Guidelines for the Investigation and Management of Metastatic Malignant Disease of Unknown Primary Origin (V 1.2)

Network Cancer Leads Group
(Incorporating Network Acute Oncology Group & Network Radiotherapy Group) V. 1.2

Agreed: November 2012
Reviewed: July 2014
Next Review Date: July 2016
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1. Introduction
Malignant disease of undefined origin (MUO) represents a very broad spectrum of presentations where evidence of a metastatic malignancy is apparent without a primary
tumour identified. NICE Clinical Guideline 104 sets out clearly the definition (Table 1) for this entity and the two refinements of this diagnosis following further investigations; namely provisional and confirmed carcinoma of unknown primary (pCUP and cCUP)\(^1\).

Historically, this clinical entity has been poorly managed with excessive and unnecessary investigation, poor information giving and delays in referral to oncology or palliative care\(^1-3\). The establishment of local CUP multi-disciplinary teams and a central specialist MDT should allow for the streamlining of investigative processes and timely triage to further specialist care. In the Mersey region, it is expected that the local Acute Oncology teams will become synonymous with the local CUP teams and take responsibility for the local CUP MDT. A central specialist MDT at Clatterbridge Centre for Oncology will enable further review for those patients with complex diagnostic problems or in whom anti-cancer therapy is contemplated.

These guidelines provide a framework to facilitate the investigation and management of MUO and CUP presentations as defined in table 1. Two MUO syndromes are exempted from this pathway as they are best managed via different site-specific MDTs:

- Squamous cell carcinoma affecting the upper/mid cervical lymph nodes should be managed through the local head/neck MDT
- Adenocarcinoma of the axillary nodes should be managed through the local breast MDT

The overarching feature of many MUO presentations is the futility of further investigations or treatment in a patient who is approaching the end of their life. Given, these factors, early holistic needs assessment and palliative care referral are important considerations. The document will be periodically reviewed in the light of experience and published evidence.
2. Patient Pathway

The majority of MUO presentations occur via an emergency admission to secondary care and the patients will be identified to the unit local CUP/AO teams. Outpatients may present through secondary care clinics, GP referrals or radiology flagging systems. Following assessment by the local CUP MDT, if further therapy is a possibility the patient should be referred through to the specialist CUP MDT hosted by Clatterbridge Cancer Centre. For the purposes of improving cancer intelligence on this condition it is expected that all presentations of MUO/CUP identified by the local CUP MDT teams will be registered at
Clatterbridge. The designated form for this specifies whether further review at the specialist CUP MDT is required.

### 2.1 Outpatient CUP MDT Assessment

All local CUP MDTs should develop their own procedures to manage MUO presentations in an outpatient setting. Most referrals will come from other site-specific MDTs or secondary care clinicians. Primary care referrals may be accepted by local arrangement with the local CUP MDT and the host Trust. The network will develop a primary care referral pathway to support direct referral to local CUP teams.

### 2.2 Inpatient CUP MDT Assessment

Inpatient referrals should be seen within one working day and it is expected that review will be by the local inpatient Acute Oncology Service. An overview of patient flow is shown in Figure 1. Concomitant with a thorough medical assessment, the patients’ holistic needs should also be assessed. Symptom control and psychological support should be offered and appropriate referrals made. The patients’ and carers’ understanding of the situation should be assessed and information given in a clear and sympathetic manner. These processes are active and ongoing throughout the patient’s journey and the CUP nurse specialist role here is fundamental. It is common for Specialist Palliative Care to be brought in during the diagnostic stage and for the majority of patients this will remain the most important intervention during their illness. Many patients can be managed as outpatients once the above needs have been met and therefore every attempt should be made to facilitate discharge.

Following specialist oncology review a management plan will be implemented and it is expected that the patient will be discussed at local CUP MDT level. Outcomes following review and/or further investigation will fall into four groups:

- **MUO/pCUP/cCUP, fit for active therapy and requiring further investigation or treatment**
- **MUO/pCUP/cCUP, not fit for further therapy and requiring best supportive care**
- Primary identified, needing review at site-specific MDT
- Non-malignant diagnosis, requiring onward referral

**REFERRAL**

Malignancy of Undefined Primary Origin (MUO)
Do not order tumour markers or further investigations unless genuine clinical need
Based upon imaging or histology

1°Care Referral  
MDT/Ward  
Radiology Flag

Urgent Referral to Local CUP/AO Team

**ASSESSMENT**

IP – within one working day of referral. Seen on ward. Patient to remain under care of admitting clinician
OP – within 14 days of referral.

**CUP Team/AO Review**

Local CUP Team
- Organise appropriate investigations
- Symptom control
- Inform patient
- Early discharge planning

Referral to palliative care for ongoing supportive care

PS 3/4 Unwell

PS 3/4 Unwell Not suitable for further therapy

**OUTCOMES**

Non-malignant
Primary Identified
“Provisional CUP”

“Confirmed CUP”

Active Therapy

Refer through to site specific oncologist/MDT

Refer on

Specialist CUP MDT

Figure 1 Patient flow for new presentations of malignancy of undefined origin
3. **Approach to Investigation**

The assessment of any MUO patient begins with a thorough history and physical examination. Most patients will be referred having had some imaging which is highly suggestive or confirmatory of malignancy. The bare minimum for further tests represents a full blood count and biochemical profile (including lactate dehydrogenase). The decision to embark on further tests from here will very much be influenced by the mode of presentation and the condition of the patient\(^4\). It should be borne in mind that most oncology decisions can be made utilising three fundamental pieces of information

- The condition, functional status and co-morbidities of the patient (history and examination)
- The stage of the cancer (cross-sectional imaging)
- The type of cancer (histology)

Further investigations should only be considered if the:

- Patient is fit for treatment
- Results affect the decision
- The patient understands the risks and benefits
- The patient is prepared to accept treatment

The use of blood tumour markers is not recommended except in a limited number of circumstances (Table 2)\(^5\)\(^-\)\(^8\). Gastrointestinal endoscopy should only be considered when a GI primary is hinted to on imaging or symptoms and where it is felt this will alter further management\(^9\)\(^-\)\(^12\). There is currently no role for positron emission tomography unless the patient has isolated cervical lymphadenopathy and is suitable for radical treatment\(^13\),\(^14\).

<table>
<thead>
<tr>
<th><strong>α-FP and β-HCG</strong></th>
<th>If germ cell tumour suspected: young men with midline lymph node metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α-FP</strong></td>
<td>If hepatocellular carcinoma suspected: evidence of chronic liver disease</td>
</tr>
<tr>
<td><strong>PSA</strong></td>
<td>Men &gt;40 with bone metastases</td>
</tr>
<tr>
<td><strong>CA125</strong></td>
<td>Women with peritoneal or pelvic metastases, ascites, pleural effusions</td>
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</tbody>
</table>

*Table 2 Indications for the ordering of blood tumour markers*
4. **Specific Presentations**

**Presentations that may benefit from radical (potentially curative) treatment:**

- Squamous carcinoma involving upper or mid neck nodes; 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 axillary nodes; Refer patients with adenocarcinoma involving the axillary nodes to a breast cancer MDT for evaluation and treatment.

- Squamous carcinoma involving inguinal nodes; 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 and consider post-lymphadenectomy radiotherapy for patients with risk factors for residual disease, for example multiple involved nodes or extrascapsular spread)
- Simple excision of clinically involved nodes, followed by radiotherapy

- A solitary, apparent metastasis. Do not investigate a tumour inappropriately because this may make radical treatment ineffective. For example, biopsy of a primary bone tumour may mean that the patient needs more extensive surgery than usual. Percutaneous biopsy of a potentially resectable liver metastasis may compromise outcome. Consider that an apparent metastasis could be an unusual primary tumour.

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

**Presentations with a poor prognosis:**

- Brain metastases as the only apparent sign of malignancy; Refer patients presenting with apparent brain metastases as the only sign of malignant disease after initial and special investigations to a neuro-oncology MDT for evaluation and treatment.

- Multiple metastases including brain involvement. 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.
4.1 Liver lesions

The finding of isolated liver metastases is a common MUO presentation and nearly half of all MUO patients will have liver involvement\(^2\). A retrospective review of carcinoma unknown primary presenting to the MD Anderson in Texas identified hepatic involvement as an independent adverse prognostic feature\(^15\). A full staging CT scan of thorax, abdomen and pelvis should be performed after history taking and physical examination. A serum \(\alpha\)-fetoprotein should be checked if there are any risk factors or clinical/radiological signs to suggest chronic liver disease.

If the distribution of metastatic disease is confined to the liver and cross-sectional imaging suggests that it may be resectable (e.g. unilobar) then a referral to the hepatobiliary MDT is recommended prior to an image-guided biopsy. If it is likely to be resectable then colonoscopy, PET CT and MRI of liver should be performed to more accurately define the extent of disease prior to surgery.

Most presentations are unlikely to be resectable and if tissue is needed an image-guided percutaneous biopsy of a lesion should be arranged.

Pitfalls: non-malignant disease

- Cirrhosis
- Haemangiomata
- Focal nodular hyperplasia
- Hepatic adenomata

4.2 Brain lesions

These are the presenting feature of around 10% of MUO presentations\(^2\). They typically present as an emergency with stroke-like symptoms and are identified on CT scanning of the brain. Immediate management with dexamethasone typically provides some relief. The key determinants of prognosis are performance status, response to corticosteroids and extent of extracerebral disease. Solitary lesions should be discussed with neurosurgical services before any further imaging is arranged. Patients who respond to steroids and are not surgical candidates should be considered for whole brain radiotherapy. Referral for whole
brain or stereotactic radiotherapy can now be done using a designated form available from the local Acute Oncology team.

**Pitfalls: non-malignant disease**

- Brain abscesses
- Cerebral infarction

### 4.3 Bone lesions

Bone lesions are seen in about a third of MUO presentations and are typically lytic in nature. They typically present as an emergency with significant skeletal events such as pathological fracture, spinal cord compression or uncontrolled pain. In many situations therefore it is imperative to arrange radiotherapy before any further investigations can be undertaken. Men over the age of 40 should have a digital rectal examination and a PSA checked. All patients with lytic bone lesions should have a serum electrophoresis and urine collection for Bence-Jones proteins. If the patient presents with a pathological fracture and is scheduled for internal fixation then ensure that you request that the surgeon sends reamings to the laboratory for histological analysis.

Bone biopsies should be arranged via the local orthopaedic services. If there is a suspicion of primary bone sarcoma (see MCCN sarcoma referral guidelines) on imaging then the images should be reviewed by the sarcoma MDT prior to an attempt at biopsy.

**Pitfalls: non-malignant disease**

- Osteomyelitis
- Paget’s Disease of Bone
- Hyperparathyroidism (Brown Tumour)
- Fibrous dysplasia

### 4.4 Lung lesions

If there is any suspicion of a lung primary, such patients should be managed by thoracic MDT. Where the distribution and appearances suggest metastatic spread tissue can be
obtained either by percutaneous needle biopsy or bronchoscopically. Consider referral for video assisted thoracic surgery if no tissue is obtained via these routes.

Pitfalls: non-malignant disease

- Sarcoidosis
- Wegener’s granulomatosis
- Tuberculosis

4.5 Peritoneal carcinomatosis

This typically presents with vague abdominal symptoms and ascites. In women it is reasonable to check a CA125 but it should be borne in mind that this will be invariably elevated even in non-malignant causes for ascites. Diagnosis can often be made on the presence of malignant cells in peritoneal fluid, particularly if a cell block is prepared, but sometimes a biopsy is required. If an image guided procedure cannot access tissue then the patient should be referred for a laparoscopy.

Imaging Assessment

Offer to patients with MUO when clinically appropriate, guided by symptoms:

- chest X-ray
- CT scan of the chest, abdomen and pelvis
- Bone scan
- MRI

Do not offer mammography routinely to women with MUO unless clinical or pathological features are compatible with breast cancer.

Do not offer PET- CT routinely unless the patient has isolated cervical lymphadenopathy and/or is suitable for radical treatment
**Histological Assessment**

It is incumbent on the local Acute Oncology teams to work closely with their local pathology laboratories to provide sufficient background information to facilitate appropriate immunohistochemical analysis. For some patients the confirmation of cancer may be sufficient on haematoxylin and eosin (H&E) staining whereas others will require a more comprehensive immunohistochemical panel to categorise the tumour.: 

a. undifferentiated malignancies. The panel of investigations will be influenced by the age and sex of the patient, the site of biopsy and morphological assessment of the H&E stained sections. In general, consider:

i. initial panel to cover possibilities of lymphoma, carcinoma, melanoma (CD45, MNF116, S-100) and germ cell tumour (OCT3/4, CD30)

ii. second line panel depending on results of (i). If probable lymphoma (CD3, CD10, CD20, CD30), carcinoma (CK7, CK20, CDX2, CA125, PSA, TTF-1, ER), melanoma (melan-A, HMB45), sarcoma (depends on suspected type, myogenin best for rhabdomyosarcoma)

iii. In the case of metastases to bone (and sometimes other sites) include TTF-1, CD10, renal carcinoma antigen, PSA

b. metastatic adenocarcinoma. Limited panel to refine possible primary site - CK7, CK20, TTF-1, PSA, ER, CDX2.

c. metastatic squamous cell carcinoma. Markers of squamous differentiation are not entirely specific but consider p63, 34BE12. Site-specific markers for origin of squamous cell carcinoma are of very limited value. The only ones worth considering are in situ hybridisation for EBER (nasopharynx) and HPV (oropharynx) in patients with metastatic neck nodes, although PET-CT scanning in patients without an obvious primary lesion should be considered before (or in conjunction with) laboratory testing.

d. Identification of predictive markers of therapeutic response. After MDT discussion, consideration should be given to requesting additional biomarkers if any of the following are suspected but only if it will have a bearing on therapy:

i. Breast: ER/Her2
ii. Lung: EGFR mutational status

iii. Colorectal: K-RAS mutational status

iv. Gastric: Her2

5. Options for Systemic Treatment of cCUP

CUP patients without a specific 'treatable syndrome, who are being considered for chemotherapy, should:

- have the balance between potential risks and benefits discussed with the if it is decided to proceed with chemotherapy, be offered entry into a clinical trial if available.
- that confirmed CUP patients with a 'treatable syndrome' and fit for treatment, should be offered chemotherapy according to the network guidelines for the management of treatable syndromes.

The evidence base for optimal systemic treatment of those patients with confirmed CUP is poor. The initial decision to treat will be based on the patients performance status and co-morbidity but there is no evidence to dictate the use of one regimen over another in cCUP. The regimen used in practice therefore, typically is a best guess approach based on where the suspected origin of the cancer. There is clear need to develop an evidence base here and where possible patients should be managed in clinical trials. As a guide some common presentations are highlighted here with suitable regimens.

<table>
<thead>
<tr>
<th>Liver or lung metastases – adenocarcinoma or poorly differentiated carcinoma</th>
<th>Gemcitabine and platinum</th>
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<tbody>
<tr>
<td></td>
<td>Gemcitabine alone</td>
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<tr>
<td></td>
<td>ECX/ECF</td>
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<td>EOX</td>
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<tr>
<td>Squamous cell carcinoma</td>
<td>Cisplatin and 5-FU/capecitabine</td>
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<tr>
<td>Poorly differentiated carcinoma with predominant midline distribution</td>
<td>ECX/ECF</td>
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<tr>
<td></td>
<td>BEP (if male)</td>
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<tr>
<td>Women with predominant peritoneal adenocarcinoma</td>
<td>Carboplatin and paclitaxel</td>
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<tr>
<td></td>
<td>Carboplatin monotherapy</td>
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<tr>
<td>Poorly differentiated neuroendocrine carcinoma</td>
<td>Platinum and etoposide</td>
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</tbody>
</table>

6. Data collection and Clinical Audit
All MUO/CUP presentations to the local CUP teams will be captured at the weekly CUP MDT and stored as part of the acute oncology data set. In addition, all MUO/CUP presentations will be registered centrally at the Clatterbridge Cancer Centre SSMDT and electronic patient record. Local CUP teams will have responsibility to register and designate whether specialist MDT review is required. The SSMDT will lead on the core dataset management and analysis.

Benchmarking audits have already been established by local AO teams. Scope and timelines of future audit projects will be set by the Acute Oncology and Unknown Primary Network Group.

An agreed CMSCN minimum dataset will be collated centrally and includes:

- Demographics and clinical factors: Age, gender, performance status, pattern of metastases, histology, LDH, final diagnosis, treatment, date of death
- Referral pathway: Cancer waiting times, date of referral, date seen by CUP team, mode of referral (OPD vs inpt), date of first CUP MDT, length of hospital stay
References

1. NICE Clinical Guideline 104: Diagnosis and management of metastatic malignant disease of unknown primary origin


16. Adenis A Fert, C Penel N. Phase II trials in patients with carcinoma of unknown primary: a pooled data analysis.. Invest New Drugs 2009
