Greater Manchester Cancer:

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

4th Edition.
For review April 2020

Contents

4th Edition.
For review April 2020

Aims of Management Guidelines:

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

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Guidelines for Good Practice:

Patient-Centred Care

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

Information

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

Communication

- Special communication training is required for all health care professionals providing direct care.
- Provision of suitable interpreters for patients whose preferred language is not English.
- Accurate documentation of key points of consultations in patients notes and swift communication of any treatment changes to all other professionals involved in care.

Supportive and Palliative care

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

Warnings and Disclaimer

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

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

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

- If you are unsure about the correct management of a situation please seek advice from a more senior member of the team.

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Definitions

Malignancy of undefined primary origin (MUO):

Metastatic malignancy identified on the basis of a limited number of tests, without an obvious primary site, before comprehensive investigation.

Provisional carcinoma of unknown primary (provisional CUP):

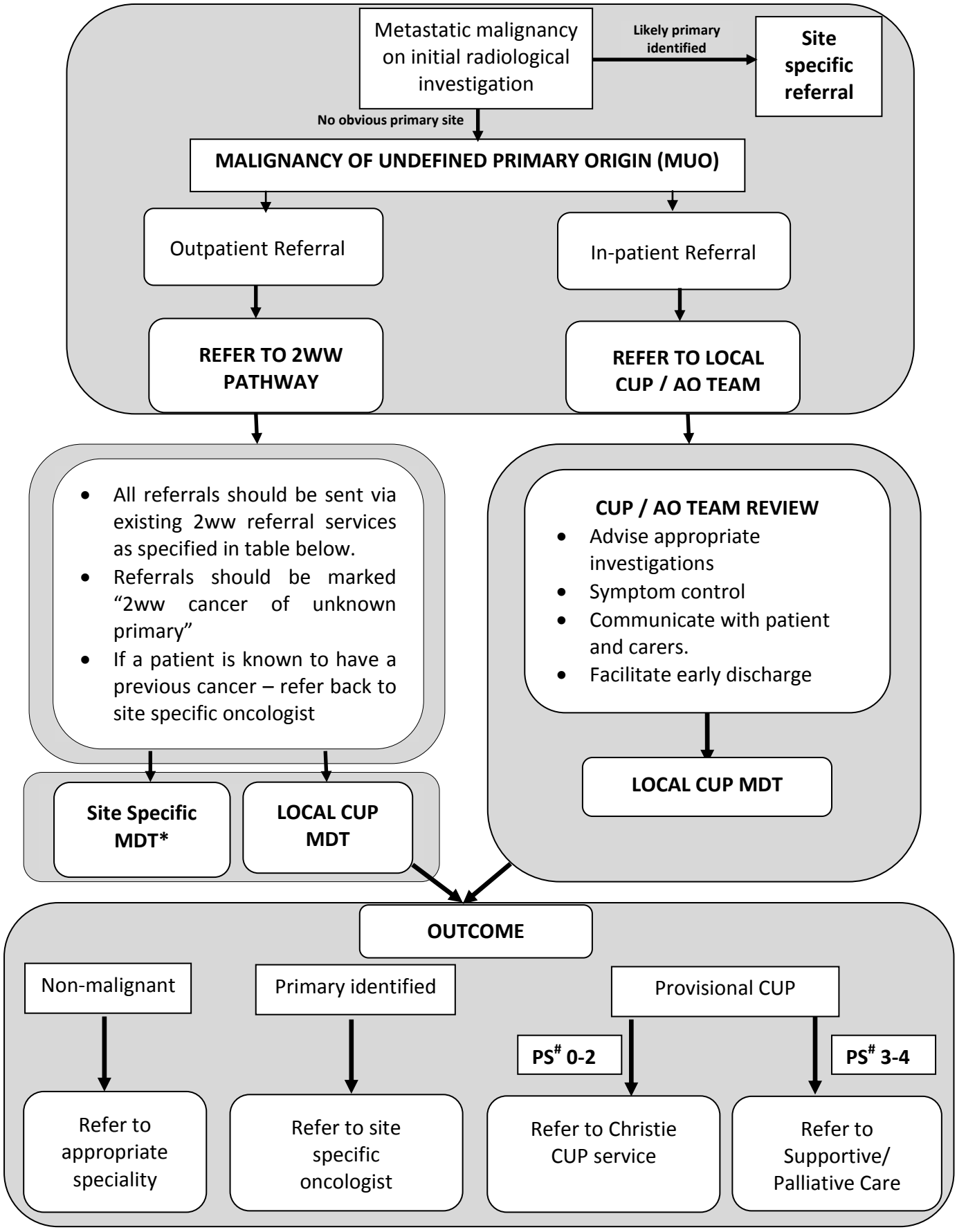
Metastatic epithelial or neuroendocrine malignancy identified on the basis of histology/cytology, with no primary site detected despite a selected initial screen of investigations, before specialist review and possible further specialised investigations.

Confirmed carcinoma of unknown primary (confirmed CUP):

Metastatic epithelial or neuroendocrine malignancy identified on the basis of final histology, with no primary site detected despite a selected initial screen of investigations, specialist review, and further specialised investigations as appropriate.

NICE definitions of MUO / CUP [1]

1. MUO Referral Pathway



* Site specific MDT may refer directly to CUP service at Christie NHS Trust

PS – WHO performance score

2. MUO: 2 week wait (2ww) specified referral pathways

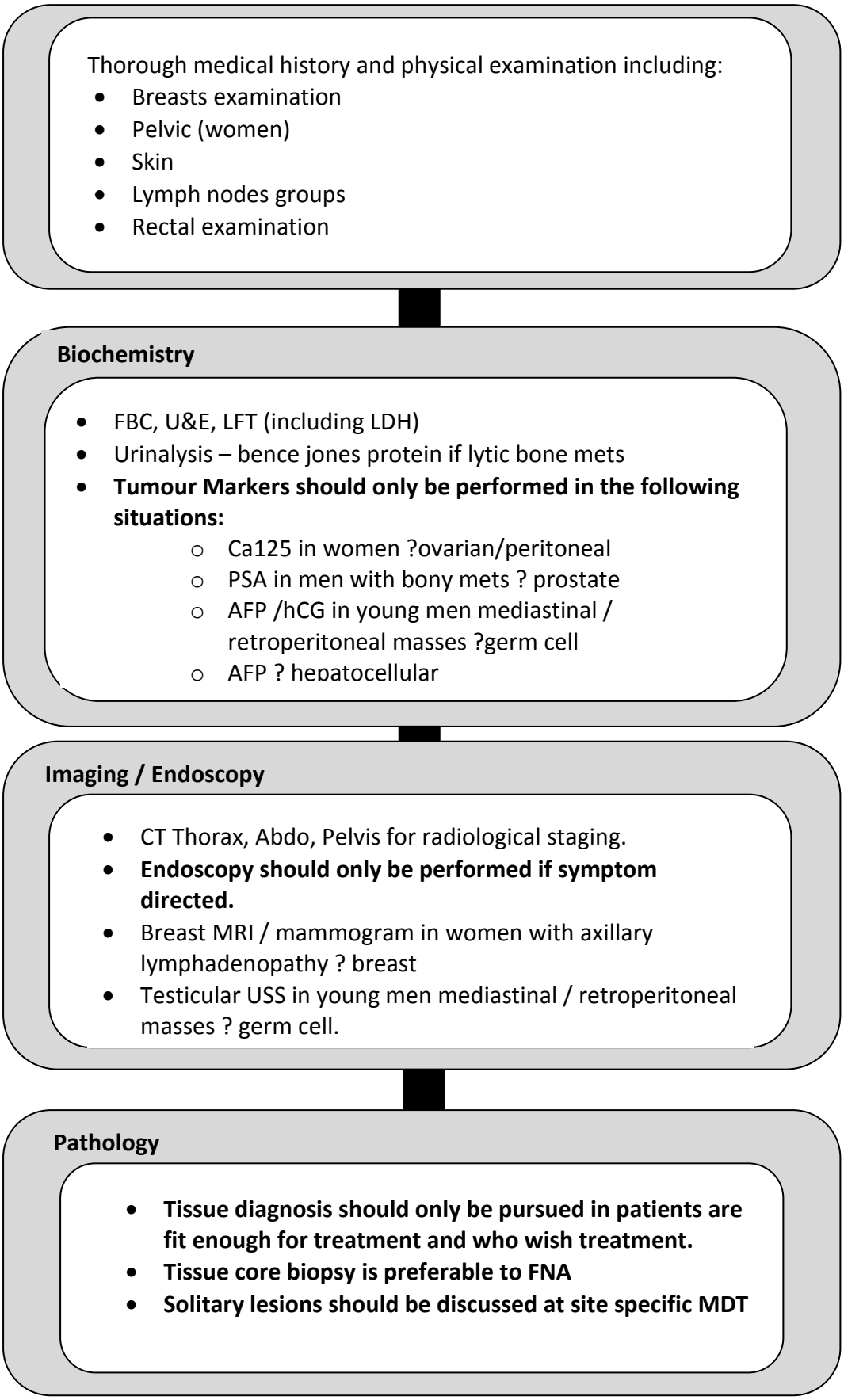
BONE	

?Metastatic	• 75% of bone metastases are from prostate kidney, breast, lung and myeloma please refer to
	  • Urology (if PSA &/or DRE abnormal)
	  • Breast
	  • Respiratory (especially if smoker)
	  • Haematology - if lytic metastases consider myeloma screen
	• Suspected spinal cord compression immediate phone call to the Acute Medic on call or send patient directly to A&E.

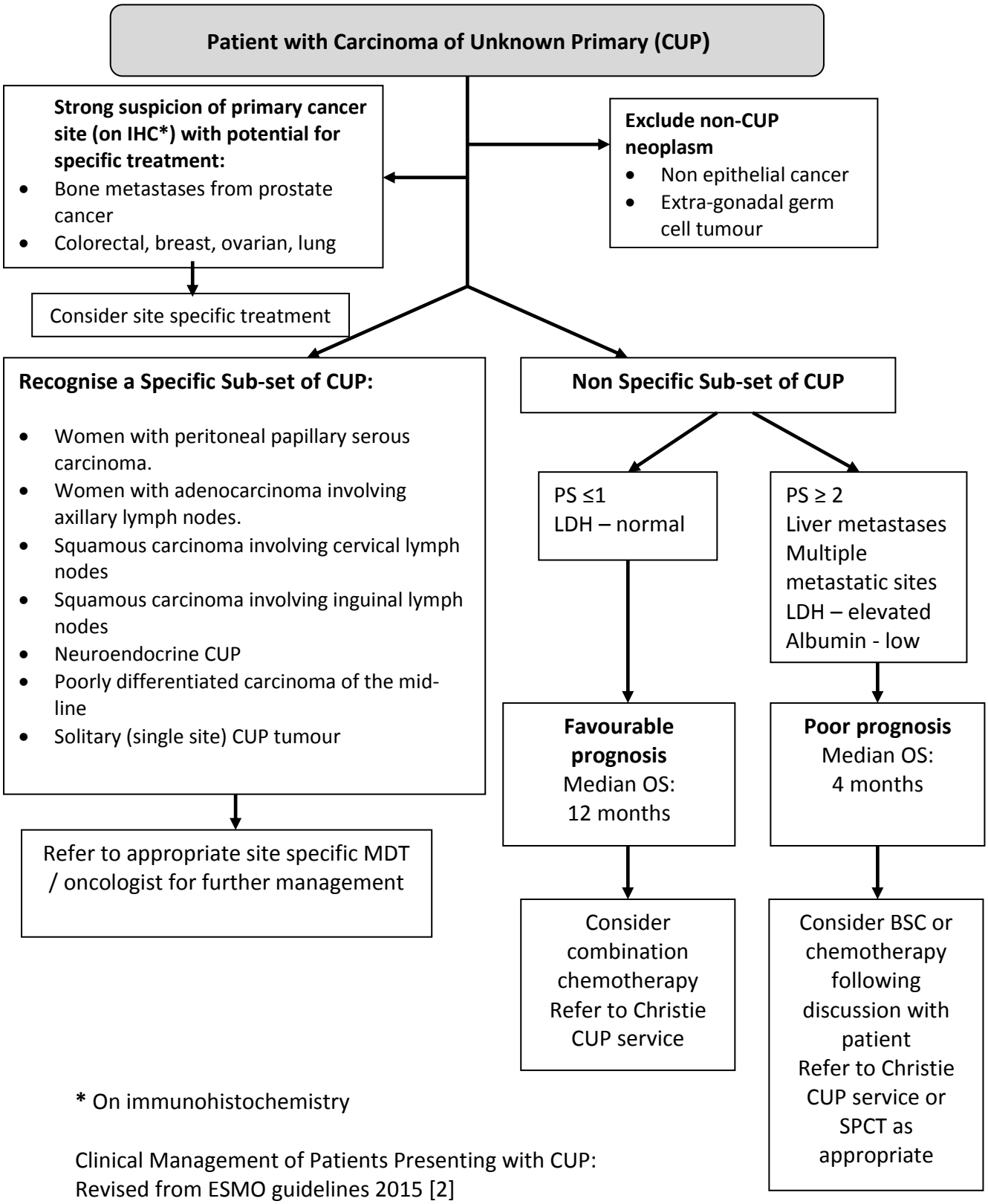
Single	If suspected primary bone tumour- Sarcoma pathway - 0161 276 8006 or fax referral form found @ http://www.cmft.nhs.uk/royal-infirmary/our-services/greater-manchester-and-oswestry-sarcoma-service
NODAL DISEASE	
Axilla	• Both sexes - Breast team
Upper/mid cervical (adeno/squamous)	• ENT team
Lower cervical	• ENT team • Upper GI if upper GI symptoms • Respiratory if chest symptoms
Inguinal (male)	• Lower GI team
Inguinal (female)	• Gynae team
Midline disease (**above** diaphragm)	• Respiratory team • Haematology team (possibly Lymphoma) • Upper GI
Midline disease (**below** diaphragm)	• Lower GI • Haematology team (possibly Lymphoma) • Urology team (if considering germ cell tumour male only)
PULMONARY	
Solitary lesion	• Respiratory team
Multiple lung lesions	• Respiratory team
Pleural effusion only	• Respiratory team
INTRA-ABDOMINAL	
Peritoneal carcinomatosis and/or ascites - Female	• Gynae team. Check CA125: CEA ratio
Peritoneal carcinomatosis and/or ascites -	• Upper/lower GI team as clinically

Male	appropriate
Portal adenopathy	• Upper GI
Multiple Liver metastases	• Upper GI(HPB)
Single Liver lesion	• Upper GI (HPB)
BRAIN	
Single	• If symptomatic admit to Acute medical team or via A&E • If asymptomatic seek advice via Neurosurgical team - Salford
Multiple brain metastases	• If symptomatic admit to Acute medical team or via A&E • If asymptomatic seek advice via Neurosurgical team - Salford
Other:	
Presentation with metastatic disease not fulfilling above criteria	• Access to oncology review via MUO/CUP clinic / clinic slot within an existing oncology clinic • Advice should be sought from CUP/AO team – contacted via hospital switchboard.

2. Investigation of Patients with MUO



3. Clinical Management Pathway of Patients with Carcinoma of Unknown Primary:



* On immunohistochemistry

Clinical Management of Patients Presenting with CUP:
Revised from ESMO guidelines 2015 [2]

Background

Patients who present with “malignancy of undefined origin” (MUO) by definition are patients who have presented with metastatic disease which has been identified on initial investigation most commonly radiological. The primary site may be subsequently identified in a significant proportion of patients, however despite extensive investigation for some patients this is not the case and they are diagnosed as being confirmed “cancer of unknown primary (CUP)”.

For some patient’s investigation to identify the primary site may not be appropriate for example patients with poor performance status or significant co-morbidities. For these patients the diagnosis will remain as MUO.

Patients who are diagnosed with “cancer of unknown primary” are those who have evidence of metastatic malignancy from an unidentified primary site. This is a very diverse patient population in which tumour type, extent of spread and outcomes vary widely. The majority of these patients will have a malignancy of epithelial lineage; patients with tumours of non-epithelial lineage (sarcoma, lymphoma, melanoma, germ cell) should be managed according to disease specific guidelines.

Cancer of unknown primary accounts for ~ 3% of new cancer diagnoses per annum, increasing to 7% in the over 85yr population. This equates to 8,930 new cases per annum in 2014. The number of recorded deaths from cancer of unknown primary in 2014 was 10,142. Six in ten deaths of cancer of unknown primary are in patients aged 75 years or older [3]. Incidence rates however are decreasing; this is likely to be due to several reasons including improvements in diagnostic methods and better registration/coding practices.

The route of presentation for CUP patients has a significant impact on outcomes and survival with CUP more likely to present as an emergency compared to all cancers; 57% of CUP patients (25,000 cases) compared to 23% for all cancers presenting via

the emergency department. A lower percentage of CUP patients are diagnosed through GP referral, 19% compared to 27% for all cancers [4]

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

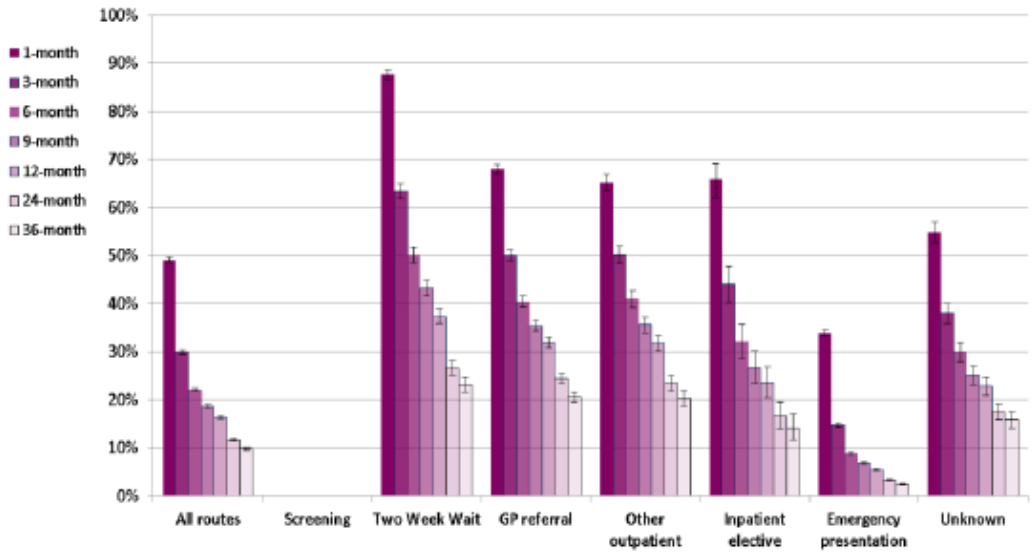


Fig 1: Relative survival estimates by presentation route and survival time, Cancer of Unknown Primary, 2006-2010 [4]

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

In many acute trusts local Acute Oncology teams are synonymous with the local CUP teams and take responsibility for the local CUP MDT and CUP clinical service. Where acute oncology teams do not provide the cover for CUP separate independent local CUP teams have been established to provide the service.

Malignancy of Undefined Origin (MUO): Referral Pathways:

Primary care referrals for patients who are diagnosed with MUO through initial investigations performed by their GP (general practitioner) should be referred to secondary care via the defined 2WW pathways as per NICE: Suspected cancer: recognition and referral guidelines [5]. It may be necessary for GP's to perform further assessments or initial investigations to determine the most appropriate referral pathway.

In order to ensure swift and appropriate referrals and reduce delay in referral the Great Manchester CUP group have recommended the following referral pathways for the most common MUO/CUP presentations:

BONE	

?Metastatic	• 75% of bone metastases are from prostate kidney, breast, lung and myeloma please refer to
	  • Urology (if PSA &/or DRE abnormal)
	  • Breast
	  • Respiratory
	  • Haematology - if lytic metastases consider myeloma screen
	• Suspected spinal cord compression immediate phone call to the Acute Medic on call or send patient directly to A&E

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Upper/mid cervical (adeno/squamous)	• ENT team
Lower cervical	• ENT team • Upper GI if upper GI symptoms • Respiratory if chest symptoms
Inguinal (male)	• Lower GI team

Inguinal (female)	• Gynae team
Midline disease (**above** diaphragm)	• Respiratory team • Haematology team (possibly Lymphoma) • Upper GI
Midline disease (**below** diaphragm)	• Lower GI • Haematology team (possibly Lymphoma) • Urology team (if considering germ cell tumour male only)
PULMONARY	
Solitary lesion	• Respiratory team
Multiple lung lesions	• Respiratory team
Pleural effusion only	• Respiratory team
INTRA-ABDOMINAL	
Peritoneal carcinomatosis and/or ascites - Female	• Gynae team. Check Ca125: CEA ratio
Peritoneal carcinomatosis and/or ascites - Male	• Upper/lower GI team as clinically appropriate
Portal adenopathy	• Upper GI
Multiple Liver metastases	• Upper GI(HPB)
Single Liver lesion	• Upper GI (HPB)
BRAIN	
Single	• If symptomatic admit to Acute medical team or via A&E • If asymptomatic seek advice via Neurosurgical team - Salford
Multiple brain metastases	• If symptomatic admit to Acute Medical team or via A&E • If asymptomatic seek advice via Neurosurgical team - Salford
Other:	
Presentation with metastatic disease not fulfilling above criteria	• Access to oncology review via MUO/CUP clinic / clinic slot within an existing clinic • Advice should be sort from CUP/AO team

These referrals pathways should be agreed by each individual trusts cancer pathway manager.

MUO presentations referred via these 2ww pathways can be discussed at either the appropriate site specific MDT or at the local CUP MDT.

If a patient is discussed at a site specific MDT and is deemed to be a provisional CUP the patient can be referred directly to the CUP service at the Christie NHS Trust. Patients do not need to be discussed at their local CUP MDT for the referral to be made – the aim of this is to reduce any delay in referral.

All patients referred to the CUP service at the Christie NHS Trust are discussed at the Central Christie CUP MDT.

Patient Presentation

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

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

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

Investigation

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

It is important when investigating patients that they are fully informed with regards the rationale and the potential outcome of investigations being performed. To

optimise the care of patients with MUO it is necessary to try and define the optimal point for ceasing diagnostic tests, based on a balance between standard clinical benefit and individual psychological need.

The following criteria should be considered when investigating patients:

- Do not offer further investigations to identify the primary site of origin of the malignancy to patients who are unfit for treatment.
- Perform investigations only if:
  - the results are likely to affect a treatment decision
  - the patient understands why the investigations are being carried out
  - the patient understands the potential benefits and risks of investigation and treatment **and**
  - the patient is prepared to accept treatment.
- Explain to patients and carers if further investigations will not alter treatment options. Provide appropriate emotional and psychological support, information about CUP, treatment options and palliative care.

Initial Assessment

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

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

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

Urinalysis for monoclonal light chains should be sent as part of a myeloma screen where there are lytic bone metastases.

Imaging

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

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

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

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

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

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

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

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

Upper and Lower GI Endoscopy

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

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

Tumour Markers

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

There are certain situations where their use is warranted:

- AFP and hCG in patients with presentations compatible with germ-cell tumours (particularly those with mediastinal and/or retroperitoneal masses and in young men).
- AFP in patients with presentations compatible with hepatocellular cancer.
- PSA in men with presentations compatible with prostate cancer.
- CA125 in women with presentations compatible with ovarian cancer/ primary peritoneal cancer (including those with inguinal nodal disease, chest, pleural, peritoneal or retroperitoneal presentations). Carefully interpret the results because of limited test specificity.

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

Histology

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

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

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

Tumours are categorised by pathology into:

• well- and moderately differentiated adenocarcinomas;

• squamous cell carcinomas;

• carcinomas with neuroendocrine differentiation;

• poorly differentiated carcinomas (including poorly differentiated adenocarcinomas);

• undifferentiated neoplasms.

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

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

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

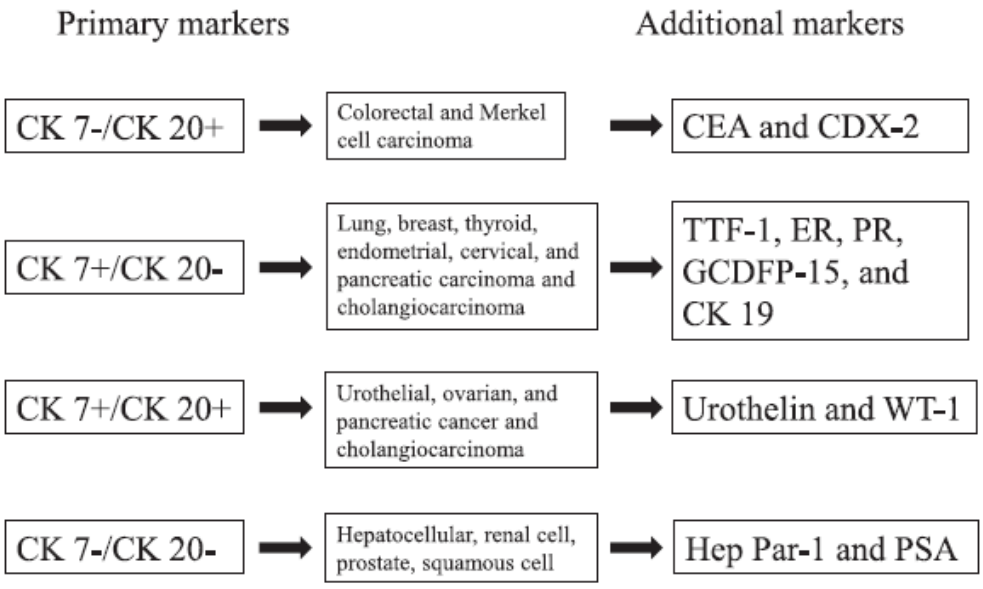

Fig 2: Basic IHC work-up of cancer of unknown primary [2]

Extended immunohistochemical panels should then be applied as felt appropriate by the reviewing histopathologist.

Potential IHC markers are described in the table below (table 2):

	Cytokeratins	PSA	ER, PgR	CDX2+, CK20+, CK7−	TTF1, NapsinA, CK7+	Thyroglobulin, calcitonin	NSE, chromogranin, synaptophysin	AFP, OCT4, hCG, PLAP	LCA	S100, HMB45	Vimentin, desmin
Undifferentiated carcinoma	+	−	±	−	−	−	−	−	−	−	±
Prostate cancer	+	+	−	−	−	−	−	−	−	−	−
Breast cancer	+	−	±	−	−	−	−	−	−	−	±
Colorectal cancer	+	−	−	+	−	−	−	−	−	−	−
Lung adenocarcinoma	+	−	−	−	+	−	−	−	−	−	−
Thyroid cancer	+	−	−	−	±	+	±	−	−	−	−
Neuroendocrine	+	−	−	−	±	±	+	−	−	−	−
Germ-cell cancer	+	−	−	−	−	−	−	+	−	−	±
Lymphoma	−	−	−	−	−	−	−	−	+	−	−
Melanoma	−	−	−	−	−	−	−	−	−	+	±
Sarcoma	−	−	−	−	−	−	−	−	−	±	+

The table shows general staining patterns but exceptions exist, especially for S100 and vimentin
Thyroid and neuroendocrine cancers often positive with CK7 and TTF1 but not with NapsinA.
PSA, prostate specific antigen; ER, oestrogen receptor; PgR, progesterone receptor; CK, cytokeratin; TTF1, thyroid transrcription factor 1; NSE, neuron-specific enolase; AFP, alpha fetoprotein; hCG, human chorionic gonadotropin; PLAP, placental alkaline phosphatase; LCA, leukocyte common antigen.

Table 2: Extended IHC work up for Cancer of Unknown Primary [2]

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

Molecular Genetic Profiling

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

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

Tissue of Origin Testing

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

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

Targetable Genetic Mutations

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

At present however the role of genetic expression based profiling has not been established in CUP and therefore it is recommended that it should only be

performed in this patient population within a clinical trial setting to allow further investigation.

Management

Prognostic Groups

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

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

CUP "SYNDROME"	Site specific Team
Isolated axillary node metastases in a female	Breast
Squamous cell carcinoma involving cervical lymph nodes	Head and Neck
Peritoneal adenocarcinomatosis in a female	Gynaecology
Squamous cell carcinoma involving inguinal lymph nodes	Urology
Poorly differentiated neuroendocrine tumour (NET) of unknown primary	NET (Specialist MDT Christie)
Well differentiated NET of unknown primary	NET (Specialist MDT Christie)
Poorly differentiated carcinoma with predominant mid-line distribution	Urology/Germ cell
Solitary CUP metastasis	Single metastasis site specific • Brain- neuro oncology • Pulmonary – lung

	• Liver – HPB • Bone – orthopaedic/sarcoma

Table 3: CUP syndromes and associated site specific teams.

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

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

Patients who present with CUP with poor prognostic features should be assessed locally by the CUP team to determine if they are suitable for consideration of systemic therapy. If there is uncertainty the case should be discussed with the CUP service at the Christie NHS Trust.

Patients who present with multiple brain metastases should be discussed at the local CUP MDT to decide if referral for whole brain radiotherapy is appropriate however there is limited evidence to support the use of whole brain radiotherapy for symptom relief in this setting [10-11].

Management of Recognisable CUP "Syndromes"

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

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

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

- **Adenocarcinoma of axillary nodes**
    - 90% of female patients presenting with adenocarcinoma of the axillary nodes are considered to have an unidentified breast primary.

- These patients should be referred to the **specialist breast MDT** and considered for radical treatment (Axillary nodal dissection, mastectomy or breast irradiation and adjuvant chemotherapy/ hormone therapy).

- **Solitary Metastases from Unknown Primary**
  - Solitary metastases even where the primary is unknown should be considered for potentially radical treatment (resection and/or RT ± systemic therapy).
  - Patients should be discussed at the **appropriate disease site specific MDT** according to the location of the metastases **PRIOR** to tissue biopsy taking place ie radiological diagnosis only.
  - Do not investigate a tumour inappropriately because this may make radical treatment ineffective. For example, biopsy of a primary bone tumour may mean that the patient needs more extensive surgery than usual. Percutaneous biopsy of a potentially resectable liver metastasis may compromise outcome.
  - Consider that an apparent metastasis could be an unusual primary tumour.

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

- **Poorly differentiated carcinoma with pre-dominant mid-line tumour**
  - Treat as per extra-gonadal germ cell tumours.

- Should be discussed at the **specialist urology / germ cell MDT**.
- Combination cisplatin based therapy / BEP in males.

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

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

Systemic Treatment of Confirmed CUP

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

All patients with confirmed CUP should be referred centrally for treatment within the CUP service at the Christie NHS Trust. Patients should only be considered for

local treatment on an individual basis and following discussion with the CUP service at the Christie NHS Trust.

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

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

Common regimens currently employed in the treatment of CUP are:

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

Clinical Trials

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

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

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

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

Supportive / Palliative Care

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

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

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

Clinical Audit and Data Collection

A minimum data set (MDS) to be collected at the local CUP MDT's will be specified to ensure that consistent high quality data is collated for all CUP patients. Trusts also need to be able to capture data on any CUP's going via site specific MDT's.

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

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

Appendices

i) Local CUP MDT's / Clinical Leads:

Cancer of Unknown Primary Pathway Sub-group Chair: Dr Claire Mitchell April 2018	
ROYAL BOLTON HOSPITAL NHS FOUNDATION TRUST	
Clinical Lead	Dr Carmel Anandadas
Core Nurse Member	Clare de Marco Masetti
MID CHESHIRE HOSPITALS NHS FOUNDATION TRUST	
Clinical Lead	Laura Horsley
Core Nurse Member	Sophie Lloyd / Sarah Latham
CENTRAL MANCHESTER UNIVERSITY HOSPITALS NHS FOUNDATION TRUST	
Clinical Lead	Dr Claire Mitchell
Core Nurse Member	Joanne Woolley
THE CHRISTIE NHS FOUNDATION TRUST	
Clinical Lead	Dr Claire Mitchell
Core Nurse Member	Andrea Spencer Shaw
EAST CHESHIRE NHS TRUST	
Clinical Lead	Dr Ganesh Radhakrishna
Core Nurse Member	Anne Allen
PENNINE ACUTE HOSPITALS NHS TRUST	
Clinical Lead	Dr Joanna Coote
Core Nurse Member	
SALFORD ROYAL NHS FOUNDATION TRUST	
Clinical Lead	Dr Claire Arthur
Core Nurse Member	Vickki Tyrrell
UNIVERSITY HOSPITAL OF SOUTH MANCHESTER NHS FOUNDATION TRUST	
Clinical Lead	Dr Yvonne Summers
Core Nurse Member	Jeena Mathews
STOCKPORT NHS FOUNDATION TRUST	
Clinical Lead	Dr Catherine Coyle
Core Nurse Member	Keven White
TAMESIDE HOSPITAL NHS FOUNDATION TRUST	
Clinical Lead	Dr
Core Nurse Member	Melanie Dadkhah-Taeidy
WRIGHTINGTON, WIGAN AND LEIGH NHS FOUNDATION TRUST	
Clinical Lead	Dr Kalena Martimarti
Core Nurse Member	Barbara Hefferon
User Representatives(x2)	
Dr Tim Cooksley	
Dr Mary O'Mara	
Imaging Specialist	
Dr Ben Taylor	

Histopathologist
Dr Pedro Oliveira
Palliative Medicine Reprsentation
Anne Marie Raferty
Administration Support
Rebecca Price
Named Member with Responsibility for User Issues
TBC
Named Member with Responsibility for Trial Recruitment
Dr Claire Mitchell

ii) ECOG / WHO Performance Status

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

iii) Referral Contacts

Dr Claire Mitchell
Consultant Medical Oncologist
CUP Service
Christie Hospital NHS Trust
Manchester
M20 4BX

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

iv) Patient Support Groups

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

2. Cancer Research UK
   www.**cancerresearch**uk.org

3. CUP Foundation – Jo's Friends
   www.cupfoundjo.org

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