Guidelines for Investigation and Management of Malignancy of Unknown Origin (MUO) / Cancer of Unknown Primary (CUP)

3rd Edition
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Contents

Contents ......................................................................................................................... 2
Aims of Management Guidelines: .............................................................................. 3
Guidelines for Good Practice: .................................................................................... 3
Patient-Centred Care ................................................................................................. 3
Information .................................................................................................................. 3
Communication ......................................................................................................... 4
Supportive and Palliative care ................................................................................... 4
Warnings and Disclaimer .......................................................................................... 5
Definitions ................................................................................................................... 6
Algorithms .................................................................................................................... 7
1: Patient Pathway ....................................................................................................... 7
2. Investigation of Patients with MUO ......................................................................... 8
3. Clinical Management Pathway of Patients with Carcinoma of Unknown Primary: . 9
   Background .............................................................................................................. 10
Malignancy of Undefined Origin (MUO) .................................................................... 12
Patient Presentation .................................................................................................... 14
Investigation ............................................................................................................... 14
Initial Assessment ...................................................................................................... 15
   Imaging ..................................................................................................................... 16
      Upper and Lower GI Endoscopy .......................................................................... 17
      Tumour Markers .................................................................................................. 17
      Histology .............................................................................................................. 18
      Molecular Genetic Profiling ............................................................................. 20
Management ............................................................................................................... 21
      Prognostic Groups ............................................................................................... 21
      Management of Recognisable CUP “Syndromes” ............................................ 23
      Systemic Treatment of Confirmed CUP ............................................................. 26
Clinical Trials ............................................................................................................. 27
Palliative Care ............................................................................................................. 28
Clinical Audit and Data Collection ........................................................................... 28
Appendices .................................................................................................................. 29
   i) Local CUP MDT’s / Clinical Leads: ................................................................. 29
   ii) Example Referral Form for Local CUP MDT: ............................................ 31
   iv) Guidelines for Referral to Local CUP MDT .................................................... 32
   v) ECOG / WHO Performance Status ............................................................... 33
Referral Contacts ........................................................................................................ 34
Patient Support Groups ............................................................................................. 34
References ................................................................................................................... 35

3rd Edition.
For review February 2018
Aims of Management Guidelines:

- To provide a simple reference manual for the management of MUO/CUP for trusts within the Greater Manchester and Cheshire (Manchester Cancer affiliated organisations).
- To update the manual as new information becomes available.
- To provide an up to date list of protocols together with outline information.
- To identify good practice guidelines in accordance with NICE guidance on *Diagnosis and Management of Metastatic Malignant Disease of Unknown Primary Origin (CG104), Improving Supportive and Palliative Care for Adults with Cancer (CSGSP) and Suspected Cancer: Recognition and Referral (NG12)*

Guidelines for Good Practice:

Patient-Centred Care

- Acknowledgement that patients want to be treated with dignity and respect, and may want choice in making decisions about their treatment and care.
- That patients should be given the name and contact details of a nurse they may access for communication and support.

Information

- Patients should receive clear, timely information, both verbal and written in keeping with their individual needs.
- Information is given regarding disease, diagnostic procedures, treatment options, effectiveness and side effects.
- Complementary and health professionals respond to patients’ desire for timing and amount of information.
• Patients have access to verbal and written information regarding support and practical help i.e. benefits, local support groups and complimentary therapies.

Communication

• Special communication training is required for all health care professionals providing direct care.
• Provision of suitable interpreters for patients whose preferred language is not English.
• Acknowledgement of difficult communication situations and adherence to Breaking Bad News policies.
• Accurate documentation of key points of consultations in patients notes and swift communication of any treatment changes to all other professionals involved in care.

Supportive and Palliative care

1. Access to information about their disease, aspect of management, available services and how to access them. This may for example include local and national patient support networks
• Advice on the practical and financial help
• Emotional and spiritual support, with specialist help for those with difficulties in adjustment and coping.
• An active rehabilitative approach to maximise functional recovery and adaptation to consequences of cancer and its treatment, including information on the effects of the treatments on physical, emotional and sexual functioning.
• A meticulous approach to the relief of pain and other symptoms at any stage. This should lead to early referral to specialist services if management of problems should prove difficult.
Warnings and Disclaimer

- This book does not attempt to be a comprehensive account of the treatment of any MUO, CUP or clinical situation. References are provided for further reading.

- Management decisions should be made only in part by the guidelines given herein: a full clinical assessment of the individual patient should be made in all cases. It is appropriate to treat outside of these guidelines/ algorithms in appropriate clinical circumstances provided that senior advice/ input is sought.

- Typing errors may be present in the text. Please inform the compilers of any errors that you may find.

- If you are not confident about what you are doing, please seek immediate advice from a more senior member of the team.
Definitions

**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 (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.

**Confirmed carcinoma 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.

NICE definitions of MUO / CUP [1]
Algorithms 1: Patient Pathway

MALIGNANCY OF UNDEFINED PRIMARY ORIGIN (MUO)

Outpatient Referral \(^1\) In-patient Referral

URGENT REFERRAL TO LOCAL CUP / AO TEAM

Malignant malignancy on initial investigation

No obvious primary site

Site specific MDT

ASSESSMENT

In-Patient:
Ward review within 24hrs (working day).
Remains under care of admitting physician.
Out-Patient\(^1\):
Seen within 14 days of referral

CUP / AO TEAM REVIEW
- Advise appropriate investigations
- Symptom control
- Communicate with patient and carers.
- Facilitate early discharge

POOR PS (3/4)
- Refer to local Palliative Care team

LOCAL CUP MDT
- Non-malignant
- Primary identified
- Provisional CUP

PS 0-2 Fit for treatment
- Refer to CUP service at Cancer Centre
- Refer to site specific MDT /oncologist
- Refer to appropriate speciality

\(^1\) Only applicable in trusts where out-patient service available.
Algorithms 2: Investigation of Patients with MUO

**Initial Assessment**

- Thorough medical history and physical examination including:
  - Breasts / pelvic (women)
  - Skin
  - Lymph nodes groups
  - Rectal examination

**Biochemistry**

- FBC, U&E, LFT (including LDH)
- Urinalysis – bence jones protein if lytic bone mets
- **Tumour Markers should only be performed in the following situations:**
  - Ca125 in women ? ovarian/peritoneal
  - PSA in men with bony mets ? prostate
  - AFP /hCG in young men mediastinal / retroperitoneal masses ? germ cell
  - AFP ? hepatocellular

**Imaging / Endoscopy**

- CT Thorax, Abdo, Pelvis for radiological staging.
- **Endoscopy should only be performed if symptom directed.**
- Breast MRI / mammogram in women with axillary lymphadenopathy ? breast
- Testicular USS in young men mediastinal / retroperitoneal masses ? germ cell.

**Pathology**

- Tissue diagnosis should only be pursued in patients are fit enough for treatment and who wish treatment.
- Tissue core biopsy is preferable to FNA
- Solitary lesions should be discussed at site specific MDT
3. Clinical Management Pathway of Patients with Carcinoma of Unknown Primary:

**Patient with Carcinoma of Unknown Primary (CUP)**

**Strong suspicion of primary cancer site (on IHC*) with potential for specific treatment:**
- Bone mets form prostate cancer
- Colorectal, breast, ovarian, lung

Consider site specific treatment

Exclude non-CUP neoplasm
- Non epithelial cancer
- Extra-gonadal germ cell tumour

**Recognise a Specific Sub-set of CUP:**
- Women with peritoneal papillary serous carcinoma.
- Women with adenocarcinoma involving axillary lymph nodes.
- Squamous carcinoma involving cervical lymph nodes.
- Squamous carcinoma involving inguinal lymph nodes.
- Neuroendocrine CUP
- Poorly differentiated carcinoma of the mid-line.
- Solitary (single site) CUP tumour

Refer to appropriate site specific MDT / oncologist for further management

**Non Specific Sub-set of CUP**

**PS ≤1**
LDH – normal

**Favourable prognosis**
Median OS: 12 months

Consider combination chemotherapy

**PS ≥ 2**
Liver mets
Multiple metastatic sites
LDH – elevated
Albumin - low

**Poor prognosis**
Median OS: 4 months

Consider BSC or chemotherapy following discussion with patient

* On immunohistochemistry

Background

Patients who are diagnosed with “cancer of unknown primary” are those who have metastatic malignancy from an undiagnosed primary site. This is a very diverse patient population in which tumour type, extent of spread and outcomes vary widely.

The majority of these patients will have a malignancy of epithelial lineage; patients with tumours of non-epithelial lineage (sarcoma, lymphoma, melanoma, germ cell) should be managed according to disease specific guidelines.

Patients who present with metastatic disease either on clinical examination or radiological imaging with an unidentified primary source are regarded as having “malignancy of undefined primary origin (MUO).” The primary site may be subsequently identified in a significant proportion of patients, however despite extensive investigation for some patients this is not the case and they are diagnosed as being confirmed “cancer of unknown primary (CUP)”.

Cancer of unknown primary accounts for ~ 3% of new cancer diagnoses per annum, increasing to 7% in the over 85yr population. This equates to 9,800 new cases per annum in 2011. The number of recorded deaths from cancer of unknown primary in 2012 was 10,625. Six in ten deaths of cancer of unknown primary are in patients aged 75 years or older [3]. Incidence rates however are decreasing this is likely to be due to several reasons including improvements in diagnostic methods and better registration practices.

Route of presentation for CUP patients has a significant impact on outcomes and survival with CUP presenting as an emergency compared to all cancers, with 57% of CUP patients (25,000 cases) compared to 23% for all cancers presenting via the emergency department. A lower percentage of CUP patients are diagnosed through GP referral, 19% compared to 27% for all cancers [4]

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One-year relative survival for CUP is 16% for patients diagnosed during 2006-2010, with the route of presentation significantly impacting on survival rates as shown below (Fig 1):

Fig 1: Relative survival estimates by presentation route and survival time, Cancer of Unknown Primary, 2006-2010 [4]

Historically, CUP patients have been poorly managed with excessive and unnecessary investigation, little provision of information given to patients and carers and delays in referral to oncology or palliative care services. The establishment of local CUP multi-disciplinary teams should allow for the streamlining of investigative processes and early referral to further specialist care.

In many acute trusts local Acute Oncology teams will become synonymous with the local CUP teams and take responsibility for the local CUP MDT. Where acute oncology teams do not provide the cover for CUP separate independent local CUP teams have been established to provide the service.
Malignancy of Undefined Origin (MUO)

Patients with MUO presentations can be further defined as follows:

- Liver tumour(s) and other intra-abdominal masses identified as likely metastatic malignancy on initial imaging, without evidence of a probable primary site.
- Bone tumour(s) identified as likely metastatic malignancy on initial imaging and not immediately considered to be related to prostate cancer by digital rectal examination (DRE) or prostate-specific antigen (PSA) or myeloma.
- Brain tumour(s) identified as likely metastatic malignancy on initial imaging, without evidence of a probable primary site.
- Lung tumour(s) identified as likely metastatic malignancy on initial imaging, without evidence of a probable primary site.
- Pleural effusion(s) diagnosed as malignant on cytology, without evidence of a probable primary site.
- Malignant ascites diagnosed on cytology, without evidence of a probable primary site.
- Skin tumour(s) confirmed as malignant on histology when primary skin cancer excluded and no obvious primary from histology or imaging.

Primary care referrals for patients who are diagnosed with MUO through initial investigations performed by their GP (general practitioner) should be referred to secondary care via defined pathways as per NICE: Suspected cancer: recognition and referral guidelines [5]. It may be necessary for GP’s to perform further assessment’s or initial investigations to determine the most appropriate referral pathway.

Example scenarios are provided below, if advice required please contact individual trusts pathway managers (Table 1):
Table 1: Examples of presentation and referral pathways for MUO presenting to primary care.

<table>
<thead>
<tr>
<th>Initial Presentation</th>
<th>Additional Assessment / Investigation</th>
<th>Referral Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone metastases on imaging in a male patient</td>
<td>History of urinary symptoms, check PSA, check FBC, U&amp;E, LFT Ca+, myeloma screen. CXR if respiratory symptom</td>
<td>Urology if PSA raised / urinary symptoms. Haematology if positive myeloma screen Respiratory if abnormal CXR</td>
</tr>
<tr>
<td>Liver metastases on imaging (USS)</td>
<td>History of gastric / bowel symptoms / weight loss. FBC, U&amp;E, LFT.</td>
<td>Gastrointestinal referral</td>
</tr>
<tr>
<td>Multiple pulmonary metastases on CXR</td>
<td>History of respiratory symptoms, weight loss, smoker</td>
<td>Respiratory referral</td>
</tr>
</tbody>
</table>

MUO presentations that are best managed via site-specific MDT’s are:

- 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
- Squamous cell carcinoma affecting the inguinal lymph nodes should be managed through specialist MDT (anal / urological/ gynae depending upon local policy).
- Solitary metastatic lesions should be referred to the site specific MDT ie brain metastasis to the neuro-oncology MDT, lung metastasis the lung MDT.
Patient Presentation

Patients may present either acutely as an emergency admission or via secondary referral pathways through GP referrals / outpatient clinics.

Those patients presenting as an emergency admission should be identified on admission by the local AO/CUP teams and early input into their management should be achieved with a view to discussing them at the local CUP MDT prior to them being referred to an oncologist if felt to be appropriate.

Those presenting via secondary referral pathways should be investigated as appropriate by the receiving team and discussed at the local CUP MDT regarding further investigation and management.

Investigation

There are numerous different clinical presentations of patients with MUO / CUP and therefore the approach in their investigation should be tailored to the individual patient rather than applying the same panel of investigations to all patients.

It is important when investigating patients that they are fully informed with regards the rationale and the potential outcome of investigations being performed. To optimise the care of patients with MUO it is necessary to try and define the optimal point for ceasing diagnostic tests, based on a balance between standard clinical benefit and individual psychological need.

The following criteria should be considered when investigating patients:

- Do not offer further investigations to identify the primary site of origin of the malignancy to patients who are unfit for treatment.
- Perform investigations only if:

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– 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.

• Explain to patients and carers if further investigations will not alter treatment options. Provide appropriate emotional and psychological support, information about CUP, treatment options and palliative care.

**Initial Assessment**

For the majority of patients with MUO a primary site will be identified in approximately 62% of patients following initial investigation. The diagnostic yield of additional tests is low in comparison to initial investigations, with significant false positive rates [6]. The evidence suggests that in patients with MUO a restricted panel of basic tests can identify most primary tumours. It follows that the use of additional tests at an early stage will not add anything in the majority of cases.

Initial assessment should be guided by patients symptoms and include a comprehensive medical history including family history and occupational history. All patients should have a thorough clinical examination performed including breast, lymph node, skin, rectal and pelvic examination.

A basic blood and biochemical survey should be sent including FBC, U&E, LFT, Ca+ albumin and LDH. Tumour markers should only be sent in specific scenarios (discussed below).

Urinalysis for bence-jones protein should be sent as part of a myeloma screen where there are lytic bone metastases.
**Imaging**

All patients presenting with MUO should have a staging CT thorax / abdomen / pelvis as part of their investigation. Most patients will have had a CXR performed on initial presentation if felt clinically appropriate.

Other radiological investigation should be employed only as indicated described below:

- **Mammography** – in patients presenting with axillary lymphadenopathy mammography is indicated to exclude a breast primary. Patients should be referred to the fast track breast service to permit mammography +/- further assessment with breast USS and biopsy as appropriate. It should not be routinely offered to all women with MUO unless there is a clinical or pathological suspicion of breast cancer.

- **Breast MRI** – in patients with isolated axillary lymphadenopathy where histology has confirmed adenocarcinoma. These patients should be managed as per breast cancer guidelines within the breast cancer MDT.

- **Testicular USS** – in men presenting with features consistent with germ cell tumour ie mid-line lymphadenopathy.

- **PET-CT** – this is not routinely indicated for patients being investigated for MUO. It should only be employed in specific scenarios following discussion at local CUP MDT. These include:

  - Patients with provisional CUP presenting with cervical lymphadenopathy with no primary tumour identified on ear, nose and throat panendoscopy if radical treatment is considered to be an option.

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Patients with provisional CUP with extra-cervical where there is a solitary site of disease and radical treatment is being considered an option.

Upper and Lower GI Endoscopy

Endoscopies of the upper and lower GI tract should not routinely be performed in all patients with MUO due to the low yield of identifying the primary tumour in an unselected population [7].

- Upper and lower GI endoscopy should only be performed in patients in patients with MUO where the symptoms, histology or radiology suggest a GI primary tumour.

Tumour Markers

The use of tumour markers can sometimes aid the identification of a cancer primary however in general their use is not routinely recommended due to their low specificity and sensitivity. Inappropriately requested tumour marker results can lead to unnecessary and costly further investigations and incorrect management as well as causing needless distress and worry to patients.

There are certain situations where their use is warranted:

- AFP and hCG in patients with presentations compatible with germ-cell tumours (particularly those with mediastinal and/or retroperitoneal masses and in young men).
- 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/ primary peritoneal cancer (including those with inguinal nodal disease, chest, pleural,
peritoneal or retroperitoneal presentations). Carefully interpret the results because of limited test specificity.

The use of additional tumour markers ie CEA, Ca19.9 and Ca15.3 should only be considered after discussion at the local CUP MDT and where it is felt they will alter the proposed management plan.

**Histology**

Pathological evaluation is required as part of the investigation of patients with MUO / CUP, where possible a tissue biopsy should be sought rather than a fine needle aspirate (FNA). Tissue biopsy should be sought for patients except where:

- Patients are not fit enough for treatment.
- Patients have expressed wish that they would not wish treatment.
- Patients have solitary metastatic lesions where surgical excision may be potentially curable ie solitary liver, brain, lung or bone metastases.

On receipt of the biopsy the histopathologist should be provided with the full clinical background including the potential diagnosis of CUP plus any significant past medical history especially any prior history of malignancy.

Tumours are categorised by pathology into:

- well- and moderately differentiated adenocarcinomas;
- squamous cell carcinomas;
- carcinomas with neuroendocrine differentiation;
- poorly differentiated carcinomas (including poorly differentiated adenocarcinomas);
- undifferentiated neoplasms.
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 (IHC) panel to categorise the tumour.

IHC staining should consist of initial panels to exclude non-epithelial lineage ie lymphoma, sarcoma, germ cell and melanoma. Tumours which appear epithelial can be confirmed using broad spectrum anti-cytokeratins panels, expanded IHC panels can then be used to distinguish between carcinoma / adenocarcinoma plus likely primary site.

Basic IHC work up of cancers of unknown primary should be performed as per the flow diagram below (Fig 2):

```
<table>
<thead>
<tr>
<th>Primary markers</th>
<th>Additional markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK 7-/CK 20+</td>
<td>Colorectal and Merkel cell carcinoma</td>
</tr>
<tr>
<td>CK 7+/CK 20-</td>
<td>Lung, breast, thyroid, endometrial, cervical, and pancreatic carcinoma and cholangiocarcinoma</td>
</tr>
<tr>
<td>CK 7+/CK 20+</td>
<td>Urothelial, ovarian, and pancreatic cancer and cholangiocarcinoma</td>
</tr>
<tr>
<td>CK 7-/CK 20-</td>
<td>Hepatocellular, renal cell, prostate, squamous cell</td>
</tr>
</tbody>
</table>
```

Fig 2: Basic IHC work-up of cancer of unknown primary [2]

Extended immunohistochemical panels should then be applied as indicated.
Potential IHC markers are described in the table below (table 2):
Table 2: Extended IHC work up for Cancer of Unknown Primary [2]

All cases should be discussed at the local CUP MDT to discuss whether further immunohistochemical / mutational analyses are warranted. These should only be undertaken where systemic anti-cancer therapy is being considered and where it would alter the potential management plan. If systemic anti-cancer therapy is being considered then additional tissue markers may be appropriate ie Her2: gastric / breast, EGFR/ALK-1: lung, KRAS: colorectal as they may impact upon choice of therapy.

Molecular Genetic Profiling

Molecular genetic profiling has been applied in 2 specific scenarios in CUP patients:

1. Tissue of Origin testing
2. Identification of targetable genetic mutations

Tissue of Origin Testing

Current treatment of cancer is based largely on determination of the organ or tissue of origin of the tumour; for example tumours arising from the lung receive different...
systemic therapy to those arising from the breast. Different tissues have different patterns of gene expression in them creating a genetic “signature” for that tissue. This genetic signature could potentially be used in patients with CUP to determine the tissue of origin of the cancer and hence provide assistance in the selection of the most appropriate systemic therapy.

Initial studies appear to show an improvement in median survival for patients receiving systemic cancer therapy according to identification of tissue of origin based on results from genetic expression based profiling [8].

**Targetable Genetic Mutations**

Genetic expression based profiling may also enable identification of abnormal/mutated cellular pathways that could be potentially targeted with therapeutic agents regardless of the primary tumour site. Limited studies have shown that at least one clinically relevant genetic mutation was identified in 96% of carcinoma of unknown primary specimens (n=192). Clinically relevant alterations were more commonly seen in adenocarcinomas of unknown primary than non-adenocarcinomas of unknown primary [9]. Further investigation of genetic profiling in CUP is on-going.

At present however the role of genetic expression based profiling has not been established in CUP and therefore it is recommended that it should only be performed in this patient population within a clinical trial setting to allow further investigation.

**Management**

**Prognostic Groups**

When deciding on treatment for cancer of unknown primary patients a decision has to be made which addresses the balance of risks (toxicity, convenience, impact upon quality of life) and the benefits (relief of symptoms, increased survival) of treatment. Decisions about commencing treatment should be made in conjunction with the
patient taking into account their wishes, the realistic aims of treatment, and prognostic factors.

Within CUP there are recognised treatable syndromes which when treated as per their presumed tissue of origin take on a more favourable prognosis (Table 3). The management of these cases is discussed further below but initially these cases should be referred on to the appropriate site specific MDT.

<table>
<thead>
<tr>
<th>CUP “SYNDROME”</th>
<th>Site specific MDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated axillary node metastases in a female</td>
<td>Breast</td>
</tr>
<tr>
<td>Squamous cell carcinoma involving cervical lymph nodes</td>
<td>Head and Neck</td>
</tr>
<tr>
<td>Peritoneal adenocarcinomatosis in a female</td>
<td>Gynaecology</td>
</tr>
<tr>
<td>Squamous cell carcinoma involving inguinal lymph nodes</td>
<td>Urology</td>
</tr>
<tr>
<td>Poorly differentiated neuroendocrine tumour (NET) of unknown primary</td>
<td>NET (Specialist MDT Christie)</td>
</tr>
<tr>
<td>Well differentiated NET of unknown primary</td>
<td>NET (Specialist MDT Christie)</td>
</tr>
<tr>
<td>Poorly differentiated carcinoma with predominant mid-line distribution</td>
<td>Urology/Germ cell</td>
</tr>
<tr>
<td>CUP with colorectal IHC</td>
<td>Colorectal MDT</td>
</tr>
<tr>
<td>Solitary CUP metastasis</td>
<td>Single metastasis site specific</td>
</tr>
<tr>
<td></td>
<td>- Brain- neuro oncology</td>
</tr>
<tr>
<td></td>
<td>- Pulmonary – lung</td>
</tr>
<tr>
<td></td>
<td>- Liver – HPB</td>
</tr>
<tr>
<td></td>
<td>- Bone – orthopaedic/sarcoma</td>
</tr>
</tbody>
</table>

Table 3: CUP syndromes and associated site specific MDT’s.

Prognostic markers can also help to identify patients with CUP who may gain benefit from anti-cancer therapy but do not fall into one of the recognisable treatable syndromes. Prognostic predictors are potentially of value in clinical decision making, allowing optimal treatment to be used in those most likely to gain the greatest benefit, whilst avoiding the unnecessary toxicity of futile anti-cancer treatment in
those unlikely to benefit. These factors may be individual physiological factors and also tumour specific factors including:

- Performance status
- Co-morbidities
- Number of metastatic sites
- Specific organ involvement ie brain / liver
- Lactate dehydrogenase levels (LDH)
- Albumin levels

Patients who present with CUP with multiple metastases including brain metastases are known to be a particularly poor prognostic group. There is no evidence to support the use of systemic chemotherapy in these patients. Patients should be discussed at the local CUP MDT to decide if referral for whole brain radiotherapy is appropriate however there is limited evidence to support the use of whole brain radiotherapy for symptom relief in this setting [10-11].

**Management of Recognisable CUP “Syndromes”**

Where appropriate patients who are fit enough for systemic therapy should be considered for entry into clinical trials; otherwise the management of recognisable CUP syndromes are summarized as follows:

- **Squamous cell carcinoma of cervical nodes**
  - A small number of CUP patients present with squamous cell carcinoma of the cervical nodes with no identified head and neck primary.
  - Pattern of disease is similar to that of patients with an identified head and neck primary.
  - These patients may benefit from radical treatment (neck dissection and/or irradiation of bilateral neck and head–neck axis. For advanced
stages induction chemotherapy with platinum-based combination or chemoradiation) with potentially curative intent.

- They should be referred to the head and neck specialist MDT.

- **Squamous cell carcinoma of inguinal nodes**
  - Rare presentation of CUP most commonly represents spread from melanomas or squamous carcinomas arising in the skin of the leg or lower trunk, external genitalia, anus, vagina, cervix, ovary and very rarely other pelvic viscera.
  - Attempt at curative treatment surgery +/- radiotherapy can occasionally be successful.
  - Patient should be referred to specialist urology MDT.

- **Adenocarcinoma of axillary nodes**
  - 90% of female patients presenting with adenocarcinoma of the axillary nodes are considered to have an unidentified breast primary.
  - These patients should be referred to the specialist breast MDT and considered for radical treatment (Axillary nodal dissection, mastectomy or breast irradiation and adjuvant chemohormonotherapy).

- **Solitary Metastases from Unknown Primary**
  - Solitary metastases even where the primary is unknown should be considered for potentially radical treatment (resection and/or RT ± systemic therapy).
  - Patients should be discussed at the appropriate disease site specific MDT according to the location of the metastases PRIOR to tissue biopsy taking place ie radiological diagnosis only.
  - 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.

- Peritoneal adenocarcinomatosis in a female
  - These patients should be discussed at the specialist gynaecology MDT.
  - Typically present with abdominal symptoms / ascites
  - They should be considered for optimal surgical debulking followed by platinum– taxane-based chemotherapy which have shown similar response rates to patients with confirmed primary peritoneal carcinoma.

- Poorly differentiated carcinoma with pre-dominant mid-line tumour
  - Treat as per extra-gonadal germ cell tumours.
  - Should be discussed at the specialist urology / germ cell MDT.
  - Combination cisplatin based therapy / BEP in males.

- Poorly differentiated NET of Unknown Primary
  - These tumours are often part of the disease spectrum of small cell carcinomas and are hence treated similarly.
  - Combination chemotherapy usually platinum based regimens are commonly utilised (platinum + etoposide combination chemotherapy).
  - Patients should be referred to the specialist NET MDT based at the Christie Hospital

- Well differentiated NET of Unknown Primary
  - These tumours tend to have a very different pattern of behaviour to carcinomas.
- Treatments may include somatostatin analogs, streptozocin + 5-FU, or oral tyrosine kinase inhibitors for example sunitinib / everolimus.
- Patients should be referred to the specialist NET MDT based at Christie Hospital

- **CUP with a colorectal IHC (CK20+ CDX2+ CK7−) or molecular profile**
  - Should be regarded as per colorectal cancer.
  - Management should be as per systemic treatment used for colorectal
  - Case should be discussed either at local CUP MDT or local colorectal MDT.

**Systemic Treatment of Confirmed CUP**

Patients who do not fall into one of the above recognised treatable syndromes may be considered for systemic therapy with the decision to treat being based on the patient’s performance status, co-morbidities and informed choice regards treatment options including best supportive care.

The evidence of benefit of chemotherapy in these patients is varied with meta-analysis of studies specific to CUP showing no statistically significant improvement in survival over best supportive care [12]. However extrapolation from studies in known primary’s that have commonly be identified as primary’s in CUP patients show a survival benefit of 3-6months in selected patients over best supportive care alone [1].

The optimal systemic therapy is yet to be determined for this group of patients. Therapy tends to be selected according to patient’s performance status, co-morbidities and suspected origin of the cancer. There is no evidence at present to dictate the use of one regimen over another in patients with confirmed CUP. Where
possible patients should be managed within a clinical trial in order to develop an evidence base for management of CUP patients.

Common regimens currently employed in the treatment of CUP are:

- Carboplatin / paclitaxel
- ECX / F (epirubicin / cisplatin / capecitabine (xeloda)/ 5FU
- EOX (epirubicin / oxaliplatin / capecitabine (xeloda)
- Gemcitabine / platinum (cisplatin/ carboplatin)
- Gemcitabine alone
- Oxaliplatin / 5FU

**Clinical Trials**

As part of the development of the CUP services and by establishment of a Pathway group the aim is to develop a research portfolio specific to CUP.

At present there are no NCRN trials or national trials currently active for CUP however proposals for further research projects being developed and the pathway group aim to be actively involved in any future trials.

Where possible and if appropriate patients are considered for entry into trials taking place within the CUP group or early phase clinical trials via the Experimental Cancer Medicine Team based at the Christie NHS Trust.

The development of future research projects within the group should be actively encouraged.
**Palliative Care**

Patients should be referred early on in their cancer pathway to palliative care services. A significant proportion of patients will not be suitable for systemic therapy and best supportive care will be the focus of their on-going management. It is therefore essential that patients and their carers receive adequate physical, psychological and spiritual input from community and central palliative care services.

Patients receiving systemic therapy also need to be referred early to palliative care services as despite systemic therapy the prognosis for these patients remains poor. Again it is essential that their physical, psychological and spiritual needs are met.

Patients should be placed on the Gold Framework Standard by their GP at initial diagnosis to highlight and ensure they receive appropriate support.

**Clinical Audit and Data Collection**

A minimum data set (MDS) to be collected at the local CUP MDT’s will be specified to ensure that consistent high quality data is collated for all CUP patients.

At present there are no clinical indicators defined for CUP within National Peer review measures

Regional audits will be agreed with contribution from all local CUP teams. The audit will be reviewed annually within the network with presentation of results upon completion.
Appendices

i) Local CUP MDT’s / Clinical Leads:

<table>
<thead>
<tr>
<th>Cancer of Unknown Primary Pathway Sub-group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair: Dr Claire Mitchell</td>
</tr>
<tr>
<td>Membership November 2015</td>
</tr>
</tbody>
</table>

| ROYAL BOLTON HOSPITAL NHS FOUNDATION TRUST |
| Clinical Lead | Dr Carmel Anandadas |
| Core nurse Member | Clare de Marco Masetti |

| MID CHESHIRE HOSPITALS NHS FOUNDATION TRUST |
| Clinical Lead | Delyth Owen |
| Core nurse Member | Sophie Lloyd / Sarah Latham |

| CENTRAL MANCHESTER UNIVERSITY HOSPITALS NHS FOUNDATION TRUST |
| Clinical Lead | Dr Claire Mitchell |
| Core nurse Member | Jenna Fletcher |

| THE CHRISTIE NHS FOUNDATION TRUST |
| Clinical Lead | Dr Claire Mitchell |
| Core nurse Member | Vikki Owen Holt / Andrea Spencer Shaw |

| EAST CHESHIRE NHS TRUST |
| Clinical Lead | Dr Catherine McBain |
| Core nurse Member | Anne Allen |

| PENNINE ACUTE HOSPITALS NHS TRUST |
| Clinical Lead | Dr Paul O'Donnell |
| Core nurse Member | Kevin White |

| SALFORD ROYAL NHS FOUNDATION TRUST |
| Clinical Lead | Dr Claire Arthur |
| Core nurse Member | Vicki Tyrrell |

| UNIVERSITY HOSPITAL OF SOUTH MANCHESTER NHS FOUNDATION TRUST |
| Clinical Lead | Dr Yvonne Summers |
| Core nurse Member | Jeena Mathews |

| STOCKPORT NHS FOUNDATION TRUST |
| Clinical Lead | Dr Catherine Coyle |
| Core nurse Member | Christine Griffiths |

| TAMEMSIDE HOSPITALS NHS FOUNDATION TRUST |
| Clinical Lead | Dr Shein Chow |
| Core nurse Member | Melanie Dadkhah-Taiedy |

| WRIGHTINGTON, WIGAN AND LEIGH NHS FOUNDATION TRUST |
| Clinical Lead | Dr Kalena Martimarti |
| Core nurse Member | Barbara Hefferon |

User Representatives(x2)
Dr Tim Crooksley

3rd Edition.
For review February 2018
<table>
<thead>
<tr>
<th>TBC</th>
<th>Imaging Specialist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Ben Taylor</td>
<td>Histopathologist</td>
</tr>
<tr>
<td>TBC</td>
<td>Consultant Palliative Medicine</td>
</tr>
<tr>
<td>TBC</td>
<td>Administration Support</td>
</tr>
<tr>
<td>Rebecca Price</td>
<td>Named Member with Responsibility for User Issues</td>
</tr>
<tr>
<td>TBC</td>
<td>Named Member with Responsibility for Trial Recruitment</td>
</tr>
<tr>
<td>Dr Claire Mitchell</td>
<td></td>
</tr>
</tbody>
</table>
## ii) Example Referral Form for Local CUP MDT:

<table>
<thead>
<tr>
<th>CUP MDT</th>
<th>Date of MDT:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATIENT DETAILS:</strong></td>
<td></td>
</tr>
<tr>
<td>Name:</td>
<td>Hospital Number:</td>
</tr>
<tr>
<td>Date of Birth:</td>
<td></td>
</tr>
<tr>
<td>Consultant:</td>
<td>If IP Ward:</td>
</tr>
</tbody>
</table>

| **CLINICAL DETAILS:**    |              |
| Symptoms:                | Performance Status: |
| Co-morbidities:          |              |
| Known sites of disease: |              |
| Bloods (including LDH):  |              |

| **RADIOLOGY / PATHOLOGY DETAILS:** |              |
| **Imaging** to be reviewed:        | Source:      |
| Modality:                           |              |
| Date of examination:                |              |

Please attach copy of original radiology report or summarise findings.

**Histopathology** to be reviewed: Source:

Date of Sample:

Please attach copy of original histopathology report or summarise findings.

**OUTCOME:**
Patients who present with the following scenarios are suitable for discussion at the local CUP MDT where there is no evidence of a primary site:

- Liver tumour(s) / intra-abdominal masses identified as likely metastatic malignancy on initial imaging
- Bone tumour(s) identified as likely metastatic malignancy on initial imaging and not immediately considered to be related to prostate cancer
- Brain tumour(s) identified as likely metastatic malignancy on initial imaging.
- Lung tumour(s) identified as likely metastatic malignancy on initial imaging.
- Pleural effusion(s) diagnosed as malignant on cytology.
- Malignant ascites diagnosed on cytology.
- Other sites of metastatic disease where the primary site is not identified can be discussed with the AO/CUP team and discussed if felt appropriate.

POINTS TO CONSIDER:

- Histology and tumour markers are **not** required prior to discussion.
- Solitary metastases should be referred to site specific MDT’s.
- Where a primary site is thought likely this should be referred via current disease specific pathways.
- In-patients should be referred to the local AO / CUP team for support and advice.
- Referrals for the MDT are reviewed and if it is felt an alternative MDT is more appropriate you will be advised accordingly. **Please ensure correct contact details are completed on the referral form.**

**IF YOU ARE UNCERTAIN PLEASE CONTACT THE AO/CUP TEAM TO DISCUSS.**
v) ECOG / WHO Performance Status

- **0** – Asymptomatic (Fully active, able to carry on all pre-disease activities without restriction)
- **1** – Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
- **2** – Symptomatic, <50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours)
- **3** – Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
- **4** – Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
- **5** – Death
Referral Contacts

Dr Claire Mitchell
Consultant Medical Oncologist – specialising in CUP
Christie Hospital NHS Trust
Manchester
M20 4BX

Tel: 0161-446-3606
Fax: 0161-446-3299

Patient Support Groups

1. MacMillan Cancer Support
   www.macmillan.org.uk

2. Cancer Research UK
   www.cancerresearchuk.org

3. CUP Foundation – Jo’s Friends
   www.cupfoundjo.org
References

1. NICE: Diagnosis and Management of Metastatic Malignant Disease of Unknown Primary Origin (CG104). 2010.