# Diagnosis and management of metastatic malignant disease of unknown primary origin

## NICE guideline

## Draft for consultation, December 2009

If you wish to comment on this version of the guideline, please be aware that all the supporting information and evidence is contained in the full version.

# Contents

# 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 heterogeneous 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 that 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.

| **Recommended terms used in this guideline** | |
|---|---|
| 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 origin (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 origin (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. |

Most patients with newly diagnosed cancer are found to have a clearly defined primary tumour after initial investigation and staging. However about 4% are eventually found to have metastatic malignancy without an identifiable primary site, despite exhaustive tests. Over 10,000 such cases occur annually in England and Wales.

Patients presenting with metastatic malignancy of undefined primary origin and those who are ultimately diagnosed with confirmed CUP are disadvantaged in many ways. There is uncertainty about the nature, timing and extent of appropriate investigation. Optimal treatment is ill-defined, with inappropriate use of some expensive palliative treatments of limited or uncertain value, or failure to use valuable, effective treatments in certain cases (for example, in occult breast cancer or extra-gonadal germ-cell

tumour). These patients are also 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 fourth most common cause of cancer death in England and Wales, is a further disadvantage for this group. No NICE cancer service guidance addresses the needs of this group of patients.

The following problems in current practice have been identified:

- lack of agreed definitions of the clinical entity
- lack of referral guidelines for suspected cancer relevant to patients without an obvious or strongly suspected primary
- lack of a system to rapidly identify patients and to ensure early specialist involvement
- lack of efficient arrangements to manage the initial diagnostic phase
- uncertainty about appropriate diagnostic tests, including the use of new technologies
- lack of a team structure to efficiently manage newly presenting patients
- lack of specialist oncology expertise
- lack of dedicated key workers/specialist nurses
- referral to inappropriate site-specific cancer teams
- lack of support and information for patients
- delays in involvement of specialist palliative care
- lack of an overarching organisational structure to ensure high-quality care
- uncertainty about optimal treatment
- lack of adequate epidemiology data
- lack of research organisation.

The aim of this guideline is to address the needs of people with CUP. This includes investigating patients with metastatic malignant disease from an undiagnosed primary cancer, defining clinical and organisational arrangements for effective management, and recommending optimal

treatment and supportive care for patients who eventually have no primary cancer identified.

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

## Patient-centred care

This guideline offers best practice advice on the care of patients with metastatic malignant disease of unknown primary origin.

Treatment and care should take into account patients' needs and preferences. People with metastatic malignant disease of unknown primary origin should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent (available from www.dh.gov.uk/consent) and the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk). In Wales, healthcare professionals should follow advice on consent from the Welsh Assembly Government (available from www.wales.nhs.uk/consent).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

# Key priorities for implementation

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

- Every CUP team should have a named lead clinician 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. [1.1.1.2]

- 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.[1.1.1.3]

- 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. [1.1.1.6]

- 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. [1.1.1.8]

**Organisation of CUP services at network and national level**

- 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 1.1.1.1)
  - 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. [1.1.2.1]

**Initial diagnostic phase**

- 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. [1.2.1.1]

- Do not use gene-expression-based profiling to identify primary tumours in patients with provisional CUP. [1.2.2.9]

**Factors influencing management decisions**

- 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. [1.3.1.2]

- Include prognostic factors in decision aids and other information for patients and carers about their treatment options. [1.3.2.3]

**Chemotherapy in patients with confirmed CUP**

- 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. [1.5.1.1]

# 1 Guidance

## *1.1 Organisation of services and support*

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

1.1.1.1 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.

1.1.1.2 Every CUP team should have a named lead clinician 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.

1.1.1.3 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.

1.1.1.4 Trusts should ensure that patients have access to an identified CUP specialist nurse/key worker when malignancy of undefined primary origin is diagnosed.

1.1.1.5 Refer patients with malignancy of undefined primary origin to the CUP team immediately.

1.1.1.6 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.

1.1.1.7 The CUP team should actively review the outcome of all investigations with the nominated pathologist and radiologist as appropriate.

1.1.1.8 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.

1.1.1.9 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.

1.1.1.10 Trusts should ensure that a system for tracking patients with malignancy of undefined primary origin is established and maintained.

1.1.1.11 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.

### 1.1.2 Organisation of CUP services at network and national level

1.1.2.1 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 1.1.1.1)
- 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.

1.1.2.2 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.

## *1.2 Diagnosis*

For patients presenting with metastatic malignancy of undefined primary origin, the diagnostic process can be divided into two phases. The aim in the initial diagnostic phase is to perform the most appropriate investigations in the most efficient fashion for relevant patients, to identify either a primary site, (which will guide treatment decisions), or a pathological subgroup for which definitive treatment can be planned regardless of primary site (the major diagnoses in this group are lymphoma, other haematologic malignancies, melanoma, sarcoma, and germ-cell tumours).

If metastatic epithelial or neuro-endocrine malignancy without an identifiable primary site is diagnosed, subsequent management 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 is defined on page 4 of this guideline.

A second phase of more specific investigations is appropriate for some patients with provisional CUP. After all subsequent tests have been completed and a primary site has not been identified, a diagnosis of confirmed carcinoma of unknown primary (confirmed CUP) can be applied. This is defined on page 4 of this guideline.

In current practice, the tests required in the initial diagnostic phase are not universally agreed. Subsequent, more complex investigations in patients with provisional CUP are similarly ill defined and are not evidence-based. In this guideline, optimal approaches to the following aspects of the diagnostic process have been examined.

- The selection of initial tests to be undertaken in patients for whom investigation is clinically relevant.
- The contribution of specialised tests.
- Optimal histological assessment of tissue samples.
- The best approaches in specific or difficult diagnostic circumstances.

### 1.2.1 Initial diagnostic phase

1.2.1.1 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.

### 1.2.2 Special tests

**Tumour markers**

1.2.2.1 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.

**Upper and lower gastrointestinal (GI) endoscopy**

1.2.2.2 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.

**Mammography**

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

**Breast magnetic resonance imaging (MRI)**

1.2.2.4 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.

**Positron emission tomography - computed tomography (PET-CT)**

1.2.2.5 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.

1.2.2.6 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.

**Immunohistochemistry**

1.2.2.7 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.

1.2.2.8 Use additional immunohistochemistry to refine the differential diagnosis, guided by the results of the panel of antibodies in recommendation 1.2.2.7 and the clinical picture.

**Gene-expression-based profiling**

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

### 1.2.3 Investigation of specific clinical presentations

**Intrapulmonary nodules without evidence of endobronchial disease**

1.2.3.1 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.

1.2.3.2 Offer video-assisted thoracoscopic surgery (VATS) exploration to patients only after a negative bronchoscopic procedure and where percutaneous biopsy is considered inappropriate.

**Investigation of malignant peritoneal disease**

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

## *1.3 Factors influencing management decisions*

### 1.3.1 When to stop investigations

1.3.1.1 Do not offer further investigations to identify the primary site of origin of the malignancy to patients who are unfit for treatment.

1.3.1.2 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.

1.3.1.3 Explain to patients and carers if further investigations will not alter treatment options. Provide appropriate emotional and psychological support.

1.3.1.4 Provide information about CUP, treatment options and palliative care to patients and carers.

### 1.3.2 Selecting optimal treatment

**Optimal treatment**

1.3.2.1 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.

1.3.2.2 Discuss the patient's prognostic factors with the patient and their carer, if appropriate, to help them make informed decisions about treatment.

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

**Decision aids**

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

**Gene-expression-based profiling**

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

## *1.4 Managing specific presentations*

### 1.4.1 Presentations that may benefit from radical treatment

**Squamous carcinoma involving upper or mid-neck nodes**

1.4.1.1 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.

**Adenocarcinoma involving the axillary nodes**

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

**Squamous carcinoma involving the inguinal nodes**

1.4.1.3 Refer patients with squamous carcinoma confined to the inguinal nodes to a specialist surgeon in an appropriate MDT, to consider treatment with curative intent.

1.4.1.4 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.

**Radical treatment for solitary metastases**

1.4.1.5 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.

1.4.1.6 Refer patients with a solitary tumour in the liver, brain, bone or lung to the appropriate MDT to consider radical local treatment.

### 1.4.2 Presentations with a poor prognosis

**Multiple metastases including brain involvement**

1.4.2.1 Refer patients presenting with brain metastases as the first sign of malignant disease to a neuro-oncology MDT for evaluation and treatment.

1.4.2.2 Do not offer chemotherapy to patients with brain metastases of unknown primary origin except as part of a controlled clinical trial.

1.4.2.3 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.

## *1.5 Systemic treatment*

### 1.5.1 Chemotherapy in patients with confirmed CUP

1.5.1.1 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.

1.5.1.2 Offer patients with CUP the opportunity to enter clinical trials.

1.5.1.3 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.

### 1.5.2 Chemotherapy for recognised treatable syndromes

1.5.2.1 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.

# 2 Notes on the scope of the guidance

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is available from www.nice.org.uk/guidance/index.jsp?action=download&o=41352

**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).
- 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.

**How this guideline was developed**

NICE commissioned the National Collaborating Centre for Cancer to develop this guideline. The Centre established a guideline development group (see appendix A), which reviewed the evidence and developed the recommendations. An independent guideline review panel oversaw the development of the guideline (see appendix B).

There is more information about how NICE clinical guidelines are developed on the NICE website (www.nice.org.uk/howwework). A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' (fourth edition, published 2009), is available from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N1739).

# 3 Implementation

NICE has developed tools to help organisations implement this guidance (see www.nice.org.uk/CGXX).

# 4 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future. The Guideline Development Group's full set of research recommendations is detailed in the full guideline (see section 5).

## *4.1 Clinical studies group for CUP*

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.

**Why this is important**

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.

## *4.2 Use of PET-CT in the malignancy of undefined primary origin diagnostic pathway*

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.

**Why this is important**

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.

## *4.3 Decision aids*

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

**Why this is important**

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.

## *4.4 Gene-expression-based profiling*

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.

**Why this is important**

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.

## *4.5 Defining optimal systemic therapy*

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

**Why this is important**

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.

# 5 Other versions of this guideline

## *5.1 Full guideline*

The full guideline, 'Diagnosis and management of metastatic malignant disease of unknown primary origin' contains details of the methods and evidence used to develop the guideline. It is published by the National Collaborating Centre for Cancer, and is available from [NCC website details to be added] and our website (www.nice.org.uk/CGXXfullguideline). **[Note: these details will apply to the published full guideline.]**

## *5.2 Quick reference guide*

A quick reference guide for healthcare professionals is available from www.nice.org.uk/CGXXquickrefguide

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1XXX). **[Note: these details will apply when the guideline is published.]**

## *5.3 'Understanding NICE guidance'*

A summary for patients and carers ('Understanding NICE guidance') is available from www.nice.org.uk/CGXXpublicinfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1XXX). **[Note: these details will apply when the guideline is published.]**

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about metastatic malignant disease of unknown primary origin.

# 6 Related NICE guidance

**Published**

- Referral for suspected cancer. NICE clinical guideline 27 (2005). Available from www.nice.org.uk/CG27
- Improving supportive and palliative care for adults with cancer. NICE service guidance (2004). Available from www.nice.org.uk/CSGSP

# 7 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations.

# Appendix A: The Guideline Development Group

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**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 (from September 2008)**
Lead Nurse and Nurse Consultant, Royal Chesterfield Hospital

**Professor Archibald Malcom**
Consultant Histopathologist, Royal Shrewsbury Hospital

**Dr Orest Mulka**
GP, Measham, Leicestershire

**Karen Pattison (May to September 2008)**
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 (from April 2009)**

Patient and carer member

**Mr Mike Williams**

Consultant General Surgeon, Cumberland Infirmary Carlisle

**Penny Wilson-Webb (May to December 2008)**

Patient and carer member

**Dr Anne Vaughan-Thomas (May 2008 to August 2009)**

Patient and carer member

# Appendix B: The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

**Dr John Hyslop (Chair)**
Consultant Radiologist, Royal Cornwall Hospital NHS Trust

**Dr Ash Paul**
Deputy Medical Director, Health Commission Wales

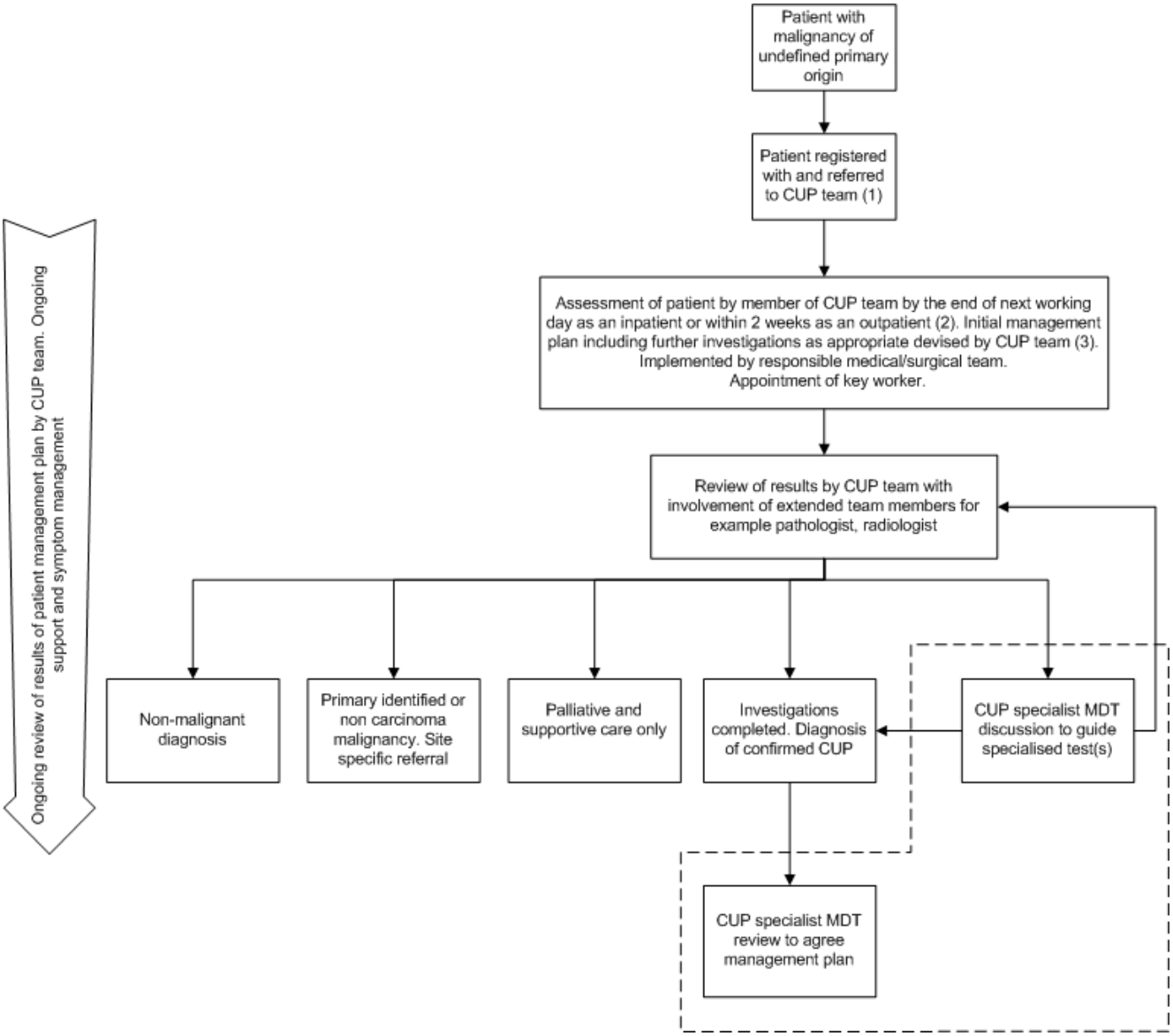
**Professor Liam Smeeth**
Professor of Clinical Epidemiology, London School of Hygiene and Tropical Medicine

**Mr Peter Gosling**
Lay member

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

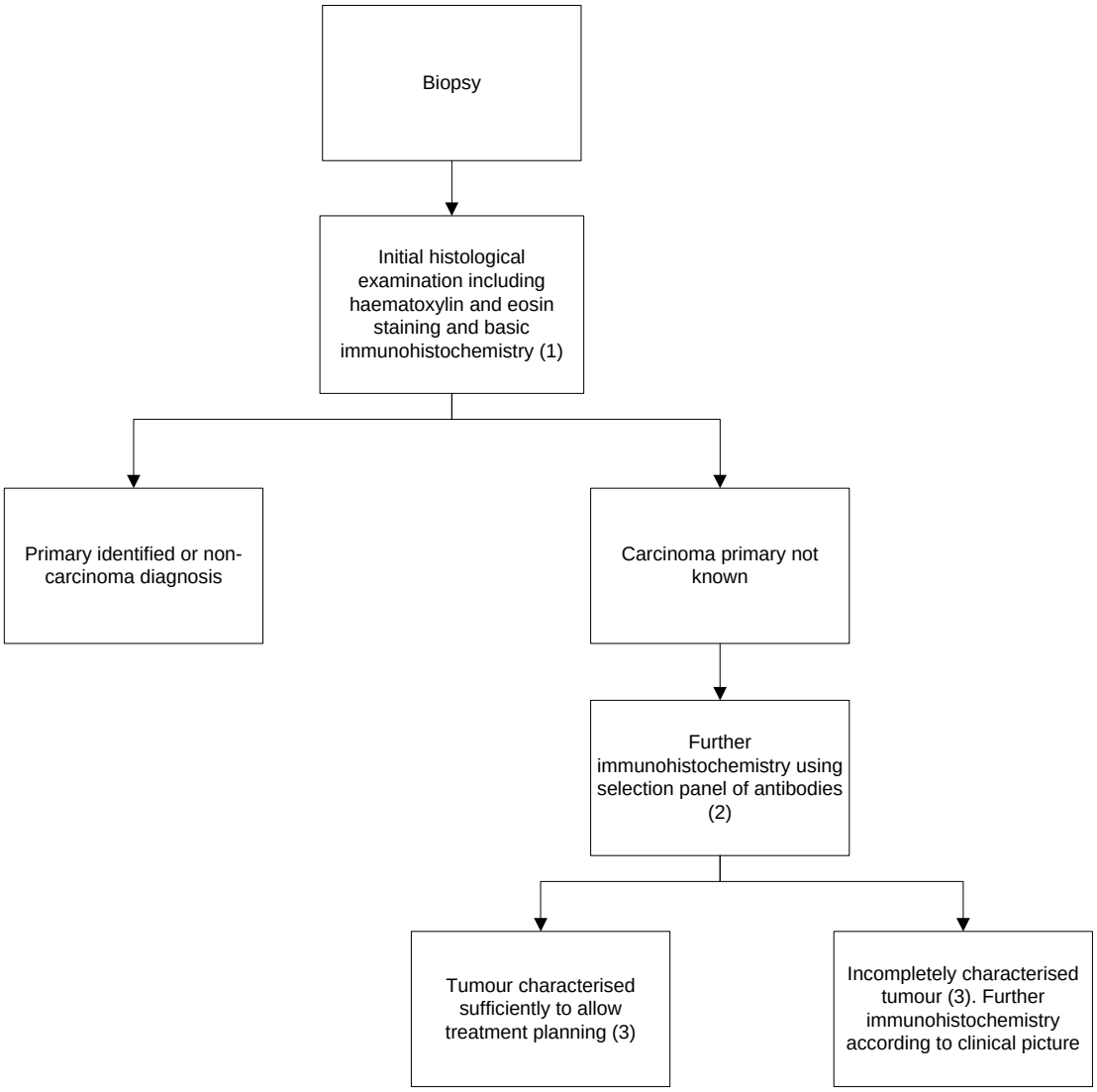
# Appendix C: The algorithms

### 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 IHC to be reviewed in conjunction with all other clinical evidence