9	0	0	05/10/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	58	2	30/09/09
BIOSIS	2008-9	18	0	30/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: What is the optimal management for patients with confirmed Cancer of Unknown Primary who present with squamous carcinoma involving upper / mid neck nodes?

Question no: 21

65. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	259	75	24/02/09
Premedline	All	1	0	24/02/09
Embase	All	394	66	25/02/09
Cochrane Library	All	4	1	24/02/09
Cinahl	All	163	8	25/02/09
Psychinfo	All	0	0	24/02/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	362	46	24/02/09
BIOSIS	All	159	23	24/02/09

Total References retrieved (after de-duplication): 152
(Also see update searches below)

Total References retrieved after Update Searching: 1

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or

micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

7. or/1-6

8. "Head and Neck Neoplasms"/

9. ((head or neck) adj (neoplas$ or tumo$ or carcinoma$ or cancer$)).tw.

10. 8 or 9

11. Carcinoma, Squamous Cell/

12. squamous.tw.

13. 11 or 12

14. 13 and 10

15. HNSCC.tw.

16. 15 or 14

17. Lymphatic Metastasis/

18. (lymph$ adj2 (metasta$ or spread$)).tw.

19. ((node$ or nodal) adj2 (metasta$ or spread$)).tw.

20. or/17-19

21. 16 and 20

22. 21 and 7

66. Health Economics Literature search details – NOT REQUIRED

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSC & ISI Proceedingsl)		

67. Any further comments:

Sifting Criteria:

68. Update Searches

New references added:

Date	Database	No. of new refs
03/08/09	Web of Science	1
27/07/09	Embase	1
08/06/09	Web of Science	2
27/05/09	Cinahl	1

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	17	1	23/09/09
Premedline	2008-9	2	0	23/09/09
Embase	2008-9	43	1	23/09/09
Cochrane Library	2008-9	3	1	23/09/09
Cinahl	2008-9	30	1	06/10/09
Psychinfo	2008-9	0	0	23/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	66	0	28/09/09
BIOSIS	2008-9	18	0	28/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: What is the optimal management for patients with confirmed Cancer of Unknown Primary who present with adenocarcinoma involving axillary nodes?

Question no: 22

69. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	51	18	10/03/09
Premedline	All	3	1	10/03/09
Embase	All	48	14	10/03/09
Cochrane Library	All	0	0	10/03/09
Cinahl	All	0	0	16/03/09
Psychinfo	All	0	0	16/03/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	43	9	16/03/09
BIOSIS	All	27	12	16/03/09

Total References retrieved (after de-duplication): 29
(Also see update searches below)

Total References retrieved after Update Searching: 0

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/

2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.

7. or/1-6

8. ACUP.tw.

9. adenocarcinoma$.tw.

10. 8 or 9

11. axillary.tw.

12. 11 and 7 and 10

70. Health Economics Literature search details

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSC & ISI ProceedingsI)		

71. Any further comments:

Sifting Criteria:

72. Update Searches

New references added:

Date	Database	No. of new refs

Database name	Dates Covered	No of references found	No of references retrieved	Finish date c search
Medline	2008-9	8	0	23/09/09
Premedline	2008-9	0	0	23/09/09
Embase	2008-9	10	0	23/09/09
Cochrane Library	2008-9	0	0	23/09/09
Cinahl	2008-9	0	0	06/10/09
Psychinfo	2008-9	0	0	23/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	7	0	28/09/09
BIOSIS	2008-9	3	0	28/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: What is the optimal management for patients with confirmed Cancer of Unknown Primary who present with squamous carcinoma involving inguinal nodes?

Question no: 23

73. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	27	4	16/03/09
Premedline	All	2	0	17/03/09
Embase	All	25	2	17/03/09
Cochrane Library	All	0	0	17/03/09
Cinahl	All	4	0	17/03/09
Psychinfo	All	0	0	17/03/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	22	1	17/03/09
BIOSIS	All	17	2	17/03/09

Total References retrieved (after de-duplication): 8
(Also see update searches below)

Total References retrieved after Update Searching: 1

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/

2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. Carcinoma, Squamous Cell/
9. squamous.tw.
10. 8 or 9
11. inguinal.tw.
12. Groin/
13. Lymph Nodes/
14. Lymphatic Metastasis/
15. 13 or 14
16. 12 and 15
17. 11 or 16
18. 17 and 7 and 10

74. Health Economics Literature search details – NOT REQUIRED

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		
EconLit		
Web of Science (SCI & SSC & ISI ProceedingsI)		

75. Any further comments:

No evidence

76. Update Searches

New references added:

Date	Database	No. of new refs

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	5	0	23/09/09
Premedline	2008-9	1	1	23/09/09
Embase	2008-9	6	0	23/09/09
Cochrane Library	2008-9	0	0	23/09/09
Cinahl	2008-9	2	0	06/10/09
Psychinfo	2008-9	0	0	23/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	6	0	28/09/09
BIOSIS	2008-9	2	0	28/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary Clinical Guideline Literature search summary

Question title: What is the benefit of radical local treatment for patients with confirmed Cancer of Unknown Primary who present with an isolated metastasis in one of the following organs: brain, bone, liver, skin, lung?

Question no: 24

77. Literature search details

Brain

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	79	34	09/06/09
Premedline	All	2	1	09/06/09
Embase	All	70	25	09/06/09
Cochrane Library	All	3	1	09/06/09
Psychinfo	All	0	0	09/06/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	47	15	10/06/09
BIOSIS	All	40	15	10/06/09

Total References retrieved (after de-duplication): 49
(Also see update searches below)

Total References retrieved after Update Searching: 0

Bone

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	29	4	09/06/09
Premedline	All	2	0	09/06/09

Embase	All	41	3	09/06/09
Cochrane Library	All	1	0	09/06/09
Psychinfo	All	0	0	09/06/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	13	2	10/06/09
BIOSIS	All	8	1	10/06/09

Total References retrieved (after de-duplication): 8
(Also see update searches below)

Total References retrieved after Update Searching: 0

Liver

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	95	2	09/06/09
Premedline	All	2	0	09/06/09
Embase	All	92	1	09/06/09
Cochrane Library	All	5	0	09/06/09
Psychinfo	All	0	0	09/06/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	82	3	10/06/09
BIOSIS	All	40	3	10/06/09

Total References retrieved (after de-duplication): 8
(Also see update searches below)

Total References retrieved after Update Searching: 0

Skin

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	124	12	22/06/09
Premedline	All	2	0	22/06/09
Embase	All	102	8	22/06/09
Cochrane Library	All	6	0	23/06/09
Psychinfo	All	1	0	23/06/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	76	9	23/06/09
BIOSIS	All	35	5	23/06/09

Total References retrieved (after de-duplication): 15
(Also see update searches below)

Total References retrieved after Update Searching: 1

Lung

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	53	5	23/06/09
Premedline	All	0	0	23/06/09
Embase	All	95	3	23/06/09
Cochrane Library	All	0	0	23/06/09
Psychinfo	All	0	0	23/06/09
Web of Science (SCI & SSCI & ISI Proceedings))	All	58	4	24/06/09
BIOSIS	All	31	3	24/06/09

Total References retrieved (after de-duplication): 8
(Also see update searches below)

Total References retrieved after Update Searching: 0

Medline search strategy *(This search strategy is adapted to each database.)*

Qu. 24a Brain
1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. exp brain neoplasms/
9. ((brain or midbrain or brainstem or intracranial or cranial or cerebell$ or cerebr$ or CNS or central nervous system) adj2 metasta$).tw.
10. glioma.tw.
11. or/8-10
12. exp Neoplasm Metastasis/
13. metastas$.tw.
14. 12 or 13
15. (solitar$ or single$ or isolat$).tw.
16. 14 and 15
17. 11 and 16
18. ((brain or midbrain or brainstem or intracranial or cranial or cerebell$ or cerebr$ or CNS or central nervous system) adj1 metastasis).tw.
19. 17 or 18
20. 7 and 19
21. (surg$ or neurosurg$ or craniotom$ or radiosurg$ or resection$ or radiotherap$ or radiation or irradiation or chemotherap$).tw.
22. (therap$ or treatment$).tw.
23. 21 or 22
24. 20 and 23

Qu. 24b Bone
1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or

malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. Bone Metastasis/
9. osseous metasta$.tw.
10. (bone$ adj2 metasta$).tw.
11. (bony adj metasta$).tw.
12. (skelet$ adj metasta$).tw.
13. or/8-12
14. (solitar$ or isolat$ or single).tw.
15. 13 and 14
16. 7 and 15

Qu. 24c Liver

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. (solitar$ or isolat$ or single).tw.
9. exp Liver Neoplasms/
10. (liver or hepatic).tw.
11. metasta$.tw.
12. exp Neoplasm Metastasis/
13. 12 and 9
14. 11 and 10
15. 13 or 14
16. 8 and 15
17. 7 and 16

Qu. 24d Skin

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ origin$1 or unidentifi$ primar$) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. exp Skin Neoplasms/
9. exp Melanoma/
10. exp Carcinoma, Squamous Cell/
11. exp Carcinoma, Basal Cell/
12. (Basal adj2 carcinoma$).tw.

13. (basal adj1 cancer$).tw.
14. (basal adj1 neoplas$).tw.
15. (basal adj1 tumo?r$).tw.
16. (basal adj1 epithelioma$).tw.
17. (basal adj1 malignan$).tw.
18. (Squamous adj2 carcinoma$).tw.
19. (squamous adj1 tumo?r$).tw.
20. (squamous adj1 cancer$).tw.
21. (squamous adj1 neoplas$).tw.
22. (squamous adj1 epithelioma$).tw.
23. (squamous adj1 malignan$).tw.
24. melanoma$.tw.
25. ((skin or derm$ or cutaneous or epithelial or epidermoid) adj1 (cancer$ or neoplas$ or carcinoma$ or tumo?r$ or malignan$)).tw.
26. or/8-25
27. (solitar$ or isolat$ or single).tw.
28. exp neoplasm metastasis/
29. 28 and 26
30. 27 and 29
31. 30 and 7

Qu. 24e Lung
1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. exp lung neoplasms/
9. (lung adj metast$).tw.
10. exp neoplasm metastasis/
11. 8 and 10
12. 11 or 9
13. (solitar$ or isolat$ or single).tw.
14. 13 and 12
15. 7 and 14

78. Health Economics Literature search details - NOT REQUIRED

(SIGN Health Economics filter added to above search)

[Indicate if SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
Psycinfo		

EconLit		
Web of Science (SCI & SSC & ISI ProceedingsI)		

79. Any further comments:

Sifting Criteria:

80. Update Searches

New references added:

Question	Date	Database	No. of new refs
24a	**03/08/09**	**Medline**	**1**

Brain

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	7	0	05/10/09
Premedline	2008-9	1	0	05/10/09
Embase	2008-9	13	0	05/10/09
Cochrane Library	2008-9	2	0	05/10/09
Cinahl	2008-9	2	0	05/10/09
Psychinfo	2008-9	0	0	05/10/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	5	0	28/09/09
BIOSIS	2008-9	2	0	28/09/09

Bone

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	4	0	05/10/09
Premedline	2008-9	1	0	05/10/09
Embase	2008-9	7	0	05/10/09
Cochrane Library	2008-9	0	0	05/10/09
Cinahl	2008-9	0	0	05/10/09
Psychinfo	2008-9	0	0	05/10/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	2	0	28/09/09
BIOSIS	2008-9	0	0	28/09/09

Liver

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	7	0	05/10/09
Premedline	2008-9	1	0	05/10/09
Embase	2008-9	11	0	05/10/09
Cochrane Library	2008-9	2	0	05/10/09

Cinahl	2008-9	0	0	05/10/09
Psychinfo	2008-9	0	0	05/10/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	11	0	28/09/09
BIOSIS	2008-9	1	0	28/09/09

Skin

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	18	0	05/10/09
Premedline	2008-9	5	0	05/10/09
Embase	2008-9	22	0	05/10/09
Cochrane Library	2008-9	4	0	05/10/09
Cinahl	2008-9	0	0	05/10/09
Psychinfo	2008-9	0	0	05/10/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	11	1	30/09/09
BIOSIS	2008-9	2	0	30/09/09

Lung

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	3	0	05/10/09
Premedline	2008-9	0	0	05/10/09
Embase	2008-9	6	0	05/10/09
Cochrane Library	2008-9	0	0	05/10/09
Cinahl	2008-9	0	0	05/10/09
Psychinfo	2008-9	0	0	05/10/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	6	0	30/09/09
BIOSIS	2008-9	2	0	30/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: For patients with confirmed Cancer of Unknown Primary who present with brain metastases, does specific treatment guided by putative site of primary origin improve outcomes, compared with generic treatment comprising supportive care ± palliative radiotherapy?

Question no: 14

81. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	256	34	03/11/08
Premedline	All	9	1	04/11/08
Embase	All	235	29	04/11/08
Cochrane Library	All	3	0	04/1108
Cinahl	All	0	0	05/11/08
Psychinfo	All	3	0	04/11/08
Web of Science (SCI & SSCI & Conference Proceedings))	All	203	16	05/11/08
BIOSIS	All	187	16	05/11/08

Total References retrieved (after de-duplication): 57

Total References after Update Searching: 0

Medline search strategy (This search strategy is adapted to each database.)

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. exp Brain Neoplasms/
9. exp Neoplasm Metastasis/
10. 8 and 9
11. ((brain or midbrain or brainstem or intracranial or cranial or cerebell$ or cerebr$ or CNS or central nervous system) adj2 metasta$).tw.
12. 11 or 10
13. 7 and 12

82. Health Economics Literature search details

(SIGN Health Economics filter added to above search)

[SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline		
Premedline		
Embase		
Cochrane Library (except NHSEED)		
NHSEED		
Cinahl		
BNI		
Psycinfo		
EconLit		
Web of Science (SCI & SSCI)		

83. Any further comments:

Sifting Criteria:

Due to lack of results, the search had to be broadened to include all treatments.

84. Update Searches

New references added:

Date	Database	No. of new refs

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	13	0	22/09/09
Premedline	2008-9	2	0	22/09/09
Embase	2008-9	28	0	22/09/09
Cochrane Library	2008-9	1	0	22/09/09
Cinahl	2008-9	0	0	06/10/09
Psychinfo	2008-9	0	0	22/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	24	0	28/09/09
BIOSIS	2008-9	9	0	28/09/09

NATIONAL COLLABORATING CENTRE FOR CANCER

Cancer of Unknown Primary **Clinical Guideline** **Literature search summary**

Question title: For patients with confirmed cancer of unknown primary with no clinical features fitting a recognised syndrome, in whom systemic treatment is being considered, does treatment improve the outcome, compared with symptomatic treatment alone?

Question title: For patients with confirmed cancer of unknown primary in whom systemic treatment is being considered, if clinical features match a recognised syndrome, does treatment guided by that syndrome result in better outcomes than generic treatment?

Question no: 27 and 28

85. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All	657	113	03/06/2008
Premedline	All	5	1	03/06/2008
Embase	All	316	77	04/06/2008
Cochrane Library	All	157	18	09/06/2008
Cinahl	All	8	2	10/06/2008
Psychinfo	All	2	1	03/06/2008
Web of Science (SCI & SSCI)	All	393	63	09/06/2008
BIOSIS	All	370	48	16/06/2008
ISI Proceedings	All	49	1	10/06/2008

Total References retrieved (after de-duplication): 210

Total References after Update Searching: 2

Medline search strategy *(This search strategy is adapted to each database.)*

1. Neoplasms, Unknown Primary/
2. ((Unknown primar$ or unknown origin$1) and (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
3. (Occult adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
4. ((Undetermined primar$ or undetermind origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
5. ((Unidentifi$ primar$ or unidentifi$ origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
6. ((Undefined primar$ or undefined origin$1) adj5 (cancer$ or neoplas$ or tumo$ or carcinoma$ or adeno$ or metasta$ or micrometasta$ or malignan$ or lymphoma$ or sarcoma$ or melanoma$)).tw.
7. or/1-6
8. Antineoplastic Combined Chemotherapy Protocols/
9. chemotherap$.tw.
10. exp Antineoplastic Agents/
11. Drug Therapy, Combination/
12. Antineoplastic Protocols/
13. Adriamycin$.tw.
14. Bevacizumab.tw.
15. Bleomycin/ or bleomycin.tw.
16. capecitabine.tw.
17. exp Carboplatin/ or (carboplatin or paraplatin).tw.

18. Cisplatin/ or cisplatin.tw.
19. Cyclophosphamide/ or cyclophosphamid$.tw.
20. exp Cytotoxins/
21. cytotoxi$.tw.
22. Dactinomycin/ or dactinomycin$.tw.
23. docetaxel.tw.
24. Doxorubicin/ or doxorubicin$.tw.
25. Epirubicin/ or epirubicin.tw.
26. Erlotinib.tw.
27. Etoposide/ or etoposide.tw.
28. exp Fluorouracil/ or (fluorouracil$ or fluoruracil$ or 5fu or 5-FU or adrucil$).tw.
29. ftorafur$.tw.
30. gemcitabine.tw.
31. Ifosfamide/ or ifosfamide.tw.
32. irinotecan.tw.
33. Leucovorin/ or leucovorin.tw.
34.exp Methotrexate/ or (methotrexate or rheumatrex or amethopterin$).tw.
35. Mitomycin/ or mitomycin$.tw.
36. Octreotide/ or octreotide.tw.
37. oxaliplatin$.tw.
38. Paclitaxel/ or (paclitaxel or taxol or taxotere).tw.
39. exp Pentetic Acid/
40. Semustine/ or semustine.tw.
41. exp Taxoids/
42. (taxoid$ or taxane$).tw.
43. topotecan/ or (topotecan or hycamtin).tw.
44. (topotecan or hycamtin).tw.
45. vinblastine.tw.
46. Vincristine/ or vincristine.tw.
47. Vindesine/ or vindesine.tw.
48. vinorelbine.tw.
49. or/8-48
50. 7 and 49
51. Meta-Analysis/
52. meta analy$.tw.
53. metaanaly$.tw.
54. meta analysis.pt.
55. (systematic adj (review$1 or overview$1)).tw.
56. exp Review Literature as Topic/
57. or/51-56
58. cochrane.ab.
59. medline.ab.
60. embase.ab.
61. (psychlit or psyclit).ab.
62. (psychinfo or psycinfo).ab.
63. (cinahl or cinhal).ab.
64. science citation index.ab.
65. bids.ab.

66. cancerlit.ab.
67. or/58-66
68. reference list$.ab.
69. bibliograph$.ab.
70. hand-search$.ab.
71. relevant journals.ab.
72. manual search$.ab.
73. or/68-72
74. selection criteria.ab.
75. data extraction.ab.
76. 74 or 75
77. Review/
78. 76 or 77
79. Comment/
80. Letter/
81. Editorial/
82. Animal/
83. Human/
84. 82 not (82 and 83)
85. or/79-81,84
86. 57 or 67 or 73 or 78
87. 86 not 85
88. Randomized controlled trials as Topic/
89. Randomized controlled trial/
90. Random allocation/
91. Double blind method/
92. Single blind method/
93. Clinical trial/
94. exp Clinical Trials as Topic/
95. or/88-94
96. (clinic$ adj trial$1).tw.
97. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
98. Placebos/
99. placebo$.tw.
100. randomly allocated.tw.
101. (allocated adj2 random).tw.
102. or/96-101
103. 95 or 102
104. case report.tw.
105. Letter/
106. Historical article/
107. review.pt.
108. or/104-107
109. 103 not 108
110. 87 or 109
111. 50 and 110

86. Health Economics Literature search details

(SIGN Health Economics filter added to above search)

[SCHARR Quality of Life filter added to above search]

Database name	No of references found	Finish date of search
Medline	3	01/10/08
Premedline	0	01/10/08
Embase	3	01/10/08
Cochrane Library (except NHSEED)	0	01/10/08
NHSEED	0	01/10/08
Cinahl	1	01/10/08
BNI	0	01/10/08
Psycinfo	0	01/10/08
EconLit	0	01/10/08
Web of Science (SCI & SSCI)	1	01/10/08

87. Any further comments:

Sifting Criteria:

Applied filters for systematic reviews and randomized controlled trials.

Excluded patients at risk of CUP
Excluded articles discussing several cancers and listing only 1 CUP case

88. Update Searches

New references added:

Date	Database	No. of new refs
27/07/09	**Embase**	**1**
03/06/09	**Web of Science**	**1**
15/04/09	**Web of Science**	**2**
15/04/09	**Embase**	**1**

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2008-9	54	1	30/09/09
Premedline	2008-9	0	0	05/10/09
Embase	2008-9	89	1	05/10/09
Cochrane Library	2008-9	7	0	30/09/09
Cinahl	2008-9	21	1	06/10/09
Psychinfo	2008-9	0	0	30/09/09
Web of Science (SCI & SSCI & ISI Proceedings))	2008-9	83	0	30/09/09
BIOSIS	2008-9	38	0	30/09/09

Appendix B – Economic Plan

National Institute for Health and Clinical Excellence

Economic Plan

This document identifies the priorities for economic analysis and the proposed methods for addressing these questions as described in section 8.1.3.1 of the Guidelines Manual (2006)

1. Guideline

Title of guideline: Metastatic malignant disease of unknown primary origin

2. Process for agreement

The economic plan was prepared by the guideline economist in consultation with the rest of the NCC technical team and GDG. It was discussed and a agreed on 06-02-2009 by the following people [a].

For the NCC and GDG:

NCC economist:	Eugenia Priedane
NCC representative(s)[b]	Andrew Champion Victoria Titshall Angela Bennett
GDG representative(s)[c]:	Andy Fowell (GDG chair) Richard Osborne (GDG Lead Clinician)

For NICE:

CCP lead [d]:	
Commissioning manager:	Nicole Elliott
Economic lead[e]:	Francis Ruiz/ Stefanie Kinsley

[a] This may be done by face-to-face meeting, teleconference or email as convenient

[b] May be the project manager, a systematic reviewer or research fellow and/or the centre director or manager, as appropriate for the NCC and guideline

[c] May be GDG chair, clinical lead and/or other members as appropriate

[d] CCP Director or Associate Director who is taking the lead for the guideline

[e] One of the CCP health economic Technical Advisors

Costing lead:

Proposals for any substantive changes will be circulated by email to this group. If revisions are agreed, they will be listed as addenda to this document (section 5 below),

Proposed economic plan

The purpose of this document is to highlight our deliberations in terms of setting the priorities for undertaking economic analyses to inform guideline development for metastatic malignant disease of unknown primary origin, or cancer of unknown primary (CUP). Previous conversations at GDG meetings have highlighted the challenges of conducting economic evaluations in this disease area, mostly because of the heterogeneity of the patient population and a lack of clinical effectiveness data in relation to interventions and procedures for CUP patients. More specifically it is considered unlikely, given the general paucity of evidence on CUP-related technologies, that we will be able to produce estimates of cost-effectiveness that are robust and reliable.

After discussions with NICE (and the Clinical Lead and Chair), we propose that development of de novo economic models may be used to estimate the value of future research for CUP-related technologies for which there may be a high level of uncertainty about the incremental effectiveness and/or cost between two or more clinical strategies. This type of analysis could help inform research recommendations within the guideline. The table below summarises and identifies topics that have been prioritised for this approach.

Clinical Topic	Requires analysis?	Comments and explanation
Topic 1 For patients with malignancy of undefined primary origin, is the existing screen of basic investigations effective in identifying the maximum number of possible primary cancers as rapidly as possible?	**Not relevant**	The shortage of studies comparing different strategies, or examining the individual contribution of individual tests, compromises the value of this PICO. An agreement has been reached among the GDG that some form of consensus-based recommendation be included in the guideline. Given these limitations, this topic is not suitable for economic evaluation.
Topic 3 For patients with malignancy of undefined primary origin undergoing initial diagnostic tests, is there benefit in terms of patient	**Low**	This topic potentially affects all CUP patients. Tumour markers are a relatively inexpensive diagnostic tool. There is no clear evidence on the sensitivity and specificity of tumour markers and their subsequent effect on health outcomes. Moreover, Varadhachary et al. states that tumour markers play more of a prognostic rather than

outcomes or speed through the process of doing serum tumour markers?		a diagnostic role. (Varadhachary et al. 2004). Therefore, it is not clear what (if any) health benefits are associated with tumour markers. Given these limitations, it would be difficult to conduct a meaningful economic evaluation.
Topic 4 For patients with malignancy of undefined primary origin, is the use of upper- and lower-GI endoscopy in all patients more effective in identifying the maximum number of possible primary cancers as rapidly as possible compared with selective, symptom-directed GI endoscopy?	**Low**	There are no economic studies and there is limited clinical evidence on the use of upper- and lower-GI endoscopy in patients with a provisional diagnosis of malignancy of unknown primary who are undergoing initial diagnostic tests and its effectiveness in identifying the primary site. Given these limitations, it would be difficult to conduct a meaningful economic evaluation.
Topic 5 For patients with malignancy of undefined primary origin does evaluation by a specialist oncology team at an earlier time than is traditionally the case improve outcomes? **Topic 6** Is consistent support from an identified key worker, e.g. a specialist nurse, from the point a patient is diagnosed with an unknown or uncertain primary cancer, more effective than no support? **Topic 7** For patients with malignancy of undefined primary origin, is it beneficial for investigations to be undertaken to end uncertainty when there is little likelihood of clinical benefit?	**Low**	Defining benefit or measuring effectiveness in quantitative terms for these topics is challenging. For each topic, it will be difficult identify discrete pathways and consequences/outcomes of each strategy or service configuration in a manner that would lend itself to economic evaluation or decision analytic techniques. The availability of economic evidence to inform these topics is also low. Given these limitations, this topic is not suitable for economic evaluation.

Topic 10 For patients with malignancy of undefined primary origin undergoing screening investigations to identify a primary site, does management by a specialist CUP MDT result in greater benefits than the existing non-MDT management?		
Topic 8 For patients with malignancy of undefined primary origin, does immuno-histochemical analysis (using CD20 and CD7) to define putative tissue/organ of origin, or hormone receptor (ER, PR) analysis to potentially predict response to hormonal therapies, result in improved outcomes?	**Low**	Based on previous discussions with RO and AF, the aim of this topic is to highlight a gold standard of managing patient in each of these subgroups, i.e. the optimal use of immuno-histochemical analysis. No evidence has been found to indicate a change in overall patient outcomes. Lack of evidence paired with relatively inexpensive competing alternatives does not render this topic a high priority.
Topic 11 For patients with provisional Cancer of Unknown Primary with clinical features compatible with metastatic breast cancer, does contrast-enhanced breast MRI improve detection of occult primary breast cancer?	**Low**	The proportion of patients covered by this topic is limited (around 500 patients). Furthermore there are no economic studies and there is limited clinical evidence on the effect of the contrast-enhanced breast MRI in patients with unknown primary on their overall survival. Given these limitations, it would be difficult to conduct a meaningful economic evaluation.
Topic 13 For patients with provisional Cancer of		If evaluated at the beginning of the patient pathway, this topic could potentially affect all patients with cancer of unknown primary. FDG

Unknown Primary does PET-CT result in improved outcomes?	**High**	PET-CT has shown to have a higher sensitivity and specificity, particularly for patients presenting with cervical lymphadenopathy (*Fogarty et. al. 2003, Johansen et. al. 2008*). There are cost implications of implementing wider use of PET-CT, but identification of the primary tumour using this imaging technique can also lead to a change in treatment decision that may result in improved patient outcomes. There are no prospective studies that have evaluated subsequent impact of PET-CT on patient outcomes, however an economic analysis using the expected value of information approach can be used to quantify the level of uncertainty and inform research recommendations into the value of PET-CT in CUP patients.
Topic 14 For patients with confirmed Cancer of Unknown Primary who present with brain metastases, does specific treatment guided by putative site of primary origin improve outcomes, compared with generic treatment comprising supportive care ± palliative radiotherapy?	**Low**	CUP patients with brain metastases have a particularly poor prognosis and chemotherapy has limited efficacy in brain metastases. Cranial irradiation may be used to provide symptomatic care. There is little available data to quantify the benefit of cranial irradiation beyond symptomatic relief. In the absence of more effective active treatments, and given that this topic affects a small proportion of CUP patients, no economic evaluation will be undertaken.
Topic 17 For patients with provisional Cancer of Unknown Primary who present with intra-pulmonary nodules without evidence of endobronchial disease, does bronchoscopy result in improved outcomes?	**Low**	This topic affects about 10% of CUP patients. There are no economic studies and there is limited clinical evidence on the effect of performing a bronchoscopy in this patient group on overall survival, thereby limiting the feasibility of conducting an economic analysis.

Topic 19 For patients with provisional Cancer of Unknown Primary who present with ascites, does cytological examination of ascitic fluid, or histological examination of malignant peritoneal tissue result in a superior clinical outcome?	**Low**	There are no economic studies and there is limited clinical evidence on the effect of the cytological examination of ascitic fluid in this patient group on overall survival. Given these limitations, this topic is not suitable for an economic evaluation.
Topic 21 What is the optimal management for patients with confirmed Cancer of Unknown Primary who present with squamous carcinoma involving upper / mid neck nodes? **Topic 22** What is the optimal management for patients with confirmed Cancer of Unknown Primary who present with adenocarcinoma involving axillary nodes? **Topic 23** What is the optimal management for patients with confirmed Cancer of Unknown Primary who present with squamous carcinoma involving inguinal nodes?	**Low**	Topics 21, 22 and 23 affect a relatively small proportion of patient in each subgroups of patients (about 5%). This topic is considered low priority since the number of patients affected is not as great as for other topics. Furthermore, the level of clinical evidence would be crucial in conducting a meaningful economic evaluation.
Topic 24	**Low**	The patient subgroups covered in this topic are very small. Based on previous discussions with RO and AF, the aim of this topic is to

What is the benefit of radical local treatment for patients with confirmed Cancer of Unknown Primary who present with an isolated metastasis in one of the following organs: brain, bone, liver, skin, lung? **Topic 25** For patients with confirmed Cancer of Unknown Primary in whom systemic treatment is being considered, are there prognostic factors that significantly influence outcome and which should be considered in treatment decisions?		highlight a gold standard of managing patients in each of these subgroups. No evidence has been found to indicate a change in overall patient outcomes. Lack of evidence paired with very small subgroups of patients render this topic a low priority.
Topic 26 For patients with confirmed Cancer of Unknown Primary in whom systemic treatment is being considered, does gene expression-based classification (according to putative tissue of origin) lead to improved outcomes (through the use of treatment chosen on the basis of the predicted primary site)?	**Low**	In recent years gene expression profiling has demonstrated the ability to identify a broad spectrum of tumour types at the molecular level. Furthermore, CUP gene expression analysis can be utilized in conjunction with, or in place of standard investigative diagnostic procedures to expedite the diagnostic process of a cancer of unknown primary. (Buckhaults et. al. 2003, Bridgewater et. al. 2008) Although this topic could all CUP patients, at present in the UK, gene expression-based classification is not common practice and there is no data to estimate resource use and health benefits associated with this diagnostic option. Given these limitations, it would be difficult to generate a meaningful estimate of cost-effectiveness and is considered a low economic priority.
Topic 27	**High**	There is little high quality evidence on the benefit of chemotherapy in CUP patients with no clinical features fitting a recognised

For patients with confirmed Cancer of Unknown Primary with no clinical features fitting a recognised syndrome, in whom systemic treatment is being considered, does treatment improve the outcome, compared with symptomatic treatment alone?		syndrome. However, given the additional costs of active treatment, an economic analysis may help reduce the level of uncertainty around the use of chemotherapy over and above supportive care in these patients. This topic was highlighted as an economic priority at the 4th GDG meeting.
Topic 28 For patients with confirmed Cancer of Unknown Primary in whom systemic treatment is being considered, if clinical features match a recognised syndrome, does treatment guided by that syndrome result in better outcomes than generic treatment?	**Medium**	For patients with confirmed CUP with clinical features matching a recognised syndrome, the use of chemotherapy is more established than for the patient population in Topic 27. Topic 28 relates to the decision between various chemotherapy regimens for 5 specific subgroups of CUP patients, whereas Topic 27 addresses the value of chemotherapy over and above best supportive care in patients with no clinical features matching a recognised syndrome. Topic 27 may inform the comparator for Topic 28, therefore it should be considered first for economic analysis. Furthermore, Topic 27 is considered a higher priority for economic analysis because there is a higher need to address the uncertainty surrounding the cost-effectiveness of chemotherapy versus best supportive care. To meet the time constraints of the guideline development process, Topic 27 has been prioritised over Topic 28.

For each question where economic analysis is proposed:

Question number(s)	*Outline proposed method of analysis*
Topic 13	**Proposed analysis** **Aim** An analysis will be carried out to assess the value of perfect information of carrying out PET-CT scan for patients with provisional cancer of unknown primary and negative initial work up, which included whole body CT and biopsy where appropriate. The findings of this analysis will be used to inform future research recommendations. **Intervention** PET-CT scan performed after negative initial diagnostic work up (including whole body CT scan and biopsy where appropriate. **Comparators** No PET-CT **Methods** PET-CT has shown to have a higher sensitivity and specificity, particularly for patients presenting with cervical lymphadenopathy (*Fogarty et. al. 2003, Johansen et. al. 2008*). Decision analysis will be used to model the clinical pathway and to estimate the expected value of perfect information of performing PET-CT in patient with provisional CUP patient who have negative initial diagnostic work up compared to not doing PET-CT will be considered in this analysis. Formal value of information analysis will provide an analytic framework which will address whether a decision on whether to adopt PET-CT scanning after initial negative diagnosis can be made on the basis of current evidence or

	whether more evidence is required to support the decision about PET-CT scanning in the future, and how much we should be prepared to pay for this evidence. (Claxton et al. 2002) There are three components in this framework: "(i) the construction of a decision analytic model to represent the decision problem; (ii) a probabilistic analysis of this model to characterize the current decision uncertainty; and (iii) establishing the value of additional information" (Briggs et al. 2006) The structure of the analytic model will be informed by the data available in the literature and in consultation with the GDG. The NHS perspective will be adopted; that is the health benefits and costs to be considered in the analysis will only be those relevant to the NHS. Relevant costs include those borne by Personal Social Services (PSS) as well as those that fall on the NHS itself. Unit costs will be derived from publicly available national sources whenever possible (e.g. NHS Reference Costs). Probability distributions will be assigned to different clinical and cost parameters within the model so that a probabilistic sensitivity analysis can be carried out to assess the overall uncertainty of the model and the robustness of the results. **Feasibility issues** Given the heterogeneity of the CUP patient population, it is not clear if a single model will be able to accommodate (mathematically) all relevant testing options and possible test results to accurately reflect clinical reality. This will require close discussions with the clinical contact and GDG to reach agreement on the appropriateness and feasibility of conducting the analysis. It is unlikely that the literature will be sufficient to populate all relevant parameters in the model. Expert elicitation will be considered where estimates from the literature are not available.

Update following 8th GDG

- The team of health economists made several attempts to draft an economic model structure for Topic 13 that is both clinically accurate and methodologically feasible for undertaking a decision analytic approach to which EVPI can be applied.
- Each version of the model was discussed in conjunction with the designated clinical contact from the GDG.
- Initial clinical guidance suggested that due to the heterogeneity of the CUP population, separate models should be considered for subgroups of CUP patients because
    - The possible outcomes of PET-CT will differ depending on the patient's initial distribution of metastases. It was considered desirable to factor in >5 possible consequences (i.e. in the context of CUP, PET-CT is viewed as a diagnostic test that does not have a binary outcome). Each outcome could result in set of follow-up tests and potentially different treatment decisions leading to different survival and QALY estimates.
    - For the comparator (do not conduct PET-CT arm in the model), different tests would be selected depending on the presentation or distribution of metastases, which would again lead to different outcomes
    - The number of possible subgroups to model was large, hence at the 7th GDG, agreement was reached to prioritise 2 subgroups for analysis: patients with liver metastases and patients with bone metastases.

At the 8th GDG, the revised draft model structures were discussed and there was consensus that the GDG should not proceed with the economic analysis for Topic 13. The following challenges contributed to this decision:

- It was difficult for the GDG to agree on an exhaustive but mutually exclusive set of pathways in the economic model. For example, in clinical practice, after conducting PET-CT, the subsequent choice of confirmatory diagnostic test or treatment decision is influenced by a complex set of patient and disease factors. There were concerns that a more simplistic approach would not adequately reflect the scope of the decision problem faced by the clinician/patient.
- There is limited data in the published literature to populate the economic model and some data would need to be elicited from experts, but the availability of experts on the GDG who have specific experience in each of these patient subgroups is limited.
- A decision was made to focus on subgroups of CUP patients to develop a model that is clinically accurate. Each subgroup analysis would require considerable resource and time commitment from the health economists and GDG members to refine and seek agreement on the model structure and elicit data to populate the model. By focusing on subgroups, the results however would only be relevant for estimating the EVPI and informing the use of PET-CT in these subgroups of patients (i.e. a small proportion of CUP patients).

Topic 27	**Proposed analysis** **Aim** An analysis will be carried out to assess the value of perfect information in a comparison of active chemotherapy vs best supportive care for the treatment of patients with confirmed cancer of unknown primary with no clinical features fitting a recognised confirmed CUP syndrome. The findings of this analysis will be used to inform future research recommendations. **Interventions** The most commonly used chemotherapy regimen(s) in current UK practice, to be defined with GDG input. **Comparators** Best supportive care, to be defined with GDG input. **Methods** Formal value of information analysis will provide an analytic framework which will address whether a decision regarding consideration of a systemic treatment can be made on the basis of current evidence or whether more evidence is required to support this decision about chemotherapy regimes in the future, and how much we should be prepared to pay for this evidence. (Claxton et al. 2002) There are three components in this framework: "(i) the construction of a decision analytic model to represent the decision problem; (ii) a probabilistic analysis of this model to characterize the current decision uncertainty; and (iii) establishing the value of additional information" (Briggs et al. 2006)

	The structure of the analytic model will be informed by the data available in the literature and in consultation with the GDG. The NHS perspective will be adopted; that is the health benefits and costs to be considered in the analysis will only be those relevant to the NHS. Relevant costs include those borne by Personal Social Services (PSS) as well as those that fall on the NHS itself. Unit costs will be derived from publicly available national sources whenever possible (e.g. NHS Reference Costs). Probability distributions will be assigned to different clinical and cost parameters within the model so that a probabilistic sensitivity analysis can be carried out to assess the overall uncertainty of the model and the robustness of the results. **Feasibility issues** It is unlikely that the literature will be sufficient to populate all relevant parameters in the model. Expert elicitation will be considered where estimates from the literature are not available.

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Addenda to economic plan

The following substantive revisions to the plans set out in the section 3 above have been agreed.

Date	*Question number(s)*	*Agreed change to number or type of analyses*
30/04/2009	Topic 13	Agreement was reached not to proceed with economic model for this topic. An explanatory note will be included in the guideline.

Appendix 3

What is the expected value of perfect information in reducing uncertainty surrounding the cost-effectiveness of systemic treatment in patients with confirmed carcinoma of unknown primary and no clinical features fitting a recognised syndrome?

1 Introduction

Patients with confirmed carcinoma of unknown primary (CUP) account for 3-5 percent of all cancer diagnoses (Assersohn et al 2003, Briasoulis et al 2000) and are often candidates for systemic chemotherapy.

For a subset of patients with CUP whose clinical and pathological features resembles one of the major tumour subtypes, treatment decisions can be guided by these features. However in the majority of CUP patients the choice of optimal treatment is not clear. Systemic chemotherapy can be given to control symptoms and to attempt to prolong survival; however there is no clear understanding of the survival benefits provided by different regimens (Golfinopoulos et al, in press). To date, studies aimed at defining optimal chemotherapy regimens in patients with CUP have been mostly small phase II trials or retrospective analyses (Parnis et al 2000).

The generally low levels of health gain and scarcity of high quality data about treatment benefits along with the considerable economic burden of chemotherapy treatment on the healthcare budget led to highlighting this topic as a priority for economic analysis.

2 Objectives

To carry out an analysis to assess the expected value of perfect information (EVPI) in a comparison of active chemotherapy versus best supportive care for the treatment of patients with confirmed CUP with no clinical features fitting a recognised syndrome. The findings of this analysis will be used to inform future research recommendations.

3 Methods

Cost-effectiveness evaluations require evidence on numerous parameters, including treatment effects, health-related preferences (utilities), healthcare resource use and costs (Sculpher and Claxton 2006). However, high quality evidence on all relevant parameters is not always available. If the evidence base used to inform a cost-effectiveness analysis is poor, decisions based upon such an analysis may be subject to a high degree of uncertainty.

Given the scarcity of high quality data about both treatment benefits and costs of chemotherapy and supportive care in patients with CUP, the economic analysis for this topic focused on two aspects: collection of data by expert elicitation to fill gaps in the published literature and inform parameters in the economic model and estimation of the EVPI to quantify the uncertainty associated with the cost-effectiveness of chemotherapy in comparison to best supportive care.

EVPI is a decision analytical approach that allows us to estimate the cost of existing uncertainty and to prioritise future research by identifying areas where collection of additional data will lead to reduction in the current level of uncertainty (Briggs et al 2006). In the context of the present analysis, EVPI was undertaken to estimate the value of future research in order to eliminate or reduce uncertainty with respect to the cost-effectiveness of chemotherapy in comparison to best supportive care in patients with CUP with no clinical features fitting a recognised syndrome.

EVPI is calculated as the difference between the expected value of the decision made with perfect information and the decision made with current information. The population EVPI is calculated by multiplying the per patient EVPI by the estimated number of patients over the effective lifetime of the treatment options included in the decision problem (Claxton et al 2001). The expected value of partial perfect information (EVPPI) estimates the value of reducing uncertainty surrounding a particular parameter or group of parameters in the decision model and allows us to focus future research around those parameters for which additional information would be most valuable.

3.1 Study population

The population of interest in this study are patients with confirmed CUP with no clinical features fitting a recognised syndrome1 and in whom systemic therapy is being considered.

3.2 Perspective

This analysis was carried out from the perspective of the National Health Service (NHS) in the UK.

3.3 Intervention

A review of the clinical literature published between 1980 and 2009 identified a number of small studies in the patient population of interest involving various single and combination chemotherapy regimens. Based on this review, members of the guideline development group (GDG) were asked to identify which of these regimens had most relevance to current UK clinical practice. The following were selected for inclusion in the economic analysis. Table 1:

- Best supportive care (BSC) alone
- Fluorouracil (5-FU) plus BSC
- Carboplatin + paclitaxel combination therapy plus BSC
- Epirubicin hydrochloride+ cisplatin + fluorouracil combination therapy (ECF) plus BSC

Table 1: Dosages assumed by the model

Agent(s)	Dosage
Fluorouracil	300 mg/m^2/day; ambulatory pump
Carboplatin/paclitaxel	Carboplatin AUC 6.0; 20–30 minute IV, Day 1 Paclitaxel 175 mg/m^2; 1-hour IV, Day 1
Epirubicin/cisplatin/fluorouracil	Epirubicin 50 mg/m^2; IV every three weeks Cisplatin 60 mg/m^2; IV every three weeks Fluorouracil 200mg/m^2 per day by continuous infusion

Source: Assersohn et al. 2003, Greco et al. 2000, Parnis et al. 2000

3.4 Structure of the model

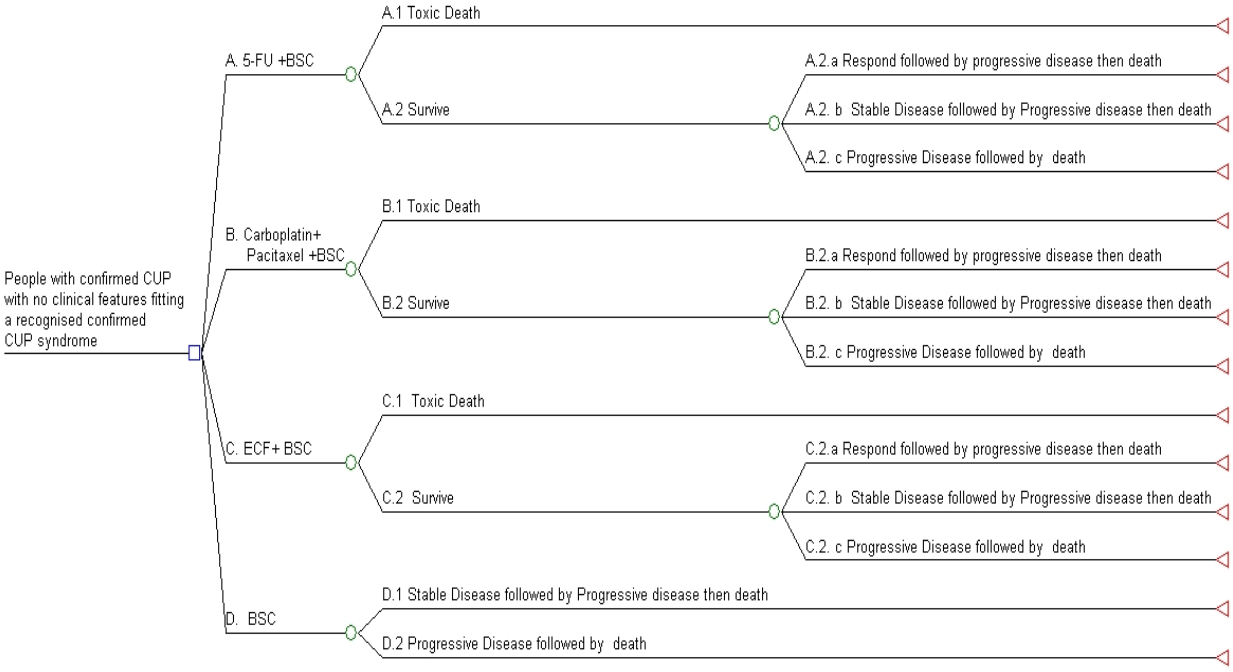
A decision tree (Figure 1) was constructed to compare the strategy of giving best supportive care alone to the strategies of administering each of the three chemotherapy regimens of interest in addition to best supportive care. The model was constructed using TreeAge Pro 2009 software.

The model includes patients with confirmed CUP who have no clinical features fitting a recognised syndrome and in whom systemic therapy is being considered. The square node at

[1] Recognised syndromes: predominantly peritoneal adenocarcinoma; unilateral axillary lymphadenopathy; midline nodal disease; cervical (neck) lymphadenopathy containing carcinoma and metastatic carcinoma with neuroendocrine differentiation .

the beginning of the decision tree shows graphically the four treatment options that have been defined as relevant to the decision problem. For patients receiving chemotherapy, the model allows for the possibility of toxic death in relation to treatment, as indicated at the first circular (chance) node. For those patients not experiencing toxic death, the initial possible outcomes of chemotherapy include response (complete or partial), stable disease or progressive disease. In the best supportive care arm of the decision tree, the possible outcomes are stable disease or progressive disease. Given this model is for patients with metastatic disease, it is assumed that patients who initially respond or experience stable disease while receiving chemotherapy or best supportive care will eventually experience disease progression prior to death.

Figure 1: Outline of the decision tree



3.5 Clinical evidence

A review of current clinical evidence was conducted to ascertain availability and quality of data to inform effectiveness parameters for the economic analysis. The evidence review showed wide variation in median survival and response rates for various chemotherapy regimens; concerns were raised about the heterogeneity among studies and potential bias associated with small sample sizes. It was also noted that the wide variation in median survival is more likely to be influenced by differences in patient selection between studies rather than efficacy of chemotherapy. Moreover, the definition of best supportive care was poorly recorded and varied considerably between earlier and later studies.

Given the limitations of these studies, clinical evidence to populate the economic model was obtained from a number of different sources. Data on rates of chemotherapy-related toxicity and utilities were obtained from the literature. Robust comparative efficacy data on the chemotherapy regimens of interest against best supportive care were not available from the literature hence response rates and duration of survival were obtained through expert elicitation. In addition, healthcare resource use associated with providing supportive care and management of treatment-related adverse events was also obtained from experts.

3.6 Expert elicitation

In the absence of quality observed evidence, one useful method to obtain estimates to inform model parameters is to elicit this information from experts who have knowledge or experience in the subject area. Importantly, expert elicitation also provides a method to obtain information about the distribution of uncertainty surrounding model parameters in order to undertake probabilistic modelling and EVPI analyses.

3.6.1 Elicitation method

Based on the structure of the model and data requirements, categories of parameters were identified for expert elicitation (Table 2). This included parameters related to effectiveness of treatment and length of treatment (number of cycles of chemotherapy). Rather than eliciting costs from experts, the elicitation exercise also included questions about volume of healthcare resource use (including resource use related to management of chemotherapy-related toxicities). Unit costs were collected separately from published sources. A complete list of parameters included in the elicitation exercise can be found in Appendix A.

Table 2: Examples of categories of parameters included in expert elicitation

Parameter Category
Proportion of patients responding/stable disease/progressive disease
Duration of response/stable/progressive disease
Number of cycles of treatment
Number of hospital inpatient/out patient days
Number of hospice days
Number of scans (CT, MRI)
Fractions of radiotherapy
Number of blood transfusions

In order to quantify uncertainty about the parameters identified above, it was necessary to elicit not only a single point estimate, but also a probability distribution for each parameter. By asking an expert for a range of estimates, it is then possible to fit an appropriate parametric distribution to represent the expert's opinion about the uncertainty of the parameter (O'Hagan et al 2006). Following the example of Leal et al. (2007), an elicitation questionnaire was constructed in Microsoft Office Excel 2007, which was chosen for its ease of use and convenience so that experts could complete the questionnaire on their own. Elicitation of scalar quantities in the questionnaire involved several steps. First, the respondent was asked to provide a minimum, maximum and most likely value for the parameter. The range was then divided into four complementary intervals and the respondent was asked to estimate the probability that the true value lay within each of these intervals. This information was used to construct a histogram to visualise the probability distribution of uncertainty. Lastly, the respondent was asked to verify if the histogram reflected his or her beliefs.

Three members of the GDG with relevant subject area knowledge and expertise in medical oncology were recruited for the elicitation exercise. Each expert answered the questionnaire individually and each expert provided answers to all questions in the exercise.

3.6.2 Combining expert opinions

Individual responses of the three experts to the elicitation questionnaire were aggregated mathematically and distributions were fitted to the aggregated results using the software package R version 2.9.0 and the distribution fitting tool developed as part of the Sheffield Elicitation Framework (SHELF) (O'Hagan 2008). However unlike SHELF, aggregation was performed as a separate step after the experts had all completed the questionnaires. Appropriate distributions were chosen to represent uncertainty (Briggs et al 2006); gamma distributions were used for parameters with non-negative values (for example, health care resource use) and beta and Dirichlet distributions were adopted for binomial and multinomial proportions respectively.

3.7 Data inputs

3.7.1 Length of treatment

There was no consistent reporting of the length of treatment for each strategy in the published literature. Therefore, duration of treatment was elicited from experts. For 5-FU, the length of treatment was elicited as the number of weeks that a patient would receive single-agent therapy. The length of treatment for combination therapies was directly elicited as the number of 3-week cycles. The estimates for mean length of treatment are shown in Table 3.

Table 3: Length of treatment

Treatment Strategy	Mean length of treatment	Distribution[2]
Fluorouracil	11.4 weeks	Gamma (3.07, 0.27)
Carboplatin/paclitaxel	3.23 cycles	Gamma (6.61, 2.05)
Epirubicin/cisplatin/fluorouracil	3.27 cycles	Gamma (4.20, 1.29)

3.7.2 Response to treatment

Based on the expert elicitation exercise, the proportion of patients who responded, achieved stable disease or experienced progressive disease is shown for each treatment strategy in Table 4 below. A Dirichlet distribution was used to characterise parameter uncertainty for response to treatment for the chemotherapy regimens and a beta distribution for best supportive care.

Table 4: Proportion of patients by response to treatment for each strategy

	5-FU	CP	ECF	BSC
	Mean	Mean	Mean	Mean
Response	10%	30%	30%	N/A
Stable	20%	20%	10%	4%
Progressive	70%	50%	60%	96%

5-FU – Fluorouracil; **CP** – Carboplatin/paclitaxel; **ECF** - Epirubicin/cisplatin/fluorouracil; **BSC** – Best supportive care; **N/A** – Not applicable

3.7.3 Duration of response, stable disease, progressive disease and overall survival

As part of the elicitation exercise, experts were asked to estimate duration of response and duration of stable disease for each of the treatment strategies. Duration was defined as the time from start of treatment until the onset of progressive disease. Separate estimates were elicited for patients who initially responded to treatment and for patients who initially achieved stable disease. For patients who initially responded to treatment, overall survival was then estimated as the sum of the duration of response to treatment and the duration of survival once the patient's disease had progressed. Similarly, for patients who initially achieved stable disease, overall survival was estimated as the sum of the duration of stable disease and the duration of survival once the patient's disease had progressed. Estimates for duration of response, duration of stable disease and progressive disease are presented by treatment strategy in Table 5.

Table 5: Duration of response, stable disease and progressive disease

Treatment strategy	Parameter	Mean (months)	Distribution[3]
	Response duration	4.4	Gamma (4.27, 0.97)
	Stable disease duration	4.1	Gamma (4.08, 1.01)
Fluorouracil	Progressive disease	3.4	Gamma (2.97, 0.89)

[2]Distribution parameters relate to requirements for TreeAge Pro software

[3] Distribution parameters relate to requirements for TreeAge Pro software.

	duration		
Carboplatin/paclitaxel	Response duration	6.4	Gamma (2.77, 0.43)
	Stable disease duration	4.7	Gamma (3.39, 0.72)
	Progressive disease duration	3.4	Gamma (2.97, 0.89)
Epirubicin/cisplatin/ fluorouracil	Response duration	4.5	Gamma (3.07, 0.69)
	Stable disease duration	4.1	Gamma (4.23, 1.04)
	Progressive disease duration	3.4	Gamma (2.97, 0.89)
Best supportive care	Stable disease duration	2.5	Gamma (6.75, 2.72)
	Progressive disease duration	3.4	Gamma (2.97, 0.89)

3.7.4 Toxicity

Rates of common Grade 3 and 4 toxicities as well as the probability of toxic death and estimated time to toxic death were all obtained from the published literature (Assersohn et al 2003, Briasoulis et al 2000, Parnis et al 2000, Huebner et al 2005, El-Rayes et al 2005) and are shown in Table 6.

Table 6: Toxicity rates, probability of toxic death and time to toxic death

Treatment strategy	Parameter	Mean	Distribution[4]
Fluorouracil *	Toxicity rates		
	Neutropenia	1%	Beta (1, 88)
	Anaemia	7%	Beta (6, 82)
	Nausea/Vomiting	1%	Beta (1, 88)
	Diarrhoea	2%	Beta (2, 86)
	Probability of toxic death	1%	Beta (1, 88)
	Time to toxic death (months)	0.125	Gamma (1, 8)
Carboplatin/paclitaxel **	Toxicity rates		
	Neutropenia	11%	Beta (8, 67)
	Anaemia	5%	Beta (4, 71)
	Nausea/Vomiting	5%	Beta (4, 71)
	Diarrhoea	3%	Beta (2, 73)
	Probability of toxic death	4%	Beta (3, 72)
	Time to toxic death (months)	2.00	Gamma (4, 2)
Epirubicin/cisplatin/ fluorouracil ***	Toxicity rates		
	Neutropenia	19%	Beta (8, 35)
	Anaemia	2%	Beta (1, 42)
	Nausea/Vomiting	2%	Beta (1, 43)
	Diarrhoea	5%	Beta (2, 41)
	Probability of toxic death	2%	Beta (1, 42)

[4] Distribution parameters relate to requirements for TreeAge Pro software.

	Time to toxic death (months)	0.75	Gamma (2.25, 3)

* Assersohn et al 2003, ** Briasoulis et al. 2000 and Huebner et al 2005, ***Parnis et al. 2000

3.7.5 Utilities

Utility weights, an index based on an individual's preference for a specific health state in relation to alternative health states, were required in the model to estimate quality-adjusted life years (QALYs), which are calculated by weighting life expectancy by a measure of associated health-related quality of life. Estimates of health state utilities specific to patients with CUP were not available in the literature hence estimates from other types of metastatic disease with similar prognosis to CUP were used as proxies (Nafees et al 2008). Beta distributions were used to characterise parameter uncertainty for utility estimates.

Table 7: Utility values

Health state	**Utility estimate (S.E.)**
Stable disease	0.6532 (0.02)
Responding to chemotherapy	0.6725 (0.02)
Progressive disease	0.4734 (0.01)
Treatment-related toxicity	**Incremental disutility estimate (S.E.)**
Neutropenia	-0.08973 (0.02)
Anaemia	-0.07346 (0.02)
Nausea and vomiting	-0.04802 (0.02)
Diarrhoea	-0.0468 (0.02)

Source: Nafees et al 2008

3.7.6 Resource use

Based on the expert elicitation exercise, resource use associated with provision of supportive care and treatment of toxicities is shown in Table 8 below.

Table 8: Resource use

	Mean	**Distribution[5]**
Supportive care		
Hospital inpatient days	13.2	Gamma (3.01, 0.23)
Outpatient visits (follow-up)	1.2	Gamma (2.65, 2.23)
Radiotherapy fractions	4.7	Gamma (3.08, 0.65)
Proportion of patient receiving Radiotherapy		Beta (32, 100)
MRI scans	0.7	Gamma (1.68, 2.46)
CT scans	1.6	Gamma (8.13, 5.18)
Hospice inpatients visits	2.0	Gamma (2.33, 1.17)
Treatment-related toxicity		
Hospital inpatient days – neutropenia	5.5	Gamma (2.94, 0.53)

[5] Distribution parameters relate to requirements for TreeAge Pro software.

Hospital inpatient days – nausea/vomiting	2.2	Gamma (3.29, 1.50)
Hospital inpatient days – diarrhoea	5.0	Gamma (2.88, 0.58)
Blood transfusions	1.7	Gamma (3.98, 2.36)

3.7.7 Unit costs

The costs considered in this analysis were only those relevant to the UK NHS, in accordance with the perspective taken by the NICE Reference Case for economic evaluations. Costs were estimated based on 2007-08 prices. When costs have been taken from other sources and are applicable to a different price year, they have been inflated using the Hospital and Community Health Services Pay and Prices Index (PSSRU, 2008). The categories of costs included:

- Cost of therapy (drug acquisition costs, administration costs)
- Cost of treating major treatment related toxicity
- Cost of healthcare resource use associated with supportive care

3.7.8 Cost of therapy

The drug acquisition cost per cycle was calculated for each chemotherapy regimen assuming that a patient received one dose per 3-week cycle for combination therapy and continuous infusion for 5-FU (Table 9). In addition to the drug acquisition costs, the cost of administering the drug was estimated from the NHS Reference Costs. Intravenous administration of 5-FU and the carboplatin / paclitaxel combination regimen was assumed to be done on an outpatient basis. The cost of administering these regimens was estimated using outpatient tariffs of £208 (HRG SB14Z) and £117 (HRG SB13Z) respectively. This cost includes hospital overheads, the administration costs of chemotherapy and clinical time. For administration of the ECF regimen, costs were estimated using the inpatient tariff of £307 (HRG SB14Z), due to toxicity. These assumptions were verified with members of the GDG.

The base case analysis uses list prices for drugs obtained from the British National Formulary (BNF). The effect of the drug discounts were explored through sensitivity analysis.

Table 9: Drug acquisition costs

Strategy	**5-FU**	**CP**		**ECF**		
Drug	Fluorouracil	Carboplatin	Paclitaxel	Epirubicin	Cisplatin	Fluorouracil
List prices, £ (BNF 57, March 2009):						
5 ml vial			111.41			
20ml vial	6.40					6.40
25 ml vial				94.54	50.22	
50 ml vial			1001.72			
60 ml vial		260				
100 ml vial						
i.v. concentrate (mg/ml)	50	10	6	2	1	50
Recommended dose (mg/m^2)	300	660	175	50	60	200
Dose per 3 weeks[6]	525[7]	-	306.25	87.5	105	350[8]
Average cost per vial(£)	6.40	260	1113.12	96.54	50.22	6.40
Number of vials	1	1	1	2	1	1
Average drug cost per cycle (£)	**134.40**	**260**	**1113.13**	**193.08**	**50.22**	**134.40**

[6] BSA 1.75 – NICE Developing Costing Tools Methods Guide Jan 2008
[7] Dose per day
[8] Dose per day

3.7.9 Cost of treatment-related toxicity

The cost of treatment-related toxicity (Table 10) was estimated by using the cost of hospital stay (for diarrhoea, nausea /vomiting and neutropenia) and blood transfusions (anaemia). The cost of hospital stay was obtained from PSSRU. The NHS Reference Costs did not provide adequate estimates of the cost of blood transfusion. An estimate of the cost of blood transfusion was obtained from a recent health technology assessment on anaemia in cancer (Wilson et al 2007).

Table 10: Unit cost of treatment related toxicity

Resource	Unit Cost (£)	Source for unit cost
Hospital stay due to toxic event	71	PSSRU 2008
Blood transfusion	277	Wilson et al 2007

3.7.10 Cost of supportive care

No published data was found that quantified healthcare resource use associated with provision of supportive care specifically in patients With CUP. Categories of relevant resource use items were defined after reviewing existing literature for treatment of malignancies with similar severity (such as metastatic non-small cell lung cancer and pancreatic cancer) (Billingham et al 2002, Maslove et al, 2005). For the purpose of this analysis, we obtained estimates of units of resource use through expert elicitation. Total number of units for each category of resource use was multiplied by the cost of providing it using PSSRU (2008). A summary of unit costs for each category of resource use are presented in Table 11.

Table 11: Unit cost of supportive care resource use

Resource	Unit cost (£)	Source for unit cost
Hospital inpatient day	249	PSSRU 2008
Outpatient visit (follow-up)	71	PSSRU 2008
Radiotherapy fraction	96	Ref Cost 2007-2008
MRI scan	262	Ref Cost 2007-2008
CT scan	135	Ref Cost 2007-2008
Hospice inpatient visit	395	Ref Cost 2007-2008

3.8 Discounting

Given an expected mean survival of less than 12 months, no discounting was applied to costs and health outcomes. For estimation of the population EVPI, a discount rate of 3.5% was applied.

3.9 Sensitivity analysis

A series of one-way sensitivity analyses were conducted to assess the robustness of the study results. One-way sensitivity analysis describes the process of changing one parameter in the model and re-running the model to see how a change in this parameter influences overall results. The sensitivity analysis included in this report considers the impact of discounts on drug acquisition costs. Whilst it is acknowledged that regional pharmacies and/or commissioners may negotiate other discounts separately, only nationally agreed discounts are considered (NICE Guide to the Methods of Technology Appraisal 2008).
Nationally-agreed drug discounts in England were as follows: the cost per dose of paclitaxel is £63.15 compared to a list price of £1113 per dose (NHS Purchasing and Supplies Agency,

PASA: August 2009). The price of carboplatin is £23.53 compared to a list price of £260 per dose. Similarly, the cost of fluorouracil, epirubicin and cisplatin are £26.04, £75.50 and £10.30 respectively compared to list prices of £134, £193 and £50. In Wales, nationally-agreed discounts were: 97% per dose for paclitaxel, 92% for carboplatin and 89%, 74% and 81% for fluorouracil, epirubicin and cisplatin respectively (personal communication from Welsh Health Supplies, August 2009). Based on these rates, the discounted cost of each regimen was calculated for England and for Wales. The average discounted cost across both regions is reported in Table 12.

Table 12: Discounted drug acquisition costs in England and Wales

Regimen	5-FU	CP	ECF
	Average cost of regimen per cycle (£)		
List price	134	1373	377
Discount price (England)	26	87	112
Discount price (Wales)	15	54	75
Discount price (Average)	20	70	93

5FU – Fluorouracil; **CP** – Carboplatin/paclitaxel; **ECF** - Epirubicin/cisplatin /fluorouracil

4 Results

A summary of expected cost, expected effectiveness and incremental cost-effectiveness ratios (ICER) estimates for each arm in the model are presented in Table 13. The cost of the strategies varies widely, ranging from the least expensive (best supportive care) at just under £580 to the most expensive (combination of carboplatin/paclitaxel) at £5842 per patient. Health outcomes, measured in terms of QALYs, ranged from 0.132 for best supportive care to 0.278 for carboplatin/paclitaxel.

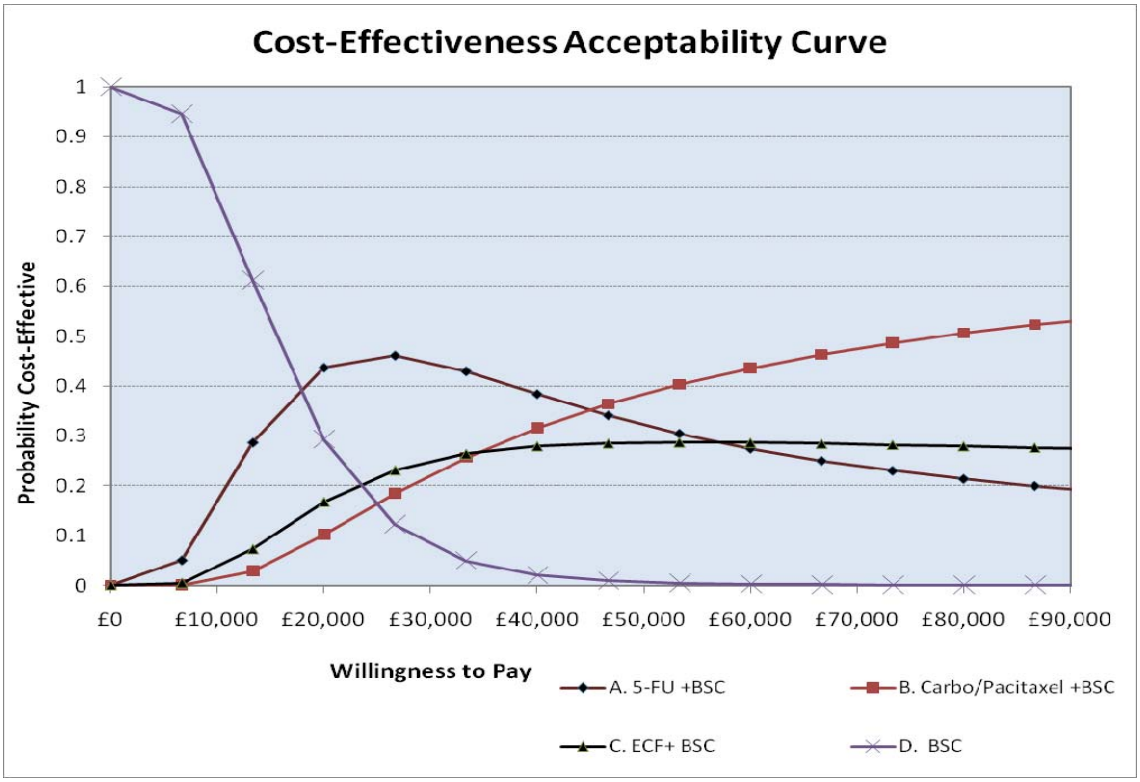
Table 13: Base case total expected cost and QALYs

Strategy	Total expected cost (£)	Total expected QALYs	Incremental CE Ratio £/QALY
Best supportive care	578	0.132	
Fluorouracil (plus supportive care)	1841	0.197	19,499
Epirubicin /cisplatin/ fluorouracil (plus supportive care)	3290	0.219	ED
Carboplatin/paclitaxel (plus supportive care)	5842	0.278	44,605

ED – extendedly dominated

The ICER estimates in Table 13 are based on mean cost and mean effectiveness for each treatment option. Combination therapy ECF is extendedly dominated by a blend of 5-FU and combination carboplatin / paclitaxel strategies. A strategy is said to be extendedly dominated if it demonstrates lower effectiveness and higher costs than a combination of two other strategies. It was recognised prior to undertaking this analysis that there was uncertainty associated with many of the data inputs in the model. This uncertainty can be characterised by estimating the probability that an option is cost-effective at different WTP values and can be shown graphically in the form of cost-effectiveness acceptability curves (CEAC). Taking 5-FU as an example, Figure 2 shows that the probability this treatment option is cost-effective at a WTP threshold of £20,000 per QALY is 43%. At the same WTP threshold, the probability that the ECF strategy and the carboplatin / paclitaxel strategy is cost-effective is 16% and 10% respectively. This suggests there is a high level of uncertainty around the cost-effectiveness of all strategies included in this model.

Figure 2: Cost-effectiveness acceptability curve



The cost-effectiveness acceptability frontier (CEAF) shows the uncertainty associated with the optimal treatment strategy over a range of WTP values and takes into account the impact of skewed distributions on the incremental net benefit function (see Appendix B).

4.1 EVPI

4.1.2 Patient level EVPI

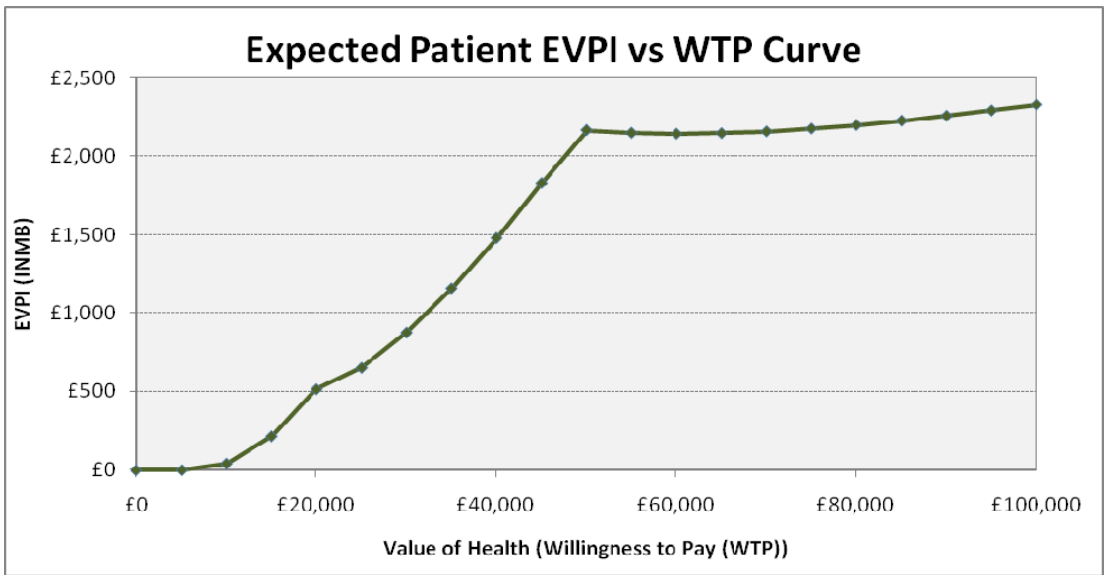
Value of information analysis was undertaken for the cost-effectiveness model by calculating the patient EVPI, population EVPI and the partial EVPI associated with particular model parameters. Table 14 summarises per patient EVPI at various WTP threshold values. For example, moving from a WTP threshold of £20,000 per QALY to £30,000 per QALY, the per patient EVPI increases from £516 to £877. A graphical representation of per patient EVPI is presented in Figure 3.

Table 14: Patient level EVPI

WTP threshold values(£)	Patient level EVPI(£)
5,000	1
10,000	42
15,000	216
20,000	516
25,000	653
30,000	877
45,000	1159
40,000	1481

50,000	2168

Figure 3: Patient EVPI



4.1.2 Population level EVPI

To calculate the population EVPI for patients with confirmed CUP and no clinical features fitting a recognised syndrome, it was necessary to estimate the annual incidence of the disease. The annual incidence was estimated from the needs assessment conducted alongside this guideline. The needs assessment reported an annual incidence of 5840 cases of malignancy without specific site of origin in England and Wales (personal communication with Dr. Paul Shaw: August 2009). After further discussion with the GDG, it was agreed that only 25% (1460 cases) of those patients would fall within the population described in the model and would be fit enough to undergo systemic treatment. The population EVPI was estimated across three time horizons: three, five and ten years. A summary of the results of population EVPI at different WTP thresholds is shown in Table 15.

Table 15: Population EVPI

WTP threshold values(£)	**Population EVPI(£)**		
	3 Year	5 Year	10 Year
5,000	5,046	7,320	12,365
10,000	235,188	341,189	576,372
15,000	1,199,717	1,740,436	2,940,127
20,000	2,866,252	4,158,086	7,024,275
25,000	3,623,276	5,256,303	8,879,499
30,000	4,867,694	7,061,586	11,929,172
35,000	6,433,452	9,333,038	15,766,347
40,000	8,217,756	11,921,536	20,139,110
50,000	12,033,193	17,456,608	29,489,535

4.1.3 Partial EVPI

The expected value of partial perfect information (EVPPI) was examined for six groups of parameters: response rate, duration of response and stable disease, length of treatment, rates of toxicity, resource use and utilities. The results of patient level EVPPI are presented in Table 16. The highest values of EVPPI are for the length of treatment and the parameters related to duration of response and stable disease, suggesting that the value of undertaking further research to reduce or eliminate uncertainty specifically for these parameters is highest.

Table 16: Patient level partial EVPI

WTP threshold values(£)	Response rates (£)	Duration (£)	Length of treatement (£)	Toxicity (£)	Resource use (£)	Utilities (£)
10,000	0.00	0.28	16.03	0.00	0.00	0.00
15,000	3.60	44.07	103.31	0.00	0.00	0.00
20,000	75.58	239.79	278.82	9.02	15.66	5.18
25,000	11.20	320.24	251.02	0.00	0.00	0.00
30,000	11.40	525.05	293.64	0.00	0.00	0.00
35,000	38.58	812.33	389.15	0.00	0.00	0.00
40,000	113.83	1148.24	525.74	0.30	0.02	0.00

4.2 Sensitivity analysis

Chemotherapy agents that are off patent may be purchased at considerable discounts in England and Wales, therefore sensitivity analysis was undertaken to assess the impact of nationally agreed price discounts on the results of the cost-effectiveness analysis and EVPI. The results of this sensitivity analysis are presented in Table 17.

Table 17: One-way sensitivity analysis: incremental cost-effectiveness ratio results

Strategy	Incremental CE ratio £/QALY	
	England	**Wales**
Best supportive care		
Fluorouracil (plus supportive care)	ED	ED
Epirubicin/cisplatin/fluorouracil (plus supportive care)	SD	SD
Carboplatin/paclitaxel (plus supportive care)	6,305	7,299

ED – extendedly dominated; SD – simple dominance

When price discounts are taken into account, the 5-FU and ECF treatment strategies are both dominated. The corresponding CEAC (Appendix B) shows that, at a threshold of £20,000 per QALY, the probability that the carboplatin/paclitaxel combination is cost-effective is almost 80%. With price discounts, the ECF strategy is dominated by the carboplatin/ paclitaxel combination (i.e. ECF exhibits lower effectiveness and incurs higher costs). Single agent 5-FU is extendedly dominated by a blend of supportive care alone and the carboplatin/ paclitaxel combination strategy.

With discounted drug prices, the probability that chemotherapy treatment is cost-effective increases and the population EVPI is now lower than in the base case analysis, as shown in Table 18.

Table 18: One-way sensitivity: population EVPI

WTP threshold values(£)	England(£)			Wales(£)		
	3 Year	5 Year	10 Year	3 Year	5 Year	10 Year
5,000	£126,293	£1,267,281	£2,140,824	£179,195	£259,959	£439,150
10,000	£873,563	£1,033,600	£1,746,065	£623,620	£904,688	£1,528,295
15,000	£712,481	£1,267,376	£2,140,985	£580,832	£842,616	£1,423,435
20,000	£873,628	£1,604,753	£2,710,917	£763,796	£1,108,042	£1,871,821
25,000	£1,106,189	£1,986,313	£3,355,488	£1,004,027	£1,456,546	£2,460,551
30,000	£1,369,206	£1,267,281	£2,140,824	£1,270,057	£1,842,478	£3,112,506

5 Discussion

This analysis was undertaken to quantify uncertainty about current information on the effectiveness and cost-effectiveness of chemotherapy compared to best supportive care in patients with CUP with no clinical features fitting a recognised syndrome and to estimate the value of undertaking future research in order to eliminate or reduce uncertainty in making a decision about the optimal treatment strategy.

An important assumption in undertaking this analysis is that the model made use of parameter estimates that reflect the most appropriate currently available sources of information. Given the paucity and poor quality of studies to date that compare the use of chemotherapy to supportive care in patients with CUP, this analysis relied on expert elicitation conducted with GDG members as the source of estimates for a number of parameters in the model. While techniques were employed to provide adequate instructions and minimise bias in the elicitation exercise, there was insufficient time and resource to explore the possible impact of including a larger number of experts beyond the GDG membership. It is also important to note that there is a considerable amount of uncertainty around consistency of coding of patients with CUP across registries, resulting in possible underestimation of annual incidence in this patient group.

For a given WTP threshold, taking parameter and decision uncertainty into account, the probability that any of the chemotherapy strategies is cost-effective is less than 50%. Further uncertainty about the optimal treatment strategy was demonstrated when the impact of discounted drug acquisition costs were explored through sensitivity analysis.

In the base case analysis, assuming a WTP threshold of £20,000 per QALY, the population EVPI ranges from £2.9 million (with a 3-year time horizon) to just over £7 million (with a 10-year time horizon). These values correspond to an upper limit of the cost of research that should be considered to reduce or eliminate uncertainty with respect to the decision problem. While EVPI is not prescriptive about the specific design of future research efforts, partial EVPI analysis suggests there is greatest value in obtaining more information specifically about the length of treatment and effectiveness of treatment in terms of duration of response for the three chemotherapy regimens included in the model (5-FU, carboplatin/paclitaxel and ECF). One-way sensitivity analysis using discounted drug acquisition costs, but maintaining base case assumptions about parameter uncertainty for all other model inputs, has the effect of reducing incremental costs and therefore lowering ICER estimates. With discounted drug costs, the population EVPI decreased in comparison to the base case, but remained positive.

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List of questions used in the elicitation exercise: Length and effectiveness of treatment

Intervention	Elicitation Question
Best supportive care	What is the proportion of patients who will achieve stable disease? For those patients who achieve stable disease while receiving supportive care only: What is the duration of stable disease (start of treatment until disease progression) in months? For those patients with progressive disease: What is the duration (time in months) from the start of disease progression until death?
5 – FU	Among CUP patients who are receiving chemotherapy treatment with single agent 5-FU: What is the length of that the treatment is given (must be > 0; number of weeks)? Out of 100 CUP patients receiving chemotherapy treatment with single agent 5-FU: What is the proportion of patients who will achieve a response (includes both partial and complete)? For those patients who achieve a response to treatment with single agent 5-FU: What is the duration of response (start of treatment until disease progression) in months? For those patients who achieve stable disease while receiving treatment with single agent 5-FU: What is the duration of stable disease (start of treatment until disease progression) in months?
Carboplatin/paclitaxel	Among CUP patients who are receiving chemotherapy treatment with single agent carboplatin/paclitaxel: What is the length of that the treatment is given (must be > 0; number of weeks)? Out of 100 CUP patients receiving chemotherapy treatment with single agent carboplatin/paclitaxel: What is the proportion of patients who will achieve a response (includes both partial and complete)? For those patients who achieve a response to treatment with single agent carboplatin/paclitaxel: What is the duration of response (start of treatment until disease progression) in months? For those patients who achieve stable disease while receiving treatment with single agent carboplatin/paclitaxel: What is the duration of stable disease (start of treatment until disease progression) in months?

ECF	Among CUP patients who are receiving chemotherapy treatment with single agent ECF: What is the length of that the treatment is given (must be > 0; number of weeks)? Out of 100 CUP patients receiving chemotherapy treatment with single agent ECF: What is the proportion of patients who will achieve a response (includes both partial and complete)? For those patients who achieve a response to treatment with single agent ECF: What is the duration of response (start of treatment until disease progression) in months? For those patients who achieve stable disease while receiving treatment with single agent ECF: What is the duration of stable disease (start of treatment until disease progression) in months?

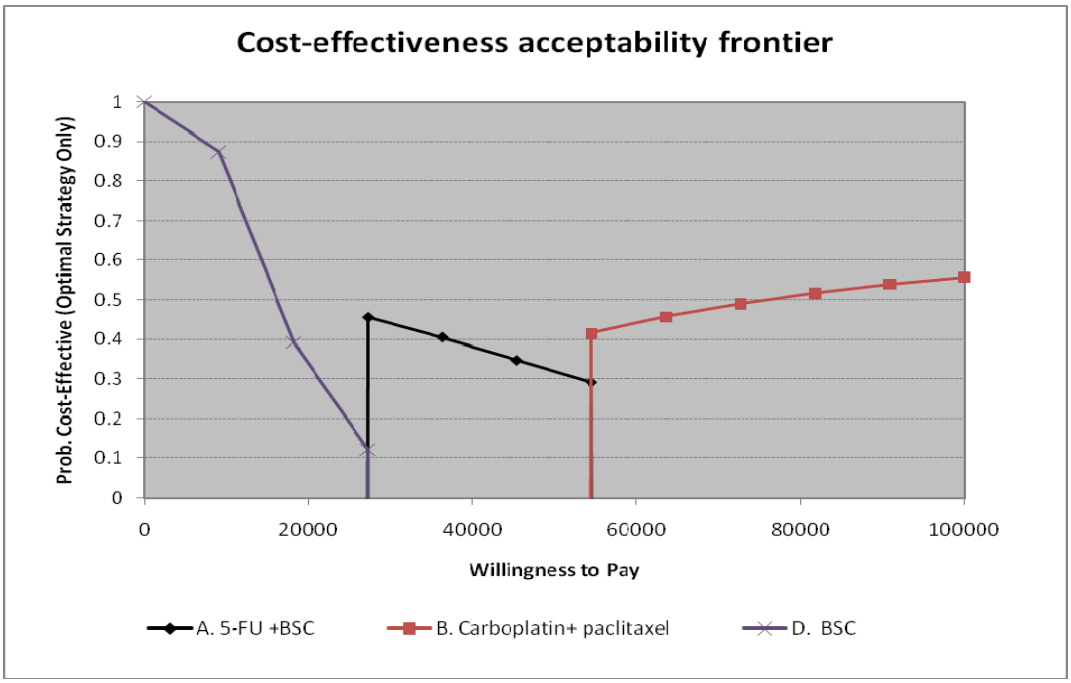
List of questions used in the elicitation exercise: Resource Use

Healthcare Resource Use Category	**Elicitation Question**
Best supportive care	In the management and provision of supportive care for CUP patients: What is the number of inpatient days that a patient spends in hospital over a 6-month period? In the management and provision of supportive care for CUP patients: What is the number of outpatient visits per patient per month? In the management and provision of supportive care for CUP patients: What is the number of inpatient days that a patient spends in hospice per month? In the management and provision of supportive care for CUP patients: What is the number of MRI scans performed per patient in a 6-month period? In the management and provision of supportive care for CUP patients: What is the number of CT scans performed per patient in a 6-month period? In the management and provision of supportive care for a cohort of 100 CUP patients: What is the number patients who will receive palliative radiotherapy?
Management of treatment related toxicity	For a patient receiving chemotherapy and who is experiencing Grade 3 or 4 neutropenia: What is the number of inpatient days that a patient spends in hospital?

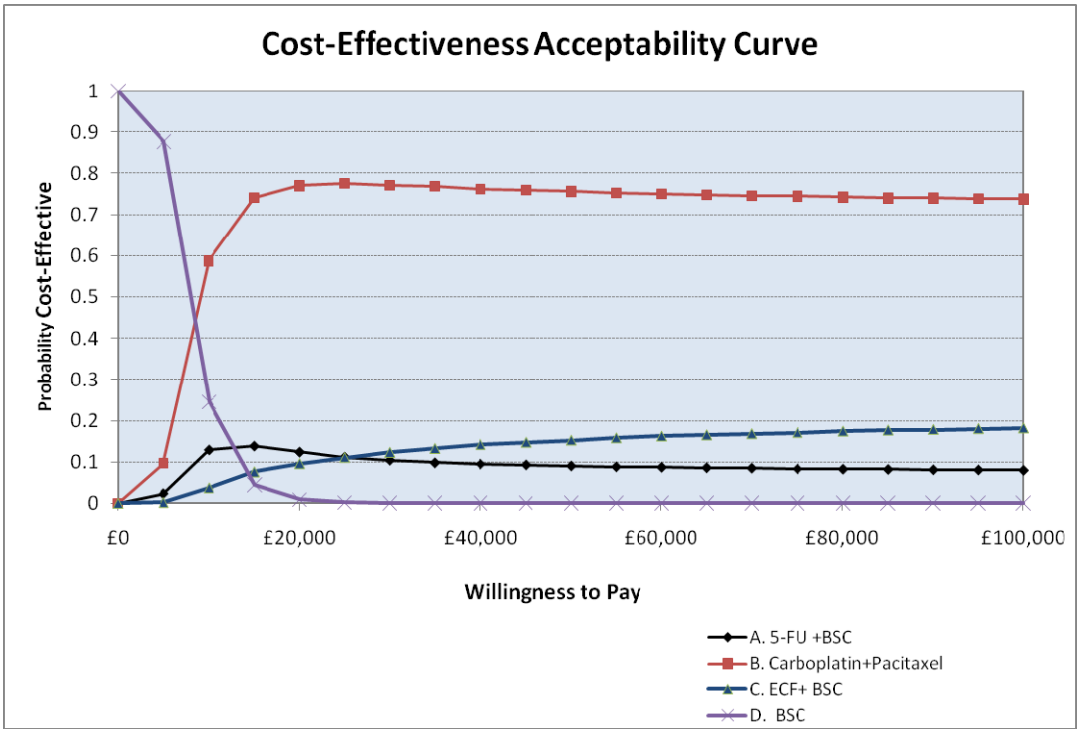
	For a patient receiving chemotherapy and who is experiencing Grade 3 or 4 anemia: What is the number of blood transfusions that a patient is given? For a patient receiving chemotherapy and who is experiencing Grade 3 or 4 nausea and vomiting: What is the number of inpatient days that a patient spends in hospital? For a patient receiving chemotherapy and who is experiencing Grade 3 or 4 diarrhoea: What is the number of inpatient days that a patient spends in hospital?

Health Economics Appendix B

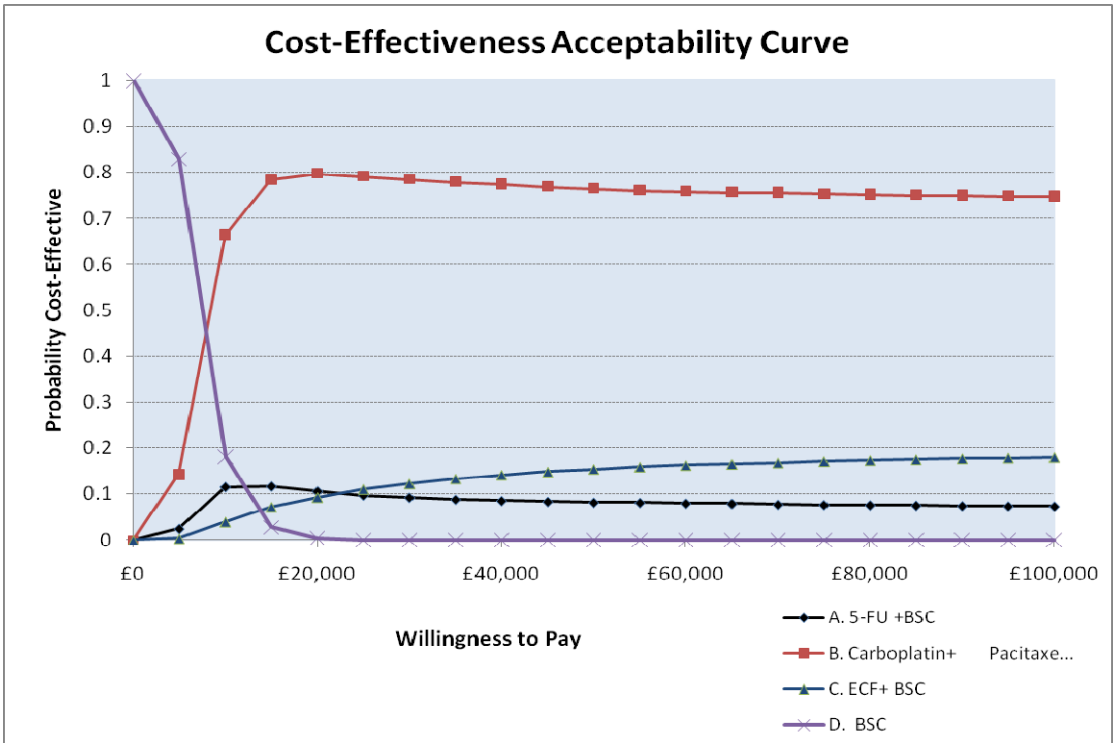
Cost-effectiveness acceptability frontier



Cost-effectiveness acceptability curve for sensitivity analysis with discounted drug acquisition costs in England



Cost-Effectiveness acceptability curve for sensitivity analysis with discounted drug acquisition costs in Wales


Cost-Effectiveness Acceptability Curve
Probability Cost-Effective
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
£0
£20,000
£40,000
£60,000
£80,000
£100,000
Willingness to Pay
A. 5-FU +BSC
B. Carboplatin+ Pacitaxe...
C. ECF+ BSC
D. BSC