

**Cancer of Unknown
Primary (CUP)**

Pathways and Guidelines (v 2)

London Cancer

April 2017

The following pathways and guidelines document has been compiled by the *London Cancer* CUP technical subgroup and agreed by the Acute Oncology ERG chair for use in all Trusts across *London Cancer*.

Agreed at the Cancer of Unknown Primary Expert Reference Group
Meeting
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1. Introduction

Cancer of Unknown Primary (CUP) sits within the remit of the Acute Oncology Service (AOS) Expert Reference Group. This document outlines the specific agreed patient pathways and the expectations for investigation and management of this subgroup of patients.

This policy has been developed using the NICE Guidance CG104: Diagnosis and management of metastatic malignancy disease of unknown primary origin, July 2010 <http://www.nice.org.uk/CG104> and the ESMO clinical practice guidelines for CUP 2015. Agreed services are in place to ensure that unnecessary investigation is avoided, and management is appropriate, with optimal patient experience

2. Definitions

Patients covered by these guidelines fall into 3 main groups:

Malignancy Of Undefined Primary Origin (MUO)	Metastatic malignancy identified on the basis of a limited number of tests, without an obvious primary site, before comprehensive investigation.
Provisional Carcinoma of Unknown Primary origin (provisional CUP)	Metastatic epithelial or neuro-endocrine malignancy identified on the basis of histology or cytology, with no primary site detected despite a selected initial screen of investigations, before 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 site detected despite a selected initial screen of investigations, specialist review, and further specialist investigations as appropriate

3. Pathways between teams and services

Preliminary investigations may have been carried out in A&E, by the patient's GP, by the AOS team or by another specialist team which raise the suspicion of MUO. Close working relationships with A&E are required since ~57% of all MUO/CUP patients present via this route. Hospital inpatients should be referred to the CUP or Acute Oncology teams if there is any suspicion of a new cancer diagnosis based on imaging suggestive of metastatic malignancy in the absence of an identifiable primary tumour.

Patients should be referred to the CUP MDT on the basis of *limited imaging* which is suggestive of metastatic disease (eg chest X ray with lung metastases, ultrasound abdomen suggesting liver metastases) without an obvious primary site. Sometimes this referral will be via the AOS team, and in other cases this will be from another team in primary or secondary care.

The CUP team will review all patients with metastatic disease from suspected or diagnosed cancer of unknown primary (MUO), including people who have been treated for cancer before. The CUP team will aim to see and assess a newly diagnosed MUO patient by the end of the next working day if an inpatient or within 2 weeks if referred as an outpatient (Appendix 1 for pathways between teams).

Following initial assessment, any further investigations should be decided by the CUP MDT in conjunction with the informed patient. The CUP/MUO teams will also assess the holistic needs of the patient and make early referral to palliative care if appropriate. The team will consider the patients' wishes and the suitability for further investigations.

All cases of MUO/CUP should be discussed at the weekly local CUP MDT but management decisions should not be delayed for those patients presenting between the MDTs. The case may also be discussed at a local site-specific MDT as appropriate depending on the clinical features.

The CUP team should ensure that for each referral a management plan exists which includes:

- a) Appropriate investigations (see below)
- b) Symptom control (early palliative care referral is advised)
- c) Access to psychological support and
- d) Access to information

The CUP team should continue to be involved in the patient's care until the patient is either:

- a) Referred to a site-specialist consultant or
- b) Referred for palliative care alone or
- c) Diagnosed with a non-malignant condition.

The CUP team will continue to manage the patient's care if confirmed CUP (cCUP) is diagnosed.

4. Patient Investigations

The investigation of all patients presenting as MUO is outlined below:

The CUP team agrees that for each patient

- a) Further investigations to identify the primary site of origin of the malignancy should not be offered to patients who are too unfit for treatment
- b) Investigations to find the primary should only be carried out if
 - a. The results are likely to affect a treatment decision
 - b. The patient understands why the investigations are being carried out
 - c. The patient understands the potential risks and benefits of investigations and treatment and
 - d. The patient is prepared to accept the eventual treatment

- c) CUP team will offer explanation to patients and carers when further investigations will not alter treatment options
- d) Provide emotional and psychological support, information about treatment options and palliative care

Confirmed CUP patients who are being considered for chemotherapy should

- a) Have the balance between potential risks and benefits discussed with them
- b) If it is decided to proceed with chemotherapy, be offered entry into a clinical trial if available

5. CUP / MUO Investigation protocols

If the patient is fit and agrees to further investigation the following are suggested based on the NICE guidance (CG104)

Initial diagnostic phase following review by MUO/CUP MDT member and guided by the patient's symptoms and performance status:

- Comprehensive History and examination (including breast / nodal regions / skin/genital/rectal and pelvic examination)
- Bloods – full blood count, urea and electrolytes, bone profile, liver function tests and clotting
- CT chest / abdomen and pelvis
- Routine measurement of tumour markers is not recommended except in certain patterns of disease
 - Myeloma screen (for isolated or multiple lytic bone lesions)
 - PSA in men
 - AFP and hCG – especially in midline nodal distributed disease (mediastinal masses and / or retroperitoneal masses)
 - AFP to aid diagnosis of hepatocellular cancer
 - Ca125 in women with peritoneal and or ascites
- Biopsy with standard histological examination, with immunohistochemical examination according to RCPATH guidelines and local departmental policy in order to distinguish carcinoma from other malignant processes

Solitary metastases:

In cases where there is evidence of an isolated lesion and solitary site of disease, further discussion at a site-specific MDT is encouraged BEFORE any biopsy which could compromise the chance of potentially curative treatment eg liver / brain / bone / skin and lung.

Second diagnostic phase: Careful consideration of further investigations should be made by the CUP MDT taking into consideration the following:

- Upper and Lower GI endoscopy
Only in patients with MUO if the symptoms, histology or radiology suggest a GI primary and its determination changes future management
- Mammography
Do not offer mammography routinely to women presenting with MUO unless clinical or pathological features are compatible with breast cancer
- Breast magnetic resonance imaging (MRI)
Patients with adenocarcinoma involving the axillary lymph nodes should be referred to the breast MDT for further evaluation and treatment. If no breast primary tumour is identified after standard breast investigations the breast MDT may recommend dynamic contrast-enhanced breast MRI to identify lesions suitable for targeted biopsy
- Positron emission tomography-computed tomography (PET)
Offer 18F-FDG PET to patients with provisional CUP presenting with cervical lymphadenopathy with no primary detected on ear, nose and throat panendoscopy if radical treatment is considered an option. Consider PET in patients with provisional CUP with extra-cervical presentations after discussion with the CUP team
- Testicular ultrasound
Only use testicular ultrasound in men with presentations compatible with germ cell tumours eg CT demonstrating enlarged para-aortic lymph nodes

Investigation of specific clinical presentations (as per CG104)

- Intrapulmonary nodules without evidence of endo-bronchial disease or other site specific disease
These patients should be referred to a specialist chest team for ongoing management and investigation
- Investigation of malignant peritoneal disease
Obtain a tissue sample for histological examination in patients with MUO presenting as ascites, if technically possible

Histopathology

Pathological work up of a suspected CUP should be undertaken in accordance with the NICE and ESMO guidance

Immunohistochemistry

Use a panel of antibodies comprising cytokeratin 7 (CK7), CK20, thyroid transcription factor-1 (TTF-1), placental alkaline phosphatase (PLAP), oestrogen receptor (ER; women only) and PSA (men only) in all patients with adenocarcinoma of unknown origin. Use additional immunohistochemistry (see ESMO guidelines) to refine the differential diagnosis, guided by the results of the panel of antibodies above and the clinical picture.

ROUTINE GENE-EXPRESSION-BASED PROFILING TO IDENTIFY PRIMARY IN PATIENTS WITH pCUP IS NOT RECOMMENDED

6. Patient Management pathway

All patients with MUO / provisional CUP should be discussed at the next CUP MDT for

- a) Discussion of further investigations
- b) Discussion of suitability for active treatment
- c) Any other relevant treatment planning decisions including early referral to palliative care if appropriate

Patients will be re-discussed following any further investigations to agree a diagnosis of confirmed CUP (cCUP). Patients may be re-discussed at any time as required for their ongoing management.

Where patients have been referred to a site-specific team (see section 7) then ongoing MDT-discussion and decision making is expected to be at the site-specific MDT meeting. They should be identified in those discussions as an MUO/CUP patient but do not need to be re-discussed at the CUP MDT as well.

7. Specific Presentations that may benefit from radical treatment and or ongoing referral to specialist MDT input

Some presentations of MUO have potentially more favourable outcome if managed appropriately. These presentations need to be identified at the CUP MDT and managed and referred on accordingly.

Squamous carcinoma involving upper- or mid-neck nodes

If the biopsy shows squamous cell carcinoma involving only upper or mid-neck nodes, and the CT scan excludes metastatic disease, the patient should be referred to the head and neck MDT for evaluation and treatment.

Offer PET-CT to patients with provisional CUP presenting with cervical lymphadenopathy with no primary tumour identified on ear, nose and throat pan-endoscopy if radical treatment is considered to be an option.

Adenocarcinoma involving the axillary nodes in females

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

Squamous carcinoma involving the inguinal nodes

Refer patients with squamous carcinoma confined to the inguinal nodes to the specialist anal MDT for review by a specialist surgeon to consider treatment with curative intent.

Solitary metastases

In cases where there is evidence of an isolated lesion and solitary site of disease, further discussion at a site-specific MDT is encouraged BEFORE any biopsy which could compromise the chance of potentially curative treatment. Consider that an apparent metastasis could be an unusual primary tumour.

Other presentations that require specialist input are

Poorly differentiated carcinoma with a midline distribution

For cases with features of extra-gonadal germ cell tumours, refer urgently to specialist germ cell tumour team for evaluation and ongoing management.

Poorly differentiated neuroendocrine carcinoma

Refer patients to the specialist neuroendocrine MDT for ongoing evaluation and treatment

Women with predominantly peritoneal adenocarcinoma

Refer patients to the specialist gynaecology MDT for ongoing evaluation and treatment.

8. Specific presentations with a poor prognosis**Brain metastases**

A significant proportion of patients presenting with brain metastases of unknown primary are likely to present as inpatients and the AOS/CUP team should be contacted for advice and to review the patient within one working day of admission. Patient should have initial investigations, including history and clinical examination, blood tests and a CT scan of the chest, abdomen and pelvis as detailed previously. Refer patients presenting with apparent brain metastases as the only sign of malignant disease after initial investigations to the specialist neuro-oncology MDT for further management advice. If there is systemic disease, a biopsy of one of the other sites of metastasis may be appropriate. Early referral to palliative care should be considered.

Multiple Metastases Including Brain

Patients diagnosed with confirmed CUP involving the brain and multiple other sites are known to have a poor prognosis. The care of these patients should be focused on optimal symptom management and palliative care support, with palliative cranial irradiation offered to some patients. Early referral to palliative care should be encouraged.

It remains important to consider more treatable primaries with a high response rate to systemic therapies and if appropriate refer to a site-specific MDT. However extensive investigations to seek a primary should not be undertaken due to evidence showing that these are unlikely to field useful results and may impair quality of life.

Patients with brain metastases of unknown primary origin and their carers should be informed that there is currently no evidence that any treatment offers improved survival and that there is limited evidence of improvement in neurological symptoms with surgery and/or whole brain radiotherapy.

9. Active treatment of CUP patients

In order to select the optimal treatment for patients with pCUP and cCUP certain prognostic factors need to be taken into account including

- Performance status of the patient
- Patient preference
- Patient comorbidities
- Presence of liver metastases
- Presence of brain metastases (see above)

The results of investigations should be reviewed by the local CUP team. If a primary is found, the patient should be referred to the site-specific MDT. If a non-epithelial malignancy such as lymphoma, melanoma, sarcoma and germ cell tumour is diagnosed the patient should be referred to the appropriate specialist MDT. Patients who fit the criteria within

section 7 should be referred to the appropriate MDT as outlined above and managed in line with those protocols and algorithms.

Otherwise confirmed CUP patients who are being considered for chemotherapy should

- a) Have the balance between potential risks and benefits discussed with them
- b) If it is decided to proceed with chemotherapy, be offered entry into a clinical trial if available

Systemic chemotherapy in patients with confirmed cCUP

If chemotherapy is being considered for patients with CUP, with no clinical features suggesting a specific treatable syndrome, the case should be discussed at the local CUP MDT. The clinical and pathological characteristics of the tumour and the toxicity profile of the drugs should be considered in treatment recommendations, along with the likely response rate. Patients should only be offered chemotherapy if of adequate performance status.

Possible regimes include:

- ECF
- ECX
- EOX
- Oxaliplatin and MDG/ capecitabine
- Irinotecan and MDG
- Single agent Capecitabine
- Cisplatin and Gemcitabine
- Carboplatin and Gemcitabine
- Cisplatin / Etoposide
- Carboplatin / Etoposide
- Carboplatin and Paclitaxel
- Single agent Paclitaxel

10. Data Collection

From January 2013, the Cancer Outcomes and Service Dataset (COSD) replaced the previous National Cancer Dataset as the new national standard for reporting cancer in the NHS in England. It incorporates a revised generic Cancer Registration Dataset, and additional clinical and pathology site specific data items relevant to different tumour types.

The CUP Subgroup agrees with the National policy for the collection of COSD, which specifies:

- when each data items should be captured on the patient pathway;
- how the data will be stored and managed within local data systems;
- that in addition to the above, each MDT should record the number of patients referred to them and each of the MDT's associated MUO/CUP assessment services should register all referrals of patients with MUO.

Appendix 1. Pathways between teams and services

