Policy and Guidelines for the Investigation, Diagnosis and management of Patients with malignancy of an Unknown Origin (MUO) and Cancer of an Unknown Primary (CUP)
This sheet is to accompany all documentation agreed by the West Midlands Strategic Clinical Network Expert Advisory Groups. This will assist the Clinical Network to endorse the documentation and request implementation.

<table>
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<tr>
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<th>Metastatic Spinal Cord Compression (MSCC), Acute Oncology (AO) and Cancer of the unknown Primary (CUP) – Expert Advisory Group (EAG)</th>
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| **EAG Chair** | Peter Correa  
Date: 22 March 2018 |
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Date: 22 March 2018 |
V1 endorsed on the 4th of December 2015.

Review planned for June 2018 or in light of revised national guidance.


The information contained in this document is a consensus of the development and consultation groups’ views on current treatment. Clinicians using this document are expected to use independent clinical judgment in the context of the presenting clinical circumstances to determine any patient’s care or treatment.

**Evidence Base Peer Review Measures:**

14-1C-105m  14- 2M-101
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1. Introduction

Metastatic cancer of unknown primary (CUP) is a common, well-recognised and heterogeneous clinical syndrome. Patients with CUP present with metastatic disease in the absence of an identifiable primary tumour despite a diagnostic work-up. Cancer of unknown primary represents 3-5% of all malignancies (Pavlidis and Fizazi 2009) and is the fourth most common cause of cancer-related death. The Routes to Diagnosis Report reviewed Hospital Episode Statistics (HES) data and found that in 2013 overall survival at 12 months for CUP patients was 16%, but only 6% for CUP patients presenting as an emergency. Overall survival at 3 years was 10% and 2% for those patients who presented as an emergency. There were 7,671 patients diagnosed with CUP in 2013 of those 54% presented as an emergency (Public Health England 2015).

These guidelines have been reviewed and endorsed by the West Midlands Strategic Clinical Network, Acute Oncology, Metastatic Spinal Cord Compression and Cancer of Unknown Primary Expert Reference Group. They have been adapted from an original document developed by the Midlands Acute Oncology Nurses Forum (MAONF). They are aligned with, and build upon, the recommendations made in the National Institute for Health and Clinical Excellence (NICE) clinical guideline 104 “Diagnosis and Management of Metastatic malignant disease of unknown primary origin” (July 2010) and the National Cancer Peer Review Programme Manual for Cancer Services: Cancer of Unknown Primary Measures Version 1.0 (January 2014)

The responsibility for the implementation of CUP/MUO guidelines lines with the trust cancer lead clinician. This document may be used as a whole or in part as trust and/or network guideline. Please ensure that the original source is recognized.

The document should be subject to organizational review and approval prior to adoption/implementation.

The measures should be applied to each relevant hospital under review.

Note: The meaning of the term 'relevant hospital' is defined for the purposes of peer review as:

- Any hospital with one or both of a) an A&E department and/or b) acute medical beds which are open to direct admissions (often locally referred to by specific terms such as 'GP take'). This can be with or without specialist oncology beds.
- Hospitals with specialist oncology beds but without either an A&E department or acute medical beds used as above. It should be noted that patients with MUO and CUP need not necessarily be acutely ill, but the above definition of relevant hospital should pragmatically cater for the vast majority of MUO and CUP patients (Peer Review 2013).

2. Purpose of the guideline.

Taking each part of the MUO/CUP patient’s pathway from GP referral through diagnosis and management and then onward referral, it outlines the points that each Trust needs to adhere to, to ensure safe and equitable MUO/CUP service provision.

The purpose of this guideline is to: -
• Provide the framework, which underpins the initial and on-going investigation and subsequent management of patients presenting as cases of MUO (malignancy of an unknown origin), aimed at improving outcomes of MUO/CUP patients across the Greater Midlands.

• Provide a guideline on the management of specific presentations of cancer of unknown primary origin, both those which may benefit from radical (potentially curative) treatment and those with a poor prognosis who may benefit from supportive and/or palliative care.

• Provide guidelines, on the systemic treatment of the following treatable syndromes within the CUP spectrum:
  o Poorly differentiated carcinoma with a midline distribution,
  o Women with predominantly peritoneal adenocarcinoma,
  o Women with adenocarcinoma involving the axillary lymph nodes,
  o Squamous cell carcinoma of lymph nodes in the neck,
  o Poorly differentiated neuroendocrine carcinoma.

• Provide direction for the following groups:
  • Primary Care Practitioners,
  • CUP MDT and CUP Service Team members,
  • Cancer site-specific MDTs,
  • Trust Emergency Departments
  • All health professionals dealing with the investigation, management and care of MUO and CUP patients.

2.1 Scope
Adult cancer patients presenting with metastatic malignant disease without an identifiable site.

3.0 The MUO/CUP Initial Management Pathway
Patients should be supported through the diagnostic pathway, their symptoms should be actively managed and they should be kept fully informed as to the purpose and results of investigations. Patients should be given the contact number of the Specialist Nurse for CUP to support them and to liaise with primary or palliative care teams as appropriate.

3.1 GP Referral
Patients who are well enough to have a planned referral from their GP should be referred and seen according to the two-week rule of patients with suspected cancer diagnosis. The referral pathway should be agreed locally but may follow one of the following routes:
  • Referral to the Trust CUP lead/MDT
  • Referral to the likely primary site specific team
General Practitioners who are concerned about the possibility of MUO/CUP should be encouraged to contact the CUP lead or CUP CNS for advice if they are unsure about referral.
3.2 Presentation
Some patients will present acutely ill and possibly via emergency services, and will be recognised early on in the diagnostic pathway as cases of MUO.

In these cases the arrangements and infrastructure for either CUP or Acute Oncology are appropriate for initial management.

In addition, the CUP assessment arrangements can be offered as part of Acute Oncology, or be a separate entity.

3.3 Referral
Outpatients with MUO should be referred to the CUP team immediately, using the rapid referral pathway for cancer, to ensure that all patients are assessed within 2 weeks of referral.

A member of the CUP team should assess in-patients with MUO by the end of the next working day after referral.

The CUP team should take responsibility for ensuring that a management plan exists, which includes:

- Appropriate investigations
- Symptom control
- Access to psychological support and
- Providing information.

4.0 MUO/CUP Investigation & Diagnosis

For patients presenting with MUO, diagnosis can be divided into two phases:

- The Initial Diagnostic Phase
- The Second Targeted investigation Phase.

4.1 Initial Diagnostic Phase
For patients presenting with MUO, diagnosis can be divided into two phases. The aim of the Initial Diagnostic Phase is to perform the most appropriate investigations efficiently, to identify one of the following:

- A primary site,
- Non-epithelial malignancy, which can be treated regardless of primary site (e.g. lymphoma, other haematological malignancies, melanoma, sarcoma and germ-cell tumours),
- Metastatic epithelial or neuro-endocrine malignancy without an identifiable site (a diagnosis of provisional CUP).

4.2 Initial Assessment and diagnostic steps (Appendix 3)

In this phase, patients with MUO should be offered the following assessment and investigations, as clinically appropriate, guided by the patient’s symptoms:
**Observations:** Temperature, pulse, blood pressure, respiration rate, O₂ saturation. Early warning score.

**History:** Full history including rate of change of symptoms. Assess and record current performance status and co-morbidities.

**Examination:** Complete clinical examination (including; breast, PR, PV, testicular, skin, nodal areas, and pelvic examination)

**Laboratory Investigations:**

- All patients: Full blood count, urea, electrolytes and creatinine; liver function tests; calcium; lactate dehydrogenase, CRP
- Men with midline disease /brain metastases: Serum Alpha-fetoprotein αFP and human chorionic gonadotrophin βhCG (Presentations compatible with germ-cell tumours)
- Women with pelvic or peritoneal disease: Cancer antigen CA125 (Presentations compatible with ovarian cancer)
- Men with bone metastases: Prostate-specific antigen (PSA) PSA (Presentations compatible with prostate cancer)
- Patients with liver only disease: Serum Alpha-fetoprotein αFP
- Consider myeloma screen - for bone lesion seen on scan with no obvious primary
- Urinalysis

**Note:** other tumour markers are generally not useful in diagnosis

**Imaging:**

- **CT thorax, abdomen and pelvis** is the staging investigation of choice in most circumstances
- Other investigations (including endoscopies) only as indicated by signs and symptoms
- Testicular ultrasound in men with presentations compatible with germ-cell tumours,

**Pathology:**

- Patients with a solitary liver lesion should be referred to the appropriate local specialist team before biopsy
- All other patients, try to get biopsy (trucut if possible) for histology to guide future treatment
- Detailed clinical information on the request form is essential

**4.3. MDT Discussion**

The CUP multidisciplinary team meeting should recommend the on-going diagnosis, treatment and care of patients with confirmed CUP (or with MUO or provisional CUP) based on the results of initial diagnosis.

Where patients present with MUO with symptoms indicating a likely but indefinite primary site, they are referred to the following tumour-site MDTs, for discussion of the investigation plan, or specialist referral routes, guided as follows:
4.4. Patterns of disease requiring URGENT specific action:
- Spinal cord compression – requires urgent admission and referral to spinal cord co-ordinator
- Men with midline disease – requires urgent referral to oncology (germ cell?)
- Superior Vena Cava Obstruction - requires urgent referral to lung MDT for consideration of stent
- Suspected lymphoma, myeloma, plasmacytoma – requires urgent referral to haematology

4.5. Patterns of disease requiring specific action:
- Men with bone metastases and elevated PSA – referral to urology MDT
- Women with axillary nodes – referral to breast surgeons/ MDT
- Women with peritoneal disease – referral to gynaecology /MDT, unless histology suggests non gynaecology origin
- Solitary liver lesion – requires referral to hepatobiliary MDT
- Neck nodes – requires referral to head and neck or neck nodes clinic as appropriate locally
- Isolated brain metastasis – requires referral to neurology MDT.

Where patients present with MUO when the possible primary diagnosis remains unclear – considered as “ambiguous” cases – the Trust CUP MDT would manage their care and treatment plan. This MDT can be a standalone, named Trust CUP MDT or that of a pre-existing Trust tumour site. If the latter, each Trust should nominate the same MDT for the discussion of all ambiguous cases.

The CUP Team should actively review the outcome of all investigations with a nominated pathologist and radiologist as appropriate.

| It should be ensured that when MUO is suspected or first diagnosed, the patient is upgraded to the existing cancer waiting times pathway. |

Every Trust undertaking diagnostic investigations of patients with MUO should ensure that services are set up for rapid and appropriate investigation of patients according to this policy, and that staff are appropriately trained.

4.6. Second Diagnostic Phase – Targeted Investigations (appendix 4.)

If further investigation is appropriate, a second phase of targeted investigations may be offered to patients with provisional CUP.

| When these are complete and if a primary site has still not been identified, a diagnosis of confirmed CUP can be made. |

4.7. Tumour Markers
Do not routinely measure tumour markers to identify primary tumours in patients with provisional CUP, as these are generally not useful in diagnosis, except for:
• αFP and βhCG in patients with presentations compatible with germ-cell tumours (particularly those with mediastinal and/or retroperitoneal masses and in young men),
• αFP in patients with presentations compatible with hepatocellular cancer, single liver lesion.
• PSA in men with presentations compatible with prostate cancer,
• CA125 in women with presentations with ovarian cancer (including those with inguinal node, chest, pleural, peritoneal or retroperitoneal presentations). Carefully interpret the results because of limited test specificity.

4.8. Upper and Lower GI Endoscopy

Do not carry out in patients with MUO unless the symptoms, histology or radiology suggest a GI primary tumour.

4.9. Mammography

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

4.10. Breast MRI

Refer patients with adenocarcinoma involving the axillary nodes to a breast cancer MDT for evaluation and treatment. If no breast primary tumour is identified after standard breast investigations, consider dynamic contrast-enhanced MRI to identify lesions suitable for targeted biopsy.

4.11. PET-CT

Offer PET-CT (18F-FDG PET-CT) to 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.

Consider 18F-FDG PET-CT in patients with provisional CUP with extra-cervical presentations after discussion with the CUP team.

4.12. Immunohistochemistry

Immunohistochemistry should be routinely applied especially in poorly differentiated cases to exclude chemo-sensitive and potentially curable tumors (i.e. lymphomas and germ cell tumors) (ESMO).

If diagnosis is adenocarcinoma, immunostaining for PSA in male patients and for oestrogen and progesterone receptors in females with axillary node metastases is advisable to rule out hormone-sensitive tumors amenable to specific therapy (ESMO).

Use additional immunohistochemistry to refine the differential diagnosis, guided by the results (Table 1).

Table 1. Immunohistochemical markers

<table>
<thead>
<tr>
<th>Immunohistochemical marker</th>
<th>Possible cancer site of origin</th>
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</thead>
</table>


<table>
<thead>
<tr>
<th>Gene</th>
<th>Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA – prostate specific antigen</td>
<td>Prostate</td>
</tr>
<tr>
<td>TTF1 – thyroid transcription factor 1</td>
<td>Lung</td>
</tr>
<tr>
<td>GcDFP-15 gross cystic disease fluid protein 15</td>
<td>Breast</td>
</tr>
<tr>
<td>CDX20</td>
<td>Colon</td>
</tr>
<tr>
<td>CK20</td>
<td>Colon, Oesophageal, Ovarian, Ampullary</td>
</tr>
<tr>
<td>CK7 cytokeratin</td>
<td>Lung, Pancreas, Cholangio, Ovarian, Breast</td>
</tr>
<tr>
<td>ER – oestrogen receptor</td>
<td>Breast, Ovarian, Endometrial</td>
</tr>
<tr>
<td>Mesothelin</td>
<td>Cholangio, Mesothelioma, Endometrial, Ovarian</td>
</tr>
<tr>
<td>CA125</td>
<td>Ovarian, Endometrial, Cholangio, Pancreas</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Cholangio, Pancreas, Lung, Stomach, Colon</td>
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4.13. **Gene-Expression-based Profiling**
Do not use to identify primary tumours in patients with provisional CUP.

4.14. **Investigation of specific Clinical Presentations**

4.14.1. **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.

4.14.2 **Investigation of Malignant Peritoneal Disease**
Obtain a tissue sample for histological examination in patients with MUO who present with ascites, if technically possible.

5.0. **Factors Influencing Management Decisions**

5.1 **Continuing/Ceasing Investigations**
Perform further investigations only if:
- The patient is fit for treatment if the primary site were found,
- 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 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.

6.0. Outcome of MUO/CUP Investigation Pathway

The MUO/CUP Investigation Pathway should ensure that the following is adhered to:

- All patients with MUO should be reported to one of the hospital’s designated members of a CUP MDT,
- All patients should be assessed face-to-face by a core member of the CUP MDT (which can be the CUP CNS) which the hospital is associated with, within two weeks of the diagnosis of MUO for outpatients and by the end of the next working day, for inpatients. (All patients presenting on a Friday or during the weekend, would require them to be seen by the end of the normal working day on Monday).
- All patients with provisional CUP should be discussed at the next CUP MDT meeting for:
  - Any advice on remaining investigations needed to confirm the diagnosis of CUP or establishment of a primary site,
  - Any necessary decision regarding suitability for “active treatment”, any treatment planning decisions.
- If a site specific MDT, is referred any MUO patients, they should refer them on for discussion by the CUP MDT.

7.0. Guidelines on the onward referral and management of specific presentations and the systemic therapy of treatable syndromes

7.1. Selecting Optimal Treatment

- Take account of prognostic factors, in particular performance status, co morbidities, likely primary site, presence of liver metastases, lactate dehydrogenase levels (optional) and serum albumin, when making decisions about further diagnostic investigations and treatment.
- Clinical features associated with an unfavourable prognosis include severely deranged organ function, multiple co-morbidities, and poor performance status. Early referral to palliative care should be considered.
- Clinical features associated with better outcomes with chemotherapy include rapid tumour growth, age less than 50 years, two or fewer areas of metastasis and normal organ function. Favourable cancer subtypes are outlined in Table 2 (p22).
- Discuss the patient’s prognostic factors with the patient and their relatives or carers, if appropriate, to help them make informed decisions about treatment.
- Do not use gene-expression-based profiling when deciding which treatment to offer patients with confirmed CUP.
7.2. Subsequent Referral and Management of Presentations that may benefit from radical treatment

- If clinical, radiological and pathological findings suggest a specific cancer primary refer to relevant MDT - Otherwise the patient will remain under the care of the unknown primary MDT

7.3. Patients who may benefit from radical (potentially curative) treatment

- Squamous carcinoma involving upper or mid neck nodes
- Adenocarcinoma involving axillary nodes
- Squamous Carcinoma involving Inguinal Nodes
- A solitary, apparent metastasis
- Lymphoma

7.4. Squamous Carcinoma involving upper- or mid-neck nodes

A small minority of CUP patients presents with squamous carcinoma in upper- or mid-neck lymph nodes from a presumed but unidentified head and neck primary. Furthermore, the pattern of nodal involvement in these patients is very similar to that seen in patients with an identified head and neck primary. Experience suggests that these groups may benefit from localised treatment with potentially curative intent.

Recommendation

Refer patients with Squamous Carcinoma involving upper- or mid-neck nodes to the Head and Neck MDT for evaluation and treatment according to agreed guidelines: please see table 4.
Table 4. Guidelines for management of Squamous Carcinoma involving upper- or mid- neck nodes (British Association of Head and Neck Oncologists standards for the process of head and neck cancer care (2009))

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SURGERY</th>
<th>RADIOThERAPY</th>
<th>CHEMOTHERAPY</th>
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<tbody>
<tr>
<td>T0N1 (No ECS)</td>
<td>Selective Neck Dissection (SND) or Modified Radical Neck Dissection (MRND)</td>
<td>No unless for Mucosal sites</td>
<td>No</td>
</tr>
<tr>
<td>T0N1 (ECS)</td>
<td>SND or MRND</td>
<td>Yes – either involved lymph nodes or ipsilateral neck and boost to involved lymph nodes.</td>
<td>Induction platinum-based chemotherapy as if head and neck cancer should be considered</td>
</tr>
<tr>
<td>T0N2a N2b N2c</td>
<td>SND or MRND +/- contralateral SND or MRND</td>
<td>Yes - ipsilateral but bilateral should be considered</td>
<td>Induction platinum-based chemotherapy as if head and neck cancer should be considered</td>
</tr>
<tr>
<td>T0N3</td>
<td>Radical or type I MRND</td>
<td>Yes - ipsilateral but bilateral should be considered</td>
<td>Induction platinum-based chemotherapy as if head and neck cancer should be considered.</td>
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7.5. Adenocarcinoma involving the axillary nodes

More than 90% of female patients presenting with adenocarcinoma involving axillary nodes are considered to harbor an unidentified breast primary. In the remainder of female patients the primary site usually becomes obvious after a careful history and examination, without recourse to extensive untargeted investigation.

Recommendation:

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

Treat with surgery/ hormones/ chemotherapy as if breast cancer.

Identical to breast cancer with similar nodal involvement as per network agreed guidelines.

7.6. Squamous Carcinoma involving the Inguinal Nodes

Metastatic carcinoma in inguinal lymph nodes most commonly represents spread from melanomas or squamous carcinomas arising in the skin of the leg or lower trunk, carcinomas of the external genitalia, anus, vagina, cervix, ovary and very rarely other pelvic viscera. This section is specifically concerned with the management of patients with squamous carcinomas, who have a relatively favourable prognosis. This is a very rare presentation of CUP and there is sparse evidence on which to base recommendations for clinical management. However, studies on groups of patients and individual patients
indicate that an attempt at curative treatment can sometimes be successful, without identification of the primary. This can be explained by spontaneous regression of an occult primary cancer or by its eradication coincidentally by treatment directed against the metastatic disease. Sometimes the primary malignancy will become evident later and may then be treatable with curative intent. If the occult primary cancer is in the midline there is an increased chance that spread to inguinal lymph nodes will be bilateral, and that sooner or later bilateral treatment will be required.

**Recommendation:**

Refer to a specialist surgeon in an appropriate MDT to consider treatment with curative intent.

<table>
<thead>
<tr>
<th>Refer to a specialist surgeon in an appropriate MDT to consider treatment with curative intent.</th>
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<tr>
<td>Offer patient with operable disease either:</td>
</tr>
<tr>
<td>• Superficial lymphadenectomy and consider post-lymphadenectomy radiotherapy (For patients with risk factors for residual disease, e.g. multiple involved nodes or extracapsular spread)</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>• Simple excision of clinically involved nodes, followed by radiotherapy+/−chemotherapy as if anal/cervical cancer</td>
</tr>
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</table>

### 7.7. Solitary Metastases

Some patients with known primary cancers who develop apparently solitary metastases can be treated successfully by radical treatment to eliminate the metastasis. If the primary cancer has been or can be successfully treated long-term remission or cure may be achieved for selected patients. There is a tendency for treatment to the metastasis to be more successful the longer the ‘disease-free interval’ following treatment to the primary, but successful outcomes can be achieved for patients who at presentation are found to have either a solitary distant metastasis or limited metastatic disease eligible for radical treatment. This is particularly the case for patients with bowel cancer who have operable metastatic disease in the liver.

Surgery is by far the most common and successful treatment modality for patients with a solitary metastasis. For some patients complete excision will combine optimal local treatment with the best way of obtaining a tissue diagnosis. Radiotherapy and radiofrequency ablation can destroy metastases in selected situations and patients, and post-operative radiotherapy may reduce the risk of local recurrence following surgery. Highly focused radiotherapy, ‘stereotactic radiosurgery’, can deliver a well-tolerated very high radiation dose to small tumours.

**Recommendation**

• 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.

**Single potentially resectable metastatic site e.g. liver, lung, node, brain - consider surgical resection (without biopsy first) or radiotherapy followed by chemotherapy or radiotherapy as appropriate**

### 7.8. Subsequent Management of Presentations with a poor Prognosis

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.

Do not offer chemotherapy to patients with brain metastases of unknown primary origin except as part of a controlled clinical trial.

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.

**7.9. Chemotherapy treatment.**

There is very little evidence about the best chemotherapy to offer in patients with CUP although a number of ‘empirical’ regimens have been adopted worldwide on the basis of weak evidence.

Choice of chemotherapy (or radiotherapy) will be dictated by the extent of disease, outcome of MDT review of imaging and pathology, the patient's performance status, organ function, co-morbidities and patient wishes.

There is increasing support (although prospective trial evidence is awaited) for the rational selection of medical therapy according to pathological subtypes, as guided by immunohistochemistry e.g. Patients with metastatic cancer with CK20 +ve, CDX20 +ve, CK 7 –ve on immunohistochemistry should be treated with chemotherapy as if colon cancer (see Tables 1 and 2).

### 7.10. Systemic treatment /Chemotherapy for Confirmed CUP Patients without a specific treatable syndrome

For patients with confirmed CUP who do not fall into one of the recognised “treatable syndromes”, it is unclear whether chemotherapy is useful or whether these patients should be managed along symptomatic lines alone.

Confirmed CUP patients without a specific “treatable syndrome” who are being considered for chemotherapy should:

- Have the balance between the potential risks and benefits explained to, and discussed with, them,
• Be offered entry into a clinical trial if available (if it is decided to proceed with chemotherapy).

If chemotherapy is offered outside clinical trials, take into account the clinical and pathological characteristics of the tumour, the toxicity profile of the drugs, their ease of administration and response rate when choosing which treatment to use.

If chemotherapy is being considered for patients with confirmed CUP, with no clinical features suggesting a specific treatable syndrome, inform patients about the potential benefits and risks of treatment.

7.11. Systemic treatment/ Chemotherapy for Confirmed CUP Patients with a treatable syndrome

Treatable syndromes are defined as follows:

• Poorly differentiated carcinoma with a midline distribution,
• Women with predominantly peritoneal adenocarcinoma,
• Women with adenocarcinoma involving the axillary lymph nodes,
• Squamous cell carcinoma of lymph nodes in the neck,
• Poorly differentiated neuroendocrine carcinoma.

Offer patients chemotherapy directed at a specific treatable syndrome if they have:
• Confirmed CUP with clinical and/or laboratory features of a specific treatable syndrome

and

• Adequate performance status.

Patients should also be offered entry into a clinical trial, if available.

7.12. Treatable Syndromes within the CUP Spectrum

For patients with confirmed CUP who fall into one of the recognised “treatable syndromes”, chemotherapy selected according to the presumed organ of origin may be more successful than generic treatment. Refer to table 3.

7.13. Poorly differentiated carcinoma with a midline distribution

Extragonadal germ cell syndrome e.g. midline/ retroperitoneal disease distribution/ raised αFP or βHCG - Combination chemotherapy: platinum based as if germ cell cancer

Patients should be offered clinical trials where this is applicable.

7.14. Women with predominantly Peritoneal Carcinoma

Features consistent with primary peritoneal origin:

Treat with Carboplatin/Taxol chemotherapy or single agent Carboplatin as per gynaecology protocols.

If mucinous treat as per colorectal with Capecitabine/Oxaliplatin.
Patients should be offered clinical trials where this is applicable.

7.15. Women with Adenocarcinoma involving the Axillary Lymph Nodes

Following discussion at Breast MDT meeting

Treat with surgery/ hormones/ chemotherapy as if breast cancer

Patients should be offered clinical trials where this is applicable.

7.16 Squamous Cell Carcinoma of Lymph Nodes in the Neck

Following discussion at Head and Neck MDT meeting

Radiotherapy +/- platinum-based chemotherapy as if head and neck cancer

Patients should be offered clinical trials where this is applicable.

7.17 Poorly-Differentiated Neuroendocrine Carcinoma

Following discussion at the appropriate Neuroendocrine MDT meeting

Combination chemotherapy: platinum/etoposide

8.0. On-going Care

The CUP Team should be involved in the patient’s care until the patient is:

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

If CUP is confirmed, the CUP team should continue managing the patient’s care, until the patient is referred for palliative care alone.

9.0 Organisation of Services, Support and Audit

9.1. The CUP Team

Every acute Trust should have a CUP Team, ensuring that patients and health care professionals should have access to it, when MUO is diagnosed.

This team should comprise of the following health care professionals as a minimum:

- An Oncologist,
- A palliative care physician
- A CUP specialist nurse/key worker
Note: a person who also has other roles such as an acute oncology assessment team nurse or cancer nurse specialist for another site-specific cancer may undertake the nurse’s role.

9.2. The CUP Multi-Disciplinary Team
The CUP MDT should comprise of those listed in 9.1 plus:

- An imaging specialist
- A histopathologist
- An MDT co-ordinator/secretary

MDT Members responsibilities:

- An NHS-employed member of the core or extended team should be nominated as having specific responsibility for users’ issues and information for patients and carers.
- A member of the core team should be nominated as the person responsible for ensuring that recruitment into clinical trials and other well-designed studies is integrated into the function of the MDT.
- At least one clinical core member of the team should have completed the training necessary to enable them to practice at level 2 for the psychological support of cancer patients and carers.

9.3. CUP Lead Clinician
There will be a named lead CUP clinician, who takes responsibility for the CUP service within the Trust.

9.4. Responsibilities of the Trust CUP Lead Clinician
The Trust CUP Lead Clinician should take full managerial responsibility for the CUP service within the Trust.
This responsibility includes ensuring that:

- There is a clinical system/pathway for the appropriate review and care of MUO and CUP patients,
- Each patient has an identified CUP Specialist Nurse/key worker and that there is a single point of contact for the patient to access the CUP team,
- There is cover for all members of the CUP team during periods of absence for provision of the hospital CUP service,
- Senior clinical input is available to inform decision making and treat patients as necessary,
- The care pathway is implemented - designated specialists working effectively together in teams such that decisions regarding all aspects of diagnosis, treatment and care of individual patients and decisions regarding the team’s operational policies are multidisciplinary decisions,
- The care pathway is utilised to help to educate other healthcare professionals in diagnosing and managing MUO and CUP,
• Care is given according to recognised guidelines (including guidelines for onward referrals) with appropriate information being collected to inform clinical decision making and to support clinical governance/audit,
• Timely and effective communication protocols between all healthcare professionals involved in the care of patients with MUO/CUP, including primary and palliative care are in place and adhered to,
• The Trust CUP MDT is effectively lead and that the attendance levels of core members are maintained, ensuring that there is cover for all members of the CUP team during periods of meeting absence,
• The target of 100% of cancer patients discussed at the MDT is met,
• The Trust CUP service meets the quality standards and lead on, or nominate a lead for service improvement,
• The outcomes of all MDT meetings are clearly recorded and clinically validated and that appropriate data collection is supported,
• An annual meeting is organised and chaired, to examine the functioning of team, review operational policies and collate any activities that are required to ensure optimal functioning of the team (e.g. training for team members),
• The notes and actions from the annual meeting are documented,
• MDT’s activities (MDT and annual meetings) are audited and results documented,
• The Trust is actively represented at the Network Acute Oncology Group by attendance at meetings or by nominating another MDT member to attend,
• The Trust contributes to regular local and network audits of the management of MUO and CUP,
• Mechanisms are in place to support entry of eligible patients into clinical trials, subject to patients giving fully informed consent,
• The target of communicating MDT outcomes to primary care is met.

9.5 Responsibilities of the Trust CUP CNS/Key Worker
On first referral to the CUP Team the Trust CUP CNS/Key Worker should take a major role in the co-ordination of the patient’s care.

If following MDT review/discussion:

• The patient is referred to a site-specific team for treatment of a specific presentation then the relevant site-specific nurse will assume the role of key worker. This should be clearly documented in the MDT discussion records.

• The patient is referred to the palliative care team for supportive and palliative care then the relevant site-specific nurse will assume the role of key worker. This should be clearly documented in the MDT discussion records.

• The patient is confirmed as CUP and the CUP team undertakes their care and management then the CUP CNS remains as the Key Worker. This should be clearly documented in the MDT discussion records.

The Key Workers responsibilities include:

• Liaise with the patient’s GP and other community support services,
- Ensure that the patient and carers can get information, advice and support about diagnosis, treatment, palliative care, spiritual and psychosocial concerns,
- Meet with the patient in the early stages of the pathway and keep in close contact with the patient, regularly by mutual agreement,
- Be an advocate for the patient at CUP team meetings by contributing to multidisciplinary discussion and patient assessment/care planning decision of the team at their regular meetings,
- Provide expert nursing advice and support to other health professionals in the nurse’s specialist area of practice,
- Be involved in clinical audit,
- Lead on patient and carer communication issues and coordinate the patient’s pathway for those patients referred to the team, acting as the key worker or taking responsibility for nominating the key worker,
- Ensure that results of the patient’s holistic needs assessment are taken into account in decision making,
- Contribute to the management of the service,
- Utilise research in the nurse’s specialist area of practice.

9.6. Responsibilities of the MDT Coordinator
The responsibilities of the Trust MDT Coordinator are to:
- Facilitate and co-ordinate the functions of the multidisciplinary team meetings,
- Ensure the appropriate proportions of patients are discussed at MDTs,
- Help with the introduction and changes to pro formas used to ensure all patients are discussed, treated appropriately and outcomes are recorded and reviewed, ensuring patients’ diagnoses, investigations, and management and treatment plans are completed and added to the patient’s notes,
- Manage systems that inform GP’s of patient’s diagnosis, decisions made at outpatient appointment etc.,
- Work with staff to ensure all patients have a booked first appointment, investigation and procedure and record details of patients coming via a different route,
- Work with key MDT members to identify areas where targets are not achieved, undertake process mapping to identify bottlenecks,
- Collect and record data,
- Manage the systems according to guidelines, monitoring milestones and submitting the required reports in the given format and required times,
- Keep a comprehensive diary of all team meetings,
- Record attendance at meetings,
- Take minutes at the multidisciplinary meetings, type notes back in the required format and distribute to all concerned,
- Be instrumental in the development of databases to capture patient information and report this to the clinicians on a weekly basis,
- Inform MDT Lead and lead cancer manager of waiting times for patients when these exceed appropriate targets,
- Ensure lists of patients to be discussed at meetings are prepared and distributes in advance,
- Ensure all correspondence, notes, x-rays, results, etc. are available for the meetings,
- Ensure action plans for patient care are produced with agreed reviews,
• Assist in capturing cancer data on all patients and assist in the development of systems to complement the cancer audit system,
• Ensure members or their deputy is advised of meetings and any changes of date, venue, etc.
Appendix 1.

Agreed pathway for the investigation and management of patients who present with Cancer of Unknown Primary Origin /Malignancy of Undefined Origin.

**REFERRAL**

- Primary Care Referral
- In-patient acute referral
- Radiology Referral

**URGENT referral to trust Acute Oncology Team**

- Phone...................................
- Email...................................

**ASSESSMENT**

In-patients are to be assessed by the end of the next working day following referral.

- Face to face assessment by a member of the acute oncology team.
- Patient to remain under the care of the admitting physician

**Acute Oncology Team assessment**

- Agree management plan and initial diagnostic investigations with managing clinical team.
- Refer patient to CUP lead and CUP CNS and arrange discussion at CUP MDT.

- Poor performance status / unwell patient - arrange urgent review by CUP clinical lead and/or palliative care team review for advice on supportive and palliative care.
- CUP CNS (identified as Key Worker) provide support and information to patients and carers

**CUP MDT Discussion**

Further management and onward referral agreed.

- Non-malignant
- Primary malignancy identified

**OUTCOME**

- Refer to appropriate clinical team.
- Provisional CUP
- Confirmed CUP

- Patterns of disease requiring specific action: Refer to appropriate site-specific oncologist/MDT for management according to agreed MAOG guidelines
- Treatment to be managed by CUP team according to agreed MAOG guidelines
- Palliative care referral for further management of, poor performance status / unwell patient, not suitable for treatment or not wishing to receive treatment.

- Refer to appropriate site-specific oncologist/MDT

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CUP Investigation and Management Guidelines V1
West Midlands SCN Acute Oncology, MSCC and CUP ERG /PJJ/ 4.12.2015
Appendix 2.

MUO/CUP Referral pathway

**GP/Primary Care referral.**
For patients who do not require emergency intervention please use the 2-week wait proforma for the relevant site-specific team or CUP MDT as per local policy.

Early discussion with the CUP MDT Lead or CUP CNS may help with referral.

**Site-specific team to;**
- Undertake initial examination and assessment.
- Initial diagnostic tests

If CUP/MUO suspected make an urgent referral to the Acute Oncology Team.

Site-specific teams must discuss this referral with the patient prior to the involvement of the CUP specialist team.

**In-patient referral.**
In patients should be referred to the acute oncology team as soon possible following suspicion of MUO/CUP

**Acute oncology team;**
The Acute Oncology team should manage all inpatients with suspicion of MUO/CUP initially.

A member of the Acute Oncology team should assess inpatients with MUO/CUP by the end of the next working day after referral.

**Acute Oncology team member receiving the referral to;**
- Visit and assess the patient within 24 hours of referral.
- Agree initial management plan, including appropriate investigations with the referring clinician
- Discuss with CUP Clinical Lead and arrange urgent review if required
- Initiate rapid referral to associated specialities e.g. palliative care team as appropriate
- List the patient for discussion at the next CUP MDT
- Inform CUP CNS and CUP Lead clinician of the referral
- Confirm that the patient is aware of the referral and the reason for referral.
Cancer of Unknown Primary Time-Line Pathway

1. Primary Care
   - Fast Track Referral
   - Radiology Referral
   - In-patient acute referral to AO or CUP team

2. Fast Track Criteria Met – Cross Sectional imaging suspicious of secondary malignant disease
   - CUP MDT Discussion
     - Initial Management Plan/Decisions i.e. BSC
     - Early Radiological review and plans, onward referrals agreed.

3. In-patient investigations – Further radiological assessment/biopsy
   - New OPA appointment with CUP Oncologist
   - Out-patient investigations – Further radiological assessment/biopsy
   - CUP MDT Discussion
     - Treatment decision and/or onward referral agreed.

4. Refer to other Site Specific Team
   - Palliative Care (Best Supportive Care)

5. Palliative Chemotherapy (Time line - dependent upon the urgency of treatment)
6. Watch and Wait Programme

7. Diagnosis/Treatment planning (In or out patient)
Appendix 3.

MUO/CUP Pathway  (Cancer of Unknown Primary Initial Management and Diagnostic Pathway)
The aim of this pathway is to enable early identification of patients that would benefit from anti-cancer treatment and to prevent unnecessary investigations in those unfit for treatment.

Please ensure early referral to Acute Oncology to discuss further management and review of the patient.

Initial Assessment and diagnostic Phase:

Observations:  Temperature, pulse, blood pressure, respiration rate, 

History:  Full history including rate of change of symptoms. Assess and record current performance status and co-morbidities.

Examination:  Complete clinical examination (including; breast, PR, PV, testicular, skin, nodal areas, and pelvic examination)

Laboratory Investigations:

•  All patients: Full blood count, U&E, LFT, Creatinine, Calcium, LDH, CRP.
•  Men with midline disease /brain metastases: Serum \alpha FP and \beta hCG (presentations compatible with germ-cell tumours)
•  Women with pelvic or peritoneal disease: CA125 (presentations compatible with ovarian cancer)
•  Men with bone metastases: PSA (presentations compatible with prostate cancer)
•  Patients with liver only disease: \alpha FP
•  Consider myeloma screen - for bone lesion seen on scan with no obvious primary
•  Urinalysis

Note:  other tumour markers are generally not useful in diagnosis

Imaging:

•  CT thorax, abdomen and pelvis is the staging investigation of choice in most circumstances
•  Other investigations (including endoscopies) only as indicated by signs and symptoms

Pathology:

•  Patients with a solitary liver lesion should be referred to the appropriate local specialist team before biopsy
•  All other patients, try to get biopsy (trucut if possible) for histology to guide future treatment
•  Detailed clinical information on the request form is essential

Further management:

If clinical, radiological and pathological findings suggest a specific cancer primary refer to relevant MDT, see guidance below. Otherwise refer to unknown primary MDT and/ or Acute Oncology Team (consider local protocol).

Please ensure patient is informed of results and plan for onward referral

Early referral to palliative care for symptom management advice and continuing care should be considered where appropriate

Patterns of disease requiring URGENT specific action:

Spinal cord compression – requires urgent admission and referral to spinal cord co-ordinator
Men with midline disease – requires urgent referral to oncology (? germ cell)
Superior Vena Cava Obstruction - requires urgent referral to lung MDT for consideration of stent
Suspected lymphoma, myeloma, plasmacytoma – requires urgent referral to haematology

Patterns of disease requiring specific action:

Men with bone metastases and elevated PSA – referral to urology MDT
Women with axillary nodes – referral to breast surgeons/ MDT
Women with peritoneal disease – referral to gynaecology /MDT, unless histology suggests non gynaecology origin
Solitary liver lesion – requires referral to hepatobiliary MDT
Neck nodes – requires referral to head and neck or neck nodes clinic as appropriate locally
Isolated brain metastasis – requires referral to neurology MDT
Appendix 4.

**Second diagnostic phase – special investigations**

If further investigation is appropriate, a second phase of targeted investigations may be offered to patients with provisional CUP.

**DO:**

- Refer patients with adenocarcinoma involving the axillary nodes to a breast cancer MDT for evaluation and treatment. If no breast primary tumour is identified after standard breast investigations, consider **dynamic contrast-enhanced MRI** to identify lesions suitable for targeted biopsy.

- Offer **PET-CT** (18F-FDG PET-CT) to 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.

- Consider **18F-FDG PET-CT** in patients with provisional CUP with extra-cervical presentations after discussion with the CUP team.

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

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**Do offer the following investigation of specific clinical presentations;**

- 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.

- Video-assisted thoracoscopic surgery (VATS) exploration to patients only after a negative bronchoscopic procedure and where percutaneous biopsy is considered inappropriate.

- Malignant peritoneal disease - obtain a tissue sample for histological examination in patients with MUO who present with ascites, if technically possible.

---

**Do NOT:**

- Carry out **Upper and Lower GI Endoscopy** in patients with MUO unless the symptoms, histology or radiology suggest a GI primary tumour.

- Offer **Mammography** routinely to women presenting with MUO, unless clinical or pathological features are compatible with breast cancer.

- Do not use **Gene-Expression-based Profiling** to identify primary tumours in patients with provisional CUP.
### Table 1. Immunohistochemical markers (ESMO 2005)

<table>
<thead>
<tr>
<th>Immunohistochemical marker</th>
<th>Possible cancer site of origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA – prostate specific antigen</td>
<td>Prostate</td>
</tr>
<tr>
<td>TTF1 – thyroid transcription factor 1</td>
<td>Lung</td>
</tr>
<tr>
<td>GcDFP-15 gross cystic disease fluid protein 15</td>
<td>Breast</td>
</tr>
<tr>
<td>CDX20</td>
<td>Colon</td>
</tr>
<tr>
<td>CK20</td>
<td>Colon, Oesophageal, Ovarian, Ampullary</td>
</tr>
<tr>
<td>CK7 cytokeratin</td>
<td>Lung, Pancreas, Cholangio, Ovarian, Breast</td>
</tr>
<tr>
<td>ER – oestrogen receptor</td>
<td>Breast, Ovarian, Endometrial</td>
</tr>
<tr>
<td>Mesothelin</td>
<td>Cholangio, Mesothelioma, Endometrial, Ovarian</td>
</tr>
<tr>
<td>CA125</td>
<td>Ovarian, Endometrial, Cholangio, Pancreas</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Cholangio, Pancreas, Lung, Stomach, Colon</td>
</tr>
</tbody>
</table>

### Table 2. Use of immunohistochemistry to guide choice of systemic therapy

<table>
<thead>
<tr>
<th>Immunohistochemical marker</th>
<th>Possible site of origin</th>
<th>Possible first line treatment strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA – prostate specific antigen</td>
<td>Prostate</td>
<td>Anti-androgen hormones</td>
</tr>
<tr>
<td>TTF1 – thyroid transcription factor 1</td>
<td>Lung</td>
<td>Platinum/Gemcitabine</td>
</tr>
<tr>
<td>GcDFP-15 gross cystic disease fluid protein 15</td>
<td>Breast</td>
<td>Anti-oestrogen hormones or Carboplatin/Paclitaxel</td>
</tr>
<tr>
<td>CDX20</td>
<td>Colon</td>
<td>Oxaliplatin/5FU</td>
</tr>
<tr>
<td>CK20</td>
<td>Colon, Oesophageal, Ovarian, Ampullary</td>
<td>Oxaliplatin/5FU, Carboplatin/Paclitaxel or Platinum/ Gemcitabine</td>
</tr>
<tr>
<td>CK7</td>
<td>Lung, Pancreas, Cholangio, Ovarian, Breast</td>
<td>Platinum/Gemcitabine or Carboplatin/Paclitaxel</td>
</tr>
<tr>
<td>ER – oestrogen receptor</td>
<td>Breast, Ovarian, Endometrial</td>
<td>Anti-oestrogen hormones or Carboplatin/Paclitaxel</td>
</tr>
<tr>
<td>Mesothelin</td>
<td>Cholangio, Mesothelioma, Endometrial, Ovarian</td>
<td>Platinum /Gemcitabine or Carboplatin/Paclitaxel</td>
</tr>
<tr>
<td>CA125</td>
<td>Ovarian, Endometrial, Cholangio, Pancreas</td>
<td>Carboplatin/Paclitaxel or Platinum /Gemcitabine</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Cholangio, Pancreas, Lung, Stomach, Colon</td>
<td>Platinum /Gemcitabine or Oxaliplatin/5FU</td>
</tr>
</tbody>
</table>
Table 3. Treatment strategies for favourable CUP subtypes

<table>
<thead>
<tr>
<th>Subtype of CUP</th>
<th>Treatment strategies</th>
<th>Outcome (when data available)</th>
</tr>
</thead>
</table>
| Extragonadal germ cell syndrome e.g. midline/ retroperitoneal disease distribution/ raised αFP or βHCG | Combination chemotherapy: platinum based as if germ cell cancer                        | RR: 50% (CR: 15-25%)  
Median survival: 13 months  
10 year survival: 15% |
| Poorly differentiated neuroendocrine adenocarcinoma of unknown primary (ACUP)   | Combination chemotherapy: platinum/etoposide                                         | RR: 50-70%  
CR: 25%  
Median survival: 14 months  
3 year survival: 24% |
| Node predominant poorly differentiated ACUP                                     | Combination chemotherapy: platinum based                                             | RR: 20-50%  
Median survival: 13 months |
| Axillary node in female                                                        | Treat with surgery/ hormones/ chemotherapy as if breast cancer                       | 5 year survival: 75%  
10 year survival: 68% |
| Neck node - squamous                                                            | Radiotherapy +/- platinum-based chemotherapy as if head and neck cancer              | 5 year survival: 5-50%  
Long term survival possible |
| Inguinal node - squamous                                                        | Lymph node dissection or radiotherapy +/- chemotherapy as if anal/cervical cancer    | |
| Bone metastasis and high PSA in males                                           | Hormonal therapy as if prostate cancer                                               | |
| Peritoneal ACUP papillary or serous histology in female                        | Surgical debulking then chemotherapy as if ovarian cancer. Similar to FIGO III ovarian cancer: platinum based chemotherapy | RR: 40-60% (CR: 30%)  
Median survival: 16 months  
5 year survival: 10% |
| Single potentially resectable metastatic site e.g. liver, lung, node, brain    | Surgical resection (without biopsy first) or radiotherapy followed by chemotherapy or radiotherapy as appropriate | |
| Predominantly abdomen/ liver metastases with CK20+, CDX20+ on immunohistochemistry | Chemotherapy as if colon cancer                                                     | RR: 40%  
CR: 5%  
Median survival: 12-18 |
| Liver, bone or multiple-site metastases of adenocarcinoma                      | Low toxicity chemotherapy of palliative orientation or best supportive care are acceptable | |
Table 4. Guidelines for management of Squamous Carcinoma involving upper- or mid- neck nodes (British Association of Head and Neck Oncologists Standards for the process of head and neck cancer care (2009)).

<table>
<thead>
<tr>
<th>STAGE</th>
<th>SURGERY</th>
<th>RADIOTHERAPY</th>
<th>CHEMOTHERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0N1 (No ECS)</td>
<td>Selective Neck Dissection or Modified Radical Neck Dissection</td>
<td>No unless for Mucosal sites</td>
<td>No</td>
</tr>
<tr>
<td>T0N1 (ECS)</td>
<td>Selective Neck Dissection or Modified Radical Neck Dissection</td>
<td>Yes – either involved lymph nodes or ipsilateral neck and boost to involved lymph nodes.</td>
<td>Induction platinum-based chemotherapy as if head and neck cancer should be considered</td>
</tr>
<tr>
<td>T0N2a N2b N2c</td>
<td>Selective Neck Dissection or Modified Radical Neck Dissection +/- contralateral Selective Neck Dissection or Modified Radical Neck Dissection</td>
<td>Yes - ipsilateral but bilateral should be considered</td>
<td>Induction platinum-based chemotherapy as if head and neck cancer should be considered</td>
</tr>
<tr>
<td>T0N3</td>
<td>Radical or type I Modified Radical Neck Dissection</td>
<td>Yes – ipsilateral but bilateral should be considered</td>
<td>Induction platinum-based chemotherapy as if head and neck cancer should be considered.</td>
</tr>
</tbody>
</table>
References:

BAHNO Standards for the process of head and neck cancer care (2009)  


National Institute for Health and Clinical Excellence (NICE) clinical guideline 104 “Diagnosis and Management of Metastatic malignant disease of unknown primary origin” (July 2010).

National Cancer Peer Review Programme Manual for Cancer Services: Cancer of Unknown Primary Measures Version 2.0 (January 2014)


Acknowledgements;

Anglia Cancer Network Acute Oncology group for sharing their draft document.

Edinburgh Cancer Centre for sharing their Metastatic Cancer Of Unknown Primary (mCUP) – Diagnosis And Management Guideline (2011)