South Yorkshire CUP Group

Cancer of Unknown Primary

South Yorkshire Guidelines for the Investigation and Management of Metastatic Malignant Disease of Unknown Primary Origin

i Document Control

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ii Information Reader Box

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iii Table of Contents

1 Introduction

Malignant disease of undefined origin (MUO) represents a very broad spectrum of presentations where evidence of a metastatic malignancy is apparent without a primary tumour identified. NICE Clinical Guideline 104 sets out clearly the definition (Table 1) for this entity and the two refinements of this diagnosis following further investigations; namely provisional and confirmed carcinoma of unknown primary (pCUP and cCUP).

Historically, this clinical entity has been poorly managed with excessive and unnecessary investigation, poor information giving and delays in referral to oncology or palliative care. The establishment of local and central CUP multi-disciplinary teams MDT should allow for the streamlining of investigative processes and timely triage to further specialist care. In the Yorkshire and Humber region, it is expected that the local Acute Oncology teams will become synonymous with the local CUP teams and take responsibility for the local CUP MDT.

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

- Squamous cell carcinoma affecting the upper/mid cervical lymph nodes should be managed through the local head/neck MDT
- Adenocarcinoma of the axillary nodes should be managed through the local breast MDT
- Squamous carcinoma involving inguinal lymph nodes only should be considered for resection and referred to the most appropriate surgical specialist, which may include discussion at a lower GI MDT
- A solitary metastasis should be discussed at an appropriate MDT (with the involvement of a member of the CUP MDT for advice) and considered for radical treatment

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

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.

To minimise the risk of delayed site-specific referral for patients who are suspected to have a specific primary, patients considered as having MUO are 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).
- 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.
- Biopsy/FNA confirmed malignancy in inguinal lymph node(s) when no obvious primary from histology or imaging.

Table 1 - Definitions of ‘malignancy undefined origin’ and ‘carcinoma of unknown primary’

2 Patient Pathway

The majority of MUO presentations occur via radiology flagging or via an emergency admission to secondary care and the patients will then be identified and referred to the unit local or central CUP/AO teams.

Outpatients may present through secondary care clinics or GP referrals. Following assessment by the CUP MDT, if further therapy is a possibility the patient should be referred through to an appropriate member of the oncology team. For the purposes of improving cancer intelligence on this condition, it is anticipated that there may be some presentations of MUO/CUP identified by the local CUP MDT teams that may be discussed with other unit CUP MDT members for an opinion regarding on-going investigations or treatments.

2.1 Outpatient CUP MDT Assessment

All local CUP MDTs should develop their own procedures to manage MUO presentations in an outpatient setting. Most referrals will come from other site-specific MDTs or secondary care clinicians. Primary care referrals may be accepted by local arrangement with the local CUP MDT and the host Trust.
All new referrals will be seen in clinic within 2 weeks.

2.2 Inpatient CUP MDT Assessment

Inpatient referrals should be seen within one working day and it is expected that review will be by the local inpatient Acute Oncology/CUP Service. An overview of patient flow is shown in Figure 1. Concomitant with a thorough medical assessment, the patients' holistic needs should also be assessed. Symptom control and psychological support should be offered and appropriate referrals made.

The patients' and carers' understanding of the situation should be assessed and information given in a clear and sympathetic manner. These processes are active and ongoing throughout the patient's journey and the CUP nurse specialist role here is fundamental. It is common for Specialist Palliative Care to be brought in during the diagnostic stage and for the majority of patients this will remain the most important intervention during their illness. Many patients can be managed as outpatients once the above needs have been met and therefore every attempt should be made to facilitate discharge.

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

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

MUO/CUP Referral Pathway

Patient flow for new presentation of malignancy of undefined origin

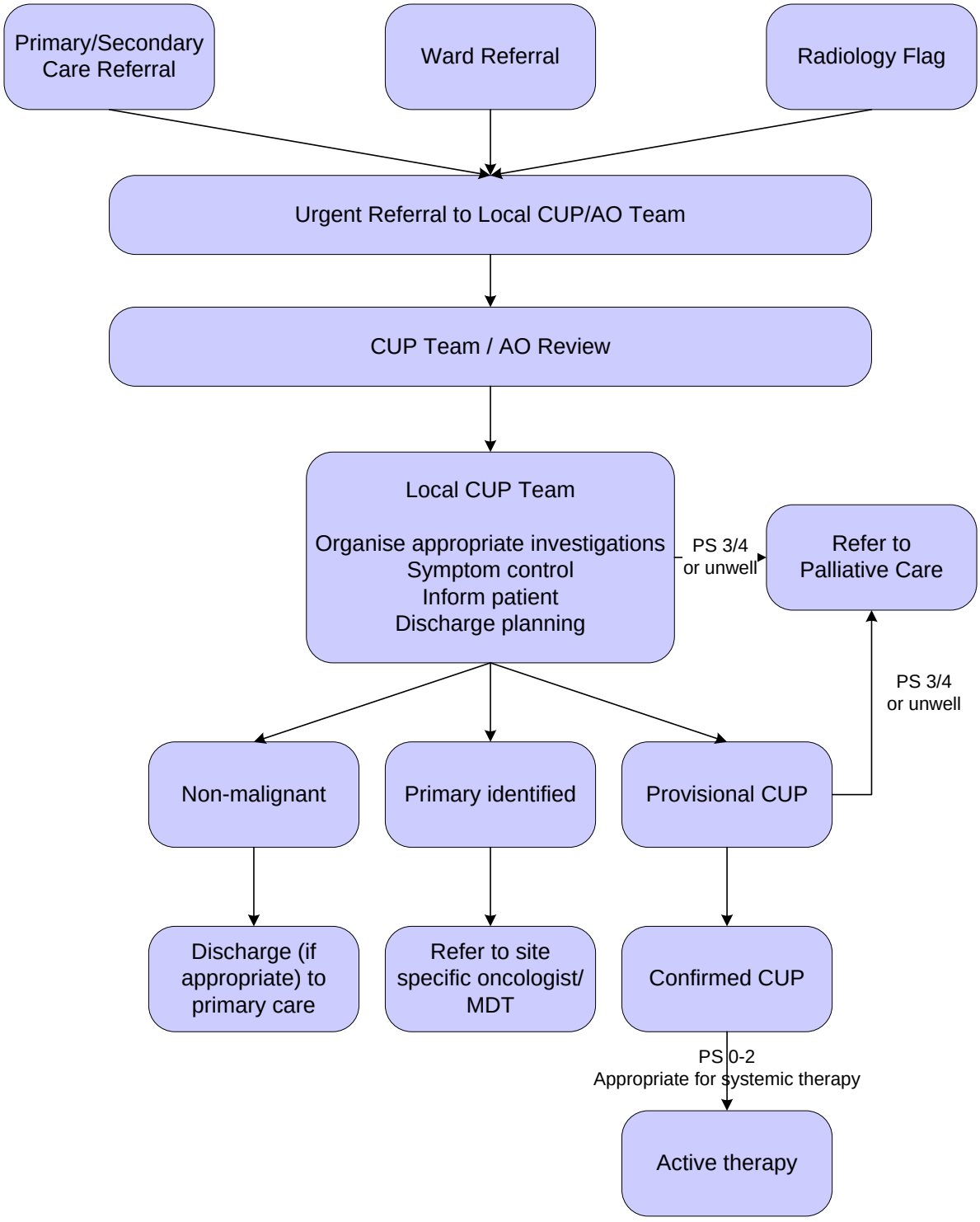


Figure 1 - Patient flow for new presentations of malignancy of undefined origin

3 Approach to Investigations

The assessment of any MUO patient begins with a thorough history and physical examination. Most patients will be referred having had some imaging which is highly suggestive or confirmatory of malignancy. The bare minimum for further tests represents a full blood count and biochemical profile.

The decision to embark on further tests from here will very much be influenced by the mode of presentation and the condition of the patient. It should be borne in mind that most oncology decisions can be made utilising three fundamental pieces of information.

- The condition, functional status and co-morbidities of the patient (history and examination). Investigations should only continue if the patient is fully informed around risks/benefits of investigations and wants to consider therapeutic options
- The stage of the cancer (cross-sectional imaging)
- The type of cancer (histology)

The use of blood tumour markers is not recommended except in a limited number of circumstances (Table 2).

Gastrointestinal endoscopy should only be considered when a GI primary is hinted to on imaging or symptoms and where it is felt this will alter further management.

There may be occasions when positron emission tomography (PET) is helpful but this should be limited to patients with isolated cervical lymphadenopathy and who may be suitable for radical treatment or following individual patient case discussion in the CUP MDT.

α-FP and β-HCG	If germ cell tumour suspected: young men with midline lymph node metastases
α-FP	If hepatocellular carcinoma (HCC) suspected: evidence of chronic liver disease
PSA	Men >40 with bone metastases
CA125	Women with peritoneal or pelvic metastases, ascites, pleural effusions

Table 2 - Indications for the ordering of blood tumour markers

4 Specific Presentations of MUO/CUP

4.1 Isolated Liver lesions

Once all relevant tests have been undertaken, if the distribution of metastatic disease is confined to the liver and cross-sectional imaging suggests that it may be resectable (e.g. unilobar) then a referral to a hepatobiliary MDT is recommended prior to an image-guided biopsy. If it is likely to be resectable then colonoscopy, PET CT and MRI of liver should be considered to more accurately define the extent of disease prior to surgery. It is also good practice to discuss with HPB Surgeon.

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

Pitfalls: non-malignant disease

- Cirrhosis
- Haemangiomata
- Focal nodular hyperplasia or hepatic adenomata

4.2 Isolated Brain lesions.

These are the presenting feature of around 10% of MUO presentations.

They typically present as an emergency with stroke-like symptoms and are identified on CT scanning of the brain. Immediate management with dexamethasone (8mg po/IV bd with PPI cover) typically provides some relief.

The key determinants of prognosis are performance status, response to corticosteroids and extent of extra-cerebral disease. Solitary lesions or less than 4 metastases should be discussed with neurosurgical services at Sheffield Teaching Hospital NHS Foundation Trust before any further imaging is arranged. Patients who respond to steroids and are not surgical candidates should be considered for whole brain radiotherapy.

Referral for whole brain or stereotactic radiotherapy should be made to the tertiary centre.

Pitfalls: non-malignant disease

- Brain abscesses
- Cerebral infarction

4.3 Isolated Bone lesions

Men over the age of 40 should have a digital rectal examination and a PSA checked.

All patients with lytic bone lesions should have a serum electrophoresis and urine collection for Bence-Jones proteins. If the patient presents with a pathological fracture and is scheduled for internal fixation then ensure that you request that the surgeon sends a pathological biopsy to the laboratory for histological analysis.

Bone biopsies should be discussed with a member of the CUP MDT and following agreement should be arranged via the local radiology or orthopaedic/spinal services. Potentially bone lesions should be discussed at the appropriate MDT prior to an attempt at biopsy. If there is a suspicion of primary bone sarcoma on imaging then the images and case should be referred urgently to the oncology team at The Royal Orthopaedic Hospital, Birmingham (http://www.roh.nhs.uk).

Pitfalls: non-malignant disease

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

4.4 Isolated Lung lesions

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

Pitfalls: non-malignant disease

- Sarcoidosis
- Wegener's granulomatosis
- Tuberculosis

4.5 Isolated Peritoneal carcinomatosis

This typically presents with vague abdominal symptoms and ascites. In women it is reasonable to check a CA125 but it should be borne in mind that this will be invariably elevated even in non-malignant causes for ascites.

Diagnosis should be made with a formal biopsy, although the presence of malignant cells in peritoneal fluid (particularly if cell block is prepared) can sometimes be helpful. If an image guided procedure cannot access tissue then the patient should be considered for a laparoscopy +/- biopsy.

5 Histological Assessment

It is incumbent on the local CUP teams to work closely with their local pathology laboratories to provide sufficient background information to facilitate appropriate immunohistochemical analysis.

For some patients the confirmation of cancer may be sufficient on haematoxylin and eosin (H&E) staining whereas others will require a more comprehensive immunohistochemical panel to categorise the tumour:

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

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

    b) second line panel depending on results of (i). If probable carcinoma (CK7, CK20, CDX2, CA125, PSA, TTF-1, ER), melanoma (melan-A, HMB45), sarcoma (depends on suspected type, myogenin best for rhabdomyosarcoma). Suspected lymphomas should be sent directly to HMDS without further immunohistochemistry in order to preserve tissue.

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

2) Metastatic adenocarcinoma. Limited panel to refine possible primary site - CK7, CK19.9, CK20, TTF-1, PSA, ER, CDX2. CA125 and WT-1 may be helpful if a primary ovarian or primary peritoneal carcinoma is suspected.

3) Metastatic squamous cell carcinoma. Markers of squamous differentiation are not entirely specific but consider p63, CK5/6, CK14 or 34BE12. Site-specific markers for origin of squamous cell carcinoma are of very limited value. The only ones worth considering are in situ hybridisation for EBER (nasopharynx) and HPV (oropharynx) in patients with metastatic neck nodes, although PET-CT scanning in patients without an obvious primary lesion should be considered before (or in conjunction with) laboratory testing.

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

    a) Breast: ER/PR/Her2
    b) Lung: EGFR/ALK mutational status
    c) Colorectal: K-RAS mutational status
    d) Gastric/Junctional: Her2

A flowchart summarising the CUP investigation and pathway policy is see in Figure 2.

MUO/CUP Investigation Pathway

Pathway for Suspected Cancer of Unknown Primary and Malignancy of Unknown Origin

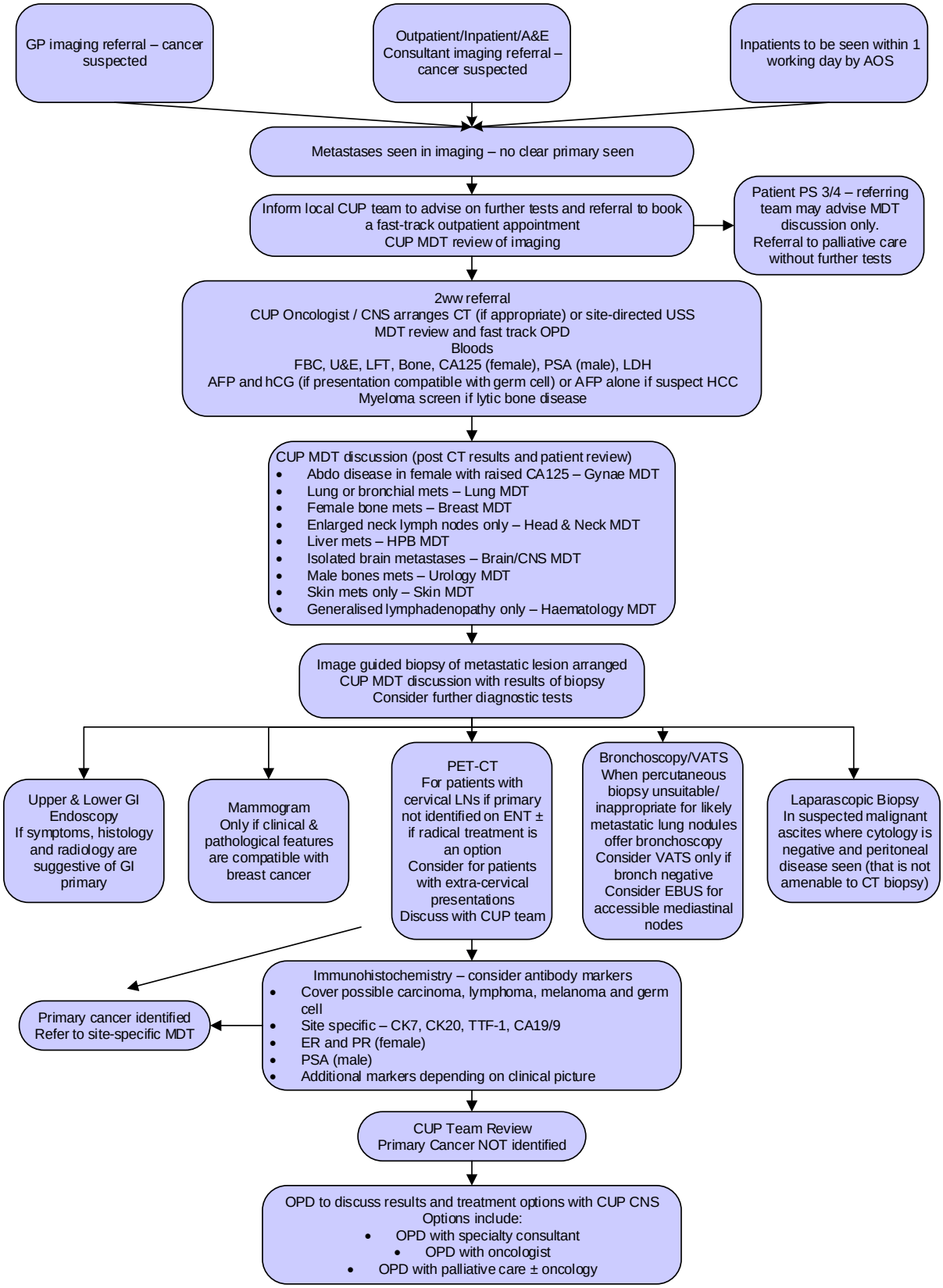


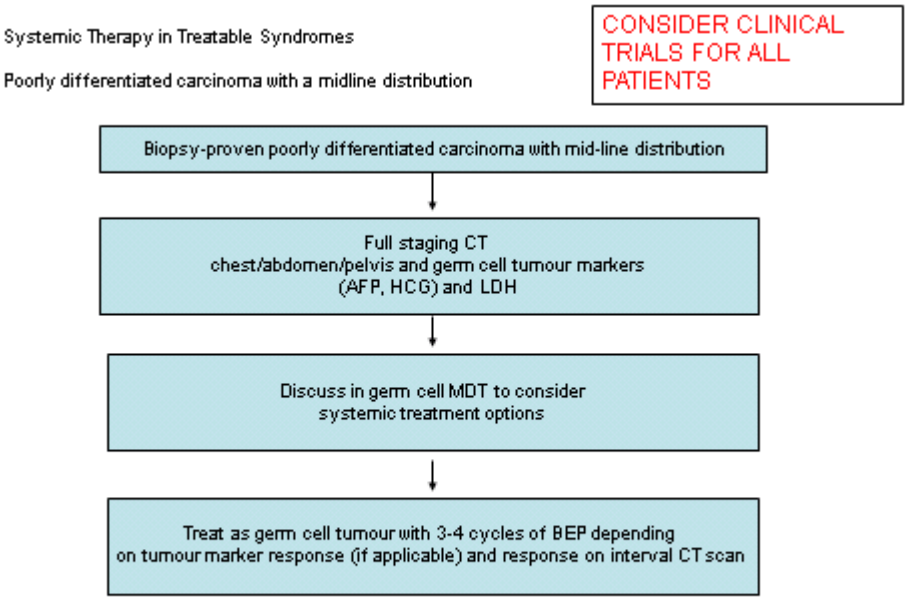
Figure 2 - MUO/CUP Investigation Pathway

6. Options for Systemic Treatment of cCUP

The evidence base for optimal systemic treatment of those patients with confirmed CUP is poor. The initial decision to treat will be based on the patients performance status and co-morbidity but there is no evidence to dictate the use of one regimen over another in cCUP. The regimen used in practice therefore, typically is a best guess approach based on where the suspected origin of the cancer.

There is clear need to develop an evidence base here and where possible patients should be managed in clinical trials. As a guide some common presentations are highlighted here with suitable regimens.

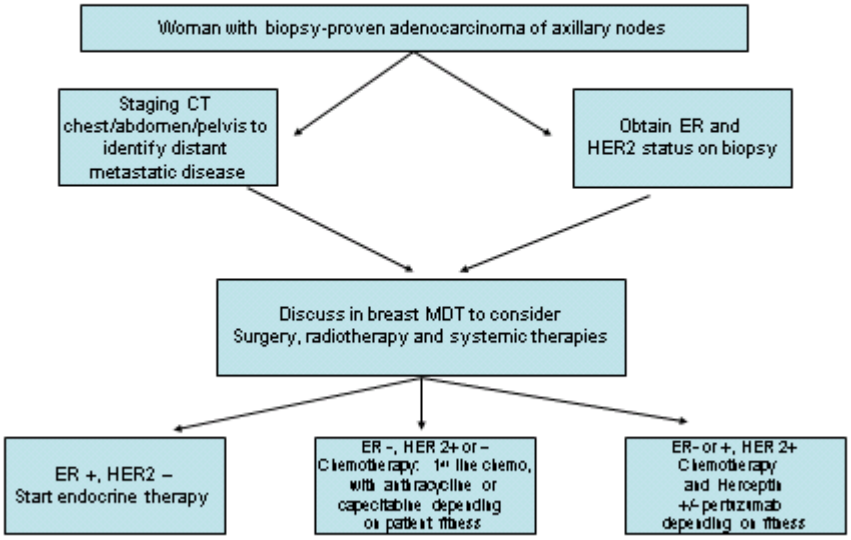
Patients who do not fit into one of the categories below but who are suitable for combination chemotherapy will usually be offered ECX/EOX based chemotherapy. All patients should be considered for clinical trials throughout their cancer journey.



Systemic Therapy in Treatable Syndromes

Women with adenocarcinoma involving the axillary lymph nodes

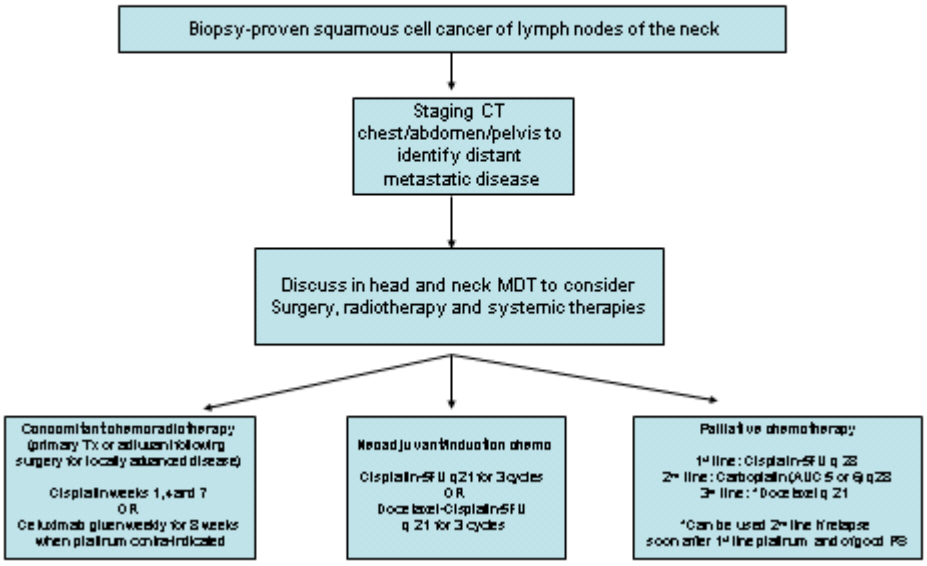
CONSIDER CLINICAL TRIALS FOR ALL PATIENTS



Systemic Therapy in Treatable Syndromes

Squamous cell carcinoma of the lymph nodes of the neck

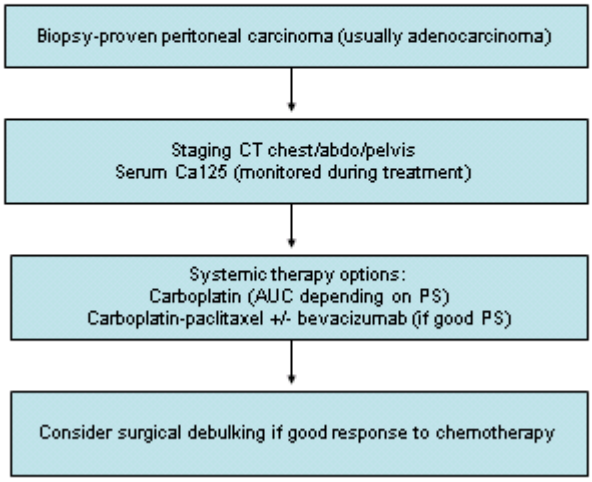
CONSIDER CLINICAL TRIALS FOR ALL PATIENTS



Systemic Therapy in Treatable Syndromes

Women with predominately peritoneal carcinoma

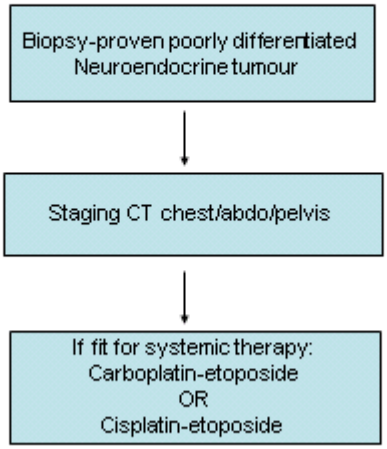
CONSIDER CLINICAL TRIALS FOR ALL PATIENTS



Systemic Therapy in Treatable Syndromes

Poorly differentiated neuroendocrine tumour

CONSIDER CLINICAL TRIALS FOR ALL PATIENTS



7. Data collection and Clinical Audit

Local CUP teams will have responsibility to register all patients.

Scope and timelines of future audit projects will be set by the South Yorkshire CUP Group and will include the following as a minimum in year one (retrospective and prospective):

- Number of cases of CUP identified within current cancer data systems
- Basic demographics
- Histology (if available)
- MDT review recorded
- Oncology/Palliative review (numbers thereof)
- Therapy (if given)

This is being supported by the Yorkshire and the Humber High Value Commissioned Pathway project.