West Yorkshire & Harrogate Cancer Alliance

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

Version 2.0

May 2017

i Document Control

Title	Network Guidelines for the Investigation and Management of Metastatic Malignant Disease of Unknown Primary Origin
Author(s)	**The West and East Yorkshire CUP Group** **Trusts involved :** Hull and East Yorkshire Hospitals NHS Trust Calderdale & Huddersfield NHS Foundation Trust The Mid Yorkshire Hospitals NHS Trust York Teaching Hospitals NHS Foundation Trust Harrogate and District Hospital NHS Foundation Trust Bradford Teaching Hospitals NHS Foundation Trust Airedale NHS Foundation Trust Leeds Teaching Hospitals NHS Trust
Owner	West Yorkshire & Harrogate Cancer Alliance

Version Control		
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0.1		First draft
0.2		Second draft – incorporating comments from first meeting of CUP NSSG
1.0		First final published version
2.0	May 2017	Review and update

Contributors to current version		
Contributor	**Date**	**Section/Contribution**
Dr Jo Dent	2013	Whole guideline
Former YCN CUP NSSG	2013	Comments on first draft version
Dr Alison Cairns	2013	Chapter 5 – Histological assessment
Dr Nick Brown	2017	Full review of guidelines

ii Information Reader Box

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1 Introduction

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

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 (Measure 12-1C-107m) 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 will be reviewed at the central CUP MDT or 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. An example of an outpatient referral form has been included in appendix 2. Individual Trusts may wish to base their referral criteria on this, but local circumstances will also impact on precise referral criteria.

2.2 Inpatient CUP MDT Assessment

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

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

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

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

MUO/CUP Referral Pathway

Patient flow for new presentation of malignancy of undefined origin

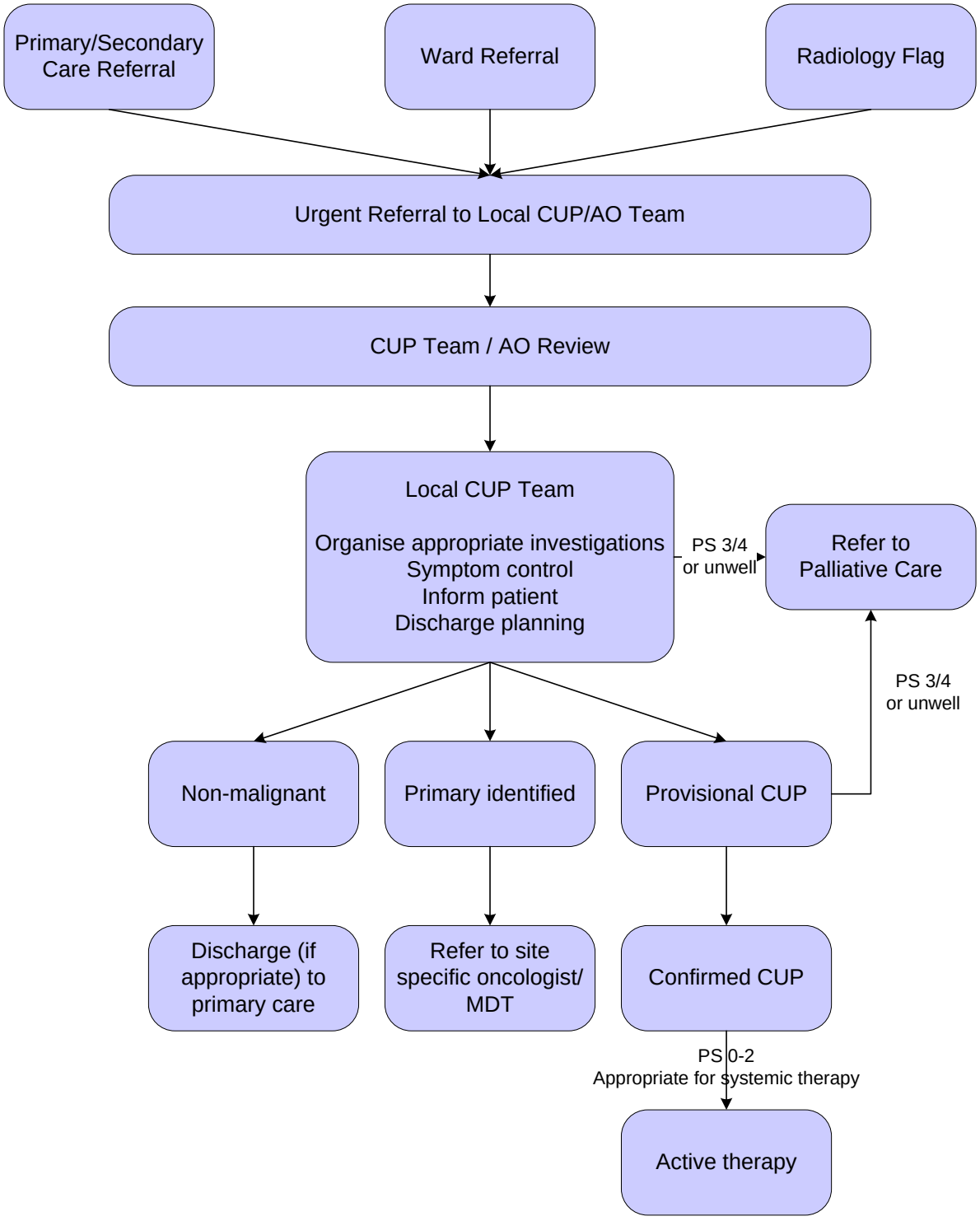


Figure 1 - Patient flow for new presentations of malignancy of undefined origin

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 (including lactate dehydrogenase- LDH).

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 with central PET radiologists.

□-FP and □-HCG	If germ cell tumour suspected: young men with midline lymph node metastases
□-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

4.1 Liver lesions

The finding of isolated liver metastases is a common MUO presentation and nearly half of all MUO patients will have liver involvement. A full staging CT scan of thorax, abdomen and pelvis should be performed after history taking and physical examination. A serum □-fetoprotein should be checked if there are any risk factors or clinical/radiological signs to suggest chronic liver disease or HCC.

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.

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 Brain lesions. Measure 12-1C-107m

These are the presenting feature of around 10% of MUO presentations. Please see Figure 2.

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 extracerebral disease. Solitary lesions or less than 4 metastases should be discussed with neurosurgical services before any further imaging is arranged. Patients who respond to steroids and are not surgical candidates should be considered for whole brain radiotherapy.

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

Pitfalls: non-malignant disease

- Brain abscesses
- Cerebral infarction

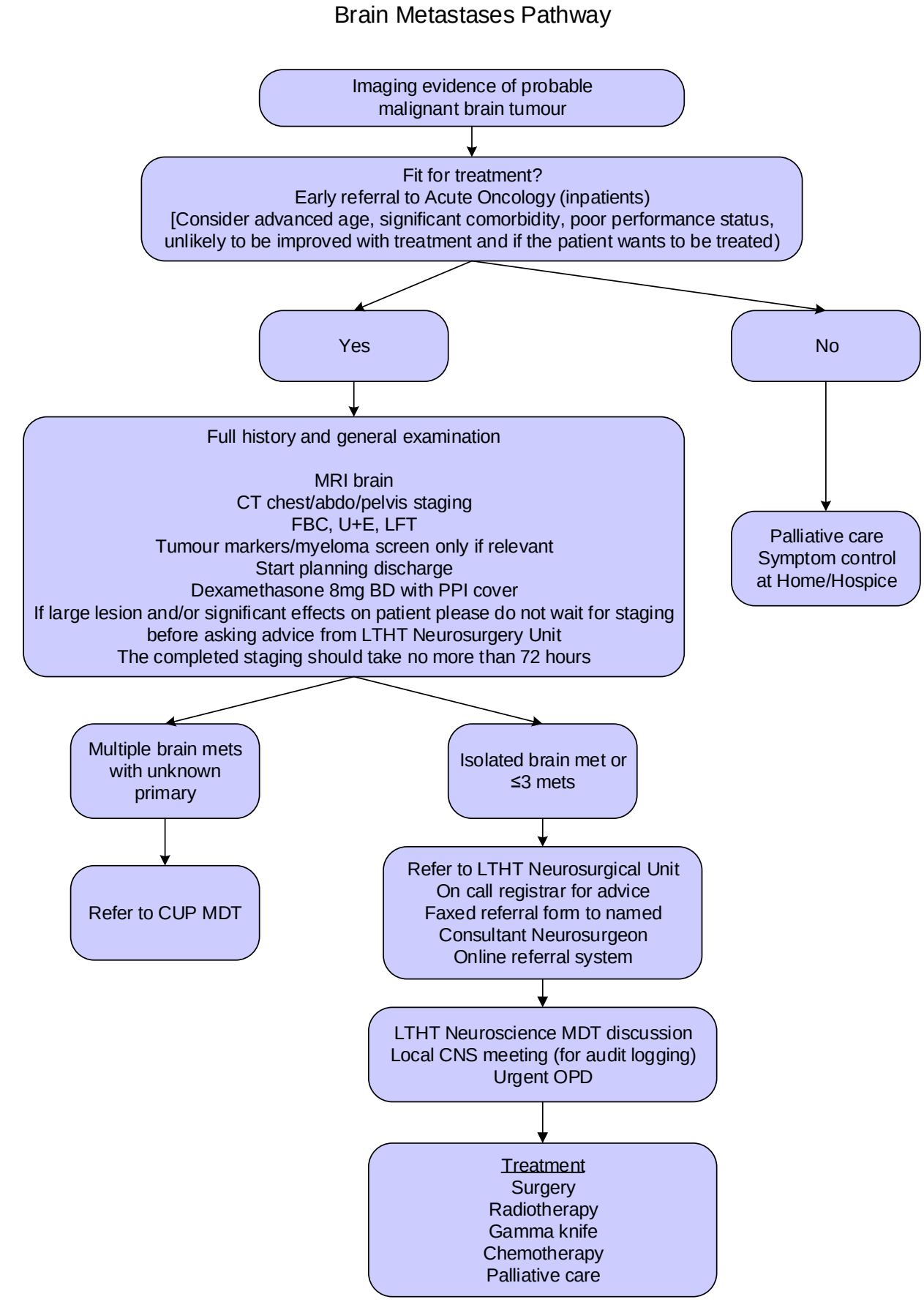


Figure 2 - Brain Metastases Pathway

4.3 Bone lesions

Bone lesions are seen in about a third of MUO presentations and are typically lytic in nature. They typically present as an emergency with significant skeletal events such as pathological fracture, spinal cord compression or uncontrolled pain. In many situations urgent local symptom control including fixation of pathological fractures for stabilisation will be required prior to discussion with clinical oncology colleagues regarding radiotherapy.

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 orthopaedic services. If there is a suspicion of primary bone sarcoma on imaging (see Yorkshire & Humber Sarcoma Referral Guideline – Appendix 1) then the images and case should be discussed with a member of the oncology team at The Royal Orthopaedic Hospital, Birmingham (http://www.roh.nhs.uk) prior to an attempt at biopsy.

Pitfalls: non-malignant disease

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

4.4 Lung lesions

If there is any suspicion of a lung primary, such patients should be managed by 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 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 Acute Oncology teams to work closely with their local pathology laboratories to provide sufficient background information to facilitate appropriate immunohistochemical analysis.

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

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. PDL-1 status if PS 0 or 1.
    c) Colorectal: K-RAS mutational status
    d) Gastric/Junctional: Her2
    e) Neuroendocrine tumours: Ki67.

A flowchart summarising the CUP investigation and pathway policy is see in Figure 3

MUO/CUP Investigation Pathway

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

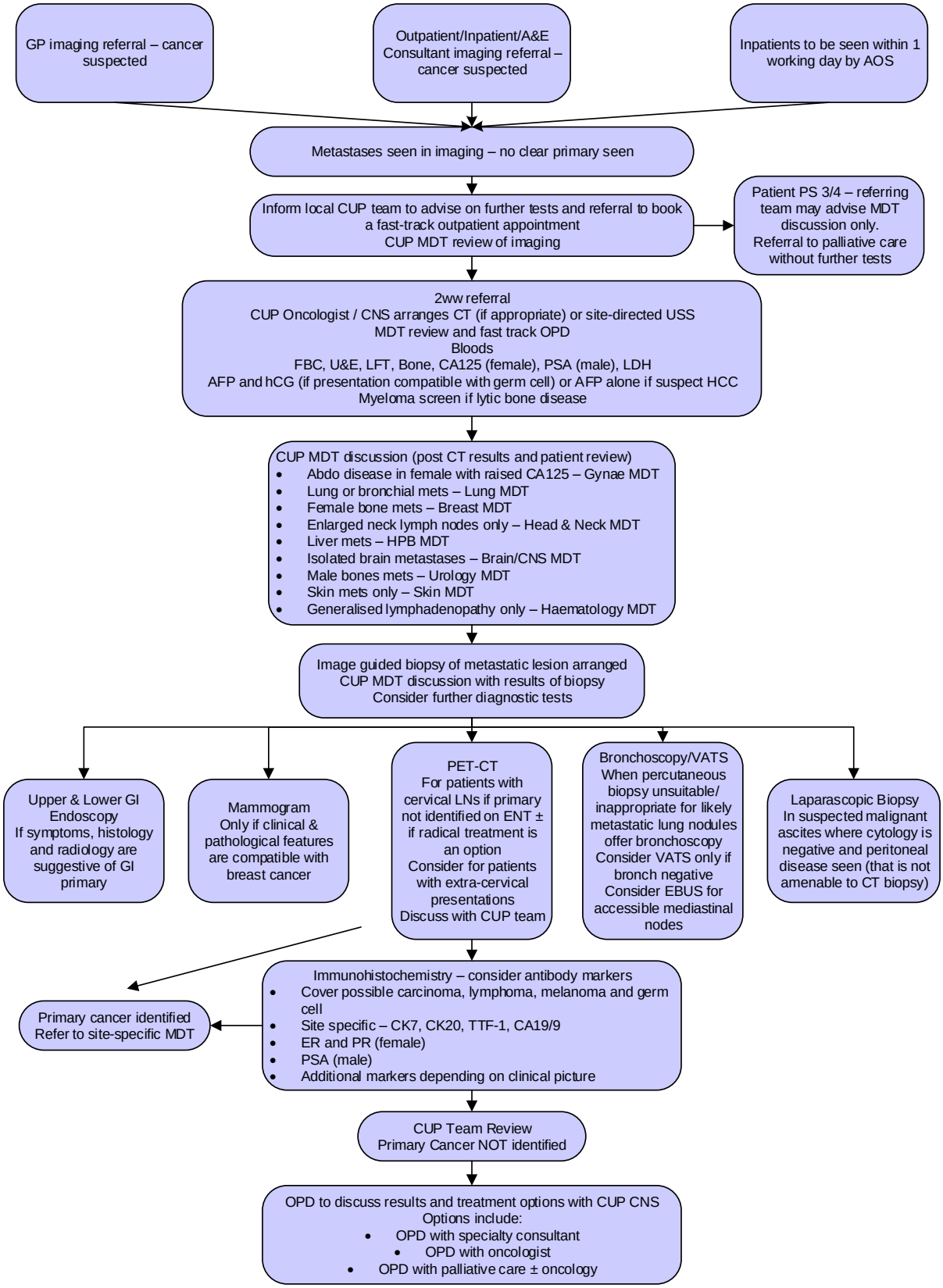


Figure 3 - MUO/CUP Investigation Pathway

6 Management of Specific Presentations

Table 3 outlines the MDT referral process when patients present with specific radiological +/- histological findings.

Presentation	MDT Referral Process
Disseminated Disease	
Multiple bone mets	CUP
Multiple liver mets	CUP/Colorectal/HPB
Multiple brain mets (>3)	CUP
Poorly differentiated midline carcinoma	Refer Germ Cell MDT LTHT
Poorly differentiated neuroendocrine ca	Refer Neuroendocrine MDT LTHT
Women with peritoneal adenocarcinoma	Refer Gynae MDT
Metastases at > one site	CUP
Localised Disease	
Squamous Ca upper- / mid-neck	Refer Head & Neck MDT
Squamous Ca inguinal nodes	Refer Lower GI MDT/LTHT Skin/Plastics MDT
Women with axillary adenocarcinoma	Refer Breast MDT
Solitary Metastasis	
Brain	Refer Neuro-Oncology MDT LTHT
Soft Tissue	Refer Sarcoma MDT LTHT
Bone	CUP/Refer to Sarcoma MDT
Liver	Refer HPB MDT
Patient not fit or declines further investigations	**Palliative care**

Table 3 – Management of specific presentations

7 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.

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

8 Data collection and Clinical Audit

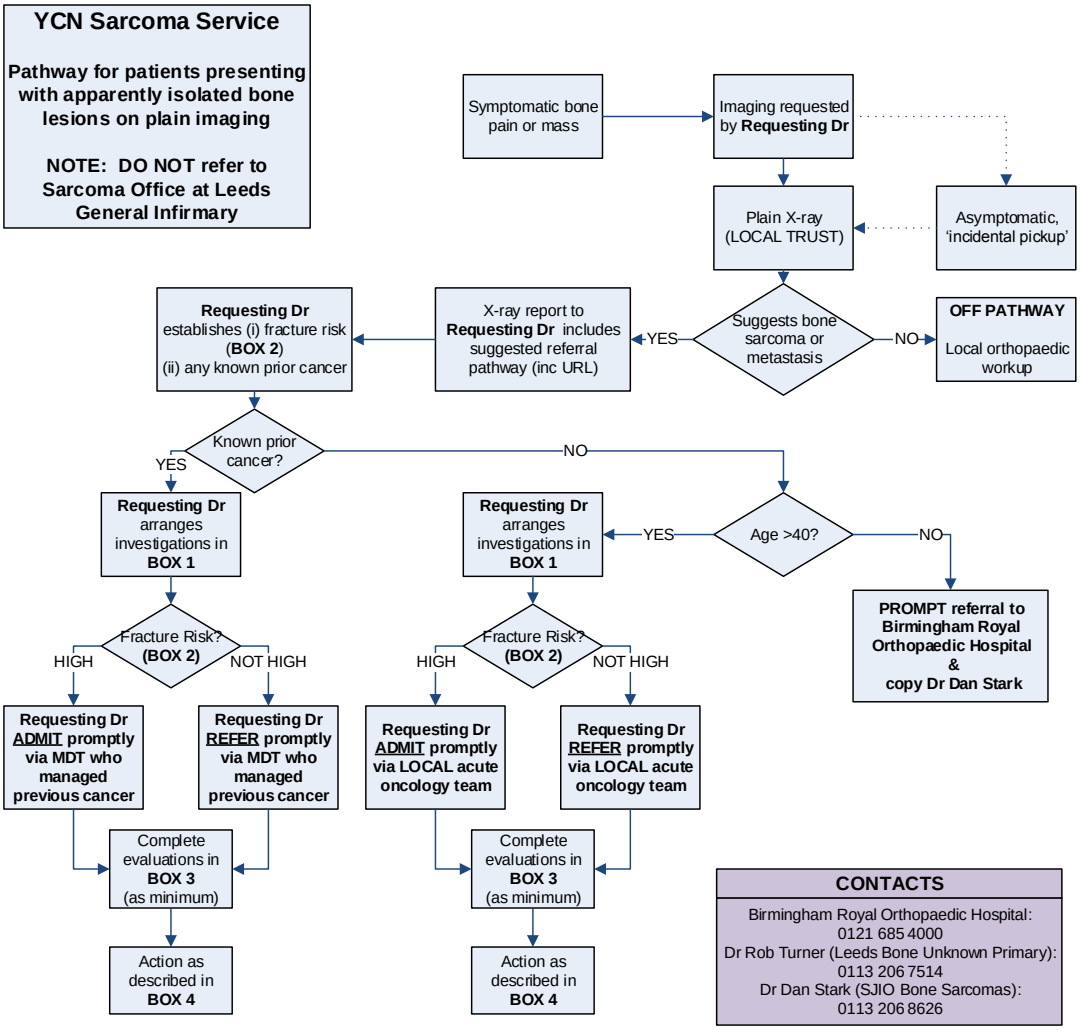
Local CUP teams will have responsibility to register all patients.

Scope and timelines of future audit projects will be set by the Unknown Primary Network Group and will include the following as a minimum (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)

Suggestions for suitable audit projects can also be found in the NHS England document: Manual for Cancer Services Cancer of Unknown Primary Measures
Version 1.1

9 Appendix 1 – Sarcoma Service



CONTACTS

Birmingham Royal Orthopaedic Hospital: 0121 685 4000
Dr Rob Turner (Leeds Bone Unknown Primary): 0113 206 7514
Dr Dan Stark (SJIO Bone Sarcomas): 0113 206 8626

BOX 1 Initial Investigations

Early bone biopsy is NOT recommended prior to discussion with oncology

Plain radiography of index lesion and other painful areas
CXR
Calculate Mirels' score (BOX 2)
Routine blood panel: FBC, U&E, LFT, Bone
Tumour markers (PSA, CEA, Ca153, AFP, βhCG)
Myeloma screen (immunoglobulins, β2-microglobulin, serum & urine electrophoresis, ESR/PV)

BOX 3 Secondary Workup

GOAL: Establish clinico-radiological diagnosis and stage

History, examination and, if indicated in addition to BOX 1 investigations, isotope bone scan, MRI of bony site and CT chest/ abdo/pelvis.

If lesion solitary, even in context of known previous malignancy, with good disease-free interval and fitness for surgery then refer to ROH Birmingham for histology and definitive surgical intervention.

BOX 2 Mirels' Scoring System

Variable	Score		
	1	2	3
Site	Upper limb	Lower limb	Peritrochanter
Pain	Mild	Moderate	Severe
Lesion	Blastic	Mixed	Lytic
Size (cortex)	<1/3	1/3-2/3	>2/3

Score	Fracture risk	Action
≤7	Low	Analgesia +/- RT
8	15%	
≥9	High	Consider surgical fixation

BOX 4 Management

Candidate Primary	Risk of fracture	Solitary	Action
Yes	High	N/A	Locality orthopaedics(*)
	Not high	N/A	Cancer site-specific MDT
No	High	Yes	ROH, Birmingham
		No	Locality orthopaedics(*)
	Not high	Yes	ROH, Birmingham
		No	Unknown primary team

For endpoints marked (*) the site-specific MDT or LOCALITY acute oncology/unknown primary team retain overall supervisory responsibility

10 Appendix 2 – Example of a CUP Referral Form

NHS
Vale of York
Clinical Commissioning Group

Suspected Cancer of Unknown Primary (MUO) - Referral Form

For patients who need to be seen within **2 weeks**

This form is to be used if imaging shows suspicion of cancer and primary site is not clear clinically or radiologically

Date of Referral			
Patient Name		Referring GP	
Patient Address		GP Address	
Patient Postcode		GP Postcode	
Date of Birth		Fax No.	
NHS No.		Surgery Tel No.	
Tel No.		Hospital No.	
Mobile No.		Please check that the patient's phone numbers are correct	

- Confirm that your patient understands that they have been referred onto a "suspected cancer pathway" ☐
- Confirm that your patient has received the information leaflet ☐
- Confirm that your patient is available to attend an appointment within 2 weeks of this referral**. ☐

** If, after discussion, your patient chooses to **not** attend within 2 weeks, when will they be available?

Please attach all imaging reports

Use this form for:

- Multiple lung metastases on CXR/CT (unless Radiology indicates lung primary) ☐
- Multiple brain metastases on CT/MRI ☐
- Multiple liver metastases on USS/CT/MRI ☐
- Multiple bone metastases on XR/CT/MRI/bone scan (**PSA not raised**) ☐
- Widespread peritoneal infiltration +/-ascites on USS CT (**CA125 not raised**) ☐
- Other disseminated disease on scan and no site of primary identified (discuss with oncology) ☐

For advice please contact oncology on call or 01904 726198

An alternative referral form should be used for the following results:

- Radiology indicates lung primary – use Suspected Lung Cancer form
- Multiple bone metastases on XR/CT/MRI/bone scan (PSA raised) – use Suspected Urological Cancer form
- Widespread peritoneal infiltration +/-ascites on USS CT (CA125 raised) – use Suspected Gynaecological Cancer form

Please give indication of patient's performance status:

0	Normal activity/well	☐
1	Normal activity but symptomatic	☐
2	Resting but <50% of the day	☐
3	Resting >50% of the day	☐
4	Bed bound/limited mobility for ADL	☐

Any additional comments:

11 Appendix 3 – Example of a Patient Information Leaflet – 2 Week Wait for CUP

NHS
Vale of York
Clinical Commissioning Group

Urgent Hospital Appointments (within 2 weeks)

Why have I been referred to hospital to be seen within 2 weeks?

It is important to find out why you have your current symptoms. You will be seen by a hospital specialist within the next 14 days, who will consider the best way to manage your care.

Does this mean I have cancer?

The 'two week' urgent referral system aims to diagnose and treat serious illnesses, including cancer, quickly. Further specialist advice and possible investigations are now needed.

What will happen next?

You will be contacted (probably by telephone) to arrange an appointment.

Why is it important for me to attend the appointment within 2 weeks?

Previous tests have found an abnormality which needs investigation now. A hospital specialist needs to see you to discuss further treatment and care options with you.

The hospital specialist that you see will be able to answer any questions that you have about the tests or treatment that you may need.

If you are unable to attend an appointment you must let the hospital know, so that alternative arrangements can be made.

If you choose to delay your appointment to go on holiday, this may affect the terms of your holiday insurance cover.

Can I bring someone with me to the appointment?

Yes, you are welcome to bring someone with you for support.

What should I do if I haven't heard anything about my referral?

If you have not heard about your referral within 7 days please contact your GP

Please make sure that your surgery has your correct contact details, including home and mobile telephone numbers.