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# CANCER OF UNKNOWN PRIMARY INVESTIGATION AND MANAGEMENT POLICY AND PROTOCOLS

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## 1. Introduction

Patients with malignancy of undefined primary origin (MUO) present in many different ways to different parts of health service organisations. The process for investigating and subsequently managing patients with MUO or CUP is complex and variable. The nature and extent of initial investigations are influenced by 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.

The purpose of this document is to provide a network wide guidance for the investigation and management of patients with a Malignancy of Unknown Origin. The Lancashire and South Cumbria Cancer of Unknown Primary Clinical Reference Group follow the NICE Clinical Guideline 104 for 'Diagnosis and Management of Metastatic Malignant Disease of Unknown Primary Origin' and have based these guidelines on those recommendations.

## 2. Key Definitions

**Confirmed Cancer of Unknown Primary (Confirmed CUP)** – Metastatic epithelial or neuroendocrine 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.

**Provisional Cancer of Unknown Primary (Provisional CUP)** - Metastatic epithelial or neuroendocrine malignancy identified on the basis of histology/cytology, with no primary site detected despite a selected initial screen of investigations, before specialist review and possible further specialised investigations.

**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.

## 3. Investigations

There are numerous different clinical presentations of MUO and it is inappropriate to apply exactly the same panel of investigations in every patient.

**DO NOT offer** further investigations if patients are unfit for treatment.

Only perform Investigations if:

- The results are likely to affect treatment decision
- The patient understands why they are being done, and the potential risks and benefits of the investigations and treatment
- The patient is prepared to accept treatment

Explain to patients and carers if further investigations will not alter treatment options.  
Provide:

- Emotional and psychological support through the CUP specialist nurse, local Acute Oncology team and palliative care teams

- Information about CUP; treatment options and palliative care if necessary.

#### **4. Initial diagnostic Tests**

Offer to patients with MUO when clinically appropriate; be guided by the patient's symptoms:

- Comprehensive history and physical examination including breast, nodal areas, skin, genital, rectal and pelvic examination
- Full blood count, urea, electrolytes and creatinine, liver function tests, calcium, urinalysis, lactase dehydrogenase
- Chest X-ray
- Myeloma screen (where isolated or multiple lytic bone lesions)
- Symptom directed endoscopy
- Computed tomography (CT) scan of the chest, abdomen and pelvis
- Tumour markers, prostate specific antigen (PSA) in men, cancer antigen 125 (CA125) in women with peritoneal malignancy or ascites, alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) in patients with midline metastatic disease
- Testicular ultrasound in men with presentations compatible with germ cell tumours
- Biopsy and standard histological examination, with immunohistochemistry, if necessary, to distinguish carcinoma from other malignant diagnoses.

## 5. Special Diagnostic Tests

Recommendations of the use of further diagnostic tests are based on recommendations from NICE Clinical Guideline 104 (2010), ESMO Clinical Guideline 2023, RCPATH Standards and datasets for reporting cancers 2018, NHSE Genomic Test Directory 2023 and NCCN Clinical Practice Guideline 1/2023 and are detailed below.

Test	Action
<b>Tumour markers</b>	<p>Only measure:</p> <ul style="list-style-type: none"> <li>• AFP and hCG in presentations compatible with germ-cell tumours (particularly mediastinal and/or retroperitoneal masses and in young men).</li> <li>• AFP in presentations compatible with hepatocellular cancer.</li> <li>• PSA in presentations compatible with prostate cancer.</li> <li>• CA125 in presentations compatible with ovarian cancer (including inguinal node, chest, pleural, peritoneal or retroperitoneal presentations). Carefully interpret the results because of limited test specificity.</li> </ul>
<b>Upper and lower gastrointestinal (GI) endoscopy</b>	Carry out only if the symptoms, histology or radiology suggest a GI primary tumour.
<b>Mammography</b>	Do not offer routinely unless clinical or pathological features are compatible with breast cancer.
<b>Breast magnetic resonance imaging (MRI)</b>	<p>Refer patients with adenocarcinoma involving the axillary nodes to a breast cancer MDT.</p> <p>If a primary tumour is not identified after standard breast investigations, consider dynamic contrast-enhanced breast MRI to identify lesions suitable for targeted biopsy.</p>
<b>Positron emission tomography-computed tomography PET CT</b>	<p>Offer to patients with cervical lymphadenopathy if:</p> <ul style="list-style-type: none"> <li>• a primary tumour is not identified on ear, nose and throat panendoscopy <b>and</b></li> <li>• radical treatment is an option.</li> </ul> <p>Consider PET scan indications in line with updated ESMO guidance- consider pet in those patients who have either isolated site of metastatic disease or oligometastases which can be treated radically.</p>
<b>Immunohistochemistry</b>	Follow Dataset for histopathological reporting of cancer of unknown primary (CUP) and malignancy of unknown primary origin (MUO) (The Royal College of Pathologists - Standards and datasets for reporting cancers, July 2018) – see Appendix 1 (Flowchart for the pathological approach to CUP/MUO)
<b>Flexible bronchoscopy and video-assisted thoracoscopic surgery (VATS)</b>	<p>When percutaneous biopsy is unsuitable or inappropriate for intrapulmonary nodules of probable metastatic origin offer:</p> <ul style="list-style-type: none"> <li>• flexible bronchoscopy with biopsy, brushings and washings even when there is no endobronchial or central nodal disease on imaging</li> <li>• VATS exploration only after a negative bronchoscopic procedure.</li> </ul>
<b>Histology to investigate malignant peritoneal disease</b>	Obtain a tissue sample for histology in patients with ascites, if technically possible.

<p><b>Gene expression profiling</b></p>	<p>Do not use to identify primary tumours.</p> <p>Consider Next -Generation Sequencing (NGS) to identify genomic aberrations that can be targeted therapeutically.</p> <p>Offer participation in clinical research if suitable trial or research study available.</p> <p>Genomic testing should be incorporated into the standard diagnostic workup in patients with confirmed CUP suitable for active treatment to identify actionable mutations.</p> <p>Whole Genome Sequencing on fresh biopsy is preferred (if feasible) and should be performed as early as possible when CUP diagnosis has been made (or suspected).</p> <p>Otherwise NGS for NTRK fusions recommended.</p> <p>Follow NHSE Genomic Test Directory for CUP.</p>
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Each local trust is responsible for developing local pathways to ensure the above diagnostic tests are carried out within their organisation.

## 6. Investigation of specific clinical presentations:

- **Intrapulmonary nodules without evidence of endobronchial disease**

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.

- **Investigation of malignant peritoneal disease**

Obtain a tissue sample for histological examination in patients with MUO who present with ascites, if technically possible.

## 7. Patient Management

- Take into account the patient's prognostic factors, particularly performance status, liver metastases, lactate dehydrogenase levels and serum albumin, when deciding about further investigations and treatment.
- Discuss prognostic factors with patients and their relatives or carers if appropriate to help them make informed decisions.
- Include prognostic factors in decision aids and other information about treatment options.

## **8. CUP/MUO patients with brain metastases**

Patients who have:

- Brain metastases as the only apparent sign of malignancy should be discussed with the CUP Team and/or referred to a Neuro-oncology MDT.
- Multiple metastases including brain involvement should be discussed with the CUP Team and offered chemotherapy only as a part of a controlled clinical trial.

Inform the patients and their carers that there is:

- No evidence that any treatment offers improved survival.
- Limited evidence that surgery and/or whole brain radiotherapy improves neurological symptoms.

## 9. Patients with favourable risk CUP

### A. Presentations that may benefit from radical treatment

Some patients with MUO/CUP will have symptoms and/or signs consistent with specific syndromes that may benefit from radical treatment. These should be discussed at the site specific local MDTs as detailed below.

Consider that an apparent metastasis could be an unusual primary tumour. Do not investigate a tumour inappropriately because this may make radical treatment ineffective. For example, biopsy of a primary bone tumour may lead to more extensive surgery than usual and percutaneous biopsy of a potentially resectable liver metastasis may compromise outcome.

Presentation		Action
1	Upper or mid neck squamous cell carcinoma	Refer to local head and neck MDT. See appendix for local contact points
2	Adenocarcinoma involving only axillary nodes	Refer to local breast MDT. See appendix for local contact points
3	Squamous cell carcinoma confined to the inguinal nodes	Refer to a specialist surgeon in an appropriate MDT to consider curative treatment. If the disease is operable offer: <ul style="list-style-type: none"><li>• superficial lymphadenectomy and consider postlymphadenectomy radiotherapy (if there are risk factors for residual disease, for example multiple involved nodes or extracapsular spread) <b>or</b></li><li>• simple excision of clinically involved nodes, followed by radiotherapy.</li></ul> See appendix for local contact points
4	Solitary metastasis in the liver, brain, bone, skin or lung	Refer to the appropriate MDT to consider radical local treatment.

### B. Systemic therapy for other favourable risk CUP subsets

Certain patterns of disease should be considered as being 'favourable risk' despite a CUP presentation. These should be discussed at the local site specific MDTs and treated according to disease specific treatment algorithms as per the network chemotherapy guidance. If available these patients should be offered entry into clinical trials.

- Poorly differentiated carcinoma with a midline distribution.
- Women with predominantly peritoneal carcinoma
- Poorly differentiated neuroendocrine carcinoma
- Well differentiated neuroendocrine tumour of unknown primary
- Men with bone metastases only and elevated PSA
- CUP with colorectal immunoprofile (CK20+, CK7-, CDX2+)



- CUP with renal cell histological and IHC profile (renal-like CUP)

## 10. Chemotherapy for patients with confirmed poor risk CUP

Offer chemotherapy only to patients with adequate performance status.

If patients do not have clinical features of a specific treatable syndrome, tell them about the potential benefits and risks of chemotherapy.

Offer patients the opportunity to enter clinical trials.

If chemotherapy is offered outside clinical trials when deciding which treatment to use take into account:

- The clinical and pathological characteristics of the tumour
- The toxicity profile of the drugs, their ease of administration and response rate

## 11. Patient Pathways between Teams and Services

- Preliminary tests for patients presenting with a suspected MUO should be performed by the A and E department or hospital specialist teams initially accepting the referral of the patient from primary care
- Once a likely diagnosis of MUO is made the CUP team should be informed and referral made to a designated member of the CUP MDT who will arrange for discussion at the next CUP MDT meeting. **Contact details for each trust in Table A.**
- The CUP MDT will:
  - Advise on remaining investigations needed to confirm the diagnosis of CUP or establishment of a primary site
  - Consider any necessary decision regarding suitability for active anti-cancer treatment
  - Consider any relevant treatment planning decisions
- The designated specialist nurse or consultant member of the CUP Assessment Service will ensure all inpatients are assessed within 1 working day of referral for inpatients and within 2 weeks of referral for outpatients
- The specialist nurse member of the CUP MDT will act as key worker for the patient until such a time as a primary tumour site is identified at which point it may be appropriate to transfer the key worker role to a site specific nurse specialist.
- Referral should be made in parallel to the appropriate site specific MDT and CUP MDT where appropriate e.g. when a likely primary site is suspected but is not clearly identified.
- Should a site specific MDT identify an MUO patient they should also be referred on for discussion at the CUP MDT.

• **TABLE A: Contact details for local CUP Teams**

Locality	Trust	Hospital	Local CUP Teams Lead Clinician
Central Lancs	Lancashire Teaching Hospitals Foundation Trust	Royal Preston Hospital	<p><b>Lead Clinician:</b> Dr Catherine Mitchell Consultant Clinical Oncologist</p> <p><b>CUP CNS:</b> Damon Hoyle Sarah Greer</p> <p><b>Contact Number:</b> 01772 523205</p>
Fylde Coast	Blackpool Teaching Hospital Foundation Trust	Blackpool Victoria Hospital	<p><b>Lead Clinician:</b> Dr Pavel Bezecny Consultant Medical Oncologist</p> <p><b>CUP CNS:</b> Karly Collins Carly Walker</p> <p><b>Contact Number:</b> 01253 657114</p>
East Lancs	East Lancashire Hospitals Trust	Royal Blackburn Hospital	<p><b>Lead Clinician:</b> Dr Ana Ferreira Consultant Medical Oncologist</p> <p><b>CUP CNS:</b> Ruth Leyland</p> <p><b>Contact Number:</b> 01254 735021</p>
Morecambe Bay	University of Morecambe Bay Hospitals Trust	Royal Lancaster Infirmary	<p><b>Lead Clinician</b> Dr Chan Ton Consultant Medical Oncologist</p> <p><b>CUP CNS:</b> Nicola White Rachel Simpson Sarah Cotter Karolina Dyminska Hannah Darwen</p> <p><b>Contact Number:</b> 01229 491289</p>

**TABLE B: Cancer of unknown primary chemotherapy protocols (ref 1-8)**

## General treatment recommendations

- 1 Patients with cancer of unknown primary should always be offered a clinical trial as an option for treatment if available
- 2 Chemotherapy for patients with cancer of unknown primary is aimed at prolonging survival and relieving any related symptoms
- 3 Chemotherapy regimen is based on the histologic type of cancer.
- 4 A recent systematic review of chemotherapy trials in patients with occult primary tumors of unfavorable presentations concluded that no specific regimen can be recommended as standard of care.

**Adenocarcinoma / Squamous Cell Carcinoma:**

Both respond to cisplatin-based combination chemotherapy. However, various studies have shown that treatment with carboplatin, gemcitabine, irinotecan, and docetaxel have also been effective.

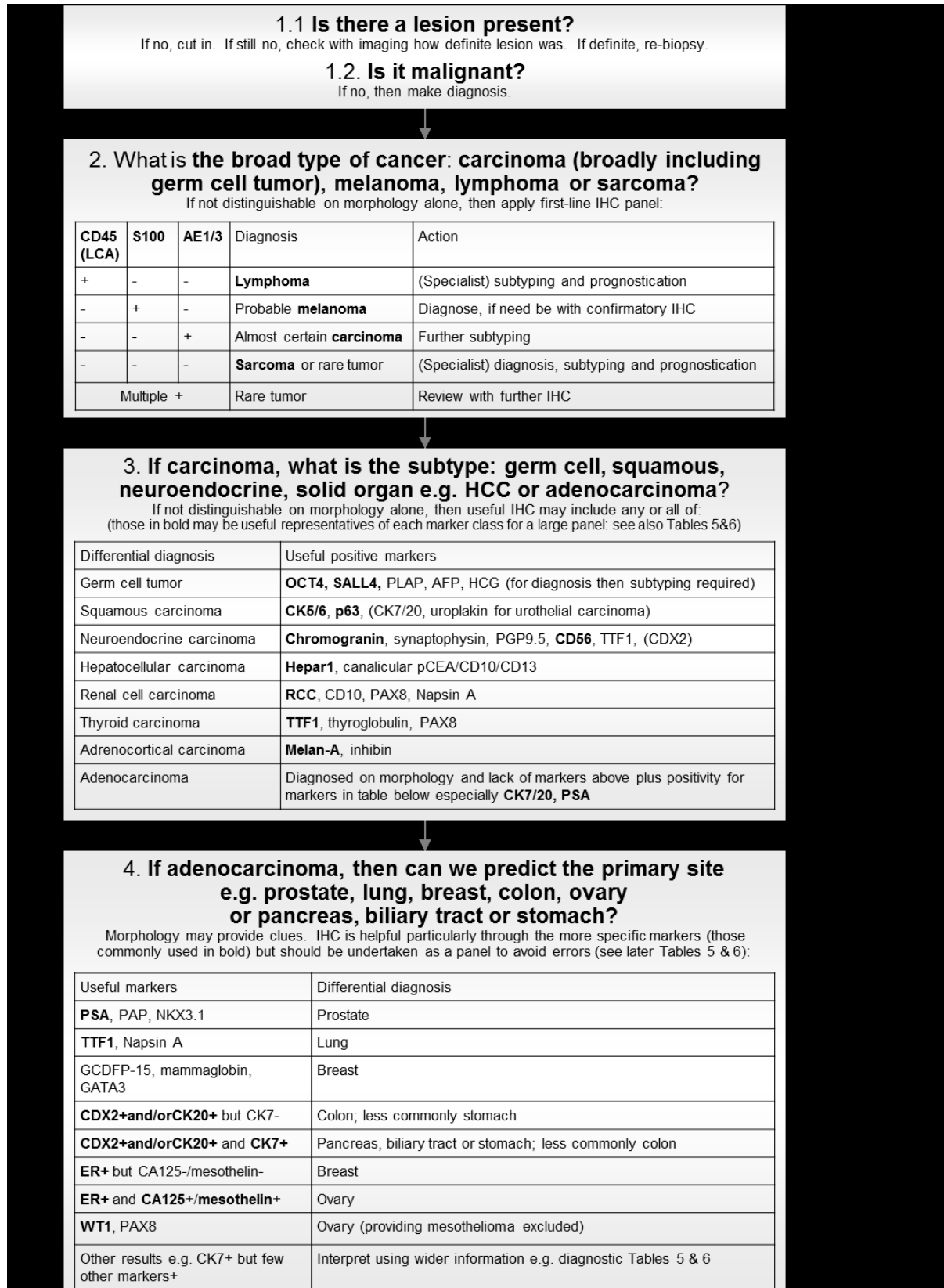
Cisplatin Gemcitabine	25 mg/m <sup>2</sup> Day 1 and Day 8 1000 mg/m <sup>2</sup> Days 1 and 8 Repeat cycle every 3 weeks
Epirubicin Cisplatin Capecitabine	50 mg/m <sup>2</sup> / IV Day 1 60 mg/m <sup>2</sup> / IV Day 1 625 mg/m <sup>2</sup> bd daily for 21 days Repeat cycle every 3 weeks
Paclitaxel Carboplatin	175 mg/m <sup>2</sup> IV Day 1 AUC = 5 Day 1 Repeat cycle every 3 weeks
Paclitaxel Carboplatin	70 mg/m <sup>2</sup> / IV Day 1 every 1 weeks AUC = 5 Day 1 every 3 weeks
Gemcitabine Cisplatin	1250 mg/m <sup>2</sup> IV Day 1 and 8 80 mg/m <sup>2</sup> IV Day 1 Repeat cycle every 3 weeks
Gemcitabine Carboplatin	1250 mg/m <sup>2</sup> IV Day 1 and 8 AUC 5 Day 1 Repeat cycle every 3 weeks
Larotrectinib Entrectinib	Larotrectinib 100 mg PO BD Entrectinib 600 mg PO OD
Oxaliplatin Capecitabine	130 mg/m <sup>2</sup> IV over 2 hours, Day 1 1000mg/m <sup>2</sup> twice daily PO for 14 Days Repeat cycle every 3 weeks
Oxal MdG	Oxaliplatin 85 mg/m <sup>2</sup> IV over 2 hours, Day 1 Calcium Folate 350 mg/m <sup>2</sup> IV over 2 hours, Day 1 5-FU 400 mg/m <sup>2</sup> IV bolus on Day 1, then 1200 mg/m <sup>2</sup> /d x 2 Days (total 2400 mg/m <sup>2</sup> over 46-48 hours) IV continuous infusion Repeat cycle every 2 weeks

**Neuroendocrine tumors:**

**Poorly** differentiated neuroendocrine tumors are generally responsive to combination chemotherapy. Commonly used chemotherapeutic agents include paclitaxel, etoposide, and platinum agents.

Etoposide Cisplatin	120 mg/m <sup>2</sup> Day 1 then 240mg/m <sup>2</sup> p.o Day 2 and 3 80 mg/m <sup>2</sup> on days 2-3 as a continuous IV infusion repeated every 4wk
Etoposide Carboplatin	100 mg/m <sup>2</sup> Day 1 then 200mg/m <sup>2</sup> p.o Day 2 and 3 AUC 5 repeated every 3wk

## Flowchart for the pathological approach to CUP/MUO



## References

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