East Midlands Clinical Networks

Cancer of Unknown Primary (CUP)

Pathways and Guidelines

V1.0

London Cancer

September 2013

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

Agreed at the Acute Oncology Services Expert Reference Group Meeting Date:
10th September 2013
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The East Midlands Acute Oncology Service Expert Clinical Advisory Group has agreed to adopt these guidelines on 26 February 2016.

INTRODUCTION

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

All CUP teams across London *Cancer* agree to adhere to the management pathway defined in the NICE guidance (CG104). Agreed services are in place to ensure that unnecessary investigation is avoided, and management is appropriate, with optimal patient experience.

DEFINITIONS

Patients covered by this pathway and guideline fall into three main categories:

- ***Malignancy of undefined primary*** *origin (MUO)*: that is metastatic malignancy diagnosed 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)*: that is 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)*: that is 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 specialised investigations as appropriate.

PATHWAYS BETWEEN TEAMS AND SERVICES

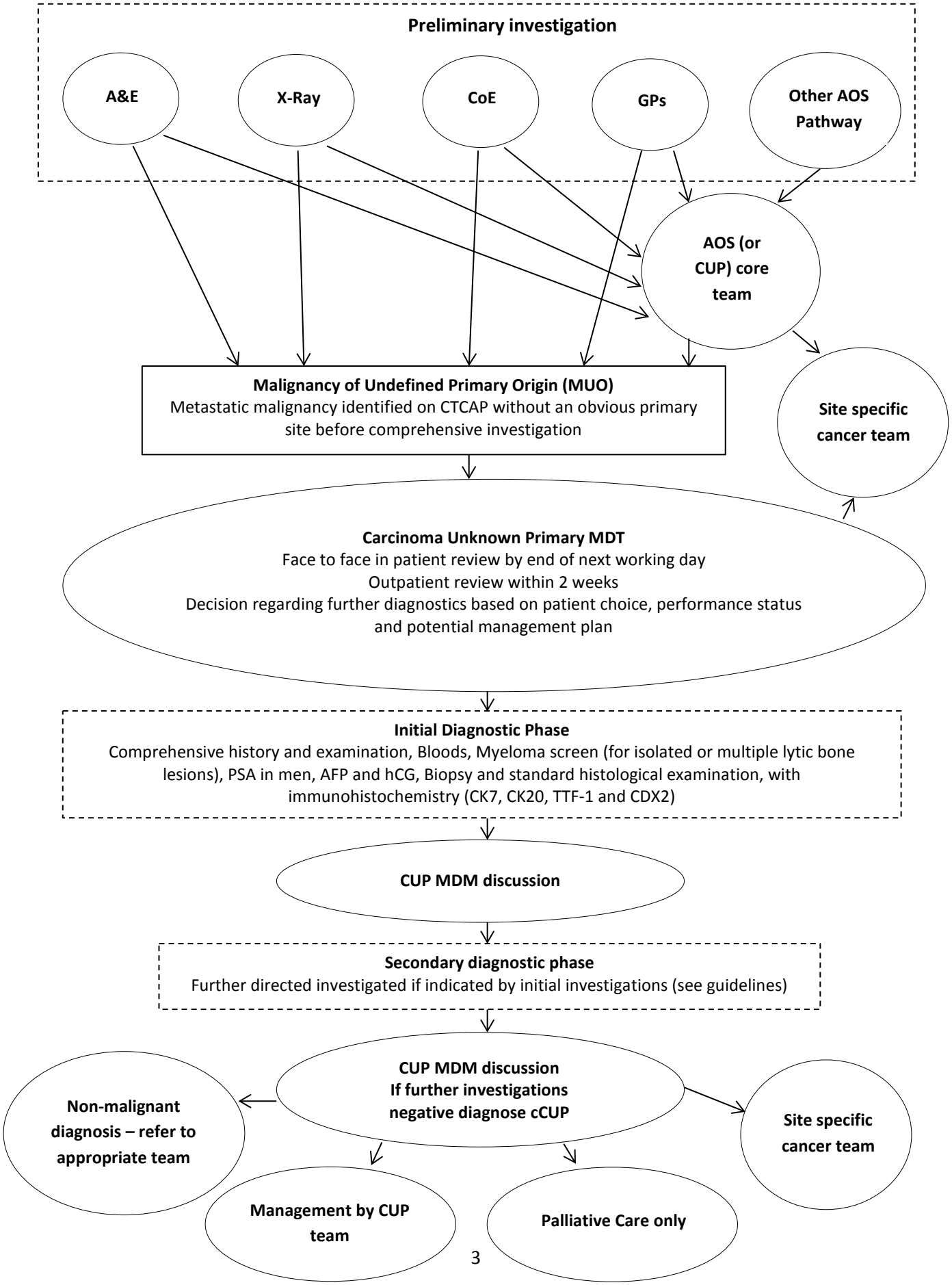
Peer review measure 12-1C-105m

Preliminary investigations may be carried out in A&E, by the patient's GP, by the AOS team or by another specialist team following referral from primary care, which raise the suspicion of MUO. Inpatients should be referred to the Acute Oncology team if there is any suspicion of a new cancer diagnosis (in some services these patients may automatically be referred to the CUP team).

Patients should be referred to the CUP MDT on the basis of CTCAP which is suggestive of metastatic disease (e.g. 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 of 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.

Figure 1


Preliminary investigation
A&E
X-Ray
CoE
GPs
Other AOS Pathway
AOS (or CUP) core team
Site specific cancer team
Malignancy of Undefined Primary Origin (MUO)
Metastatic malignancy identified on CTCAP without an obvious primary site before comprehensive investigation
Carcinoma Unknown Primary MDT
Face to face in patient review by end of next working day
Outpatient review within 2 weeks
Decision regarding further diagnostics based on patient choice, performance status and potential management plan
Initial Diagnostic Phase
Comprehensive history and examination, Bloods, Myeloma screen (for isolated or multiple lytic bone lesions), PSA in men, AFP and hCG, Biopsy and standard histological examination, with immunohistochemistry (CK7, CK20, TTF-1 and CDX2)
CUP MDM discussion
Secondary diagnostic phase
Further directed investigated if indicated by initial investigations (see guidelines)
CUP MDM discussion
If further investigations negative diagnose cCUP
Non-malignant diagnosis – refer to appropriate team
Site specific cancer team
Management by CUP team
Palliative Care only

Following initial assessment, any further investigations should be decided by the CUP MDT in conjunction with the informed patient. The CUP team should ensure that for each referral a management plan exists which includes:

a) Appropriate investigations
b) Symptom control
c) Access to psychological support and;
d) Providing information

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

Referred to a site-specialist Consultant or
Referred for palliative care alone or
or Diagnosed with a non-malignant condition.

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

The pathway is outlined in **figure 1**. Further details of investigation and management policy are contained within the remainder of this document.

PATIENT INVESTIGATION AND MANAGEMENT POLICY

The investigation and subsequent management of all patients presenting as cases of Malignancy of Unknown Origin (MUO).

Peer review measure 12-1C-104m

The CUP team agrees that for each patient referred that:

1. Continuing investigations to find the primary should only be carried out if
   a) The patient is fit for treatment should the primary be found
   b) The results are likely to affect a treatment decision
   c) The patient understands why the investigations are being performed and the potential risks and benefits of investigation and treatment and
   d) The patient is prepared to accept the eventual treatment

2. Confirmed CUP patients without a specific "treatable syndrome" who are being considered for chemotherapy, should
   a) Have the balance between potential risks and benefits discussed with them and
   b) If it is decided to proceed with chemotherapy, be offered entry into a clinical trial if available

3. Confirmed CUP patients with a "treatable syndrome" and fit for treatment should be offered chemotherapy according to Network guidelines for the management of specific subgroups.

NETWORK CUP INVESTIGATION PROTOCOLS

Peer review measures 12-1C-106m, 12-1C-10m, 12-1C-108m

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 CUP MDT member and guided by the patient's symptoms and performance status:

Comprehensive history and examination (including breast/nodal areas (groin, axilla and neck)/skin/genital/rectal and pelvic examination)

Bloods – full blood count, urea and electrolytes, liver function tests, bone profile, clotting

Routine measurement of tumour markers is not recommended except in certain patterns of disease:

Myeloma screen (for isolated or multiple lytic bone lesions)
PSA and PSAP in men
AFP and hCG – especially in midline nodal distributed disease (mediastinal masses and/or retroperitoneal masses)
AFP to help diagnose hepatocellular cancer

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.

If a provisional CUP diagnosis is made at this stage then the patient should be discussed at the next CUP MDT meeting.

- **Solitary metastases**. Do not investigate a tumour inappropriately because this may make radical treatment ineffective. Refer patients with a solitary tumour in the liver, brain, bone, skin or lung to the appropriate MDT to consider radical local treatment.

Second diagnostic phase. Careful consideration of further investigations should be made by CUP MDT, in line with the following:

Upper and Lower GI endoscopy

Only carry out upper and lower GI endoscopy in patients with MUO if the symptoms, histology or radiology suggest a GI primary tumour and its determination changes future management.

Mammography

Only offer mammography to patients presenting with MUO if clinical or pathological features are compatible with breast cancer, do not offer this routinely.

Breast magnetic resonance imaging (MRI)

Only offer breast MRI to patients presenting with MUO if clinical or pathological features are compatible with breast cancer, do not offer this routinely.

Positron emission tomography-computed tomography

Offer PET-CT of the neck to patients with pCUP presenting with cervical lymphadenopathy with no primary tumour identified on ear, nose and throat panedoscopy if radical treatment is considered to be an option.

Testicular ultrasound

Only use testicular ultrasound in men with presentations compatible with germ cell tumours

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

Investigation of specific clinical presentations

- Intrapulmonary nodules without evidence of endobronchial disease or other site systemic disease. Patients should be referred to a specialist chest team for expert investigation and management.

- Investigation of malignant peritoneal disease. Obtain a tissue sample for histological examination in patients with MUO who present with ascites, if technically possible.

DISCUSSION AT CUP MDT

As detailed above, all patients with provisional CUP (pCUP) should be discussed at the next CUP MDT for

- Discussion of further investigations
- Discussion of suitability for active treatment and any other relevant treatment planning decisions

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 on-going management.

Where patients have been referred to site specific team (see below) then on-going MDT discussion and decision making is expected to be at the site specific MDT meeting. They should be identified in that discussion as an MUO/CUP patient, but do not need to be re-discussed at the CUP MDT as well.

MANAGEMENT PATHWAY

Peer review measures 12-1C-106m, 12-1C-107m, 12-1C-108m

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

- Performance status of the patient
- Patient preference
- Patient comorbidities
- Presence of liver metastases

Referral of pCUP patients to site specific teams

Patients with these specific subgroups should be referred to the indicated team for best management:

Poorly differentiated carcinoma with a midline distribution	Germ cell tumour team
Squamous carcinoma involving inguinal nodes	Anal team
Women with predominately peritoneal adenocarcinoma	Gynaecological team
Adenocarcinoma involving the axillary lymph nodes	Breast team

Squamous carcinoma of lymph nodes in the upper or mid neck	Head and neck team
Poorly differentiated neuroendocrine carcinoma	Neuroendocrine team
Brain metastases are the only apparent sign of malignancy	Neuro-oncology MDT
Multiple brain metastases with no other signs of systemic disease	Neuro-oncology MDT

Where the clinical profile fits a certain primary, even if it is not confirmed, then consider referral to the appropriate site specific MDT.

Chemotherapy in patients with confirmed CUP

If chemotherapy is being considered for patients with confirmed CUP, with no clinical features to suggest a treatable syndrome, inform patients of the potential benefits and risks of treatment. Offer patients with confirmed CUP the opportunity to enter clinical trials. If chemotherapy is offered outside clinical trials take into consideration the clinical and pathological characteristics of the tumour, the toxicity profile of the drugs and response rate when choosing which treatment to use.

Standard regimens for the first line treatment of CUP include:

- ECX/EOX
  +/- Epirubicin 50mg/m^2 iv bolus
  Cisplatin 60mg/m^2 or Oxaliplatin 130mg/m^2 iv with hydration every 3 weeks
  Capectabine 1250mg/m^2 po in 2 divided doses daily or 5FU 300mg/m^2/day CI

All Patients

Patients should be offered clinical trials where this is applicable.

DATA COLLECTION

Peer review measures 12-1C-103m

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.

Further details are available at
http://www.ncin.org.uk/collecting_and_using_data/data_collection/cosd