Clinical Guideline

Diagnosis and management of metastatic malignant disease of unknown primary origin

Full Guideline

Draft for consultation

Contents

Key priorities

1. Every CUP team should have a named lead clinican who should:
   - take managerial responsibility for the CUP service within the cancer unit or hospital
   - ensure there is a clinical system for the appropriate care of patients with malignancy of undefined primary origin or CUP
   - ensure that each patient has an identified CUP specialist nurse/key worker
   - ensure there is cover for all members of the CUP team at all times
   - ensure that senior clinical input is available to inform decision making and treat patients as necessary
   - ensure that there is a single point of contact for the patient to access the CUP team
   - represent the hospital in CUP matters at the CUP network site specific group and specialist CUP network MDT
   - implement the care pathway and make other healthcare professionals aware about appropriately diagnosing and managing malignancy of undefined primary origin, and CUP
   - ensure timely and effective communication between all healthcare professionals involved in the care of patients with malignancy of undefined primary origin or CUP, including primary and palliative care **and**
   - contribute to regular local and network audits of the management of malignancy of undefined primary origin or CUP.

2. Assign a CUP specialist nurse/key worker to patients diagnosed with malignancy of undefined primary origin or CUP. The CUP specialist nurse/key worker should:
   - take a major role in coordinating the patient's care in line with this guideline
   - ensure that the patient and their carers can get information, advice and support about diagnosis, treatment, palliative care, spiritual and psychosocial concerns
   - meet with the patient in the early stages of the pathway and keep in close contact with the patient regularly by mutual agreement
   - be an advocate for the patient at CUP team meetings.

3. A member of the CUP team should see inpatients with malignancy of undefined primary origin by the end of the next working day after referral. Outpatients should be seen within 2 weeks. The CUP team should take responsibility for ensuring that a management plan exists which includes:
   - appropriate investigations
   - provision of information
   - symptom control
   - access to psychological support.

4. A specialist network CUP MDT should be set up at regional level to review the treatment and care of patients with confirmed CUP, or with complex diagnostic or treatment issues. This team should carry out established specialist MDT responsibilities.

5. Every cancer network should establish a network site specific group responsible for managing all stages of CUP. The group should:
   - advise the cancer network on all matters related to CUP, recognising that many healthcare professionals have limited experience of CUP
   - ensure that the local care pathway for diagnosing and managing CUP is in line with this guideline
   - ensure that every CUP team in the network is properly constituted (see recommendation on p. 32, line 3)
   - ensure that patients have appropriate points of contact with the CUP team, because they present through a variety of routes

- maintain a network-wide audit of the incidence of CUP, its timely management, and patient outcomes
- arrange and hold regular meetings to report patient outcomes and review the local care pathway.

6. Offer the following investigations to patients with malignancy of undefined primary origin, if appropriate:
   - comprehensive history and physical examination including breast, nodal areas, genital, rectal and pelvic examination
   - full blood count; urea, electrolyte and creatinine; liver function; calcium; urinalysis; lactate dehydrogenase
   - chest X-ray
   - immunoglobulin levels (where there are isolated or multiple lytic bone lesions)
   - symptom-directed endoscopy
   - computed tomography (CT) scan of the chest or abdomen or pelvis
   - prostate-specific antigen (PSA) in men
   - cancer antigen (CA) 125 in women with peritoneal malignancy or ascites
   - alpha-fetoprotein (AFP) and human chorionic gonadotrophin (HCG) (particularly in the presence of midline nodal disease)
   - biopsy and standard histological examination to distinguish carcinoma from other malignant diagnoses.

7. Do not use gene-expression-based profiling to identify primary tumours in patients with provisional CUP.

8. Perform investigations only if:
   - the results are likely to affect a treatment decision
   - the patient understands why the investigations are being carried out
   - the patient understands the potential benefits and risks of investigation and treatment **and**
   - the patient is prepared to accept treatment.

9. Include prognostic factors in decision aids and other information for patients and carers about their treatment options.

10. If chemotherapy is being considered for patients with confirmed CUP, with no clinical features suggesting a specific syndrome, inform patients about the potential benefits and risks of treatment.

Key research recommendations

1. **A clinical studies group should be established at National Cancer Research Network (NCRN) level for CUP, to coordinate and direct a broad portfolio of research examining basic science, clinical studies, organisational processes and patient-centred topics.**

   The existence of a national organisation to guide and facilitate research has revolutionised cancer care in the UK. High-quality, rapidly accruing trials have resulted in improved outcomes for patients with all common cancers. Patients with CUP cannot benefit from similar advances because there is no national research strategy addressing their needs. Establishing an NCRN clinical studies group for CUP with a comprehensive portfolio of relevant trials would redress this inequality.

2. **Further research is needed to determine whether the use of PET-CT early in the CUP management pathway reduces the number of investigations that the patient is subjected to.**

   Tests early in the diagnostic pathway of patients with malignancy of undefined primary origin are selected on the basis of clinical factors (suspicion about a possible primary site) and test-related factors (expected yield, ease of access, ease of use, cost). Investigation is an iterative process in which the results of one round of tests inform the selection of subsequent tests. PET-CT is a new test that provides information not available from other investigations. In some circumstances it may reveal a primary tumour that would either not be detected using standard tests, or that would have been detected only after a protracted and costly series of other tests.Using PET-CT early in the diagnostic pathway may reveal useful clinical information more quickly and more cost effectively than current diagnostic strategies. Comparison of established methods of investigation with early use of PET-CT is therefore warranted.

3. **Decision aids should be developed and research carried out to evaluate their benefit.**

   Decision aids have been shown to help breast cancer patients when they face difficult choices. Such aids could be of even greater value to patients with CUP. Research to evaluate the benefits, ease of use and acceptability of such tools to both clinicians and patients should be conducted. Such a study could be an adjunct to a larger trial of chemotherapy.

4. **Prospective randomised trials should be undertaken in patients with confirmed CUP to evaluate whether chemotherapy treatment guided by gene-expression-based profiling is superior to treatment guided by conventional clinical and pathological factors .**

   Selection of optimal chemotherapy for patients with cancer is largely based on knowing the organ of origin of the tumour. For patients with CUP this is not known and decisions are therefore based on the likely organ of origin, as determined by tests such as histology. The limited benefit of treatment selected on this basis highlights the ineffectiveness of current tests in guiding treatment. If the likely organ of origin were more accurately defined there may be a greater chance that treatment would be more effective. Gene-expression-based profiling reliably defines the organ of origin of tumour samples, and the information this test provides in cases of CUP may translate into superior outcomes. Comparing the outcome of chemotherapy treatment selected using conventional factors with the outcome of chemotherapy based on a putative organ of origin defined by gene-expression-based profiling would determine whether this technique would be a beneficial addition to standard management in CUP.

5. Randomised controlled clinical trials should be undertaken in patients with confirmed CUP to define optimal systemic therapy.

The evidence currently used to guide selection of systemic treatment for patients with CUP is very limited, and mainly based on phase II non-comparative studies. In some patients it is uncertain whether systemic treatment offers any advantages over supportive care alone. Randomised controlled trials comparing different interventions should be conducted in well-defined groups of patients with CUP to define optimal treatment. Such trials should include in their design methods to assess cost-effectiveness and patient-centred factors such as quality of life.

Methodology

Introduction

What is a Clinical Guideline?
Guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances – from prevention and self-care through to primary and secondary care and onto more specialised services. NICE clinical guidelines are based on the best available evidence of clinical and cost effectiveness, and are produced to help healthcare professionals and patients make informed choices about appropriate healthcare. While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

Clinical guidelines for the NHS in England, Wales and Northern Ireland are produced as a response to a request from the Department of Health (DH). They approve topics for guideline development and before deciding whether to refer a particular topic to the National Institute for Health and Clinical Excellence (NICE) they consult with the relevant patient bodies, professional organisations and companies. Once a topic is referred, NICE then commissions one of four National Collaborating Centres (NCCs) to produce a guideline. The Collaborating Centres are independent of government and comprise partnerships between a variety of academic institutions, health profession bodies and patient groups. The National Collaborating Centre for Cancer (NCC-C) was referred the topic of metastatic malignant disease of unknown primary origin in April 2007 as part of NICE's fourteenth wave work programme. However, the guideline development process began officially on 8 May 2008 when sufficient capacity became available at the NCC-C.

Who is the Guideline Intended For?
This guideline does not include recommendations covering every detail of the diagnosis and management of metastic malignant disease of unknown primary origin. Instead we have tried to focus on those areas of clinical practice that are (i) known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high quality evidence; or (iv) where NICE guidelines are likely to have most impact. More detail on how this was achieved is presented later in the section on 'Developing Clinical Evidence Based Questions'.

This guideline is relevant to all healthcare professionals who come into contact with patients with metastic malignant disease of unknown primary origin, as well as to the patients themselves and their carers. It is also expected that the guideline will be of value to those involved in clinical governance in both primary and secondary care to help ensure that arrangements are in place to deliver appropriate care to this group of patients.

The Remit of the Guideline
Guideline topics selected by the DH identify the main areas to be covered by the guideline in a specific remit. The following remit for this guideline was received as part of NICE's fourteenth wave programme of work:

- *'To prepare a clinical guideline on the diagnosis and management of metastatic malignant disease of unknown primary origin, including service delivery where appropriate."*

What the Guideline Covers - The Scope
The remit was then translated into a scope document by the Guideline Development Group (GDG) Chair and Lead Clinician and staff at the NCC-C. The purpose of the scope was to:

- provide an overview of what the guideline would include and exclude
- identify the key aspects of care that must be included
- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C and the remit

- inform the development of the clinical questions and search strategy
- inform professionals and the public about the expected content of the guideline.

Prior to the commencement of the guideline development process, the scope was subject to a four week stakeholder consultation in accordance with processes established by NICE in the 'NICE guidelines manual' (NICE 2005, NICE 2006, NICE 2007). The full scope is shown in Appendix 4. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from registered stakeholder organisations and the NICE Guideline Review Panel (GRP). Further information about the GRP can also be found on the NICE website. The NCC-C and NICE reviewed the scope in light of comments received, and the revised scope was reviewed by the GRP, signed off by NICE and posted on the NICE website.

Involvement of Stakeholders

Key to the development of all NICE guidance are the relevant professional and patient/carer organisations that register as stakeholders. Details of this process can be found on the NICE website or in the 'NICE guidelines manual' (NICE 2007). In brief, their contribution involves commenting on the draft scope, submitting relevant evidence and commenting on the draft version of the guideline during the end consultation period. A full list of all stakeholder organisations who registered for the metastic malignant disease of unknown primary origin guideline can be found in Appendix 6.2.

Needs Assessment

As part of the guideline development process the NCC-C invited a specialist registrar, with the support of the GDG, to undertake a needs assessment (see Appendix 6.3). The needs assessment aims to describe the burden of disease and current service provision for patients with carcinoma of unknown primary in England and Wales, which informed the development of the guideline. This document forms a supplement to the full guideline and also appears on the accompanying CD-ROM to this guideline.

Assessment of the effectiveness of interventions is not included in the needs assessment, and was undertaken separately by researchers in the NCC-C as part of the guideline development process.

The information included in the needs assessment document was presented to the GDG. Most of the information was presented in the early stages of guideline development, and other information was included to meet the evolving information needs of the GDG during the course of guideline development.

The Process of Guideline Development – Who Develops the Guideline?

Overview

The development of this guideline was based upon methods outlined by the 'NICE guidelines manual' (NICE 2007). A team of health professionals, lay representatives and technical experts known as the GDG (see Appendix 6.1), with support from the NCC-C staff, undertook the development of this clinical guideline. The basic steps in the process of developing a guideline are listed and discussed below:

- using the remit, define the scope which sets the parameters of the guideline
- forming the Guideline Development Group
- developing clinical questions
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence

- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- updating the guideline.

The Guideline Development Group (GDG)

The CUP GDG was recruited in line with the existing NICE protocol as set out in the 'NICE guidelines manual' (NICE 2007). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and candidates were interviewed prior to being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Requests for applications were sent to the main stakeholder organisations and patient organisations/charities (see Appendix 6.2). Individual GDG members were selected by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline. At the start of the guideline development process all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded (see Appendix 6.1).

Guideline Development Group Meetings

Thirteen GDG meetings were held between 8 May 2008 and 5 October 2009. During each GDG meeting (either held over one or two days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GDG workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GDG in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations prior to presenting it to the GDG as a whole. Each clinical question was led by a GDG member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GDG subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/Carer Members

Individuals with direct experience of carcinoma of unknown primary services gave an integral user focus to the GDG and the guideline development process. The GDG included four patient/carer members. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline and bringing service-user research to the attention of the GDG.

Sadly during development of the guideline two of the patient members of the group passed away and an additional patient member was recruited.

Expert Advisers

During the development phase of the guideline the GDG identified areas where there was a requirement for expert input on particular specialist clinical questions. The clinical questions were addressed by formal presentations by a recognised expert who had been identified by the GDG. A full list of recognised experts who contributed to the guideline can be found in Appendix 6.4.

Developing Clinical Evidence-Based Questions

Background

The scope, as described in Appendix 4, needs to be very clear about which patient groups are included and which areas of clinical care should be considered. But within these boundaries it does not usually specify which topics are considered a priority.

It was recognised by the NCC-C at an early stage that in order to complete the guideline development work to an appropriate standard the GDG needed to restrict its work to approximately 20 clinical questions. Previously this prioritisation would have been carried out by the GDG at its first two meetings but it was clear from some guidelines already published that this approach had resulted in a much larger number of questions than 20 being addressed.

Clinical guidelines should be aimed at changing clinical practice and should avoid ending up as 'evidence-based textbooks' or making recommendations on topics where there is already agreed clinical practice. It was therefore felt important that the 20 clinical questions should be prioritised into areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where NICE guidelines were likely to have most impact.

Method

An extensive list of potential topics for the guideline to investigate was compiled by the NCC-C Director and GDG Chair and Lead Clinician. This list was incorporated into a questionnaire which asked respondents to rate each topic on a three point Likert scale ranging from 0 (low priority) to 2 (high priority). It was made clear that respondents would be rating the priority for each topic to be included in a clinical guideline to be published in two years' time. The questionnaire also asked respondents to suggest any additional topics they would like to see included with an equivalent assessment of their priority.

Questionnaires were subsequently sent to the CUP GDG in advance of the first GDG meeting.

The scores from each completed questionnaire were aggregated by NCC-C staff and ranked. These results together with information on identifiable practice variation (see needs assessment) were presented to the GDG at its first meeting. The list of prioritised topics produced via the questionnaire survey was in no way definitive and the GDG used these results to agree their final priorities for the clinical questions.

For clinical questions about interventions, the PICO framework was used. This structured approach divides each question into four components: the patients (the population under study – P), the interventions (what is being done - I), the comparisons (other main treatment options – C) and the outcomes (the measures of how effective the interventions have been – O). Where appropriate, the clinical questions were refined once the evidence had been searched and, where necessary, sub-questions were generated.

The final list of clinical questions can be found in Appendix 5.

Care Pathway

Early in the development process the GDG drafted an outline care pathway (or algorithm) in order to explore how patients with CUP might access and be treated by the NHS.

Review of Clinical Literature

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions. Additionally, stakeholder organisations were invited to submit evidence for consideration by the GDG, provided it was relevant to the agreed list of clinical questions.

In order to answer each question the NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GDG. When required, the health economist searched for supplementary papers to inform detailed health economic work, for example modelling (see section on 'Incorporating Health Economic Evidence').

Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence. Search filters, such as those to identify systematic reviews (SRs) and randomised controlled trials (RCTs) were applied to the search strategies when there was a wealth of these types of studies. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1950 onwards
- Excerpta Medica (Embase) 1980 onwards
- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1982 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- British Nursing Index (BNI) 1994 onwards
- Psychinfo 1806 onwards
- Web of Science 1970 onwards. [specifically Science Citation Index Expanded
- (SCI-EXPANDED) and Social Sciences Citation Index (SSCI)]
- System for Information on Grey Literature In Europe (SIGLE) 1980–2005
- Biomed Central 1997 onwards
- National Research Register (NRR)
- Current Controlled Trials.

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

Searches were updated and re-run 6–8 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, 9 October 2009 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review (and appear on the accompanying CD-ROM to this guideline).

Critical Appraisal

Following the literature search one researcher independently scanned the titles and abstracts of every article for each question, and full publications were obtained for any studies considered relevant or where there was insufficient information from the title and abstract to make a decision. The researcher then individually applied the inclusion/exclusion criteria to determine which studies would be relevant for inclusion and subsequent appraisal. Lists of excluded papers were generated for each question and the rationale for the exclusion was presented to the GDG when required.

The researcher then critically appraised the full papers. Critical appraisal checklists were compiled for each paper and one researcher undertook the critical appraisal and data extraction.

For all the relevant appraised studies for a particular question, data on the type of population, intervention, comparator and outcomes (PICO) was recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review). All the evidence was considered carefully by the GDG for accuracy and completeness.

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual' (NICE 2007). In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details.

Incorporating Health Economics Evidence

The aim of providing economic input into the development of the guideline was to inform the GDG of potential economic issues relating to CUP. It is important to investigate whether health services are both clinically effective and cost effective, i.e. are they 'value for money'.

Prioritising topics for economic analysis

In addition to the review of the relevant clinical evidence, the GDG were required to determine whether or not the cost-effectiveness of each of the individual clinical questions should or could be investigated. After the clinical questions were decided, and with the help of the health economist, the GDG agreed which of the clinical questions were an economic priority for analysis. These 'economic priorities' were chosen on the basis of the following criteria, in broad accordance with the NICE guidelines manual (NICE 2007):

Overall relevance of the topic:

- *The number of patients affected*: interventions affecting relatively large numbers of patients were given a higher economic priority than those affecting fewer patients
- *The health benefits to the patient:* interventions that that were considered to have a potentially significant impact on both survival and quality of life were given a higher economic priority
- *The per patient cost:* interventions with potentially high financial (cost/savings) implications were given high priority compared to interventions expected to have lower financial implications
- *Likelihood of changing clinical practice:* priority was given to topics that were considered likely to represent a significant change to existing clinical practice.

Uncertainty:

- *High level of existing uncertainty*: higher economic priority was given to clinical questions in which further economic analysis was considered likely to reduce current uncertainty over cost-effectiveness. Low priority was given to clinical questions when the current literature implied a clearly 'attractive' or 'unattractive' incremental cost-effectiveness ratio, which was regarded as generalisable to a UK healthcare setting
- *Likelihood of reducing uncertainty with further analyses (feasibility issues):* when there was poor evidence for the clinical effectiveness of an intervention, then there was considered to be less justification for an economic analysis to be undertaken.

For each topic that was prioritised for economic analysis a comprehensive systematic review of the economic literature was conducted. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence wherever possible. For those clinical areas reviewed, the information specialists used a similar search strategy as used for the review of clinical evidence but with the inclusion of a health economics and quality of life filter. Each search strategy was designed to find any applied study estimating the cost or cost effectiveness of the topic under consideration. A health economist reviewed abstracts and relevant papers were ordered for appraisal.

Published economic evidence was obtained from a variety of sources:

- Medline 1966 onwards
- Embase 1980 onwards
- NHS Economic Evaluations Database (NHS EED)

- EconLit 1969 onwards.

Economic Modelling

Once the priority topics for economic analysis had been agreed by the GDG, the health economist investigated whether or not a cost-effectiveness analysis of each topic could be carried out. Cost-effectiveness evaluations require evidence on numerous parameters, including treatment effects, health-related preferences (utilities), healthcare resource use and costs. However, high quality evidence on all relevant parameters within an economic analysis 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 and therefore cost effectiveness analysis would not be appropriate.

Expected Value of Perfect Information (EVPI)

Given the scarcity of high quality data to inform a cost effectiveness analysis in the CUP guideline the GDG agreed instead to assess the expected value of perfect information (EVPI) on one of the prioritised topics in the guideline (see Appendix 1).

EVPI is a decision analytical approach that allows health economists to estimate the cost of existing uncertainty within a particular clinical area (Briggs et al. 2006). It also enables the health economist to prioritise future research by identifying areas where collection of additional data will lead to a reduction in that current level of uncertainty. EVPI is calculated as the difference between the expected value of the decision made with perfect information and the decision made with current information.

Once the GDG had agreed to this approach the next task was to perform a systematic review of the literature. When relevant published evidence was identified and considered to be of sufficient quality, this information was used to inform the economic analysis. Assumptions and designs of the economic analysis were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

The details of the model are presented in the evidence review and Appendix 1. During the analysis the following general principles were adhered to:

- the GDG Chair and Clinical Lead were consulted during the construction and interpretation of the analysis
- the analysis was based on the best evidence from the systematic review
- assumptions were reported fully and transparently
- the results were subject to thorough sensitivity analysis and limitations discussed
- costs were calculated from a health services perspective.

Agreeing the Recommendations

For each clinical question the GDG were presented with a summary of the clinical evidence, and where appropriate economic evidence, derived from the studies reviewed and appraised. From this information the GDG were able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicit in the accompanying qualifying statement.

Qualifying Statements

As clinical guidelines are currently formatted, there is limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and costeffectiveness. To make this process more transparent to the reader, the NCC-C felt the need for an explicit, easily understood and consistent way of expressing the reasons for making each recommendation.

The way we have chosen to do this is by writing a ‘qualifying statement’ to accompany every recommendation and will usually cover:

- the strength of evidence about benefits and harms for the intervention being considered
- the degree of consensus within the GDG
- the costs and cost-effectiveness (if formally assessed by the health economics team).

Where evidence was weak or lacking the GDG agreed the final recommendations through informal consensus. Shortly before the consultation period, ten key priorities and five key research recommendations were selected by the GDG for implementation and the patient algorithms were agreed. To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

Consultation and Validation of the Guideline

The draft of the guideline was prepared by NCC-C staff in partnership with the GDG Chair and Lead Clinician. This was then discussed and agreed with the GDG and subsequently forwarded to NICE for consultation with stakeholders.

Registered stakeholders (see Appendix 6.2) had one opportunity to comment on the draft guideline and this was posted on the NICE website between 2 December 2009 and 2 February 2010. The GRP also reviewed the guideline and checked that stakeholder comments had been addressed.

The pre-publication check process

Following stakeholder consultation and subsequent revision, the draft guideline was then subject to a pre-publication check. The pre-publication check provides registered stakeholders with the opportunity to raise any concerns about factual errors and inaccuracies that may exist in the revised guideline after consultation.

During the pre-publication check the full guideline was posted on the NICE website for 15 working days, together with the guideline consultation table that listed comments received during consultation from stakeholders and responses from the NCC-C and GDG.

All stakeholders were invited to report factual errors using a standard proforma. NICE, the NCC and the GDG Chair and Lead Clinician considered the reported errors and responded only to those related to factual errors. A list of all corrected errors and the revised guideline were submitted to NICE, and the revised guideline was then signed off by Guidance Executive. The list of reported errors from the pre-publication check and the responses from the NCC-C were subsequently published on the NICE website.

The final document was then submitted to NICE for publication on their website. The other versions of the guideline (see below) were also discussed and approved by the GDG and published at the same time.

Other Versions of the Guideline

This full version of the guideline is available to download free of charge from the NICE website (www.nice.org.uk) and the NCC-C website (www.wales.nhs.uk/nccc).

NICE also produces three versions of the CUP guideline which are available from the NICE website:

- the NICE guideline, which is a shorter version of this guideline, containing the key priorities, key research recommendations and all other recommendations
- the Quick Reference Guide (QRG), which is a summary of the main recommendations in the NICE guideline. For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk

- 'Understanding NICE Guidance' ('UNG'), which describes the guideline using non-technical language. It is written chiefly for patients with CUP but may also be useful for family members, advocates or those who care for patients with advanced breast cancer. For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk

Updating the Guideline

Literature searches were repeated for all of the clinical questions at the end of the GDG development process, allowing any relevant papers published before 9 October 2009 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Three years after publication of the guideline, NICE will commission a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update.

Funding

The National Collaborating Centre for Cancer was commissioned by NICE to develop this guideline. Health economic analysis for this guideline was provided by the London School of Hygiene and Tropical Medicine and funded by the National Collaborating Centre for Cancer.

Disclaimer

The GDG assumes that healthcare professionals will use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.

The NCC-C disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

References

Briggs, A., Claxton K, Sculpher M, Decision Modelling for Health Economic Evaluation. 2006, Oxford: Oxford University Press

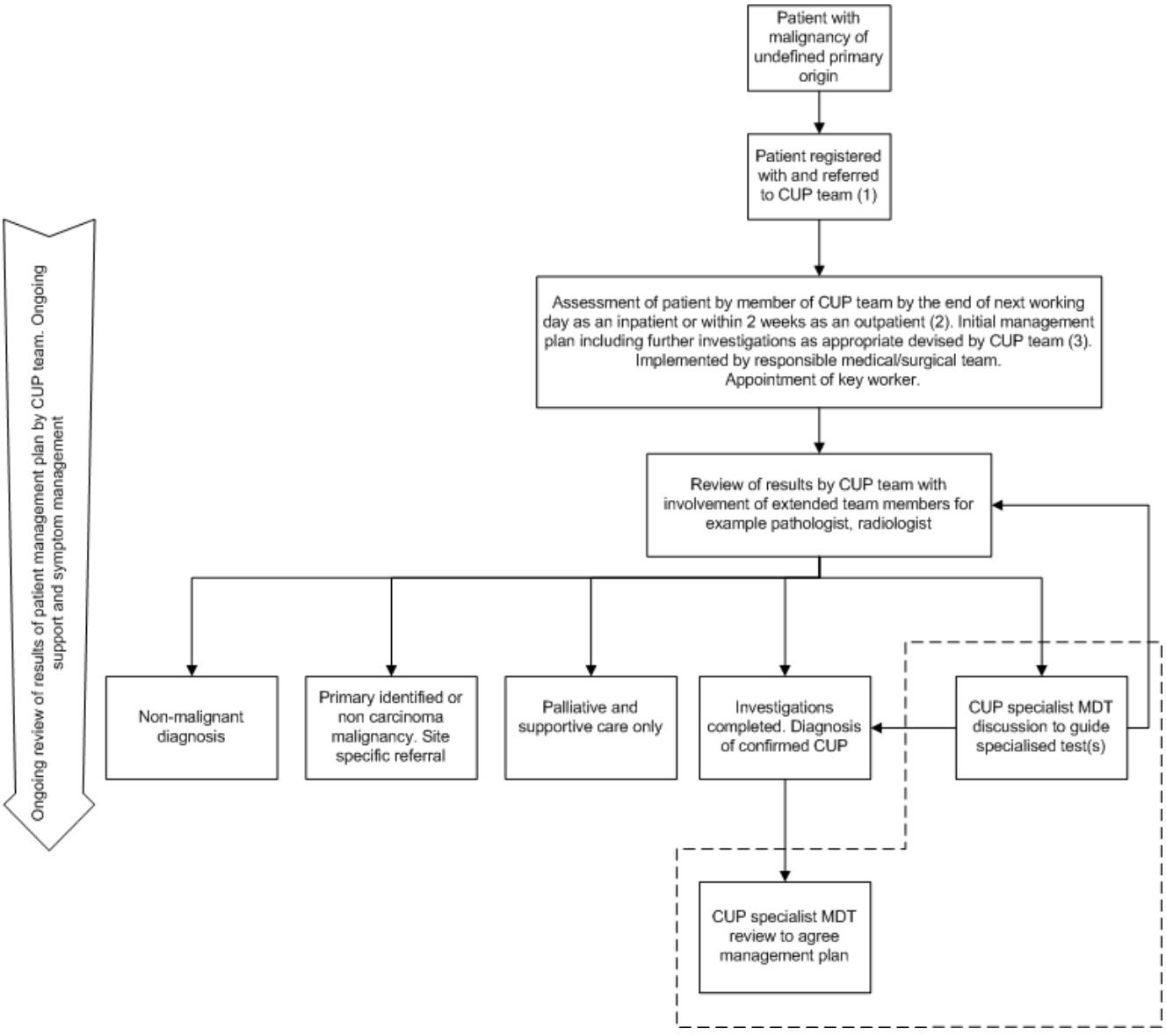
National Institute for Health and Clinical Excellence (2005) The guidelines manual. London: National Institute for Health and Clinical Excellence.

National Institute for Health and Clinical Excellence (2006) The guidelines manual. London: National Institute for Health and Clinical Excellence.

National Institute for Health and Clinical Excellence (2007) The guidelines manual. London: National Institute for Health and Clinical Excellence.

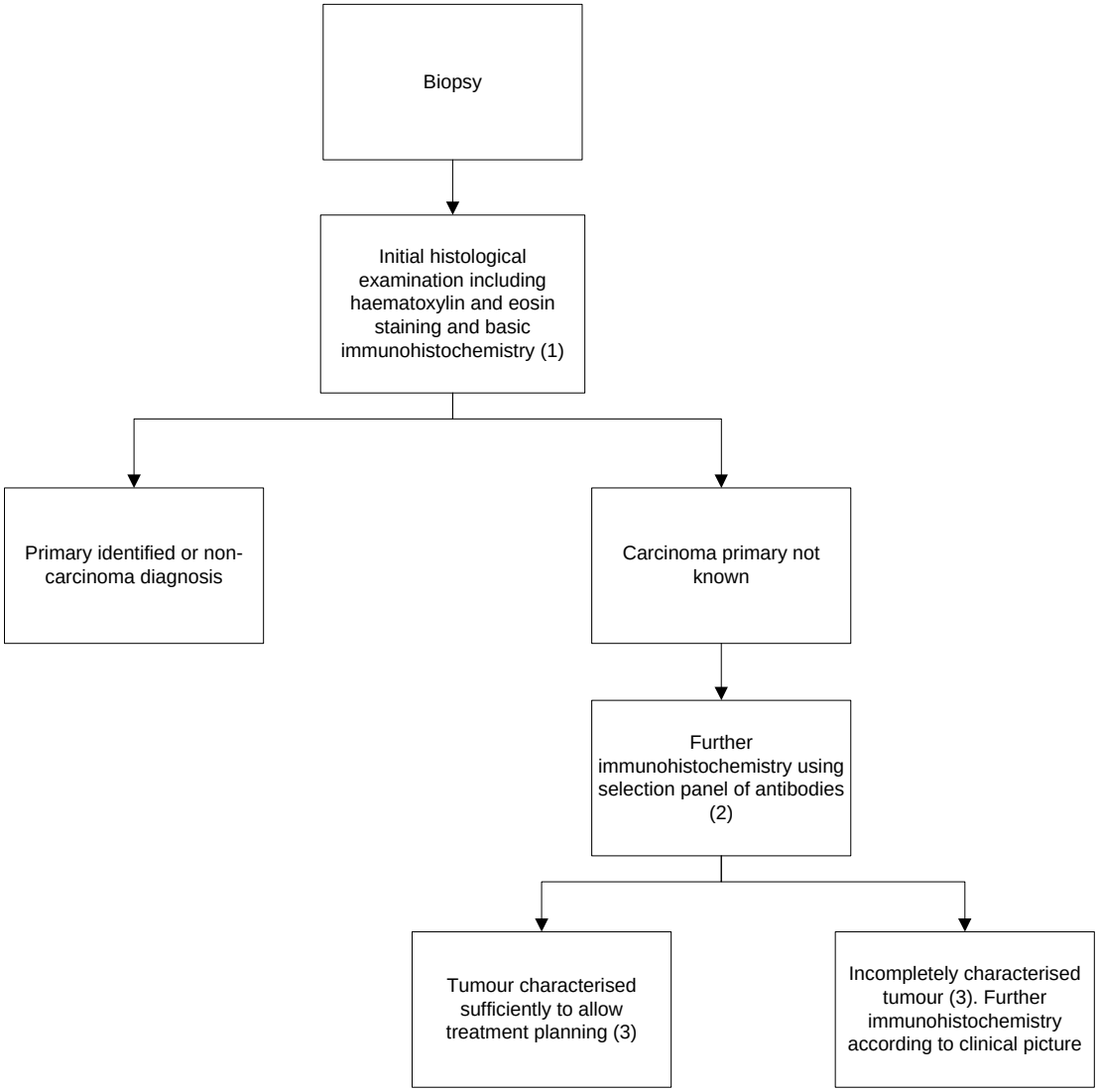
Algorithms

Patient pathway



Key:
1. CUP team comprising an oncologist, a palliative care physician and a CUP specialist nurse, as a minimum.
2. Standard cancer guidelines relating to time to treatment apply
3. Includes information, support, and symptom control.
----- Function of CUP multidisciplinary team (MDT)

Pathology



Key:
1. To distinguish between epithelial and non-epithelial malignancy
2. CK7, CK20, TTF-1, PLAP, ER (women only), PSA (men only)
3. Results of immunohistochemistry to be reviewed in conjunction with all other clinical evidence

Epidemiology

Carcinoma of unknown primary origin (CUP) is an orphan disease. Patients presenting with malignancy of undefined primary origin and those who are ultimately diagnosed with confirmed CUP are largely denied the medical and other benefits afforded to those with site-specific cancers because of the lack of specific, dedicated clinical services, the lack of information and understanding about the disease and the lack of a formal structure to support research. The consistently poor prognosis seen in CUP, which is the third most common cause of cancer death in England and Wales, is a further disadvantage for this group.

Improvements in the care of patients with malignancy of undefined primary origin or CUP spectrum of disease can be achieved by:

- Developing a robust definition for this clinical entity
- Collecting accurate epidemiological data
- Improving organisation of the diagnostic process
- Evaluating the use of new diagnostic techniques particularly applicable to this group
- Developing clinical expertise and systems for effective delivery of all aspects of care
- Evaluating optimal treatment strategies
- Establishing a research organisation dedicated to this condition

This Guideline has been developed to raise the standard of care for patients with CUP to the level experienced by patients with other cancers.

Introduction

Cancer of unknown primary origin (CUP) does not have a discrete classification within the International Classification of Disease (ICD) nomenclature[1]. The ICD codes which will usually cover registrations of CUP are ICD C77 to C80. Full definitions of these ICD codes are included in Box 1. Unfortunately, as there is no agreed definition of CUP, these codes may not capture all CUP diagnoses because they may also be included within other ICD codes. Hence it may be difficult to make direct comparisons with site specific tumours. And because there is no single ICD code to capture these diagnoses, analyses looking at the burden of disease may omit CUP[2].

Box 1: ICD codes covering CUP diagnoses

ICD-10 C77	*Secondary and unspecified malignant neoplasm of lymph nodes* (excludes malignant neoplasm of lymph nodes specified as primary) Head, face and neck (supraclavicular lymph nodes), intra-thoracic, intra-abdominal, axillary and upper limb nodes (pectoral lymph nodes), inguinal and lower limb nodes, intra-pelvic lymph nodes, lymph nodes of multiple regions, unspecified
ICD-10 C78	*Secondary malignant neoplasm of respiratory and digestive sytems* (lung, mediastinum, pleura, other and unspecified respiratory organs, small intestine, large intestine and rectum, retro-peritoneum and peritoneum, liver, other and unspecified digestive organs)
ICD-10 C79	*Secondary malignant neoplasm of other sites* (kidney and renal pelvis, bladder and other unspecified urinary organs, skin, brain and cerebral meninges, unspecified parts of nervous system, one and bone marrow, ovary, adrenal gland, other specified sites)
ICD-10 C80	*Malignant neoplasm without specification of site* (cancer, carcinoma, carcinomatosis, generalised cancer or malignancy, malignancy, multiple cancer, malignant cachexia and primary site unknown)

[1] International Classification of Disease 10. World Health Organisation
[2] Leading causes of death in England and Wales - how should we group causes. Health Statistics Quarterly No. 28: Office of National Statistics. 2005

Cancer registration

All cancer registries in the UK aim to deliver timely, comparable and high-quality data by collecting information on every new diagnosis of cancer (or more specifically condition considered to be registrable[3]) occurring in their populations.

The information is acquired from a variety of sources including hospitals, cancer centres, treatment centres, hospices, private hospitals, cancer screening programmes, other cancer registers, primary care, nursing homes and death certificates. In many instances more than one source of information is available to cancer registries from within a single organisation, for example the hospital patient administration system (PAS), pathology laboratories, medical records departments and radiotherapy databases.

Analysing the data involves checking its validity and completeness and running a complex process of clinical data linkage and consolidation. The number of new registrations made each year depends on the population size covered by the individual registry. To give an example, for a registry with a population of 5 million people, approximately 30,000 new registrations are likely to be added to the database each year.

All registries collect a common minimum dataset[4]. Cancer registries in England are also required to collect cancer registration items from the new National Cancer Dataset, which has been formally agreed and published in Dataset Change Notice (DSCN) 2005/09[5]. Work is currently under way to ensure that registries have systems in place to allow them to receive and process this extended list of data items[6].

Incidence

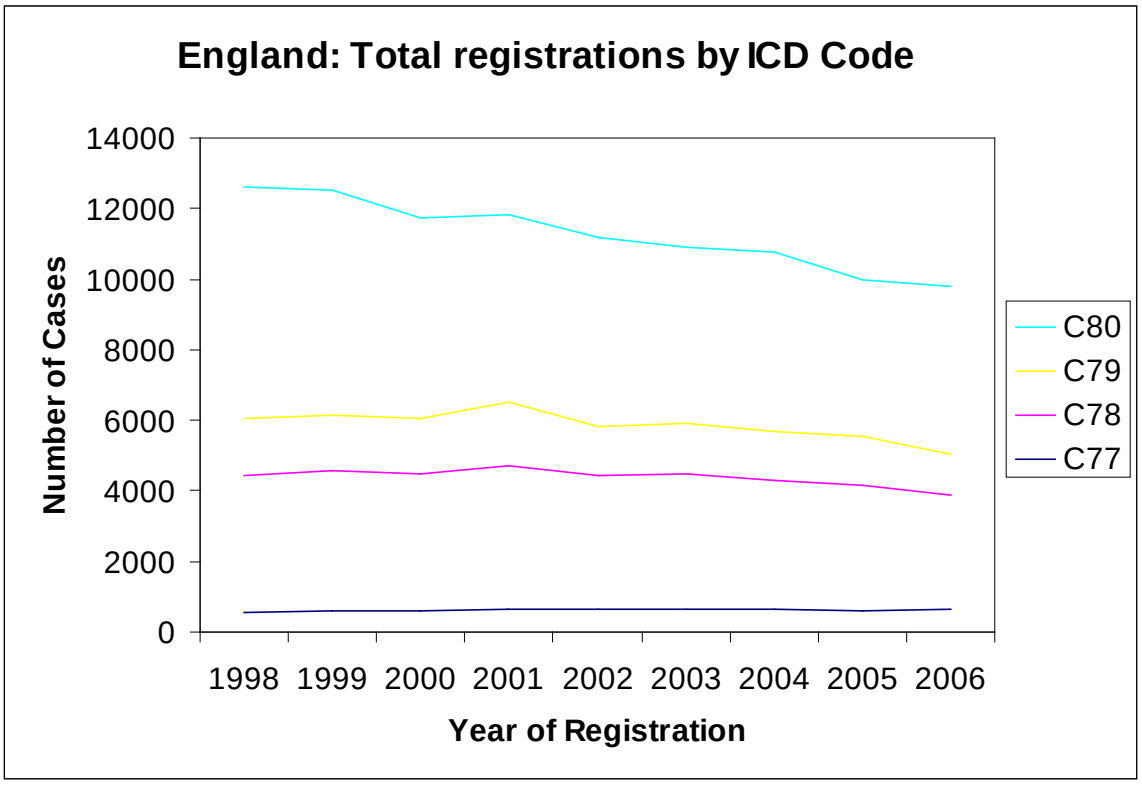
Using the ICD codes presented in Box 1, there were a total of 9,778 new cases of CUP registered in England for 2006[7]. This constituted 2.7% of total cancers registered in England for that year. Of the CUP cases registered 46.3% (4,523) were men and 53.74% (5,255) were women. For Wales there were a total of 3,229 cases of CUP registered between 2002 and 2006. This gives an average of 807 cases per year and represented 3.9% of all cancers registered during this four year period.

Data in Figure 1 shows the total number of registrations in England for individual ICD codes C77 to C80 between 1998 and 2006. These data show that the total number of CUP cases has been falling year on year. The greatest reduction in cases appears to be in the C80 coding, which accounts for around 50% of cases. This decrease in recent years may be due to improved diagnosis, with cases previously diagnosed as CUP now having primary cancer site diagnosis. However there may be other explanations for this decline, for example a change in cancer registry coding practice or changes in clinical practice due to the formation of site specific MDTs. These possible explanations will require further analysis.

Although these data provide the best current information available on the incidence of cancer of unknown primary they do not present the complete picture of the burden of disease of malignancy of undefined primary origin (MUO) or CUP to the NHS. What is represented by current cancer registration is as complete a classification as is possible. Many more patients will present to the NHS with an initial diagnosis of MUO but over time their primary site will be identified and will never appear within these statistics.

[3] UK Association of Cancer Registries. Available at: http://82.110.76.19/registration/registrable.asp
[4] UK Association of Cancer Registries. Available at: http://82.110.76.19/registration/dataset.asp
[5] NHS Connecting for Health. Available at: http://www.connectingforhealth.nhs.uk/dscn/dscn2005/092005.pdf
[6] UK Association of Cancer Registries. Available at: http://82.110.76.19/registration/role.asp
[7] MB1 Office for National Statistics (2006)

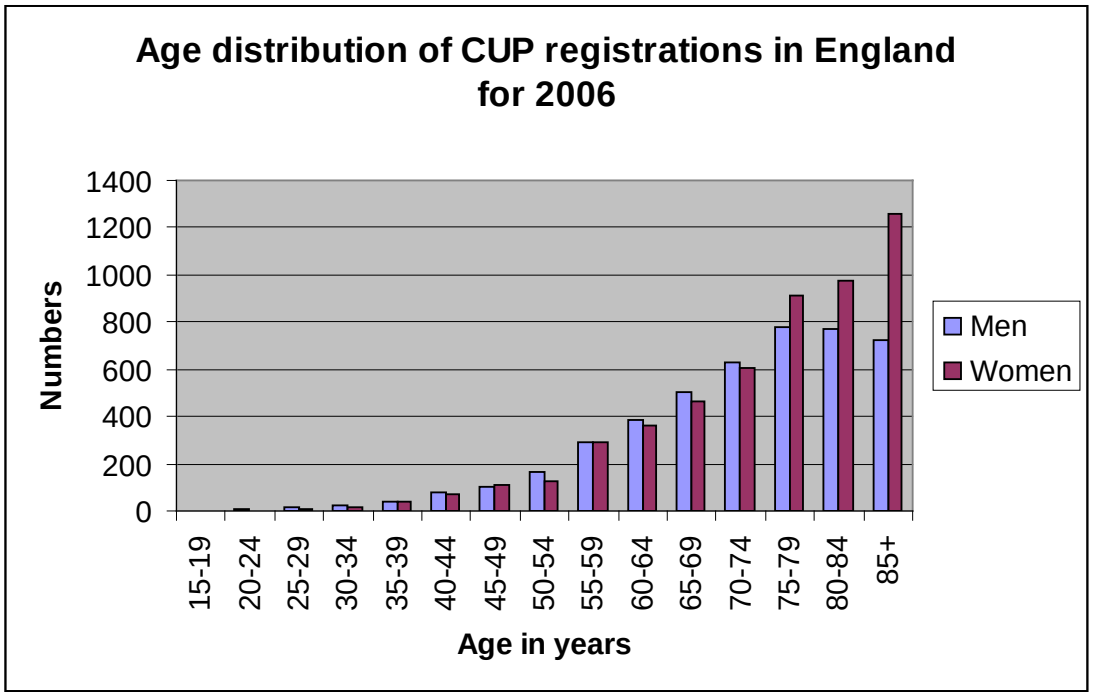
Figure 1 Total number of registrations in England for indivudal ICD codes (1998-2006)



Source MB1 Office for National Statistics

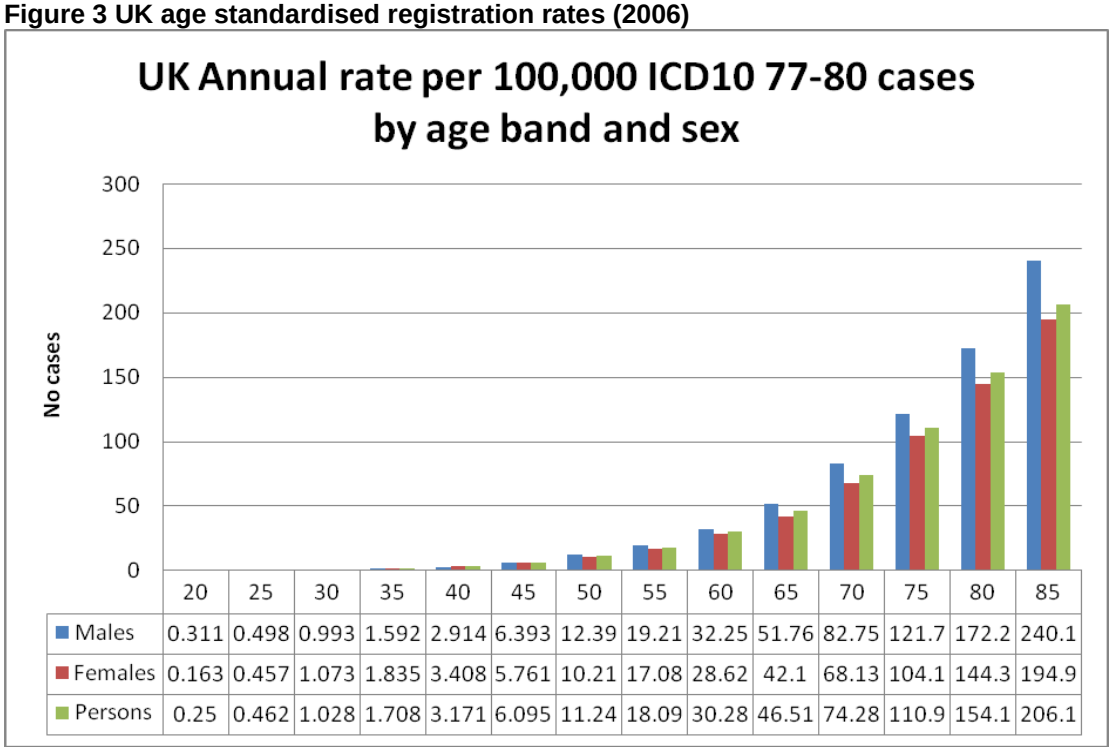
Figure 2 shows the age distribution of registrations by sex in England for 2006. This shows that for women the number of cases increased steadily with age. However for men the highest number of cases were in the 75-79 years age group with the numbers subsequently falling in the older age ranges. This contrasts with the age standardized registration rates for both men and women during the same period (Figure 3), which are both shown to increase, with the incidence rates for men being higher at all ages.

Figure 2 Age distribution of registrations by gender in England (2006)



Source MB1 Office for National Statistics

Figure 3 UK age standardised registration rates (2006)

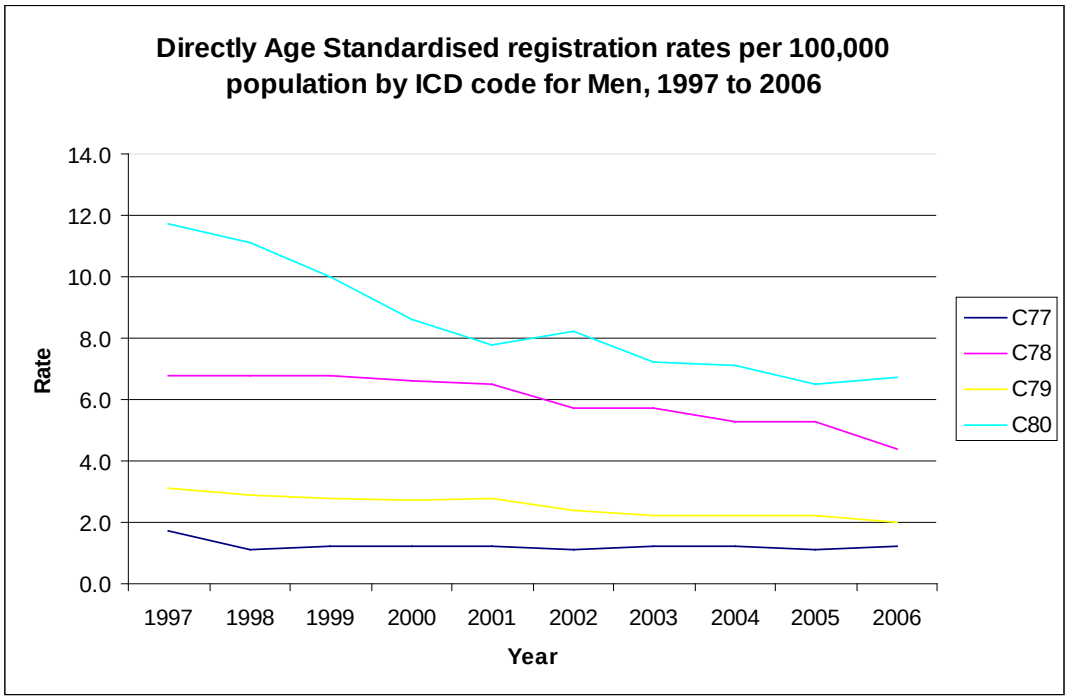


	20	25	30	35	40	45	50	55	60	65	70	75	80	85
Males	0.311	0.498	0.993	1.592	2.914	6.393	12.39	19.21	32.25	51.76	82.75	121.7	172.2	240.1
Females	0.163	0.457	1.073	1.835	3.408	5.761	10.21	17.08	28.62	42.1	68.13	104.1	144.3	194.9
Persons	0.25	0.462	1.028	1.708	3.171	6.095	11.24	18.09	30.28	46.51	74.28	110.9	154.1	206.1

Source: Data from all UK cancer registries

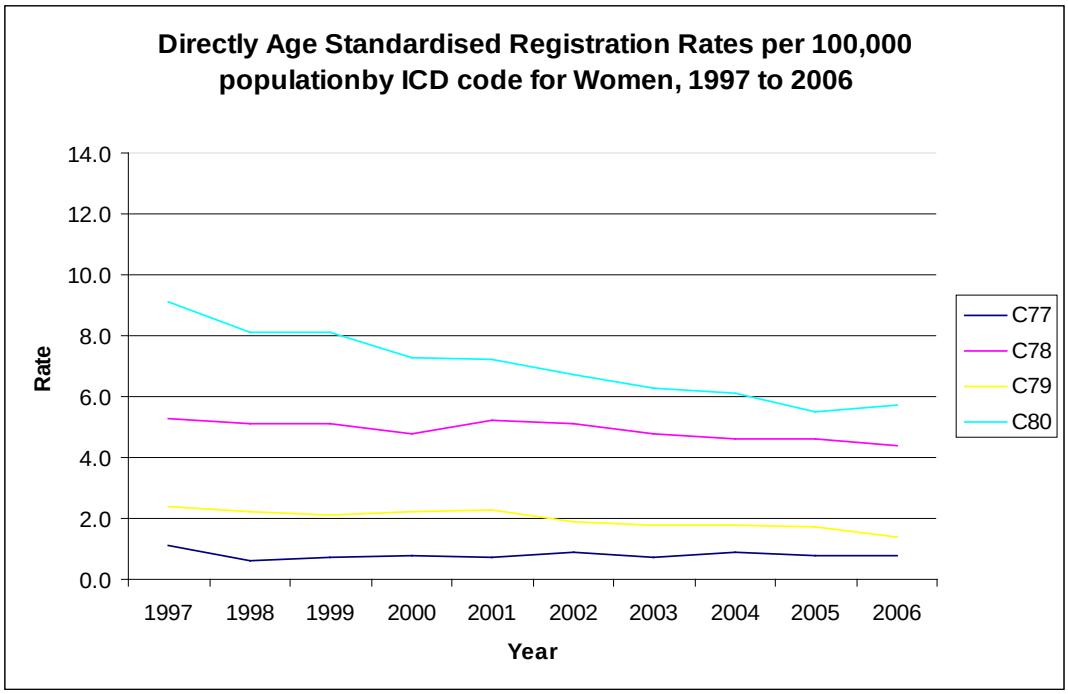
Directly standardized registration rates for men and women in the UK between 1997 and 2006 are shown in Figures 4 and 5 respectively. These show that rates have fallen over the last 10 years for ICD codes C78 and C80 but have fallen considerably less for ICD codes C77 and C79.

Figure 4 Directly age standardised registration rates per 100,000 population by ICD code for men (1997-2006)



Source: Data from all UK cancer registries

Figure 5 Directly age standardised registration rates per 100,000 population by ICD code for women (1997-2006)



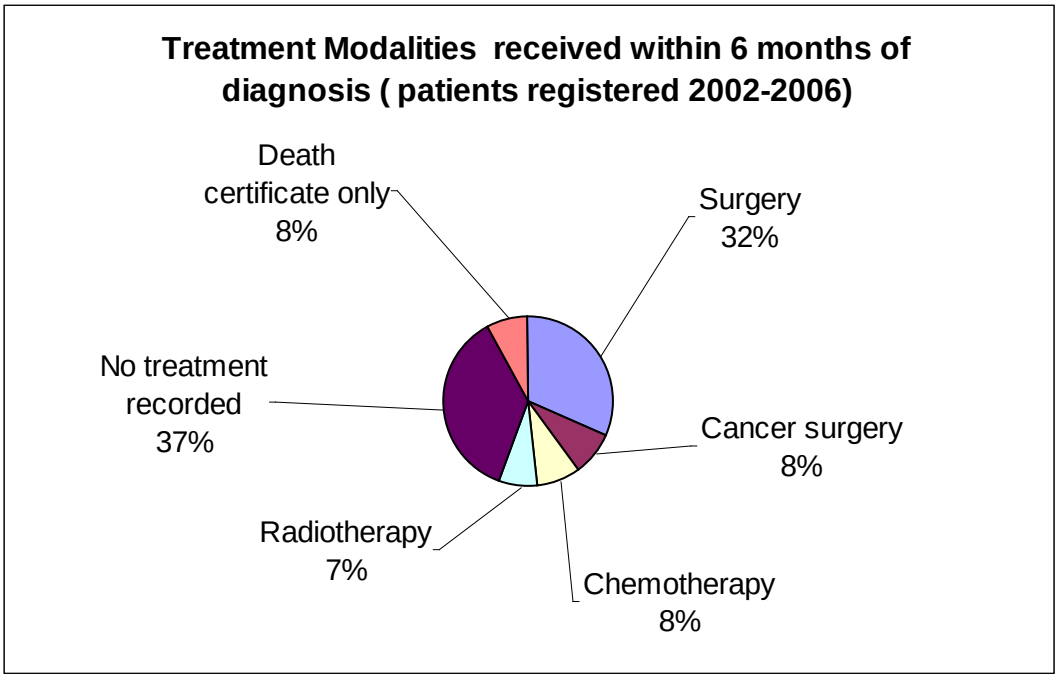
Source: Data from all UK cancer registries

Treatment data

UK cancer registries collect information on the treatment that patients have received for their cancer within six months of registration. Figure 6 below shows the range of treatments received by patients who were registered with ICD codes C77 to 80 between 2002 and 2006 in the Thames Region of England. It should be noted that patients may have received more than one form of treatment. The data presented here relate to the type of treatment and not to the proportion of patients receiving that treatment.

It is of note that 37% of these patients are recorded as receiving no treatment. This may be due to under ascertainment of treatment data but is still a significant proportion. A further 8% were only registered through their death certificate and no further information was available. Only 23% of recorded treatments appear to have been definitive or curative i.e. chemotherapy, radiotherapy or cancer surgery. It is possible that more than one of these treatment modalities relate to a single patient i.e. it was the same patient that received cancer surgery, radiotherapy and chemotherapy. A further 32% of treatments were surgical, but it is unknown if these were diagnostic or therapeutic procedures. Further investigation of these data is now required.

Figure 6 Treatment modalities received within 6 months of diagnosis (2002-2006)



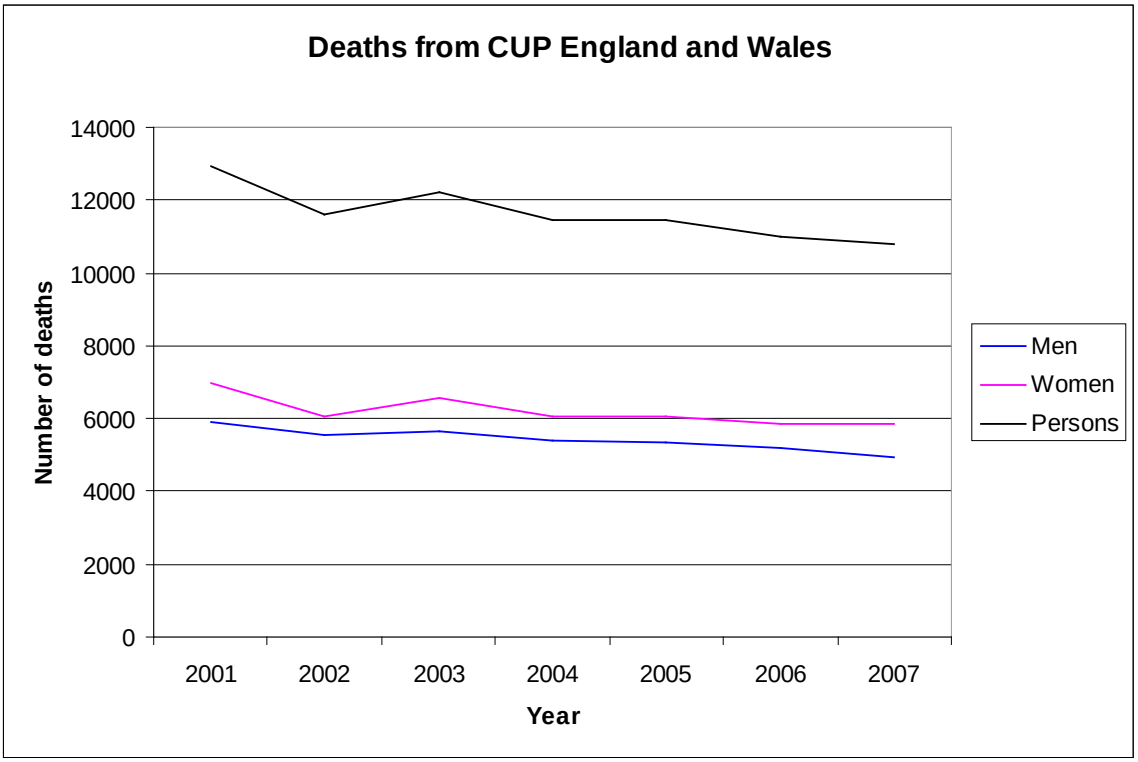
Source: Thames Cancer Registry for patients registered 2002-2006.

Mortality data

During 2006 there were 11,018 deaths within the C77 to C80 codings for CUP patients in England and Wales[8] (Figure 7). This represented 2.2% of all deaths within that year. Of these total deaths 5,183 were in men and 5,935 in women and this represented 7.3% (men) and 9.0% (women) of all cancer-related deaths during that year.

[8] Table 5.2; Deaths: underlying cause, sex and age group 2006. Chapter 2. Neoplasms. Office of National Statistics.

Figure 7 Deaths from CUP in England and Wales (2001-2007)

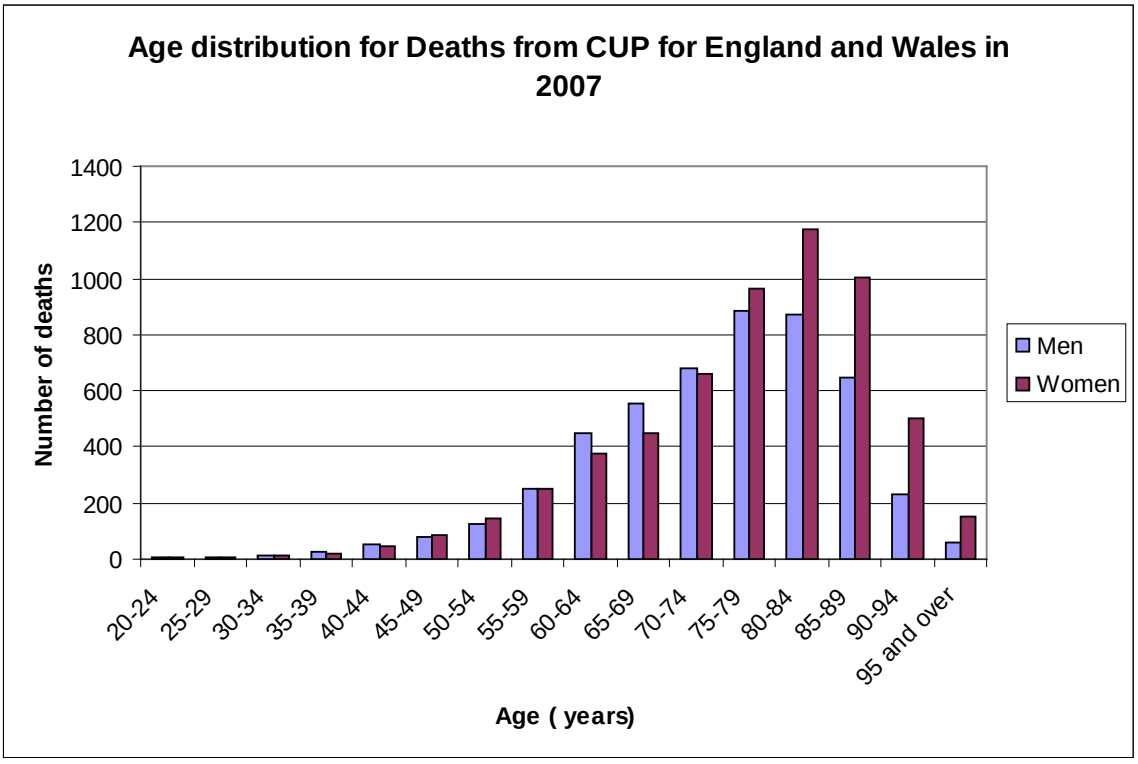


Source : Mortality by Cause: England & Wales

Figure 7 shows that there has been a fall in the total numbers of deaths attributed to CUP from 12,916 in 2001 to 10,813 in 2007. This fall reflects the reduction already seen in CUP cancer registrations (Figure 1) and may be due to an improvement in identifying the site of the primary cancer.

Figure 8 shows the age distribution for deaths attributed to CUP in England and Wales for 2007. This also reflects the distribution of the age at registration which appears to show a younger modal value in men than women for both deaths and registrations.

Figure 8 Age distribution for deaths from CUP for England and Wales (2007)



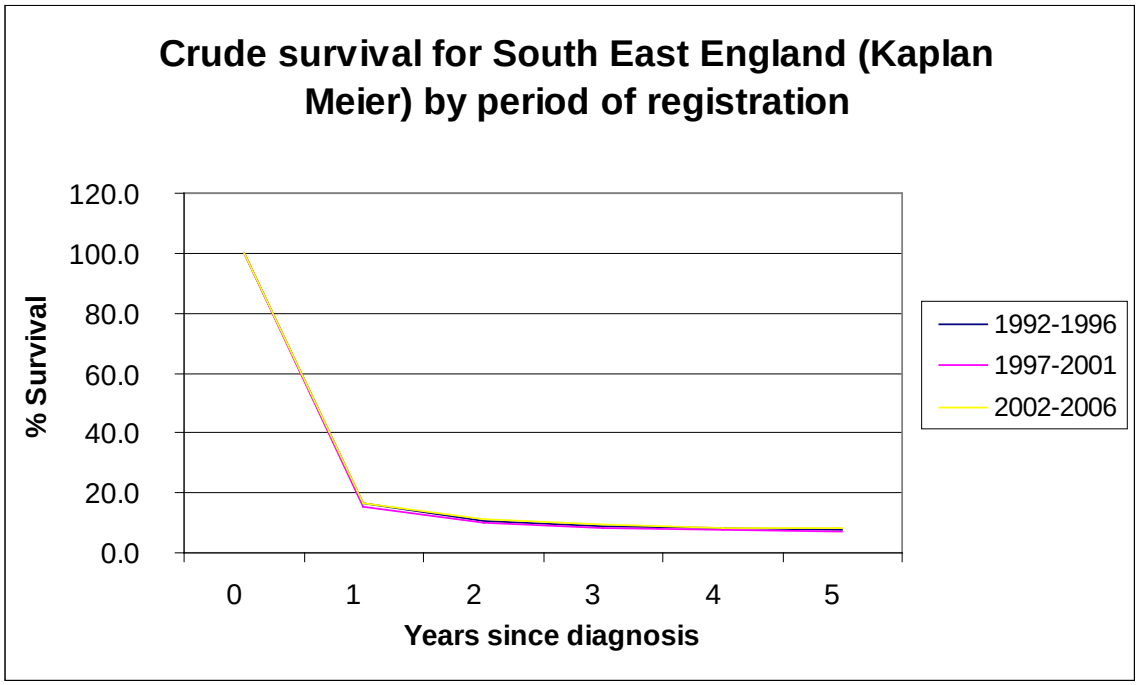
Source: Table 5.2; Deaths by Cause. Office of National Statistics (2006)

Survival

Figure 9 shows the Kaplan Meier survival curves for patients registered in the South East England between 1991 and 2006. This shows the rapid fall in survival during the first 12 months after diagnosis to around 16%, with a more gradual fall in survival over the next 5 years to 8%. What is also noticeable is that there appears to be no detectible change in the survival of CUP between 1992 and 2006. This is in stark contrast with the mortality rate from all cancers in the UK which fell by 15% for men and 11% for women between 1993-5 and 2002-4.[9]

[9] Health Statistics Quarterly. No. 38 Office of National Statistics. Summer 2008

Figure 9 Crude survival for South East England by period of registration



Source: Thames Cancer Registry

1 Introduction

The term “cancer of unknown primary” refers to a condition in which a patient has metastatic malignancy without an identifiable primary source. This is a hetereogeneous illness in which the type of tumour, the extent of spread, and the outcome of treatment all vary widely. When categorising cancer of unknown primary, one important factor initially considered is the cell type of origin of the metastatic disease. The majority of patients have malignancy which appears to derive from epithelial cells, hence these patients are regarded as having carcinoma of unknown primary origin. Patients with tumours of non-epithelial lineage (melanoma, sarcoma, lymphoma, germ-cell) form a distinct and important minority because management of these tumours can often be satisfactorily undertaken even in the absence of an identifiable primary source. Such patients are not considered in this guideline because their care is adequately defined in existing guidelines for their specific tumour type. We have used the term “carcinoma of unknown primary” (CUP) to refer to those patients with metastatic malignancy of epithelial, neuro-endocrine or undifferentiated lineage whose investigation, treatment and care is considered within the scope of this guideline.

Carcinoma of unknown primary is currently an inexact term because it is often applied to patients in whom only limited investigations have been performed. Further testing in such patients may reveal a primary tumour, or may demonstrate a non-epithelial malignancy. Because the process of investigation is a continuum from initial presentation with the results of limited tests, to a final diagnosis after all relevant investigations have been completed, a more precise terminology reflecting the different phases of investigation would be advantageous.

A patient who presents with metastatic malignancy (in the form of tumour masses or effusions) on clinical examination or by imaging, without an obvious primary site, can be regarded as having “malignancy of undefined primary origin”. Although a primary site is subsequently found in most of these patients, or an uncommon non-epithelial malignancy is diagnosed, some patients will ultimately be diagnosed with “true” carcinoma of unknown primary after extensive testing.

For the purpose of defining optimal management during the various phases from initial presentation to completion of testing, the following definitions have been devised for this guideline.

Definitions

Malignancy of undefined primary origin:
Metastatic malignancy identified on the basis of a limited number of tests, without a probable primary site, prior to comprehensive investigation.

Provisional carcinoma of unknown primary (provisional CUP)
Metastatic epithelial or neuro-endocrine malignancy identified on the basis of histology/cytology, with no primary detected despite a selected initial screen of investigations, prior to specialist review and possible further specialised investigations.

Confirmed carcinoma of unknown primary (confirmed CUP)
Metastatic epithelial or neuro-endocrine malignancy identified on the basis of final histology, with no primary detected despite a selected screen of investigations, specialist review, and further specialised tests as appropriate.

To minimise the risk of delayed site-specific referral for patients who are suspected to have a specific primary, patients considered as having malignancy of undefined primary origin are further defined as follows:

- Liver tumour(s) and other intra-abdominal masses identified as likely metastatic malignancy on initial imaging, without evidence of a probable primary site.
- Bone tumour(s) identified as likely metastatic malignancy on initial imaging and not immediately considered to be related to prostate cancer (by DRE or PSA).
- Brain tumour(s) identified as likely metastatic malignancy on initial imaging, without evidence of a probable primary site.
- Lung tumour(s) identified as likely metastatic malignancy on initial imaging, without evidence of a probable primary site.
- Pleural effusion(s) diagnosed as malignant on cytology, without evidence of a probable primary site.
- Malignant ascites diagnosed cytology, without evidence of a probable primary site.
- Skin tumour(s) confirmed as malignant on histology when primary skin cancer excluded and no obvious primary from histology or imaging.
- Biopsy confirmed malignancy in cervical lymph node(s) when head and neck primary excluded and no obvious primary from histology or imaging.
- Biopsy confirmed malignancy in axillary lymph node(s) when no obvious primary from histology or imaging.
- Biopsy confirmed malignancy in inguinal lymph node(s) when no obvious primary from histology or imaging.

Patients for whom a specific primary site is supected, who do not satisfy these criteria, are managed along conventional lines by site-specific referral and investigation.

2 Organisation of services and support

Introduction

Patients with malignancy of undefined primary origin present in many different ways to different parts of the health service. There is a small proportion for whom treatment will make a significant difference and they need to be identified promptly and treatment commenced. But the experience of many is going through a lengthy diagnostic process with little new information discovered. They voice disquiet at a string of investigations which seem to have no logic and which may cause discomfort, add little to their care or subsequent treatment. They speak of confusion as to who is in charge of their care and who is directing progress. They are often in hospital for long periods of time with little perceived benefit. On being told that they have a cancer but that the primary source is unclear they feel further lack of fitting into a defined system. They meet other cancer patients with a named oncology consultant, named specialist nurses, MDT decision making, targets for time to treatment, organised support systems, major national charities, patient advocate groups and often feel added disenfranchisement. The absence of an organised research programme is a further disadvantage for this group of patients.

> *"When I went from colorectal MDT to gynae MDT, there was a ten day gap until my appointment. I was then sent back, now having an ultrasound confirmed taking up most of my upper abdomen. I had to wait a week for appointment, then another three weeks while MDTs quibbled about whose surgery time would be used for my op"*

Some patients present with advanced disease when further investigations and thoughts of systemic treatment are wholly inappropriate. Often there is a lack of an appropriately skilled clinician to explain the futility of invasive tests with no prospect of beneficial anti-cancer treatment.

> *" The whole time, my symptoms were getting increasingly worse and I did not have any symptom control. What will (would) also make a huge difference is early oncology and palliative care input"*

For those patients who are offered treatment it is not clear whether they are fully aware of the limitations and potential side effects of treatment, and whether they are able to make informed decisions.

Current deficiencies in the management of patients with carcinoma of unknown primary (CUP)

The process for investigating and subsequently managing patients with malignancy of undefined primary origin or CUP is complex, variable and imperfect. The shortcomings in existing strategies for initial management of patients without a "site-specific" diagnosis can be attributed to the following:

a) Lack of agreed definitions of the clinical entity
b) Lack of referral guidelines for suspected cancer relevant to patients without an obvious or strongly suspected primary
c) Lack of a system to rapidly identify patients and to ensure early specialist involvement
d) Lack of efficient arrangements to manage the initial diagnostic phase
e) "Orphan" status of the clinical entity
f) Lack of a team structure to efficiently manage newly presenting patients
g) Lack of specialist oncology expertise
h) Referral to inappropriate site-specific cancer teams

i) Lack of support and information for the defined patient group
j) Delays in involvement of specialist palliative care
k) Lack of an overarching organisational structure to ensure high-quality care
l) Lack of adequate epidemiology data
m) Lack of research organisation

Resolution of these problems has been approached by examining whether, for newly-presenting patients with malignancy of undefined primary origin undergoing initial investigations to establish a primary site, there are organisational and support arrangements which can improve outcomes.

The carcinoma of unknown primary (CUP) team and its functions

Traditional approaches in medicine are being revised, through the establishment of teams responsible for rapid assessment and diagnosis. Alert systems exist which notify clinical teams of new admissions, and real-time tracking of patients can be used to streamline care. Newly presenting patients are investigated in a timely fashion, with early assessment by senior clinicians to refine the diagnostic process. These innovations can deliver advantages both to patients and hospitals, in terms of more rapid treatment and more efficient resource use.

> *"My late wife's journey could have been so much better and handled much better"*

Some problems encountered in managing patients with malignancy of undefined primary origin might be similarly improved by ensuring early expert assessment by senior oncology clinicians. Undertaking relevant investigations in a rational order, using specialised tests at an appropriate stage and implementing expert decision-making to inform treatment plans could all contribute to an improved outcome.

The provision of support from a specialist nurse is now an accepted intervention for patients with the major common cancers as there is evidence that this reduces patient concerns and suffering. Patients with CUP undergoing investigations are not currently provided with the support 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.

> *"Very little information either written or verbal on the difficulties of this condition were available. Not many of the specialist nurses had much knowledge of this type of problem and dealt only on a day to day basis with the affects of the cancer rather than the huge crisis we were facing due to an unknown outcome"*

The optimum organisation of a system to rapidly identify and then manage newly presenting patients with malignancy of undefined primary origin has been examined. Key considerations were:

- development of mechanisms for early identification of patients and subsequent tracking
- the role of a small specialist team ("CUP team") responsible for guiding decision making and orchestrating care for problems related to a new diagnosis of cancer, particularly of an unidentified primary site.

Recommendations

- Trusts should establish a CUP team, consisting of an oncologist, a palliative care physician and a CUP specialist nurse/key worker as a minimum. The team should have administrative support and sufficient designated time in their job plans for this specialist role.
- Every CUP team should have a named lead clinican who should:
  - take managerial responsibility for the CUP service within the cancer unit or hospital
  - ensure there is a clinical system for the appropriate care of patients with malignancy of undefined primary origin or CUP
  - ensure that each patient has an identified CUP specialist nurse/key worker
  - ensure there is cover for all members of the CUP team at all times
  - ensure that senior clinical input is available to inform decision making and treat patients as necessary
  - ensure that there is a single point of contact for the patient to access the CUP team
  - represent the hospital in CUP matters at the CUP network site specific group and specialist CUP network MDT
  - implement the care pathway and make other healthcare professionals aware about appropriately diagnosing and managing malignancy of undefined primary origin, and CUP
  - ensure timely and effective communication between all healthcare professionals involved in the care of patients with malignancy of undefined primary origin or CUP, including primary and palliative care **and**
  - contribute to regular local and network audits of the management of malignancy of undefined primary origin or CUP.

Qualifying statement: There is evidence that specialist referral improves care for cancer patients. The GDG also considered recent reports and took evidence from experts, it concluded that patients with malignancy of undefined primary origin would benefit from early intervention and active tracking to ensure timely care in line with standard practice for site specific cancers.

- Assign a CUP specialist nurse/key worker to patients diagnosed with malignancy of undefined primary origin or CUP. The CUP specialist nurse/key worker should:
  - take a major role in coordinating the patient's care in line with this guideline
  - ensure that the patient and their carers can get information, advice and support about diagnosis, treatment, palliative care, spiritual and psychosocial concerns
  - meet with the patient in the early stages of the pathway and keep in close contact with the patient regularly by mutual agreement
  - be an advocate for the patient at CUP team meetings.
- Trusts should ensure that patients have access to an identified CUP specialist nurse/key worker when malignancy of undefined primary origin is diagnosed.

Qualifying statement: There is little evidence on the effect of key workers for people with cancer, however they have become standard practice for site-specific cancers and the GDG felt that CUP patients should not be disadvantaged and should also have benefit of key worker input.

- Refer patients with malignancy of undefined primary origin to the CUP team immediately.
- A member of the CUP team should see inpatients with malignancy of undefined primary origin by the end of the next working day after referral. Outpatients should be seen within 2 weeks. The CUP team should take responsibility for ensuring that a management plan exists which includes:
  - appropriate investigations
  - provision of information
  - symptom control
  - access to psychological support.
- The CUP team should actively review the outcome of all investigations with the nominated pathologist and radiologist as appropriate.

- A specialist network CUP MDT should be set up at regional level to review the treatment and care of patients with confirmed CUP, or with complex diagnostic or treatment issues. This team should carry out established specialist MDT responsibilities.
- The CUP team should be involved in the patient's care until the patient is:
  - referred to a site-specialist consultant **or**
  - referred for palliative care alone **or**
  - diagnosed with a non-malignant condition.

  If CUP is confirmed, the CUP team should continue managing the patient's care.
- Trusts should ensure that a system for tracking patients with malignancy of undefined primary origin is established and maintained.
- Every trust undertaking diagnostic investigations of patients with malignancy of undefined primary origin should ensure that services are set up for rapid and appropriate investigation of patients according to this guideline, and staff are appropriately trained.

Qualifying statement: There is evidence that specialist referral improves care for cancer patients. The GDG also considered recent reports and took evidence from experts, it concluded that patients with malignancy of undefined primary origin would benefit from early intervention and active tracking to ensure timely care in line with standard practice for site specific cancers.

There is evidence that site specific MDTs improve outcomes and cancer patient satisfaction with their care. The GDG also took evidence from experts who demonstrated reduced length of stay in hospital for patients with malignancy of undefined primary origin whose care was influenced by a CUP team.

Clinical evidence

There was no direct evidence about the early referral of people with malignancy of undefined primary origin to specialist oncologists. Evidence supports specialist cancer care in general, however (Grilli; Gruen) and it is reasonable to assume that early referral to a specialist could mean earlier initiation of therapy and the avoidance of inappropriate tests or treatment.

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.

The NHS Institute for Innovation and Improvement (NHSIII, 2009) published a report 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 NICE Improving Outcomes series of cancer service guidance consistently recommends that people with cancer should have a named key worker. There is relatively little evidence from randomised trials, however, about their effectiveness.

Two randomised trials investigated 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. A randomised trial of palliative care coordinators found they had little

effect on the severity of symptoms of terminally ill patients with cancer when compared with usual care (Addington-Hall et al, 1992).

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

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Organisation of CUP services at network and national level

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 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 patients.

> *"During my investigations (before I was diagnosed with cancer following an exploratory laparotomy), I became aware that some MDTs are very dependent on their meetings, with not a lot of communication happening in between meetings and limited or no cross-talk between MDTs when the picture was confusing"*

Patients with malignancy of undefined primary origin and confirmed CUP are not currently "owned" by a specific MDT, and hence their management and support is fragmented and poorly coordinated. Organisation of data collection, trial entry, patient experience data and assessment of outcomes are similarly lacking. Some patients are discussed at varying points in their diagnostic course at disease specific MDTs, but the lack of defined policies and pathways result in poor outcomes

Formal application of an MDT approach to patients with malignancy of undefined primary origin early in their clinical course may be advantageous, but needs to take into account the very different clinical scenario faced by patients and clinicians in the rapidly moving early diagnostic phase. Formal multidisciplinary review of individual cases should not delay this phase, nor should there be a requirement for too frequent re-discussion in MDT meetings. Development of a structure incorporating the best features of conventional MDT working, at critical points in the management of a patient with CUP, offers the best way to provide the maximum benefit and efficiency.

High-level organisation of services, in the form of guidelines for the referral of suspected cancer (NICE 2005), Network site-specific groups, peer review processes, and national research programmes have all contributed to increased quality of care and clinical outcomes for patients with cancer from a recognised primary site. Extension of these administrative structures and resources to patients with malignancy of undefined primary origin or CUP is a logical extension of existing policies.

Recommendations

- Every cancer network should establish a network site specific group responsible for managing all stages of CUP. The group should:
  - advise the cancer network on all matters related to CUP, recognising that many healthcare professionals have limited experience of CUP
  - ensure that the local care pathway for diagnosing and managing CUP is in line with this guideline
  - ensure that every CUP team in the network is properly constituted (see recommendation on p. 32, line 3)
  - ensure that patients have appropriate points of contact with the CUP team, because they present through a variety of routes
  - maintain a network-wide audit of the incidence of CUP, its timely management and patient outcomes
  - arrange and hold regular meetings to report patient outcomes and review the local care pathway.
- Data definitions should be further developed to allow capture of malignancy of undefined primary origin and CUP as distinct clinical entities. CUP should have the same information gathering and analysis systems at local and national level as for site-specific tumours.

Qualifying statement: The GDG considered expert advice and agreed that services for CUP patients should be organised along similar lines to those site-specific cancers with cancer network site specific groups. Significant deficiencies in epidemiological data, and the almost complete absence of organised research for CUP patients was noted.

Clinical evidence

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 (Stephens et al 2005, 2006) observed large improvements in overall survival associated with MDT management, but the weight of evidence suggests a more modest beneficial effect (Coory et al, 2008; Morris et al 2006, 2008).

Evidence from two patient questionnaire studies suggests that patients managed by MDT report greater satisfaction than those managed elsewhere (Coory et al 2008; Gabel et al, 1997)

There was some evidence that the time from diagnosis to treatment was shorter (of the order of a couple of weeks) when patients were managed by an MDT (Coory et al 2008; Gabel et al, 1997) although none of the studies directly addressed the diagnostic process.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Research recommendation

- A clinical studies group should be established at National Cancer Research Network (NCRN) level for CUP, to coordinate and direct a broad portfolio of research examining basic science, clinical studies, organisational processes and patient-centred topics.

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3 Diagnosis

Introduction

Patients are frustrated by having one test, waiting for the result and the subsequent decision to do a further test, the usefulness of which may be questionable. Are there strategies that would reach the same conclusion in a timely, efficient and cost effective manner? Can clinicians be guided in their thinking by algorithms? Which tests are essential, and which are only appropriate in certain circumstances?

> *"Since the tests that have been run fail to turn up a location, and since I haven't presented any symptoms that would indicate the presence of cancer elsewhere, they have just chalked it up to a mystery. For me that is probably the scariest part. The image that often comes to mind is a time bomb ticking away somewhere. You know that a bomb may exist but you don't know if it really does nor do you know where it is and when it will go off"*

Patients with carcinoma of unknown primary (CUP) are usually diagnosed by the detection of metastatic malignancy (in the form of tumour masses or effusions) on clinical examination or by imaging, without an obvious primary site.

The process for investigating patients with malignancy of undefined primary origin is complex and variable. The nature and extent of initial investigations are influenced by the experience of the responsible clinician, the nature of the presentation, the clinical state of the patient and the availability of facilities for special tests. The aim is to identify a primary site (if possible), and to define the histological type of tumour, since these are the main factors influencing treatment and outcome.

> *" We were told the implications of not finding the primary site. In fact we were not even told that she was actually only receiving palliative treatment through her cancer journey"*

The diagnostic process can be divided into two phases. The initial diagnostic screen will often define a primary site, and/or a specific histological type of tumour, allowing definitive treatment to be planned. At the completion of a broad screen of initial investigations, several clinicopathologic groups can be identified, predominantly subdivided according to the pathologic diagnosis:

- Lymphoma and other haematologic malignancies
- Metastatic thyroid cancer
- Metastatic melanoma
- Sarcoma
- Metastatic germ-cell tumour
- Metastatic epithelial or neuro-endocrine malignancy, primary revealed during screening investigations
- Metastatic epithelial or neuro-endocrine malignancy, no primary revealed during screening investigations

Specific management can be employed for the first six entities on this list. Management of the final group, which comprises the CUP spectrum, initially depends on the appropriateness of further investigation. Prior to any further tests, this group can be termed "provisional carcinoma of unknown primary (provisional CUP) and defined as follows:

- Provisional carcinoma of unknown primary
  Metastatic epithelial or neuro-endocrine malignancy identified on the basis of histology, with no primary detected despite a selected initial screen of investigations, prior to specialist review and possible further specialised investigations.

A second phase of more specific investigations is appropriate for some patients. After all relevant tests have been completed and a primary site has not been identified, a diagnosis of confirmed carcinoma of unknown primary (confirmed CUP) can be made. This is defined as follows:

- Confirmed carcinoma of unknown primary
  Metastatic epithelial or neuro-endocrine malignancy identified on the basis of definitive histology, with no primary detected despite a selected screen of investigations, specialist review, and further specialised tests as appropriate.

In current clinical practice, the basic tests required in the initial diagnostic phase are not universally agreed, and subsequent investigations are not evidence-based. Accordingly, there is currently no consensus on the optimal strategy for rapidly achieving a detailed diagnosis. Uncertainty exists about the usefulness of some investigations performed in some patients, and not in others, for example serum tumour marker levels, mammography and positron emission tomography combined with computed tomography (PET-CT).

The approach used to improve the efficiency and precision of the diagnostic phase (within the limits posed by variation between individual patient presentations) is:

1) to define a core of initial tests usually undertaken in the majority of patients (for whom investigation is clinically relevant)
2) to examine the best approaches in difficult diagnostic circumstances
3) to examine the contribution of specialised tests
4) to define optimal histological assessment of tissue samples.

Initial diagnostic phase

" What are all these tests I need? What do I tell family/work"

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 CUP has emphasised the importance of avoiding certain tests which were perceived as invasive, or low-yield (for instance endoscopy or barium studies). However, the advent of more modern approaches to diagnosis (for example. same-day upper- and lower-GI endoscopy), and the wider availability of complex yet high-yield tests (for example CT scanning) has altered this perception. These developments, together with the importance of identifying 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 requires continual updating.

An optimal strategy would maximise the number of diagnoses made for which specific valuable interventions could be offered, identify as many primary tumours as possible and be rapidly and easily applied. It would also minimise the risk of over-investigation in patients for whom exhaustive testing is unlikely to improve outcome.

Recommendation

- Offer the following investigations to patients with malignancy of undefined primary origin, if appropriate:
  - comprehensive history and physical examination including breast, nodal areas, genital, rectal and pelvic examination
  - full blood count; urea, electrolyte and creatinine; liver function; calcium; urinalysis; lactate dehydrogenase
  - chest X-ray
  - immunoglobulin levels (where there are isolated or multiple lytic bone lesions)
  - symptom-directed endoscopy
  - computed tomography (CT) scan of the chest or abdomen or pelvis
  - prostate-specific antigen (PSA) in men
  - cancer antigen (CA) 125 in women with peritoneal malignancy or ascites
  - alpha-fetoprotein (AFP) and human chorionic gonadotrophin (HCG) (particularly in the presence of midline nodal disease)
  - biopsy and standard histological examination to distinguish carcinoma from other malignant diagnoses.

Qualifying statement: The GDG noted the recent reviews of diagnostic strategies in malignancy of undefined primary origin. It noted the importance of stressing the basic requirements to carry out a full history and examination as a precursor to more invasive investigations. The GDG reached a consensus that beyond the basic tests the process should be guided by the CUP team.

Clinical evidence

Sixteen studies proposed panels of diagnostic tests for routine use people with malignancy of undefined primary origin, but without supporting evidence. There was consensus that the basic panel of tests should include: history and 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

Eight observational studies reported the diagnostic yield of tests in patients with malignancy of undefined primary origin. Five included only patients presenting with bone metastases (Alcalay et al, 1995; Jacobsen et al, 1997; Katigiri et al, 1999; Rougraff et al, 1993 and Simon et al 1986) and three included any malignancy of undefined primary origin (Kirsten et al 1987; Le Chevalier et al 1988 and Losa Gaspa 2002). Of the 556 primary tumours identified in the eight studies, 424 (76%) were identified by initial tests. The proportion of patients who had a primary tumour identified by initial tests 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 malignancy of undefined primary origin. 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%).

Although none of the studies reported a comparison of an expert diagnostic strategy with arbitrary diagnostic test order, the evidence suggests that in patients with malignancy of undefined primary origin a restricted panel of basic tests can identify most primary tumours. 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.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Special tests

> *"…as a difficult to diagnose patient it was really easy to start feeling that I was a 'problem' when I was being moved around between MDTs. This was hard to balance against the desperation I felt being 'stuck' in a system when I just wanted to know what was wrong with me and whether I could be treated"*

Patients can be subjected to multiple investigations in the hope of identifying the primary origin of the carcinoma. Often these take place as an in-patient and can result in a protracted stay in hospital. Other tests are relatively simple but the yield and resultant change in management is not clear.

An investigation that was highly accurate in identifying the primary might result in shorter hospital stays and quicker access to treatment. Similarly if unnecessary tests are performed there is inevitable delay and resultant frustration.

Tumour markers

Identification of elevated serum tumour marker levels can sometimes facilitate diagnosis of certain treatable cancers and their timely measurement in some circumstances can be associated with significant clinical gain.

In general however, tumour marker measurements are not 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. However inappropriately requested tumour marker results can lead to unnecessary and costly further investigations and incorrect management as well as causing needless distress and worry to patients.

Clarifying which tumour markers should be measured and awareness of their significant limitations are critical to their use in the diagnosis and management of patients with CUP.

Recommendation

- Only measure tumour markers during diagnosis in the following circumstances:
  - AFP and HCG in patients with presentations compatible with germ-cell tumours (particularly those with mediastinal and/or retroperitoneal presentations).
  - AFP in patients with presentations compatible with hepatocellular cancer.
  - PSA in men with presentations compatible with prostate cancer.
  - CA125 in women with presentations compatible with ovarian cancer (including those with inguinal node, chest, pleural, peritoneal or retroperitoneal presentations). Carefully interpret the results because of limited test specificity.

Qualifying statement: Evidence to support recommendations on measurement of serum tumour markers for patients with malignancy of undefined primary origin is sparse and of low quality. These recommendations therefore rely on additional evidence of the diagnostic utility of these markers in patients who do not have malignancy of undefined primary origin.

Clinical evidence

There was very little evidence about the use of serum tumour markers in the diagnosis of primary tumours in patients with malignancy of undefined primary origin: only nine case series were included.

Evidence suggests that elevated levels of the serum tumour markers AFP and PSA (Losa Gaspa et al, 2002; Destombe et al 2007; Tsukushi et al 2006) have reasonably high specificity for metastatic liver/germ-cell and prostate tumours respectively.

One small study (Losa Gaspa et al, 2002) found 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 (Losa Gaspa et al, 2002; Tsukushi et al, 2006; Koch & McPherson, 1981; De Wit et al, 1991) and CA 19-9 had low specificity for the primary tumour site in patients with metastatic cancer, suggesting they would not be useful in diagnosing primary tumour site.

Losa Gaspa et al (2002) reported elevated serum CA-125 in all ten women with metastatic ovarian cancer in their prospective series. The low specificity of elevated serum CA-125 in this study, however, suggests it would not be useful in diagnosing ovarian cancer.

Research recommendation

- Further prospective research is required into the efficacy (including effect on time to diagnosis and cost effectiveness) of measuring AFP, hCG, PSA and CA125 in patients with malignancy of undefined primary origin.

Upper and lower gastrointestinal (GI) endoscopy

Upper and lower gastrointestinal (GI) endoscopy are recognised procedures to confirm or exclude GI malignancy in malignancy of undefined primary origin when symptoms suggest a GI primary. Upper GI endoscopy is a single defined procedure to examine oesophagus, stomach and duodenum; all being potential sites for the primary tumour. Lower GI endoscopy covers three different procedures; rigid sigmoidoscopy, flexible sigmoidoscopy and full colonoscopy, which examine increasing areas of the colon from distal to proximal.

The identification of a primary site in the GI tract could lead to the use of specific systemic therapy or occasionally potentially curative surgery (for example in colon cancer with isolated liver metastases) and hence potentially improving outcomes.

Recommendation

- Do not carry out upper or lower GI endoscopy in patients with malignancy of undefined primary origin unless the symptoms, histology or radiology suggest a GI primary tumour.

Qualifying statement: No directly relevant studies were found to support the routine use of upper and lower GI endoscopy in asymptomatic patients. A consensus was reached to recommend such procedures only if there were symptoms suggestive of a GI primary.

Clinical evidence

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

Four small studies reported the diagnostic yield of gastrointestinal endoscopy in patients with CUP, but without specifying histology or presentation (Katagiri et al 1999 ; Kirsten et al 1987: Schapira et al 1995; Yamada et al, 1975). 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 (Froehlich et al, 1999) 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.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Mammography

Breast cancer may present as malignancy of undefined primary origin. In some circumstances, for instance presentations with axillary adenopathy, there is such a high likelihood that a breast primary is present that investigation specifically to identify this is warranted.

In the majority of patients however there is uncertainty whether the diagnostic yield from a relatively complex and potentially uncomfortable test such as mammography is sufficiently high to justify its use in all cases. The application of this test to selected groups, based on clinical and pathological features, may be more appropriate.

Recommendation

- Do not offer mammography routinely to women presenting with malignancy of undefined primary origin, unless clinical or pathological features are compatible with breast cancer.

Qualifying statement: The GDG recognised that mammography is readily accessible, acceptable and relatively cheap. However the evidence from retrospective and prospective studies showed little impact, when widely applied, on increased identification of breast cancer and furthermore no change in action.

Clinical evidence

The quality of the included studies was low. They were almost all retrospective series, not designed to evaluate mammography and 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.

There was inconsistent evidence about the usefulness of mammography for as a routine test for women with malignancy of undefined primary origin, without a palpable breast mass. In three studies the diagnostic yield in this population was zero (Kirsten et al 1987; Leonard et al 1993 and Stevens et al 1999). In two other studies it ranged from 6% (Le Chevalier et al 1988) to 14% (Losa Gaspa et al 2002). 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% (Galimberti et al 2004, Knapper et al 1991, Merson et al 1992 and Pananero et al 2006). 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 in patients presenting with malignancy of undefined primary origin.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Research recommendation

- Further prospective studies are required to evaluate the diagnostic yield, impact on management and cost-effectivness of mammography in patients with malignancy of undefined primary origin.

Breast magnetic resonance imaging (MRI)

In women presenting with isolated axillary adenopathy with adenocarcinoma at biopsy, the most likely diagnosis is metastases from primary breast carcinoma. Initial investigations, including specialist breast examination, mammography and ultrasound, will identify the primary breast tumour in the majority of cases. However, in a proportion of patients, these investigations will not identify a primary tumour. Surgical series show that approximately 2/3 of these patients will have an occult primary tumour identified on histopathological analysis of mastectomy specimens. With appropriate treatment, the prognosis of these patients is equivalent to, or better than, (other) patients with stage II breast cancer.

If a primary tumour can be identified in the breast, then appropriate patients can be offered breast conserving surgery rather than mastectomy, with potentially equivalent mortality, but reduced morbidity. Dynamic contrast enhanced magnetic resonance imaging (MRI) has been shown to have a high sensitivity (but low specificity) for detection of primary breast cancer.

Recommendation

- Refer patients with adenocarcinoma involving the axillary nodes to a breast MDT for evaluation and treatment. If no breast primary tumour is identified after standard investigations, consider dynamic contrast-enhanced breast MRI to identify breast lesions suitable for targeted biopsy.

Qualifying statement: The GDG noted the high prevalence of primary breast cancer in patients presenting with axillary nodes, however there was little evidence to demonstrate that there was any change in outcomes following MRI, though it may alter management. The GDG reached a consensus that these patients should be managed within a breast MDT and MRI considered as per local guidelines dependent on availability.

Clinical evidence

All the included 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. 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. Pooling the two

studies 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 studies, breast MRI has a positive likelihood ratio of 1.57 and a negative likelihood ratio of 0.22 for breast primary tumours.

Evidence from four case series suggests MRI influences treatment decisions. Evaluation of the extent of disease on breast MRI has been used to plan breast surgery (Buchanan et al 2005; Ko et al 2007 and McMahon et al 2005) and select candidates for adjuvant therapy (Henry-Tillman, 1999; Ko et al, 2007).

There was a lack of evidence comparing outcomes in patients who had breast MRI with those who did not have breast MRI.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Research recommendation

- Further research should be carried out to investigate the value of breast MRI in locating primary breast cancers in women presenting with axillary adenopathy together with other sites of metastases, or in other patients with manifestations of CUP suspected of being of breast origin.

Positron emission tomography – computed tomography (PET-CT)

18FDG-PET-CT is a hybrid imaging modality which 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 provisional CUP is different from that in patients with an identified primary. In provisional CUP the purpose is still to identify occult disease, but with the aim of identifying a primary tumour undetected by all previous tests. Identification of an occult primary is presumed to result in improved treatment outcomes as compared with empirical therapy for confirmed CUP. It is desirable to establish the nature and magnitude of any benefits of PET-CT in provisional CUP, which would be expected to vary according to clinical subtypes.

Recommendations

- Offer 18-FDG-PET-CT to patients with provisional CUP presenting with cervical lymphadenopathy with no primary tumour identified on panendoscopy if radical treatment is considered to be an option.
- Consider 18-FDG-PET-CT in patients with provisional CUP with extra-cervical presentations after discussion with the CUP team or specialist network CUP MDT.

Qualifying statement: The GDG recognised the developing evidence base for using 18-FDG-PET-CT in CUP diagnosis. There was some evidence of change of management though none of improvement in outcomes. The GDG consensus was that there was already an established practice for patients with cervical lymphadenopathy who had the potential for curative treatment. In other patients careful consideration needs to be given as to whether 1-8FDG-PET-CT will alter management.

Clinical evidence

The quality of the evidence was moderate to 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 (35 studies) or PET-CT (12 studies). There were no studies designed to study the effect of a PET scan on a patient's survival.

The pooled data suggest relatively high sensitivity and specificity (of the order of 80% for PET and 85% for PET-CT) for the detection of the primary tumour in patients with provisonal CUP. The results of the individual studies, however, were significantly heterogeneous. Two recent systematic reviews considered PET-CT for the identification of unknown primary tumours, and reached similar conclusions. Kwee and Kwee (2009) reported pooled sensitivity and specificity of PET-CT as 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 meta-analysis identified significant heterogeneity. The estimated tumour detection rate for PET-CT was 37% in Kwee and Kwee (2009) and 31% in Dong et al (2008).

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%].

Eighteen studies reported the rate at which PET or PET-CT revealed previously unknown metastases. Previously occult metastases were revealed by PET or PET-CT in approximately 28% of cases. Twenty studies reported the proportion of patients whose management was changed as a result of PET or PET-CT findings. 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).

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Research recommendations

- Further research is needed to determine whether the identification of a primary tumour site with PET-CT modifies treatment and improves patient survival and quality of life.
- Further research is needed to determine whether the use of PET-CT early in the CUP management pathway reduces the number of investigations that the patient is subjected to.

Immunohistochemistry

Basic haematoxylin and eosin staining (H+E) can lead to a firm histological diagnosis in many instances. However in patients with a biopsy showing a malignancy of unknown origin a simple panel of immunohistochemistry tests is essential to exclude melanoma, lymphoma or sarcoma. Once a diagnosis of carcinoma is established the H+E stain may not be sufficient to determine its origin. Immunohistochemical analysis of the expression of cytokeratin 20 (CK20) and cytokeratin 7 (CK7) can result in greater certainty about the likely tissue of origin and the use of these antibodies has been validated in patients in whom the primary site of malignancy was identified. In addition the antibody thyroid transcription factor 1 (TTF-1) is commonly used to confirm or exclude a bronchial carcinoma. Placental alkaline phosphatase (PLAP) is a useful marker for germ-cell tumours, some of which have the appearance of an adenocarcinoma. Antibodies to oestrogen receptors (ER) are often used as an adjunct to the diagnosis of metastatic breast carcinoma, especially when used in conjunction with CK20 and CK7. Antibodies to prostate-specific antigen (PSA) are useful in the diagnosis of metastatic prostatic adenocarcinoma. There are many other antibodies, which may be of value in certain circumstances to further define the diagnosis.

Recommendations

- Use a panel of antibodies comprising CK7, CK20, TTF-1, PLAP, ER (women only) and PSA (men only) in all patients with adenocarcinoma of unknown origin.
- Use additional immunohistochemistry to refine the differential diagnosis, guided by the results of the panel of antibodies in the previous recommendation and the clinical picture.

Qualifying statement: The GDG was presented with good evidence from retrospective reviews on the use of a basic set of histological markers such that an algorithm could be recommended to aid the identification of tumour origin.

Clinical evidence

There was consistent evidence, from 32 retrospective reviews of primary or metastatic tumour samples, to support the use of CK7, CK20, TTF-1, ER and PSA in narrowing the differential diagnosis of metastatic adenocarcinoma. Data were sparse for certain primary tumour types (for example salivary gland and oesophagus) and there was potential for bias because samples were selected retrospectively on the basis of their histology and primary site.

Data from the individual studies were pooled, for each tumour site, to estimate proportions of tumours positive for the tumour markers CK7, CK20, TTF-1, ER, PR, PSA and combinations of CK7/CK20 (see evidence review). The positive predictive values of each marker for each tumour site were also calculated.

Two markers were highly specific: TTF1 had a positive predictive value of 91% or greater for lung cancer in nine of the ten studies that considered it (Dennis et al 2005; Drlicek et al 2004; Hecht et al 2001; Jang et al 2001; Ng et al, 2002; Park et al 2007; Roh et al 2002; Saad et al, 2004; Srodon et al, 2002; Strickland-Marmol et al, 2007). PSA had a positive predictive value ranging from 86% to 100% for prostate cancer (Dennis et al 2005; Giordana et al 2000; Torenbeek et al 1998).

The combination of CK20+/CK7- had a positive predictive value of ranging from 83% to 93% for colon primary tumour (Azoulay et al, 2005; Chu et al, 2002; Drlicek et al, 2004; Jang et al, 2001; Kendle et al, 2003; Tot et al, 2002; Vang et al, 2006).

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Research recommendation

- Further research should be carried out to identify further antibodies that have good sensitivity and specificity for different types of adenocarcinoma.

Gene-expression-based profiling

Different tissues (for example. breast, lung, prostate) display different patterns of gene expression, with greater or lesser expression of some genes in one tissue compared to another. The individual pattern of expression of a panel of genes can be regarded as a “signature” for that tissue. Tumours (for example breast cancer, lung cancer, prostate cancer) tend to share the same signature (or gene-expression based profile) as their tissue of origin.

Treatment of cancer is to a large extent governed by knowledge of the organ or tissue from which the tumour arises. In general, this classification is more important in determining choice of treatment than the morphological appearance of a tumour.

Morphological classification of CUP, (with additional immunohistochemical analysis), provides some guidance about the nature of a tumour, and allows informed speculation about the tissue of origin, but by definition, a crucial determinant of optimal therapy (identification of a definite primary site) is lacking in confirmed CUP. The possible role of GEBP in providing additional useful information about a putative tissue of origin, or in assisting identification of a previously undetected primary has been examined in CUP.

Recommendations

- Do not use gene-expression-based profiling to identify primary tumours in patients with provisional CUP.

Qualifying statement: The GDG noted that this is a rapidly changing field, having noted the limited evidence at the present time and taken expert advice. Currently there is no evidence that gene-expression based profiling improves the management or changes the outcomes for patients with CUP.

Clinical evidence

Literature searches identified five gene profiling tests designed to identify the primary tumour tissue of origin in patients with CUP. CupPrint and Pathwork Tissue of Origin use oligonucleotide microarrays measuring hundreds of genes. The others, GeneSearch, Theros CancerType ID and miRview Mets are real time RT-PCR assays, measuring between 10 and 92 genes.

The classification accuracy of these tests exceeded 80%, in validation samples of tumours of known primary (Dumur et al, 2008; Horlings et al, 2008; Li et al 2006; Ma et al, 2006; Rosenfeld et al, 2008; Talantov et al, 2006). There were no studies directly comparing the diagnostic performance of these tests.

Two of the tests, CupPrint and GeneSearch, have been used in patients with provisional CUP or confirmed CUP (Talantov et al, 2006; Varadhachary et al, 2008; Horlings et al 2008; Bridgewater et al 2006; Huebner et al 2007). In these patients the molecular diagnostic tests produced a putative tissue of origin in most cases, but the lack of a primary tumour prevents the verification of these diagnoses. The number of unclassifiable cases ranged from 11% to 48%, often due to poor quality RNA from tissue samples.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Research recommendation

- The contribution of gene-expression based profiling to improving conventional diagnostic strategies should be investigated.

Investigation of specific clinical presentations

Intrapulmonary nodules without evidence of endobronchial disease

The lung is a common site for metastatic malignancy. The pattern of disease may be helpful in directing attention to candidate primary sites but in the absence of an identified primary it is logical to consider obtaining tissue from the parenchymal lung deposits. Bronchoscopy is the investigation of first choice where there is clinical evidence also of endobronchial or central nodal disease, but the value of bronchoscopy is less clear where intra-pulmonary nodules are the only apparent abnormality.

Recommendations

- Offer flexible bronchoscopy with biopsy, brushings and washings to patients presenting with intrapulmonary nodules of probable metastatic origin that are unsuitable for percutaneous biopsy, even in the absence of endobronchial or central nodal disease on imaging.
- Offer video-assisted thoracoscopic surgery (VATS) exploration to patients only after a negative bronchoscopic procedure and where percutaneous biopsy is considered inappropriate.

Qualifying statement: Both bronchoscopy and VATS may achieve a useful diagnostic yield but there was no evidence for superiority for one investigation over the other, and VATS was associated with greater morbidity. A GDG consensus was reached to recommend VATS only after negative bronchoscopy and in patients unsuitable for percutaneous biopsy.

Clinical evidence

Evidence came from retrospective case series 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 visible on chest X-ray (Argyros et al, 1994; Diaz et al, 2003; Poe et al, 1985). 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.

Lin et al (1999) performed video-assisted thoracic surgery (VATS) for diagnosis of pulmonary metastases in 78 patients when percutaneous needle biopsy was unfeasible or unsuccessful. They reported that VATS resection obtained adequate tissue for diagnosis in all cases.

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 reviews of observational studies suggests that both procedures carry a risk of complications. For example the reported rates of perioperative mortality were between 1 and 2% for VATS (Imperatori et al, 2009) compared with 0.1 to 0.2% for bronchoscopy (Geraci et al, 2007).

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Investigation of malignant peritoneal disease

Ascites is a common manifestation of CUP 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 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.

Recommendation

- Obtain a tissue sample for histological examination in patients with malignancy of undefined primary origin who present with ascites, if technically possible.

Qualifying statement: Evidence to support recommendations for patients with CUP who present with ascites is sparse and of low quality, being mostly from small, retrospective single institutional studies spread over 20 years. Therefore these recommendations are based on the quoted safety of percutaneous and laparoscopic biopsy; the fact that FNA has a lower tumour yield, requiring further tissue sampling; and that biopsy of tumour tissue as opposed to cytology of fluid alone is more likely to yield pathological information which will guide treatment.

Clinical evidence

Evidence came from observational studies of patients with malignant ascites or peritoneal carcinomatosis of unknown origin. None of the studies compared cytology and histology in the same group of patients, with consistent use of a reference standard diagnostic test. The diagnostic rate of cytomorphology plus immunocytochemistry, for primary tumour tissue of origin, ranged from 57% and 87% (Longato-Filho et al, 1997; Mottolese et al 1988, 1992; Pomjanski et al 2005). In comparison, histopathology plus immunohistochemistry had a diagnostic rate between 93% and 97% (Hewitt et al 2007; Spencer et al 2001).

There were no data about complications of cytology. Percutaneous core biopsy was associated with minor local bruising and discomfort in one study (Hewitt et al, 2006). There was no useful data about the influence of either procedure on the overall duration of diagnostic process.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Research recommendation

- Further research is required to determine the relative sensitivities of fine needle cytology and core biopsy in patients with malignancy of undefined primary origin presenting with ascites.

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4 Factors influencing management decisions

Introduction

Patients with carcinoma of unknown primary (CUP) face many dilemmas. They have to live with the uncertainty of not knowing where the cancer originated, despite what may have been an exhaustive series of investigations, the utility of which may be open to criticism. Patients may not understand the limitations of anti-cancer treatment and may feel abandoned when told there is no further treatment. They often find a lack of information, guidance and support which heightens their feelings of abandonment.

The uncertainty which surrounds almost all aspects of care for malignancy of undefined primary origin or CUP patients is most clearly seen when decisions are being made about investigation and treatment. The diagnostic process has no well-defined end point in those patients in whom a primary is never found. The selection of treatment modality (ranging from symptomatic care alone through to protracted intensive chemotherapy) will, in the best circumstances, be made through an informed dialogue between patient and doctor, but these decisions are hampered by the heterogeneity of CUP, the lack of established pathways of care and limited information about outcomes.

The approach used to improve the decision-making process for investigation and treatment is:

1) to examine ways to limit the investigation pathway when further benefits will not emerge from protracted testing
2) to examine methods for selecting optimal treatment.

When to stop investigations

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 may conflict with 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.

> *"…I know when one surgeon told me that there was nothing that could be done for me in his view and just said he 'admired my spirt' when I said that I would undergo any trial treatment and then told me to try not to be angry over the next few weeks, I went through feelings that I can't possibly describe"*

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.

Recommendations

- Do not offer further investigations to identify the primary site of origin of the malignancy to patients who are unfit for treatment.
- Perform investigations only if:
  - the results are likely to affect a treatment decision
  - the patient understands why the investigations are being carried out
  - the patient understands the potential benefits and risks of investigation and treatment **and**
  - the patient is prepared to accept treatment.
- Explain to patients and carers if further investigations will not alter treatment options. Provide appropriate emotional and psychological support.
- Provide information about CUP, treatment options and palliative care to patients and carers.

Qualifying statement: The GDG found a lack of evidence to confidently place limits on the extent of investigations but gained much useful information from the experience of the patient and carer members of the group. There was strong GDG consensus that better support and clearer information would be more likely to address patients concerns and anxieties than further investigations that would not affect treatment decisions.

Clinical evidence

There is evidence, from observational studies, that people with CUP sometimes receive excessive diagnostic evaluation (for example Shaw et al, 2007) but very few studies reported the psychological effect of diagnosis of the primary tumour in people with CUP. No studies directly compared minimal versus exhaustive diagnostic evaluation in terms of patients' quality of life.

The best evidence came from a qualitative study of a group of ten people with provisional CUP or confirmed CUP (Boyland and Davis, 2008). Using patient interviews and questionnaires, Boyland and Davis (2008) identified several important themes in the patients' experience of CUP. There was evidence that people with carcinoma of unknown primary experience uncertainty and distress. Patients had to deal with the uncertainty about the origin of their disease, its future course and the benefit of treatment. Some patients felt that they were missing the chance of targeted therapy if their primary is not found. One patient, with a suspected ovarian primary tumour, found some benefit in having at least a probable diagnosis.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Selecting optimal treatment

Optimal treatment

For all cancer patients, decisions to introduce treatments are based on the balance of burdens (toxicity, inconvenience) and benefits (relief of symptoms, increased of survival). The same principle applies to patients with CUP, although the more limited efficacy of treatment means that the greatest care should be taken in weighing the factors in these patients. In patients with CUP, accurate prognostic predictors are potentially of value in clinical decision making, allowing optimal treatment to be used in those most likely to gain the greatest benefit, whilst avoiding the unnecessary toxicity of futile anti-cancer 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 involvement, performance status and co-morbidity. Tumour-specific factors

(for example chemosensitivity, tumour burden and specific organ involvement) influence the likelihood of a satisfactory outcome of treatment. In many instances the factors referred to are unknown, or difficult to quantify. Consideration of these prognostic factors needs to influence decisions about the appropriateness, extent and duration of investigation as well as choice of subsequent management.

> *"We most definitely would have approached her treatment in a very different way had we been made aware of the facts as they were at the time"*

Recommendations

- Take account of prognostic factors, in particular performance status, presence of liver metastases, lactate dehydrogenase levels and serum albumin, when making decisions about further diagnostic investigations and treatment.
- Discuss the patient's prognostic factors with the patient and their carer, if appropriate, to help them make informed decisions about treatment.
- Include prognostic factors in decision aids and other information for patients and carers about their treatment options.

Qualifying statement: The GDG were presented with good evidence from retrospective studies that prognostic factors can be used to guide treatment decisions. Further information from the National Confidential Enquiry into Patient Outcome and Death report(NCEPOD, 2008) strengthens the recommendation that performance status needs to guide discussions with patients about possible treatment options.

Clinical evidence

Meta-analysis of univariate overall survival analyses in 50 case series and clinical trials in patients with CUP suggested several adverse prognostic factors. Adverse factors prognostic included: poor performance status (HR = 2.00; 95% C.I. 1.69 to 2.33), elevated serum LDH (HR = 1.64; 95% C.I. 1.41 to 1.92), liver metastases (HR =1.51; 95% C.I. 1.36 to 1.67), metastases not confined to lymph nodes (HR=1.43; 95% C.I. 1.23 to 1.64), more metastatic sites (HR = 1.33; 95% C.I. 1.20 to 1.47), adenocarcinoma histology (HR = 1.32; 95% C.I. 1.18 to 1.47), older age group (HR = 1.27; 95% C.I. 1.11 to 1.45), lung metastases (HR = 1.26; 95% C.I. 1.09 to 1.44) and male sex (HR = 1.23; 95% C.I. 1.10 to 1.37).

Eleven studies reported multivariate analysis of overall survival. The adverse prognostic factors that were statistically significant in the majority of these multivariate analyses were: poor performance status, liver metastases, low serum albumin and elevated LDH.

Six studies reported prognostic models (Culine et al 2002; Hess et al 1999; Ponce-Lorenzo et al 2007; Seve et al 2006; Trivanovic et al 2009; Van der Gaast et al 1995), which classify patients with CUP into risk groups according to their estimated time to death. There were statistically significant differences between the risk groups in terms of overall survival, but the clinical significance was unclear as there were no studies evaluating whether these models influence treatment decisions.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Research recommendation

- The value of prognostic factors in predicting response to treatment should be analysed in all future clinical trials of systemic treatments for patients with CUP.

Decision aids

For all patients with cancer decisions about whether to undergo extensive investigations or potentially toxic treatments with limited benefits are difficult. The generally poor outcomes seen in patients with CUP mean these decisions are even more troubling for this group. The proven benefit of decision aids in cancer where the primary is identified may usefully translate to patients with CUP.

Recommendation

- Develop decision aids to help patients and their carers make informed decisions about continuing investigations and using anticancer treatment after CUP has been diagnosed.

Qualifying statement: The GDG noted the high level evidence for using decision aids in site-specific cancers, however there was no evidence to support their use in CUP. The GDG consensus view, strongly supported by the patient and carer members, was that there was a need to develop such aids and to conduct research into their use.

Clinical evidence

Literature searches found no published studies of decision aids for people with cancer of unknown primary. There was good evidence, from systematic reviews of randomised trials (O'Brien et al 2009; O'Connor et al 2009) 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.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Research recommendation

- Decision aids should be developed and research carried out to evaluate their benefit.

Gene-expression-based profiling

> *"To me, CUP is no different from any other advanced metastatic cancer, except that we don't know where it started. Many of the dilemmas are the same and I know that when I run out of therapies, I will be facing the same situation as them again and I will have had some time to prepare for it. If diagnostics one day allow us to get away from finding the site and instead finding more about the tumour (receptors etc), then hopefully CUP patients will be able to access some life-extending drugs that are currently accessible to breast, kidney cancers etc"*

Different tissues (for example. breast, lung, prostate) display different patterns of gene expression, with greater or lesser expression of some genes in one tissue compared to another. The individual pattern of expression of a panel of genes can be regarded as a "signature" for that tissue. Tumours (for example breast cancer, lung cancer, prostate cancer) tend to share the same signature (or gene-expression based profile) as their tissue of origin.

Treatment of cancer is to a large extent governed by knowledge of the organ or tissue from which the tumour arises. In general, this classification is more important in determining choice of treatment than the morphological appearance of a tumour.

Gene-expression based profiling of confirmed CUP may identify a pattern which correlates strongly with a particular tissue of origin, and this information may be useful in selecting treatment

approaches with a higher success rate than treatment chosen based on conventional factors (tumour morphology, tumour distribution, tumour marker profiles).In addition, gene-expression based profiling might lead to additional specific investigations and subsequent detection of an otherwise unsuspected primary tumour. However, validation of this approach is required before treatment decisions in confirmed CUP can be reliably based on gene-expression based classification.

Recommendations

- Do not use gene-expression-based profiling when deciding which treatment to offer patients with confirmed CUP.

Qualifying statement: The GDG noted that this is a rapidly changing field, having noted the limited evidence at the present time and taken expert advice. Currently there is no evidence that gene-expression based profiling improves the management or changes the outcomes for patients with CUP.

Clinical evidence

Literature searches identified five gene profiling tests designed to identify the primary tumour tissue of origin in patients with CUP. CupPrint and Pathwork Tissue of Origin use oligonucleotide microarrays measuring hundreds of genes. The others, GeneSearch, Theros CancerType ID and miRview Mets are real time RT-PCR assays, measuring between 10 and 92 genes.

There was limited evidence about the impact of gene profiles on treatment outcomes. One observational study (Varadhachary et al, 2008) and several case reports (Bridgewater et al, 2006; Horlings et al, 2006; Tothill et al, 2005), suggested that gene profiling could allow more effective chemotherapy tailored to the primary tissue of origin.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Research recommendations

- Prospective randomised trials should be undertaken in patients with confirmed CUP to evaluate whether chemotherapy treatment guided by gene-expression based profiling is superior to treatment guided by conventional clinical and pathological factors.
- Comparative trials of gene-expression based profiling technologies should be undertaken to identify the most effective test in terms of reliability, sensitivity, specificity and cost-effectiveness.
- Studies of the use of gene-expression based profiling to define clinical subsets of malignant disease treated in different ways should include patients with confirmed CUP.

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5 Managing specific presentations

Introduction

Patients presenting with malignancy of undefined primary origin do not fit into the existing site-specific MDT structure. They often get passed from one MDT to another resulting in frustration, wasted time, prolonged stays in hospital and lack of ownership of the clinical problem. This inefficiency is compounded by the fact that some presentations, with isolated metastatic disease, have potentially more favourable outcomes if managed appropriately.

Presentations that may benefit from radical treatment

Squamous carcinoma involving upper- or mid-neck nodes

A small minority of CUP patients present with squamous carcinoma in upper- or mid-neck lymph nodes from a presumed but unidentified head and neck primary. Furthermore, the pattern of nodal involvement in these patients is very similar to that seen in patients with an identified head and neck primary. Experience suggests that these groups may benefit from localised treatment with potentially curative intent.

Radical neck dissection, with subsequent radiotherapy, is the most common treatment for this group of patients. However, the extent of surgery and radiotherapy delivered is variable and dependent upon the risk status of the patient (which is dependent upon the number and size of lymph nodes, tumour histology and extracapsular nodal spread). The benefit of surgery and radiotherapy over surgery alone is contentious. Radiotherapy may be to the ipsilateral neck only, or to a wider field including likely sites of the primary tumour within the pharynx and larynx. If the primary site can be accurately identified, by imaging or by endoscopy and biopsy, then radiotherapy can be appropriately targeted.

Recommendation

- Refer patients presenting with upper- or mid-neck squamous cell carcinoma and an unidentified primary tumour to a head and neck MDT for evaluation and treatment.

Qualifying statement: The GDG found little evidence on which to base its recommendation. However there was GDG consensus that standard practice does lead to a significant disease survival and that there is a need for further studies to determine the refinement of this approach within head and neck MDTs.

Clinical evidence

There was a lack of studies designed to evaluate post operative treatment in patients with squamous carcinoma in upper or mid neck lymph nodes and unknown primary. Evidence was limited to observational studies, with sparse data about patients treated with surgery alone. It is likely that the choice of adjuvant therapy was influenced by a patient and disease characteristics, so direct comparison between these observational studies is not appropriate.

Case series suggest that five year post-operative overall survival of between 22% and 60% in patients treated with adjuvant radiotherapy (Boscolo-Rizzo et al, 2007; Colletier et al, 1998; Davidson et al, 1994; Fernandez et al, 1998; Grau et al, 2000; Issing et al, 2003; Mistry et al, 2008; Patel et al, 2007; Strojan et al 1998)

In two small series of patients treated with surgery alone, five year overall survival ranged from 65% to 66% (Grau et al, 2000; Mistry et al 2008). Two studies of surgery plus chemoradiotherapy reported five year overall survival of 75% (Argiris et al, 2003) and 89% (Shehadeh et al, 2006).

Treatment related morbidity was common after radiotherapy and most patients experienced varying degrees of 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.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Research recommendation

- Prospective studies are needed to determine the best management of patients presenting with upper- and mid-neck squamous cell carcinoma with an unidentified primary tumour.

Adenocarcinoma involving the axillary nodes

More than 90% of female patients presenting with adenocarcinoma involving axillary nodes are considered to harbour an unidentified breast primary. In the remainder of female patients the primary site usually becomes obvious after a careful history and examination, without recourse to extensive untargeted investigation.

Recommendation

- Refer patients with adenocarcinoma involving the axillary nodes to a breast MDT for evaluation and treatment.

Qualifying statement: The GDG found little evidence to guide recommendations. There was GDG consensus that these patients are best managed within a breast MDT.

Clinical evidence

There was no direct evidence regarding the optimal management of patients presenting with adenocarcinoma involving axillary nodes and unknown primary tumour. The best available evidence came from a small number of retrospective case series studies (Ellerbroek et al 1990; Kemeny et al 1986; Knapper 1991;Jackson et al 1995; Medino-Franco et al 2002; Merson et al 1992; Rosen and Kimmel 1990; van Ooijen et al 1993; Varadarajan et al 2006; Whillis et al 1990). The survival outcomes reported in these studies suggest that patients with unknown primary adenocarcinoma involving axillary nodes could be managed in the same way as patients with stage II breast cancer.

The use of adjuvant treatment was not associated with a statistically significant improvement in survival or local control in three studies (Ellerbroek et al 1990, Knapper 1991, Merson et al 1992). The studies were not designed to evaluate adjuvant therapy, however, and were too small to allow conclusions about the use of adjuvant therapy in this patient group.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Squamous carcinoma involving the inguinal nodes

Metastatic carcinoma in inguinal lymph nodes most commonly represents spread from melanomas or squamous carcinomas arising in the skin of the leg or lower trunk, carcinomas of the external genitalia, anus, vagina, cervix, ovary and very rarely other pelvic viscera. This section is specifically concerned with the management of patients with squamous carcinomas, who have a relatively favourable prognosis. This is a very rare presentation of CUP and there is

sparse evidence on which to base recommendations for clinical management. However, studies on groups of patients and individual patients indicate that an attempt at curative treatment can sometimes be successful, without identification of the primary. This can be explained by spontaneous regression of an occult primary cancer or by its eradication coincidentally by treatment directed against the metastatic disease. Sometimes the primary malignancy will become evident later and may then be treatable with curative intent. If the occult primary cancer is in the midline there is an increased chance that spread to inguinal lymph nodes will be bilateral, and that sooner or later bilateral treatment will be required.

Recommendations

- Refer patients with squamous carcinoma confined to the inguinal nodes to a specialist surgeon in an appropriate MDT, to consider treatment with curative intent.
- Offer patients with operable disease either:
  - superficial lymphadenectomy plus consideration of post-lymphadenectomy radiotherapy (for patients with risk factors for residual disease, for example multiple involved nodes or extrascapsular spread) **or**
  - simple excision of clinically involved nodes, followed by radiotherapy.

Qualifying statement: The GDG found little evidence to guide recommendations. There was GDG consensus that specialist surgery should be considered, along with possible post-operative adjuvant therapy, guided by a relevant MDT.

Clinical evidence

There was sparse evidence about treatment for people with metastatic squamous cell carcinoma of unknown primary who present with inguinal lymphadenopathy. Three observational studies, including 80 patients, reported outcomes in patients treated for inguinal lymphadenopathy of unknown primary (Guarishi et al, 1987; Wallack and Reynolds, 1981; Zaren and Copeland, 1978).

In the series reported by Zaren and Copeland (1978) none of the seven patients who received superficial inguinal node dissection 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. In this 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.

Guarishi et al (1987) reported a series of 56 patients with inguinal node CUP. Following excisional biopsy, a minority (14%) received inguinal lymph node dissection, the remainder received radiotherapy (63%), chemotherapy (7%) or no further treatment (16%). Overall survival at five years for all patients was 27%. 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.

Evidence about complications came from a single study (Guarishi et al 1987). Superficial lymph node dissection was associated with minor leg swelling. Severe acute toxicity was seen in 6% of those treated with radiotherapy and 31% of women older than 50 experienced a hip fracture in the radiotherapy treatment field.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Radical treatment for solitary metastases

Some patients with known primary cancers who develop apparently solitary metastases can be treated successfully by radical treatment to eliminate the metastasis. If the primary cancer has

been or can be successfully treated long-term remission or cure may be achieved for selected patients. There is a tendency for treatment to the metastasis to be more successful the longer the 'disease-free interval' following treatment to the primary, but successful outcomes can be achieved for patients who at presentation are found to have either a solitary distant metastasis or limited metastatic disease eligible for radical treatment. This is particularly the case for patients with bowel cancer who have operable metastatic disease in the liver.

Surgery is by far the most common and successful treatment modality for patients with a solitary metastasis. For some patients complete excision will combine optimal local treatment with the best way of obtaining a tissue diagnosis. Radiotherapy and radiofrequency ablation can destroy metastases in selected situations and patients, and post-operative radiotherapy may reduce the risk of local recurrence following surgery. Highly focused radiotherapy, 'stereotactic radiosurgery', can deliver a well tolerated very high radiation dose to small tumours.

Recommendations

- Do not confound radical therapy by investigating the nature of a tumour inappropriately. For example, biopsy of a primary bone tumour may mean that the patient needs more aggressive surgery than usual. Percutaneous biopsy of a liver metastasis may disseminate the tumour, making a cure impossible. Consider an unusual primary tumour masquerading as a metastasis.
- Refer patients with a solitary tumour in the liver, brain, bone or lung to the appropriate MDT to consider radical local treatment.

Qualifying statement: The GDG found no evidence in the form of randomised trials for benefit from radical treatment for isolated metastasis but reviewed case series which reported favourable outcomes. The GDG formed a consensus recommendation based on experience and accepted practice. For liver metastasis there was more evidence from multicentre series but no direct comparison of outcomes from different treatment modalities.

Clinical evidence

Brain metastases

There were no comparative studies comparing localised therapy for isolated brain metastases of unknown primary, evidence was limited to case series (Bartelt et al, 2003; Debevec et al, 1992; Khansur et al, 1997; Maesawa et al, 2000; Maiuri et al, 1998; Nguyen et al, 1998; Petrovich et al, 2002; Ruda et al, 2001; Salvati et al, 1995; Yardeni et al,1984). Overall survival was better in patients treated with localised therapy (median ranged from 10 to 21 months) than in those receiving only palliative radiotherapy (median 6 to 15 months). It is likely, however, that patients treated with surgery had better pretreatment prognosis than those who received palliative radiotherapy only.

One systematic review (Hart et al, 2007) considered evidence from three randomised trials about the benefit of surgery for single 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). There was insufficient evidence to say which of the treatment options had the lowest complication rate.

Liver Metastases

Surgery for liver metastases from unknown primary tumour 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.

Bone, lung and skin metastases

There was no direct evidence about the radical local treatment of isolated bone, lung or skin metastases from unknown primary.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Presentations with a poor prognosis

Multiple metastases including brain involvement

Patients with confirmed CUP involving the brain in addition to other sites pose particular problems because of the generally bad prognosis associated with this presentation. The management of this group of patients currently involves providing symptomatic care with palliative cranial irradiation offered to some patients. However there is no clear consensus on patient selection or clinical benefit. While a more aggressive approach combining whole brain radiotherapy and systemic chemotherapy is offered to some patients again there is no consensus on patient selection or clinical benefit and patients have little information on which to base their informed consent to any treatment offered. 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 approach.

If it emerged that specific treatment guided by putative site of primary origin 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. If treatment guided by putative primary site of origin proved unsuccesful then extensive investigation to identify such a site is not supported and clinical care could be focused on support and palliation from an earlier stage in the patient’s limited remaining life. However it would remain important to exclude primary cerebral tumours which can masquerade as metastases and more treatable primaries with a high response rate to systemic therapy.

Recommendations

- Refer patients presenting with brain metastases as the first sign of malignant disease to a neuro-oncology MDT for evaluation and treatment.
- Do not offer chemotherapy to patients with brain metastases of unknown primary origin except as part of a controlled clinical trial.
- Inform patients with brain metastases of unknown primary origin and their carers that there is no evidence that any treatment offers improved survival and there is limited evidence of improvement in neurological symptoms with surgery and/or whole brain radiotherapy

Qualifying statement: Evidence to support recommendations for patients with brain metastases of unknown origin is sparse and of poor quality. Direct evidence in patients with brain metastases of unknown origin is from small, case series spread over 20 years. Evidence from the few randomised trials investigating the addition of chemotherapy to whole brain radiotherapy for the treatment of brain metastases of known primary, typically in patients with non-small cell lung cancer has been taken into account in developing the recommendations.

Clinical evidence

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.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Research recommendation

- Randomised controlled trials of whole brain radiotherapy +/- chemotherapy versus best supportive care should be conducted that measure impact on quality of life and neurological function as well as survival.

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6 Systemic treatment

Introduction

Patients with confirmed CUP who have gone through a prolonged and frustratingly negative diagnostic process may find themselves being offered treatment for which there is no evidence of benefit and potential for harmful side effects.

In this population, 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 patients with confirmed CUP. On the other hand, the recognition of certain "treatable syndromes" with consistent and considerable benefit from chemotherapy (for example extragonadal germ-cell tumour, peritoneal malignancy analogous to ovarian cancer) means that appropriate use of chemotherapy can be justified in selected cases. The validity of the "recognised" syndromes is however open to question, and requires confirmation.

Chemotherapy in patients with confirmed CUP

For patients with confirmed CUP who do not fall into one of the recognised "treatable syndromes", it is unclear whether chemotherapy is useful or whether these patients should be managed along symptomatic lines alone.

Recommendations

- If chemotherapy is being considered for patients with confirmed CUP, with no clinical features suggesting a specific syndrome, inform patients about the potential benefits and risks of treatment.
- Offer patients with CUP the opportunity to enter clinical trials.
- If chemotherapy is given outside clinical trials, take into account the clinical and pathological characteristics of the tumour, the toxicity profile of the drugs, their ease of administration and response rate when choosing which treatment to use.

Qualifying statement: Evidence for superiority of any particular regimen in terms of survival prolongation is lacking. The current literature fails to support the hypothesis that palliative chemotherapy improves survival and/or quality of life in patients with CUP not belonging to specific syndromes. The literature is heavily influenced by small non-randomised, single institution trials with varying patient selection criteria.

Considering that the commonest primary tumours identified in CUP patients tend to be lung, pancreatic and gastrointestinal, one may extrapolate from these tumour types where studies have shown that chemotherapy prolongs survival by an average of 3-6 months over best supportive care alone. Furthermore response to chemotherapy is associated with a well-documented improvement in symptoms and quality of life. However high-quality evidence to support this is lacking from the current literature in CUP.

Clinical evidence

Evidence about chemotherapy for patients with confirmed CUP not belonging to a recognised subgroup was limited to small phase II trials. No published studies were 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 (Lofts et al 1999; Mousseau et al 1991; Shaw et al 2007; Sumi et al 2001). However, evidence suggests that fitter patients tend to receive chemotherapy (Seve et al, 2006) and this probably contributes to the observed differences.

There was no strong evidence about the optimal chemotherapy regimen. Golfinopoulos et al (2009) used multiple comparisons meta-analysis to estimate the relative effectiveness of the regimens used in ten randomised phase II 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

Adenis 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 study design or methodology 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.

Research recommendation

- Randomised controlled clinical trials should be undertaken in patients with confirmed CUP to define optimal systemic therapy.

Qualifying statement: An economic analysis using expected value of perfect information (EVPI) methodology examining common chemotherapy regimens demonstrated considerable uncertainty about optimal treatment and indicated that research to define optimal treatment would be of value.

Health economic evaluation

Patients with confirmed carcinoma of unknown primary (confirmed CUP) account for 3-5 percent of all cancer diagnoses (Assersohn et al 2003, Briasoulis et al 2000). For a subset of patients with CUP whose disease resembles one of the major tumour types, treatment decisions can be guided by clinical and/or pathological features. However in the majority of patients with CUP, 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 2009). The generally low levels of health gain and scarcity of high quality data about treatment benefits along with the cost implications of administering chemotherapy treatment led to highlighting this topic as a priority for economic analysis.

Cost-effectiveness evaluations require evidence on numerous parameters, including treatment effects, health-related preferences (utilities) and healthcare resource use and costs (Sculpher et al 2005). 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: 1) collection of data by expert elicitation to fill gaps in the published literature in order to inform parameters in the economic model and 2) estimation of the expected value of information (EVPI) to quantify the uncertainty associated with the cost-effectiveness of chemotherapy in comparison to best supportive care in order to inform research recommendations aimed at reducing this uncertainty.

A decision tree was constructed to compare the strategy of giving best supportive care alone to giving three different chemotherapy regimens: fluorouracil (5-FU), carboplatin in combination with

paclitaxel (CP), and epirubicin in combination with cisplatin and fluorouracil (ECF). These regimens were selected after reviewing the available published literature and after discussion with the guideline development group (GDG) to determine which regimens were of most relevance to current UK clinical practice.

The clinical evidence required to populate the model was obtained from a number of different sources. Effectiveness of treatment and supportive care in terms 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 were also obtained from experts. Rates of toxic events (Grade 3 and 4) and toxic death were obtained from clinical review of published literature.

Utility weights were required in the model to estimate quality adjusted life years (QALYs). 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.

The costs considered in the analysis were those relevant to the UK NHS, and included drug acquisition costs, administration costs, costs of treating adverse events and costs associated with healthcare resource use for provision of supportive care. Unit costs were based on NHS Reference Costs 2007-2008. When necessary, costs were uplifted using the Hospitals and Community Health Services Pay and Prices Index (PSSRU, 2008).

Given an expected mean survival of less than 12 months, costs and benefits were not discounted for the calculation of incremental cost-effectiveness ratios (ICERs). For the EVPI analysis, a rate of 3.5% was applied.

The base case results of the model (Table 6.1) show that the cost of the different treatment strategies ranged from £578 for best supportive care alone to £5,842 for the combination of carboplatin and paclitaxel. Effectiveness, measured in terms of QALYs, ranged from 0.132 for best supportive care to 0.278 for the combination of carboplatin and paclitaxel.

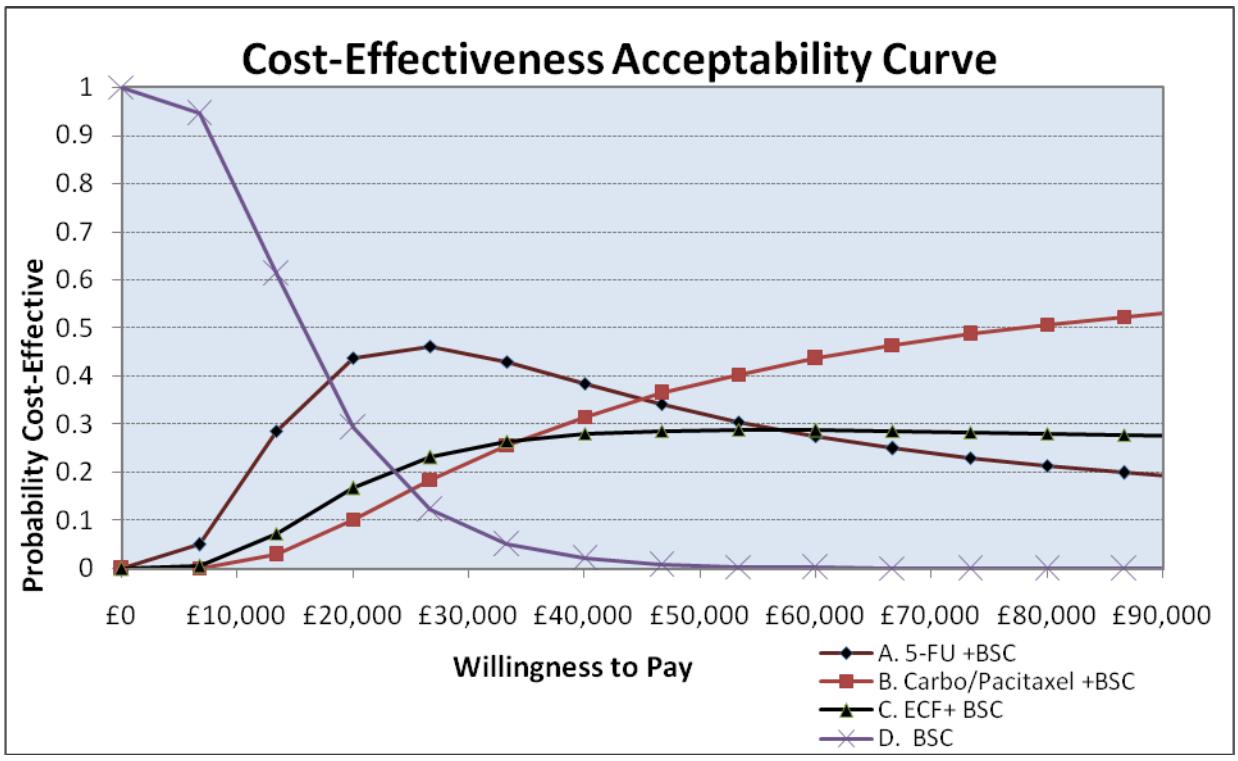
Table 6.1: Results of the base case analysis

Strategy	Total Expected Cost (£)	Total Expected QALYs	ICER
BSC	578	0.132	
5-FU +BSC	1,841	0.197	19,499
ECF+ BSC	3,290	0.219	ED
Carboplatin/paclitaxel + BSC	5,842	0.278	44,605

ED, extendedly dominated

The estimate of incremental cost-effectiveness ratios (ICER) are based on mean cost and mean effectiveness for each treatment option. At a given willingness to pay (WTP) threshold, taking parameter and decision uncertainty into account, the probability that any one of the chemotherapy strategies was cost-effective was less than 50% (Figure 6.1).

Figure 6.1: Cost-effectiveness acceptability curves



Population EVPI was estimated across three time horizons: three, five and ten years (Table 6.2). Taking into account the annual incidence of this patient group and a three year time horizon, the population EVPI was estimated as £2,866,252 at a threshold of £20,000 per QALY. The population EVPI can be interpreted as the upper estimate on the amount that should be spent to undertake additional research that will reduce uncertainty in the decision between the treatment strategies that were included in this model.

Table 6.2: Population EVPI

WTP threshold values(£)	Population EVPI (£)		
	3 Year	5 Year	10 Year
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

An analysis of the expected value of partial perfect information (EVPPI) showed that there was greater uncertainty surrounding parameters related to length of the treatment and effectiveness of treatment (in terms of duration of response to therapy), suggesting that the value of reducing uncertainty associated with these parameters through future research is highest.

Sensitivity analysis on the cost of the chemotherapy regimens was undertaken to explore the impact of price volume discounts in England and Wales. With discounted prices, the population EVPI fell from £2,866,252 to £873,628 for a 3-year time horizon (at a threshold of £20,000 per QALY).

Chemotherapy for recognised treatable syndromes

For patients with confirmed CUP who fall into one of the recognised "treatable syndromes", chemotherapy selected according to the presumed organ of origin may be more successful than generic treatment.

Recommendations

- Offer patients chemotherapy directed at a specific syndrome if they have:
  - confirmed CUP with clinical and/or laboratory features of a specific syndrome **and**
  - good performance status.

Qualifying statement: Evidence for the superiorty of syndrome specific treatment over generic treatment has not been found in randomised controlled trials. Current clinical practice supports the use of syndrome-specific treatments.

Clinical evidence

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.

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.

Health economic evaluation

The GDG did not consider this topic a priority for health economic evaluation (see Appendix B of the Evidence Review), therefore no further economic analysis was undertaken. However the GDG did consider the economic consequences when agreeing their recommendations.

Research recommendation

- Encourage researchers to design prospective randomised controlled trials, with quality of life analysis, to compare new treatments to the current best syndrome-specific chemotherapy.

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Appendix 1

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 syndrome10 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

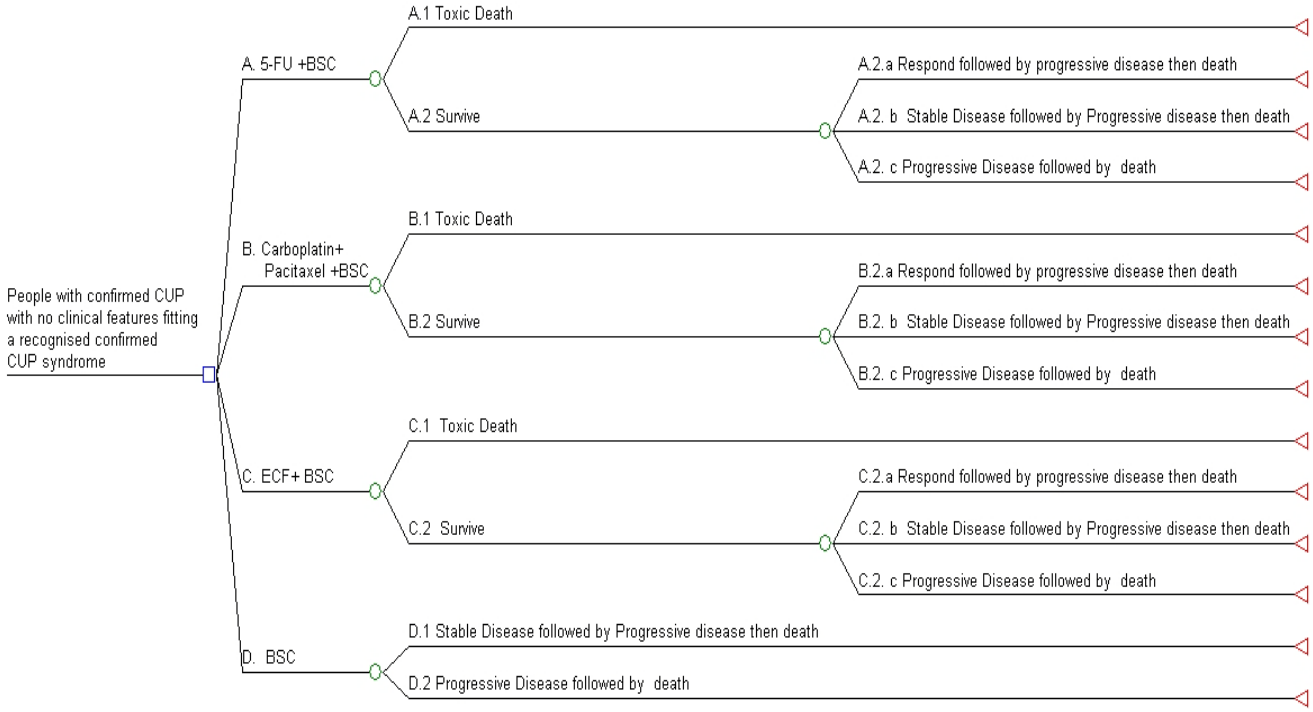
[10] Recognised syndromes: predominantly peritoneal adenocarcinoma; unilateral axillary lymphadenopathy; midline nodal disease; cervical (neck) lymphadenopathy containing carcinoma and metastatic carcinoma with neuroendocrine differentiation .

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 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[11]
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

[11] Distribution parameters relate to requirements for TreeAge Pro software

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[12]
Fluorouracil	Response duration	4.4	Gamma (4.27, 0.97)
	Stable disease duration	4.1	Gamma (4.08, 1.01)
	Progressive disease duration	3.4	Gamma (2.97, 0.89)
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[13]
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)

[12] Distribution parameters relate to requirements for TreeAge Pro software.
[13] Distribution parameters relate to requirements for TreeAge Pro software.

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)
	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[14]
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)
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.

[14] Distribution parameters relate to requirements for TreeAge Pro software.

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[15]	525[16]	-	306.25	87.5	105	350[17]
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**

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

[15] BSA 1.75 – NICE Developing Costing Tools Methods Guide Jan 2008
[16] Dose per day
[17] Dose per day

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.

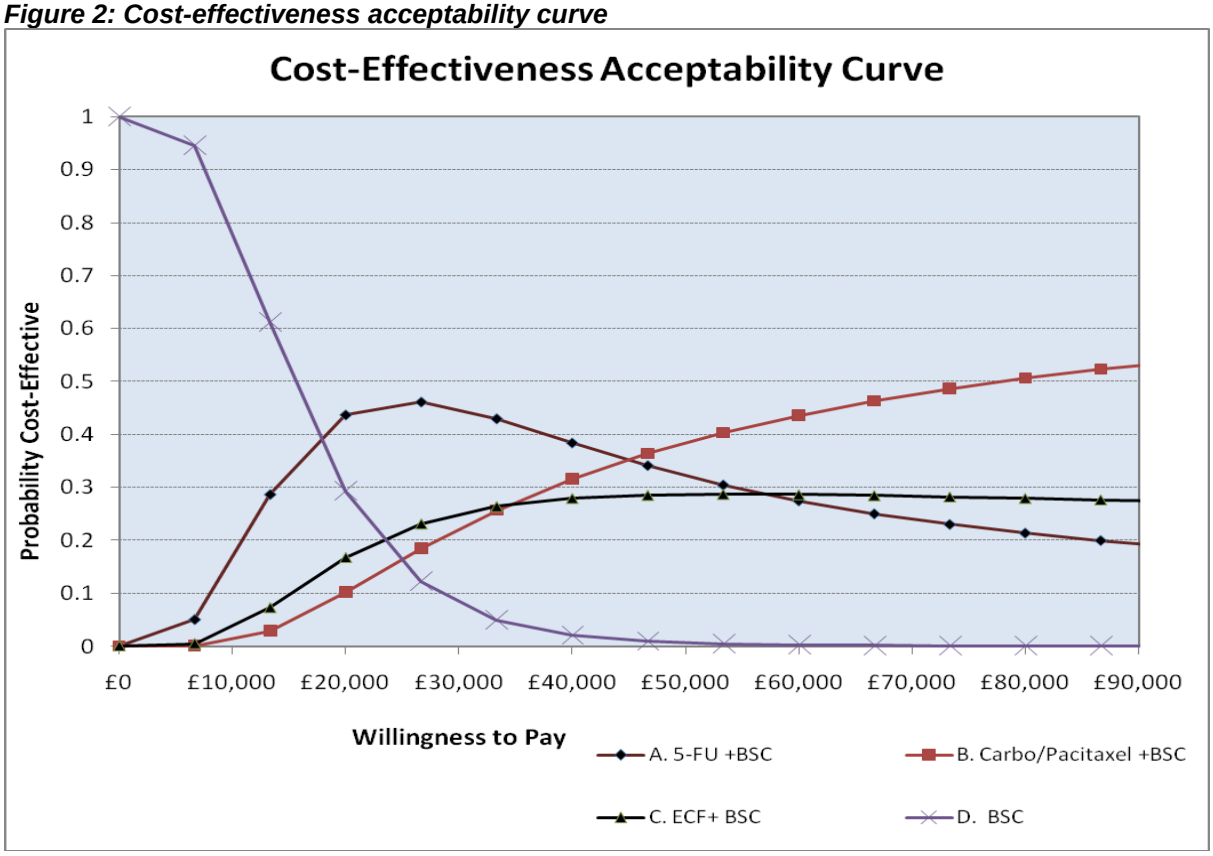
Table 13: Base case total expected cost and QALYs

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

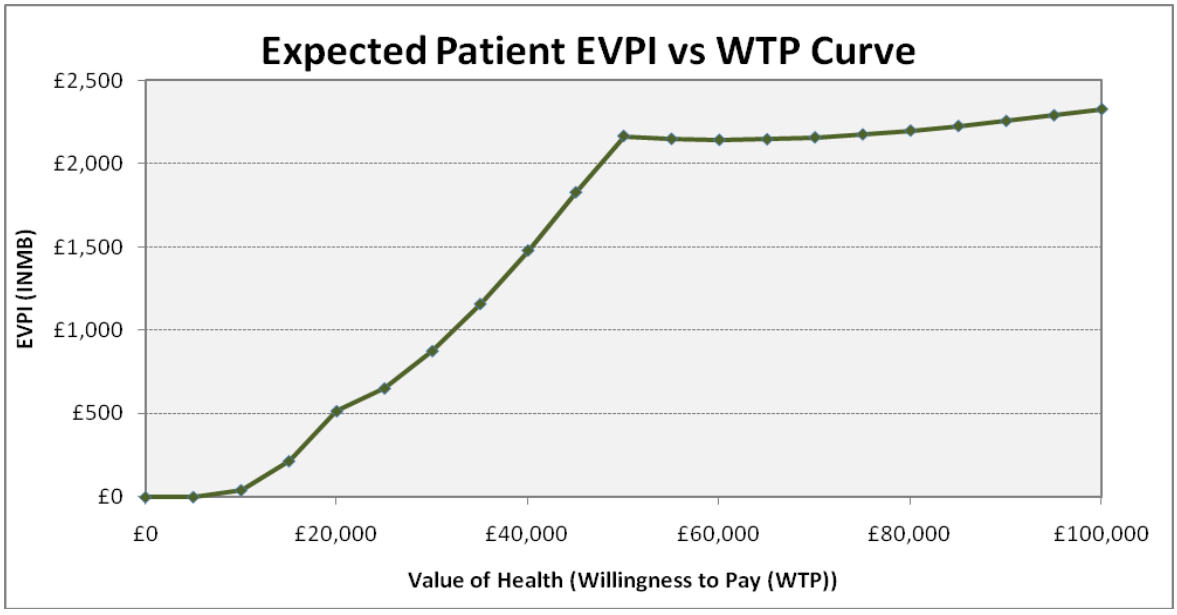
4.1.1 Patient level EVPI

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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Health Economics Appendix A

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

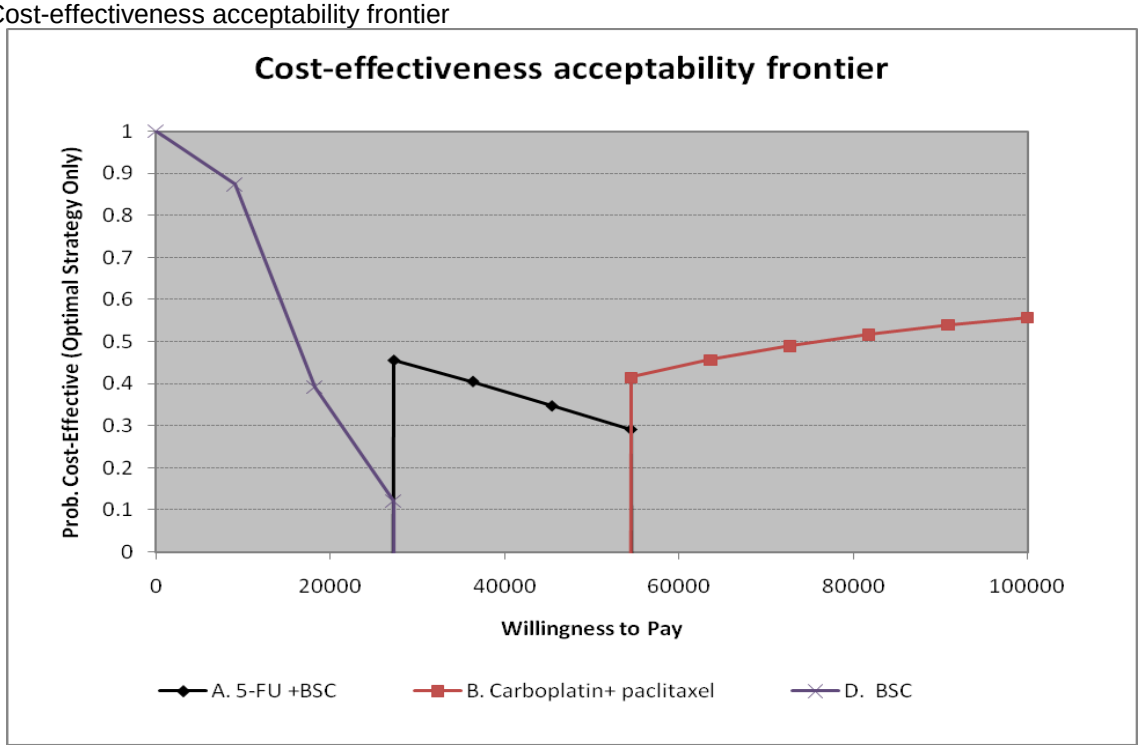
Healthcare Resource Use Category	Elicitation Question
Best supportive care	In the management and provision of supportive care for CUP patients: What is the number of inpatient days that a patient spends in hospital over a 6-month period? In the management and provision of supportive care for CUP patients: 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?

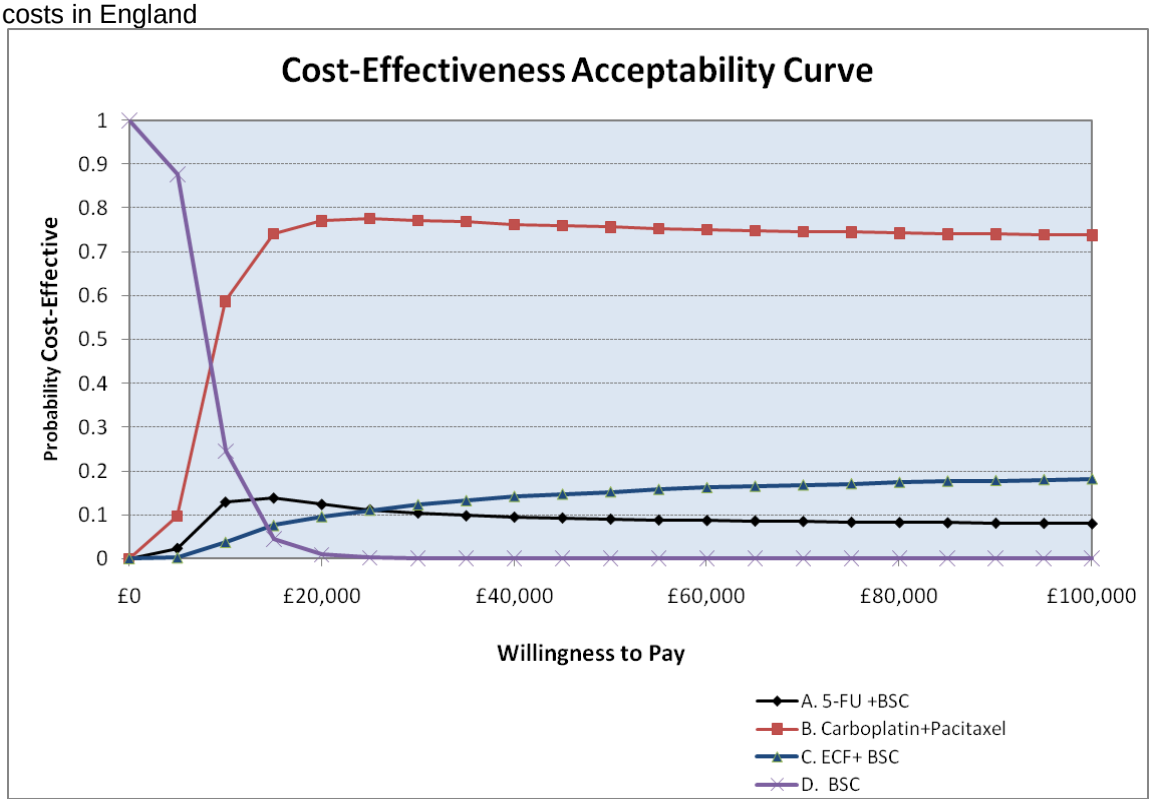
1

Health Economics Appendix B

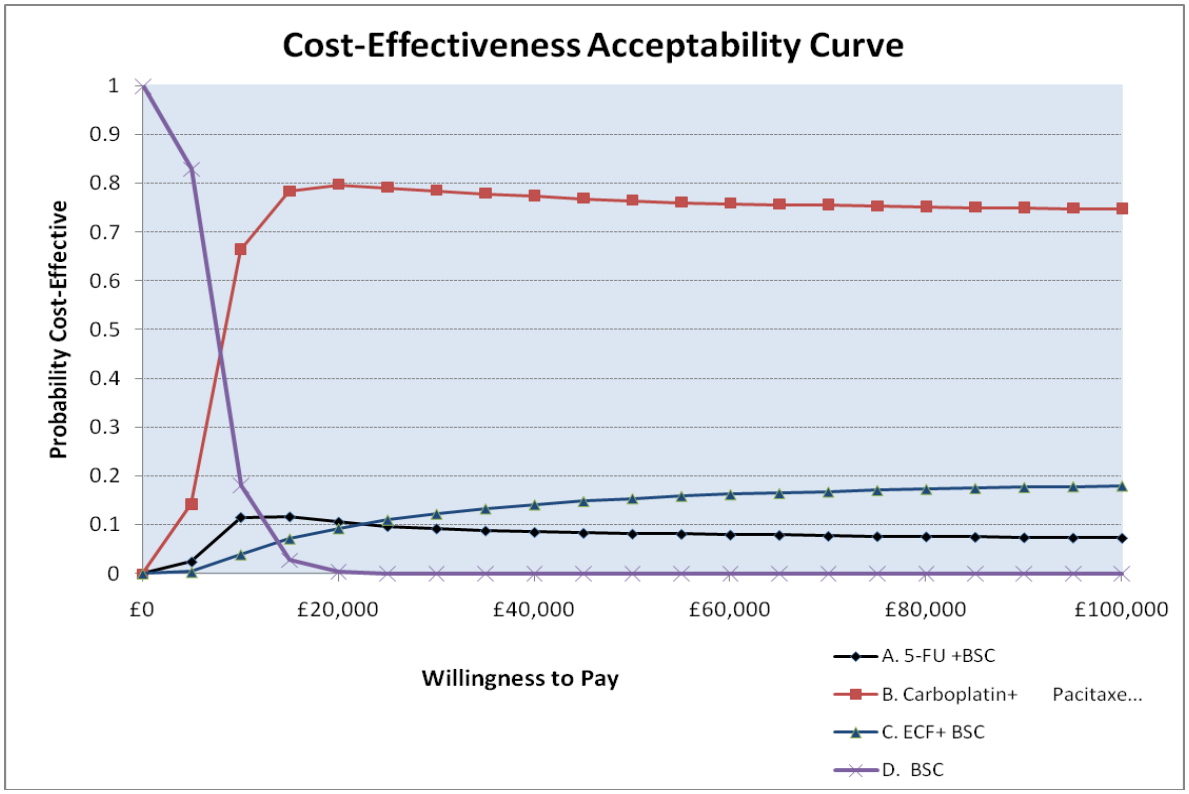
Cost-effectiveness acceptability frontier



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



Appendix 2

Abbreviations

AFP	alpha-fetoprotein
CA19-9	carbohydrate antigen 19-9
CA125	cancer antigen 125
CEA	carcinoembryonic antigen
CK	cytokeratin
CT	computed tomography
CUP	carcinoma of unknown primary
DRE	digital rectal examination
ER	oestrogen receptor
FBC	full blood count
HCG	human chorionic gonadotrophin
H&E	haematoxylin and eosin staining
H&N	head and neck
IHC	immunohistochemistry
LDH	lactate dehydrogenase
LFT	liver function tests
MDT	multidisciplinary team
MRI	magnetic resonance imaging
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
PSA	prostate-specific antigen
PET	positron emission tomography
PET-CT	positron emission tomography combined with computed tomography
PLAP	placental alkaline phosphatase
PR	progesterone receptor
TTF-1	thyroid transcription factor
confirmed CUP	confirmed carcinoma of unknown primary
provisional CUP	provisional carcinoma of unknown primary
RCT	randomised controlled trial
U&E	urea and electrolyte
VATS	video assisted thoroscopic surgery
WBRT	whole brain radiotherapy

Appendix 3

Glossary

Adenocarcinoma
A malignant tumour originating in glandular tissue.

Adenopathy
Disease of a gland.

Adjuvant treatment
Treatment as a follow-up to surgery designed to remove any microscopic traces of tumour which may have been left behind.

Ascites
An abnormal accumulation of fluid in the abdominal cavity.

Biopsy
Removal of a sample of tissue from the body to allow diagnosis of a disease.

Bronchoscopy
The procedure in which a cylindrical fiberoptic instrument is inserted into the airway that allows the visual examination of the lower airways.

Carcinoma
Cancer arising from the lining tissue that covers all body organs.

Chemotherapy
A chemical that kills tumour cells.

Colonoscopy
The procedure in which a long, flexible, fiberoptic instrument is used to view the entire inner lining of the colon and the rectum.

Comorbidity
The presence of more than one disease or health condition in an individual at a given time.

Computed tomography (CT)
A diagnostic imaging technique that uses X-rays and a computer to produce a detailed picture of a cross section of the body.

Confirmed carcinoma of unknown primary (confirmed CUP)
Metastatic epithelial or neuro-endocrine malignancy identified on the basis of final histology, with no primary detected despite a selected screen of investigations, specialist review and further specialised tests as appropriate.

Cytology
The study of cells, their origin, structure, function and pathology.

Cytomorphology
The study of the shape of cells.

Decision aids
A variety of resources which can help patients participate in decisions about their health for example information booklet, CD-ROM.

Endoscopy
Visual examination of interior structures of the body with a flexible fibreoptic tube.

Haematology
The scientific study of blood and blood-forming tissues.

Histology
An examination of the cellular characteristics of a tissue using a microsope.

Immunohistochemistry
A technique that uses antibodies and dyes to identify specific molecules in tissues which are analysed by a pathologist using a microscope.

Lesion
A pathologic change in body tissue.

Lymphadenopathy
An abnormal enlargement of the lymph nodes.

Magnetic resonance imaging (MRI)
A diagnostic imaging technique that uses powerful electromagnets, radio waves and a computer to produce well-defined images of the body's internal structures.

Malignancy of undefined primary origin
Metastatic malignancy identified on the basis of a limited number of tests, without a probable primary site, prior to comprehensive investigation

Malignant
Cancerous cells which can invade into nearby tissue and spread to other parts of the body.

Mammography
The process of taking a mammogram – a soft tissue X-ray of the breast which may be used to evaluate a lump or which may be used as a screening test in women with no signs or symptoms of breast cancer.

Markers
Substances found in increased amounts in the blood, other body fluids or tissues which may be associated with the presence of a certain type of cancer in the body

Meta-analysis
A method of summarising previous research by reviewing and combining the results of a number of different clinical trials.

Metastases
Spread of cancer away from the primary site to somewhere else, usually via the bloodstream or the lymphatic system.

Multidisciplinary team (MDT)
A team with members from different healthcare professions (including for example, oncology, pathology, radiology, nursing).

Occult
Hidden or difficult to observe.

Oncology
The study and treatment of cancers.

Oncologist
A doctor who specialises in treating cancer.

Palliative
Anything which serves to alleviate symptoms due to the underlying cancer but is not expected to cure it.

Pathologist
A doctor who examines tissues and cells using a microscope.

Percutaneous
The method of obtaining a tissue sample through the skin.

Pleural effusions
Occurs when fluid collects in the pleural space.

Positron emission tomography (PET)
A diagnostic imaging technique using a radio-active tracer which shows increased tissue metabolism.

Prognosis
A prediction of the likely outcome or course of a disease.

Provisional carcinoma of unknown primary (provisional CUP)
Metastatic epithelial or neuro-endocrine malignancy identified on the basis of histology/cytology, wit no primary detected despite a selected initial screen of investigations, prior to specialist review and possible further specialised investigations.

Radiotherapy
A treatment for cancer that uses high energy ionising radiation (usually X-rays) to kill cells.

Randomised controlled trials (RCTs)
A clinical trial in which subjects are randomised to different groups for the purpose of studying the effect of a new intervention, for example a drug or other therapy.

Sarcoma
A malignant tumour arising from connective tissues.

Sigmoidoscopy
A procedure whereby a short and rigid or slightly longer and flexible fiberoptic tube is inserted into the rectum to examine the lower portion of the large intestine/bowel.

Supportive care
Treatment that is given to prevent, control, or relieve side effects in order to improve a patient's quality of life.

Systematic review
A review of the literature carried out in order to address a defined question and using quantitative methods to summarise the results.

Systemic treatment
Treatment, usually given by mouth or by injection, that reaches and affects tumour cells throughout the body rather than targeting a specific area.

Thoracotomy
Opening the chest wall.

Triage
A process in which patients are sorted according to their need for care.

Ultrasound
An imaging method in which high-frequency sound waves are used to outline a part of the body.

Appendix 4

Guideline scope

Guideline title

Diagnosis and management of metastatic malignant disease of unknown primary origin

Short title

Metastatic malignant disease of unknown primary origin

Background

The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Cancer to develop a clinical guideline on the diagnosis and management of metastatic malignant disease of unknown primary origin for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health (see appendix). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

The Institute's clinical guidelines support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued have the effect of updating the Framework.

NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment. Clinical need for the guideline

Most patients with newly diagnosed cancer are found to have a clearly defined primary tumour after initial investigation and staging. However, a significant minority (about 5%) are eventually found to have metastatic malignancy without an identifiable primary site, despite exhaustive tests. On the basis of figures from the Office for National Statistics for 2000, at least 10,000 such cases occur annually in England and Wales. These 'unknown primary' cases pose additional problems to those encountered when a primary tumour is evident and where recognised management processes have been defined. These problems include:

- uncertainty about the nature, timing and extent of appropriate investigation
- over- or under-investigation
- failure to use valuable, effective treatments in certain cases (for example, in occult breast cancer or extra-gonadal germ-cell tumour)
- inappropriate use of some expensive palliative treatments of limited or uncertain value
- unstructured use of potentially valuable but costly new technologies such as positron emission tomography (PET) scanning, genetic profiling and targeted therapies
- inadequate reporting of data such as incidence and waiting time
- poor patient access to cancer information and support facilities
- the absence of a structured research programme.

There are no national clinical guidelines on this topic currently being developed in the UK. Neither the NICE guideline 'Referral guidelines for suspected cancer' (NICE clinical guideline 27) nor any of the NICE cancer service guidance addresses the needs of this group of patients.

Most patients with cancer currently benefit from a multidisciplinary approach to management of their disease, based on agreed local guidelines for investigation and treatment. One quite large

subset of patients is those who present with metastatic cancer without an identified primary site. However, the heterogeneous nature of patients with an undiagnosed primary cancer and their varied clinical problems mean that current management is likely to be very variable and inefficient. Therefore, specifically designed guidelines would improve the management of this group of patients.

The aim of this guideline is to clarify the investigation of patients with metastatic malignancy disease from an undiagnosed primary cancer, to define optimal treatment for patients who eventually have no primary cancer identified, and to include appropriate supportive care for this group of patients.

The guideline

The guideline development process is described in detail in two publications that are available from the NICE website (see 'Further information'). 'The guideline development process: an overview for stakeholders, the public and the NHS' describes how organisations can become involved in the development of a guideline. 'The guidelines manual' provides advice on the technical aspects of guideline development.

This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health (see appendix).

The areas that will be addressed by the guideline are described in the following sections.

Population

Groups that will be covered

Adults (18 years and older) who have a provisional diagnosis of metastatic malignant disease with or without histological or cytological confirmation, in whom a primary site has not been identified and in whom further investigation is needed.

Adults who, following appropriate investigation, are found to have histologically or cytologically confirmed metastatic carcinoma but no apparent site of primary tumour, and for whom subsequent management needs to be considered.

Adults who have had a previous diagnosis of cancer treated with a curative intent, who present with metastatic malignant disease and in whom it is uncertain whether this is a recurrence or related to a new primary tumour.

No patient subgroups needing special consideration have been identified.

Groups that will not be covered

Children (younger than 18) with metastatic malignant disease of unknown primary site.

Adults with histologically or cytologically confirmed malignant lymphoma.

Adults with an established or highly probable primary site of malignant carcinoma or sarcoma on the basis of clinical examination or imaging, with or without histological or cytological confirmation.

Healthcare setting

Primary care.

Secondary care, including all departments and specialties where these patients may present and be managed, such as general acute medicine (and its subspecialties); general surgery; orthopaedic surgery; ear, nose and throat surgery; gynaecology and care of the elderly.

Tertiary care in cancer centres and regional specialties such as neurosurgery and plastic surgery.

Clinical management (including service delivery where appropriate)

Diagnosing the primary site of metastatic malignant disease using:

- histological, cytological and molecular techniques
- imaging techniques
- endoscopic techniques
- invasive operative techniques (such as image-guided biopsy or laparoscopy)
- biochemical tests (such as 'tumour markers').

How investigations are best sequenced and organised to reach the most rapid diagnosis.
Which groups of patients are unlikely to benefit from extensive investigation.

What systemic or locoregional therapy, if any, is effective in treating patients who, following appropriate investigation, are found to have histologically or cytologically confirmed metastatic carcinoma but no apparent site of primary tumour. Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only where clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform their decisions for individual patients.

What appropriate psychological and supportive care addresses the particular needs of this patient group and their carers.

The Guideline Development Group will consider making recommendations on the principal complementary and alternative interventions or approaches to care relevant to the guideline topic.

The Guideline Development Group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, or changing the approach to care to make more efficient use of resources, can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

Status

Scope

This is the final scope.

Guideline

The development of the guideline recommendations will begin in May 2008.

Further information

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'
  'The guidelines manual'.

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

Appendix: Referral from the Department of Health

The Department of Health asked the Institute:

"To prepare a clinical guideline on the diagnosis and management of metastatic malignant disease of unknown primary origin, including service delivery where appropriate."

Appendix 5

List of topics covered by each chapter

Chapter 2 – Organisation of services and support

- For patients with malignancy of undefined primary origin does a evaluation by a specialist oncology team at an earlier time than is traditionally the case single point of contact improve outcomes?
- 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?
- 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?

Chapter 3 – Diagnosis

- For patients with malignancy of undefined primary origin, is there an optimal initial diagnostic strategy?
- For patients with malignancy of undefined primary origin undergoing initial diagnostic tests, is there benefit in terms of duration of diagnostic process or patient outcomes through measuring serum tumour markers?
- 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?
- For women with malignancy of undefined primary origin undergoing initial investigations to establish a primary site, does a policy of mammography in all patients convey benefits (in terms of more frequent detection of clinically unsuspected primary breast cancer, and avoidance of unnecessary other tests,) than a policy of only performing mammography in patients selected on the basis of histological or clinical features suggesting possible occult breast cancer
- 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?
- For patients with provisional cancer of unknown primary does PET-CT result in improved outcomes?
- For patients with malignancy of undefined primary origin, does immuno-histochemical analysis result in improved outcomes?
- 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?
- 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?

Chapter 4 – Factors influencing management decisions

- 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?
- 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?
- Decision aids for people with cancer of unknown primary
- 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?

- For patients with confirmed cancer of unknown primary in whom systemic treatment is being considered, does gene-expression based profiling (to define putative tissue of origin) lead to improved outcomes (through the use of treatment chosen on the basis of the predicted primary site)?

Chapter 5 – Management for specific presentations

- What is the optimal management for patients with confirmed cancer of unknown primary who present with squamous carcinoma involving upper / mid neck nodes?
- What is the optimal management for patients with confirmed cancer of unknown primary who present with adenocarcinoma involving axillary nodes?
- What is the optimal management for patients with confirmed cancer of unknown primary who present with squamous carcinoma involving inguinal nodes?
- 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?
- 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?

Chapter 6 – Systemic treatment

- 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?
- 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?

Appendix 6

People and organisations involved in production of the guideline

Appendix 6.1

Members of the Guideline Development Group (GDG)

GDG Chair	
Dr Andrew Fowell	Macmillan Consultant in Palliative Medicine, Eryri Hospital, Caernarfon
GDG Lead Clinician	
Dr Richard Osborne	Consultant in Medical Oncology, Dorset Cancer Centre
Group Members	
Dr Philip Barber	Consultant Respiratory Physician, University Hospital of South Manchester and Christie Hospital Manchester
Dr Kathie Binysh	Cancer Network Lead Clinician, West London Cancer Network
Dr David Brooks	Macmillan Consultant in Palliative Medicine, Chesterfield and North Derbyshire Hospital NHS Trust
Dr David Farrugia	Consultant Medical Oncologist, Cheltenham General Hospital
Nicola James[18]	Lead Nurse and Nurse Consultant, Royal Chesterfield Hospital
Prof Archibald Malcom	Consultant Histopathologist, Royal Shrewsbury Hospital
Dr Orest Mulka	GP, Measham, Leicestershire
Karen Pattison[19]	Lead Cancer Nurse/Head of Service for Chemotherapy, South Tyneside NHS Foundation Trust
Dr Gareth Rees	Consultant in Clinical Oncology, Royal United Hospital Bath
Dr Catherine Sturgeon	Clinical Scientist, Department of Clinical Biochemistry, Royal Infirmary of Edinburgh
Dr John Symons	Patient and carer member
Dr Marcus Ben Taylor	Consultant Radiologist, Christie Hospital Manchester
Janie Thomas[20]	Patient and carer member
Mr Michael Williams	Consultant General Surgeon, Cumberland Infirmary Carlisle
Penny Wilson-Webb[21]	Patient and carer member
Dr Anne Vaughan-Thomas[22]	Patient and carer member

[18] From September 2008 – present
[19] From May 2008 – September 2008
[20] From April 2009 – present
[21] From May 2008 – December 2008
[22] From May 2008 – August 2009

Declarations of interest

The Guideline Development Group were asked to declare any possible conflicts of interest which could interfere with their work on the guideline. The interests that were declared are as follows:

GDG Member	Interest Declared	Type of Interest	Decisions Taken
David Brooks	Trust receives a grant from Macmillan Cancer Relief to evaluate management of patients with CUP	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics
	Received an honorarium from Cephalon for giving a lecture on analgesia	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the lecture was not specific to CUP
David Farrugia	Received an honorarium from Roche for attending an advisory board on Erlotinib (Tarceva)	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include tyrosine kinase inhibitors until December 2008[23]
	Received expenses from Roche for attending the ASCO conference in May/June 2008	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
John Symons	Director of CUP Foundation - Jo's Friends	Personal, non-pecuniary	Declare and can participate in discussions on all topics
	Member of Cancer 52	Personal, non-pecuniary	Declare and can participate in discussions on all topics
	Received sponsorship from Pathwork Diagnostics for an evening reception for the CUP foundation conference in October 2009	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics
	received sponsorship from Biotheranostics and Rosetta Genomics for the CUP foundation conference in October 2009	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics

[23] Tyrosine kinase inhibitors were not included in any of the topics investigated by the guideline and were therefore not discussed by the GDG.

Anne Vaughan-Thomas	Shareholdings in GlaxoSmithKline	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include GSK interventions until one year after shares have been sold
	Joint grant holder for research projects in veterinary healthcare from Pfizer Animal Health, Schering-Plough, and Meriel	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics
Paul Shaw	Expenses paid by American Association for Cancer Research, American Society for Clinical Oncology and European Cancer Organisation to go to a course	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts.
	Co-investigator and receives drugs from AstraZeneca, Novartis and Abbott to carry out a research project on colorectal cancer	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics
Fergus Macbeth	Expenses paid by AstraZeneca, Novartis and Abbott to travel to meetings	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
	Received testing kit from GE Healthcare related to colorectal cancer research	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics
	Principle investigator for FRAGMATIC trial in lung cancer patients	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics

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Appendix 6.2

Organisations invited to comment on guideline development

The following stakeholders registered with NICE and were invited to comment on the scope and the draft version of this guideline.

3 Counties Cancer Network Palliative Care Lead Clinicians Group
Abbott Laboratories Ltd
ABI
Acute Care Collaborating Centre
Afiya Trust, The
Arden Cancer Network
Association of Chartered Physiotherapists in Oncology and Palliative Care
Association for Clinical Biochemistry
Association for Palliative Medicine of Great Britain & Ireland
Association of the British Pharmaceuticals Industry (ABPI)
Barnsley Hospital NHS Foundation Trust
BASO ~ The Association for Cancer Surgery
Bedfordshire PCT
Birmingham Cancer Network
Boehringer Ingelheim Ltd
Bolton Council
Bournemouth and Poole PCT
Breakthrough Breast Cancer
British Association for Counselling and Psychotherapy
British Association of Dermatologists
British Orthopaedic Association
British Association of Otolaryngologists Head & Neck Surgeons
British Dietetic Association
British Gynaecological Cancer Society
British Liver Trust
British National Formulary (BNF)
British Nuclear Medicine Society
British Society for Human Genetics
British Thoracic Society
Calderdale PCT
Cambridge University Hospitals NHS Foundation Trust
Cancer of Unknown Primary (CUP) Foundation
Cancer Research UK
Cancer Services Collaborative
Cancerbackup
Care Quality Commission
CASPE
Central South Coast Cancer Network
Chronic Conditions Collaborating Centre
Commission for Social Care Inspection
Connecting for Health
Department for Communities and Local Government
Department of Health
Department of Health, Social Security and Public Safety of Northern Ireland
Derby-Burton Cancer Network
Derbyshire Mental Health Services NHS Trust
Grunenthal UK Ltd

Harrogate and District NHS Foundation Trust
Health Commission Wales
Heart of England NHS Foundation Trust
Humber and Yorkshire Coast Cancer Network
GE Healthcare
Get A-Head Charitable Trust
Imaging Equipment Ltd
Imperial College Healthcare NHS Trust
Institute of Biomedical Science
Johnson & Johnson Medical
Kirklees PCT
Leeds PCT
Lilly UK
Macmillan Cancer Support
Marie Curie Cancer Care
Medicines and Healthcare Products Regulatory Agency
Mental Health Collaborating Centre
Ministry of Defence
Mouth Cancer Foundation
Nation Cancer Network Clinical Directors Group
National Council for Palliative Care
National Patient Safety Agency
National Public Health Service – Wales
NCRI
NHS Clinical Knowledge Summaries Service (SCHIN)
NHS Direct
NHS Health and Social Care Information Centre
NHS Improvement
NHS Plus
NHS Purchasing & Supply Agency
NHS Quality Improvement Scotland
NHS Sefton
NHS Sheffield
North East London Cancer Network
North Tees & Hartlepool Acute Trust
North Tees PCT
North Trent Cancer Network
North Yorkshire and York PCT
Nottingham University Hospitals NHS Trust
Nucletron UK Ltd
Nursing & Supportive Care Collaborating Centre
PERIGON Healthcare Ltd
Pfizer Limited
Primary Care Collaborating Centre
Robert Jones & Agnes Hunt Orthopaedic Hospital NHS Trust
Roche Diagnostics Ltd
Royal Brompton & Harefield NHS Trust
Royal College of General Practitioners
Royal College of Midwives
Royal College of Nursing
Royal College of Paediatrics and Child Health
Royal College of Pathologists
Royal College of Physicians of London
Royal College of Radiologists
Royal Pharmaceutical Society of Great Britain
Royal Society of Medicine

Sandwell PCT
Sanofi-aventis
Sarcoma UK
Scottish Intercollegiate Guidelines Network (SIGN)
Sheffield PCT
Sheffield Teaching Hospitals NHS Foundation Trust
Siemens Medical Solutions Diagnostics
Skin Care Campaign
Social Care Institute for Excellence (SCIE)
Society and College of Radiographers
Society of British Neurological Surgeons
Society for Cardiothoracic Surgery
South East Wales Cancer Network
Specialist Advisory Committee on Antimicrobial Resistance (SACAR)
Sussex Cancer Network
Thames Valley Cancer Network
University Hospital Birmingham NHS Foundation Trust
University of North Tees and Hartlepool NHS Trust
Welsh Assembly Government
Welsh Scientific Advisory Committee (WSAC)
West & East & North Hertfordshire PCTs
Western Cheshire PCT
Western Health and Social Care Trust
Wiltshire PCT
Women's & Children's Collaborating Centre
Wyeth Pharmaceuticals
York Hospitals NHS Trust
Yorkshire and Humber Specialised Commissioning Group

Appendix 6.3

Individuals carrying out literature reviews and complementary work

Overall Co-ordinators

Dr John Graham[24]	Director, National Collaborating Centre for Cancer, Cardiff
Dr Andrew Champion	Centre Manager, National Collaborating Centre for Cancer, Cardiff
Dr Fergus Macbeth[25]	Clinical Practice Centre Director, NICE

Project Manager

Angela Bennett[26]	Assistant Centre Manager, National Collaborating Centre for Cancer, Cardiff
Victoria Titshall[27]	Project Manager, National Collaborating Centre for Cancer, Cardiff
Helen Pearson[28]	Project Manager, National Collaborating Centre for Cancer, Cardiff

Researcher

Dr Nathan Bromham	National Collaborating Centre for Cancer, Cardiff
Dr Susan O'Connell	National Collaborating Centre for Cancer, Cardiff
Angela Melder	Senior Reviewer, National Collaborating Centre for Cancer, Cardiff

Information Specialist

Stephanie Arnold	National Collaborating Centre for Cancer, Cardiff

Health Economist

Eugenia Priedane	Research Assistant, London School of Hygiene and Tropical Medicine
Bernadette Li	Research Fellow, London School of Hygiene and Tropical Medicine

Needs Assessment

Dr Paul Shaw	Clinical Research Fellow, Cardiff University
Dr Kathie Binysh	Cancer Network Lead Clinician, West London Cancer Network

[24] From March 2009 – present
[25] From May 2008 – September 2008
[26] From February 2009 – present
[27] From May 2008 – February 2009
[28] From August 2009 – present

Appendix 6.4

Expert advisers to the Guideline Development Group

Professor Peter Clark	Co-chairman of the National Chemotherapy Advisory Group
Dr Ernie Marshall Knowsley Hospitals,	Macmillan Consultant in Medical Oncology Clatterbridge Centre for Oncology & St Helens & Merseyside & Cheshire Cancer Network
Karin Oien	Clinical Senior Lecturer in Molecular Pathology & Honorary Consultant Pathologist, University of Glasgow
Dr Harpreet S. Wasan	Consultant and Hon Reader in Medical Oncology, Department of Cancer Medicine, Hammersmith Hospital/Imperial College of Science, Technology and Medicine, London

Appendix 6.5

Members of the Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring its quality. The members of the Guideline Review Panel were as follows:

Dr John Hyslop – Chair
Consultant Radiologist, Royal Cornwall Hospital NHS Trust

Dr Ash Paul
Deputy Medical Director, Health Commission Wales

Professor Liam Smeeth
Professor of Clinical Epidemiology, London School of Hygiene and Tropical Medicine

Mr Peter Gosling
Lay member

Mr Johnathan Hopper
Medical Director (Northern Europe), ConvaTec Ltd