Peninsula Cancer Alliance

Cancer of Unknown Primary (CUP) and Acute Oncology

Site Specific Group

Clinical Guidelines for the Investigation,

Diagnosis and Management of Patients with CUP

Approved: May 2020

Review Date: May 2022

Peninsula Cancer Alliance

VERSION CONTROL

THIS IS A CONTROLLED DOCUMENT. PLEASE DESTROY ALL PREVIOUS VERSIONS ON RECEIPT OF A NEW VERSION.

Please check the Peninsula Cancer Alliance website for the latest version available: www.peninsulacanceralliance.nhs.uk

VERSION	DATE ISSUED	SUMMARY OF CHANGE	NAME
0.1	18th February 2016	First Draft	PCA CUP SSG
0.2	January 2018	Updated following the formation of the Peninsula Cancer Alliance (PCA)	PCA CUP SSG
0.3	May 2020	Final draft updated	PCA CUP AND AOS SSG
1	May 2020	Guidelines Approved	PCA CUP AND AOS SSG
1.2	July 2020	Correction made pg. 11	BKINGSHOTT

This version has been edited by:

Dr Anne McCormack
Consultant Oncologist-Royal Devon & Exeter Hospital NHS Foundation Trust

Naomi Clatworthy
Acute Oncology Nurse Consultant and AOS lead - Northern Devon Healthcare NHS Trust
Chair of the Peninsula Cancer Alliance Cancer Unknown Primary and Acute Oncology SSG

Nina Kamalarajan
Peninsula Cancer Alliance SSG Support Manager until 2019

Beth Kingshott
Peninsula Cancer Alliance SSG Support Manager

These updated clinical guidelines have been agreed by the following MDT Leads:

Name	Position	Trust
Dr Ian Fraser	Consultant Clinical Oncologist MDT Lead	North Devon Healthcare NHS Trust
Dr David Sherriff	Consultant Clinical Oncologist MDT Lead	Plymouth Hospitals NHS Trust
Dr Charlotte Thompson	Consultant Medical Oncologist MDT Lead	Royal Cornwall Hospitals NHS Trust
Dr Anne McCormack	Consultant Clinical Oncologist MDT Lead	Royal Devon and Exeter NHS Foundation Trust
Dr Louise Medley	Consultant Clinical Oncologist MDT Lead	Torbay and South Devon NHS Foundation Trust

CUP Clinical Guidelines Content

References and Acknowledgement	17

1.0 Introduction

Approximately 10,000 people per annum will present with metastatic malignancy where the primary site of disease remains unidentifiable. Established 2-week wait pathways exist for all site-specific presentations, ensuring timely and effective diagnosis. However, no such pathway exists for patients presenting with metastatic malignancy of unknown primary. These patients are at a significant disadvantage, due to a lack of referral guidance or specialist teams to oversee the process. This leads to significant delays in diagnosis and management with consequent poor outcomes and patient satisfaction.

The following guidelines pertain to the local management of cancer of unknown primary malignancies for the Peninsula Cancer Alliance CUP and Acute Oncology SSG.

The SSG refers to the National Institute for Health and Care Excellence (NICE-July 2010) Guidelines: *"Diagnosis and Management of Metastatic Malignant Disease of Unknown Primary Origin".*

Summary guidelines are available here; https://www.nice.org.uk/guidance/CG104

Full guidelines are available here;

https://www.nice.org.uk/guidance/cg104/resources/metastatic-malignant-disease-of-unknown-primary-origin-in-adults-diagnosis-and-management-pdf-35109328970437

The aims of this document are to ensure the development of robust infrastructure to ensure equitable service provision for patients presenting with advanced metastatic malignancy and to provide clear guidance to enable appropriate and timely investigations and management suitable to the patient's condition.

The ultimate goal is:

1. To provide clear guidance for the initial and on-going investigations and subsequent management of patients presenting with malignancy of unknown primary origin.

2. To identify those patients with favourable or potentially curable conditions that may benefit from treatment, such as;

    a. Poorly differentiated carcinoma with a midline distribution
    b. Women with peritoneal adenocarcinoma
    c. Women with adenocarcinoma in axillary lymph nodes
    d. Squamous cell carcinoma of lymph nodes in the neck
    e. Poorly differentiated neuroendocrine carcinoma.

3. To identify those patients with a poor prognosis who may benefit from supportive/palliative care and fast track discharge for end of life care.

2.0 Provision of Hospital CUP Services

2.1 Configuration of Services

The Peninsula Cancer Alliance (PCA) CUP and Acute Oncology SSG covers a total catchment population of approximately 1,729,700;

Devon: 1.178million[1]

Cornwall and IOS: 551,700[2]

Its associated acute service provider trusts and Clinical Commissioning Groups (CCGs) are:

Organisation	Referring CCG
University Hospitals Plymouth NHS Trust	NHS Devon CCG
Northern Devon Healthcare NHS Trust	NHS Devon CCG
Royal Cornwall Hospitals NHS Trust	NHS Kernow CCG
Torbay & South Devon Healthcare NHS Foundation Trust	NHS Devon CCG
Royal Devon & Exeter NHS Foundation Trust	NHS Devon CCG

2.2. Roles and Responsibilities

The responsibilities of Lead CUP Clinician are to ensure;

- There is a clinical system/pathway for the review and care of MUO/CUP patients.
- Each patient has an identified CUP specialist nurse with a single point of access.
- There is adequate cover for members of the team during absence to ensure continued smooth running of the service.
- Care is given according to recognised guidelines with appropriate collection of information to aid clinical decision making and to support clinical governance/audit.
- Timely and effective communication takes place between CUP team members and colleagues within primary & secondary care and palliative care.
- The CUP MDT is effectively led with attendance maintained, ensuring adequate cover during absences.

[1] https://new.devon.gov.uk/factsandfigures/data-table/?postId=mid-year-population-estimates&geography=464)

[2] https://www.cornwall.gov.uk/council-and-democracy/data-and-research/data-by-topic/population/

- The MDT aims to discuss 100% of patients.
- An annual meeting is organised and chaired to review operating procedures, ensure optimal functioning and identify action points for future development.
- The Trust contributes to regular local and network audits of the management of MUO/CUP.

Team responsibilities include:

- Acting as coordinators for all patient referrals for MUO/CUP between departments within the hospital and primary care.
- Ensuring the implementation and continued development of a quality CUP service.
- Developing clear guidance for the investigation and subsequent management of MUO/CUP.
- Ensuring timely review of patients presenting with MUO/CUP within two weeks for outpatients and by the end of the next working day for inpatients.
- Reporting to the NAOG and hospital management team.

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, or
- diagnosed with a non-malignant condition

3.0 Referrals

The CUP team accepts referrals from the emergency department, acute medical/surgical wards and local GP's. First referral should be made to the specialist nurse, who will offer advice regarding appropriate investigations and co-ordinate on-going review and management. Please refer to each individual CUP service for further information on referrals.

3.1 GP Referral

If the patient is well enough, they should be referred and seen within 2 weeks. This may be through either of the following routes;

- Referral to the likely primary site specific team.
- Referral to the CUP team via an initial phone call and emailed referral letter/form.

If the patient is acutely unwell and requires inpatient management, they should be referred via the acute medical unit, who will ensure on-going referral to the CUP team as an inpatient.

The only exception to this rule is in the case of suspected malignant spinal cord compression when a direct call to the spinal cord co-ordinator or Acute Oncology service should be made during working hours, or to the spinal registrar on call via switchboard if presenting out of hours.

3.2 Inpatient Referral

Patients presenting acutely unwell via emergency services should be referred to the acute oncology/CUP team, where a member of the team will offer advice and arrange to review the patient within 24 hours, if appropriate. The team will advise on appropriate investigations, symptom control and provide information and support to the patient. The patient will remain under the care of the admitting physician throughout the diagnostic process, with support from the CUP team.

Where a potential primary source is identified on initial investigations, the patient should be discussed at the relevant site-specific MDT. The CUP specialist nurse will ensure that the appropriate CNS is informed.

If, after appropriate investigations, a primary site cannot be identified, then the patient should be discussed at the CUP MDT. Currently, requests for discussion should be made via the CUP team.

4.0 MUO/CUP Patient Investigation and Management Policy

4.1 Investigations & Diagnosis

Investigations should only be performed if;

- The patient is fit for treatment if the primary site were identified
- The results of an investigation is 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 investigations and treatment and is prepared to accept treatment.

At all points throughout the pathway, the team should provide adequate symptom control for the patient, referring to palliative care at an early stage to ensure that all areas of need are addressed (including psychosocial and spiritual).

Investigation of MUO can be subdivided into two phases;

- The initial diagnostic phase
- The second targeted investigation phase

4.2 Initial Diagnostic Phase

The aim of the initial diagnostic phase is to arrange the most appropriate investigations to identify one of the following;

- A primary site.
- Non-epithelial malignancy which can be treated regardless of primary site (e.g. lymphoma, melanoma, sarcoma & germ cell tumours).
- Confirm epithelial or neuro-endocrine malignancy without an identifiable site (provisional CUP).

The following assessments and investigations should be completed, where possible guided by the patient's symptoms;

Observations: Temperature, pulse, blood pressure, respiratory rate, oxygen saturations, documented Early Warning Score (EWS).

History: Full history including onset and rate of change of symptoms, Co-morbidities and Performance status (see Appendix 3).

Examination: Full clinical examination (Breast, PR, genital, skin, nodal areas & pelvic)
Investigations

Laboratory

- All patients; FBC, U&E's, LFT's, calcium, LDH & CRP.
- Men – midline disease/brain mets; Serum alpha-fetoprotein, βHCG (germ cell).
- Men – bone metastases; PSA (prostate cancer).
- Women – pelvic or peritoneal disease Ca125 (ovarian carcinoma).
- Liver only disease – αFP (hepatoma).
- Bone lesions only – myeloma screen.
- Urinalysis.

Please note, other tumour markers are unhelpful in diagnosis and should not be requested unless specifically advised by the CUP team.

Imaging

- CT Thorax Abdomen and Pelvis
- Testicular ultrasound in men with midline disease (germ cell?)
- Other investigations (including endoscopies) only as indicated by signs & symptoms

- Patients with a solitary liver lesion should be referred to the HPB MDT *BEFORE* biopsy.
- For all other patients, please discuss with the CUP team before arranging a biopsy as comorbidities, performance status and risk of proceeding may influence the need to biopsy.

Where a possible primary site is identified, the patient should be referred to the appropriate tumour-site MDT. Certain clinical presentations require discussion at specific MDT's as follows;

Presentation	**MDT**
Men with bone mets and elevated PSA	Urology MDT
Women with axilliary nodes	Breast MDT
Women with peritoneal disease on histology	Gynae MDT (unless non-gynae)
Solitary liver lesion	HPB MDT
Neck nodes	Head and Neck MDT
Isolated brain mets	Neuro-oncology MDT
Intrapulmonary nodules	Lung MDT

Those patients where a primary source cannot be identified are discussed at the dedicated weekly Carcinoma of Unknown Primary MDT.

The CUP team will continue to recommend on-going investigations, treatment and care of patients with confirmed CUP based on the results of the initial phase investigations.

4.3 Second Diagnostic Phase (Targeted)

A second phase of targeted investigations can be offered where appropriate. These would generally be offered *after* discussion at an MDT and should not be requested without discussing with the CUP team first.

Upper & Lower GI endoscopy

- Only appropriate in patients with symptoms, histology or radiology suggesting a GI source.

Mammogram

- Should only be arranged if clinical or histopathological features consistent **with a breast primary**

Breast MRI

- In patients with axillary node adenocarcinoma where a breast primary has not been identified by standard imaging (mammogram/ultrasound).

PET-CT

- In patients presenting with cervical lymphadenopathy where no primary tumour identified on panendoscopy.
- Extra –cervical presentations after discussion with the CUP team

Bronchoscopy

- In patients presenting with intrapulmonary nodules of probable metastatic origin unsuitable for percutaneous biopsy

Immunohistochemistry

A wide panel of immunohistochemical markers are applied in the first instance to identify those tumours which are chemosensitive and potentially curable, such as lymphoma and germ cell tumours. If the initial panel identifies an epithelial cancer, a further panel of tests may help to identify the likely source of origin (see table below).

Immunohistochemical marker	Possible cancer site of origin
CK20	Colorectal, Appendix, Merkel Cell
CK7	Lung, Pancreas, Cholangiocarcinoma, Gastro-oesophageal Ovary, Breast
PSA (prostate specific antigen)	Prostate
TTF-1	Lung, Thyroid
ER (oestrogen receptor)	Breast, Ovary, Endometrial
Ca125	Ovary, Endometrial, , Pancreas
Calretinin/WT-1	Mesothelioma, Ovary
CEA	GI tract, Pancreas, Lung,

5.0 Outcome of MUO/CUP Investigation Pathway

Patients in whom the primary site has been identified should be assessed by a member of the appropriate site-specific MDT. The CUP CNS will ensure that the appropriate CNS is informed of the diagnosis.

Where a primary site remains unidentified, the patient will remain under the care of the CUP Oncologist for on-going management.

When it is determined that a patient is not suitable for active oncological management, then the patient should be seen by a member of the hospital or community palliative care team to ensure they receive suitable and timely end of life care.

6.0 Treatment Options

The following factors should be considered when selecting the optimal treatment for patients with MUO/CUP;

- Rapidly growing tumours, age < 50, ≤2 sites of disease and normal organ function are associated with better outcomes and should be considered for active treatment.
- Multiple co-morbidities, deranged organ function and poor performance status are associated with poor prognosis. Early referral for palliative care should be considered.

Full and active discussion with patients and their carers should take place to aid in the decision making process.

6.1 Management of patients with a specific treatable syndrome

Management of patients with specific treatable syndromes should be discussed through the relevant MDT as detailed below. Treatment may involve surgery, chemotherapy and/or radiotherapy.

Treatable Specific Syndrome	Relevant MDT for Discussion
Poorly differentiated carcinoma with midline distribution	Urology MDT
Women with predominantly peritoneal adenocarcinoma	Gynae MDT
Women with adenocarcinoma of the axillary nodes	Breast MDT
Squamous cell carcinoma of lymph nodes in the neck	Head & Neck MDT
Poorly differentiated neuroendocrine carcinoma	Lung MDT

6.2 Systemic Chemotherapy for Patients without a specific treatable syndrome

There is no clear consensus on the most suitable chemotherapy regime to offer to patients with true CUP. A number of broad spectrum ‘empirical’ regimes are used, although evidence remains poor. Regimes are generally selected based on the immunophenotype of the cancer (see above).

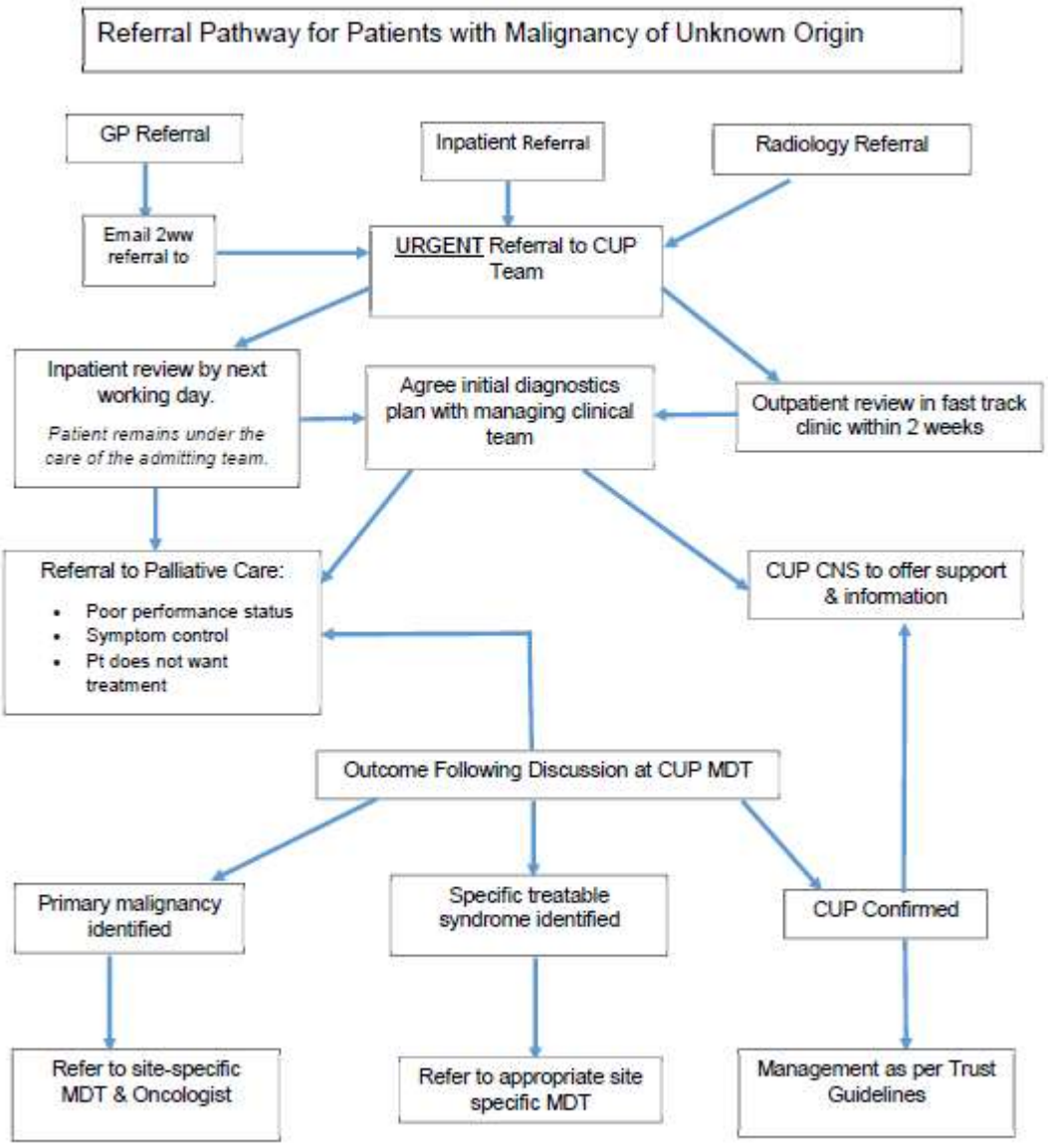
The potential risks and benefits of embarking on chemotherapy should be discussed at length with the patient and their carers. Where possible, patients should be offered entry into suitable clinical trials. In some cases, symptomatic management only may be the most appropriate course of action and appropriate referrals to palliative care services should be made.

The following Chemotherapy regimes are in use across the peninsula both in first and second line settings. Please refer to the Peninsula Cancer Alliance website for up to date regimes.

Regimen	Drug Doses	Cycle Length
Carboplatin & Paclitaxel	• Carboplatin AUC 6 day1 • Paclitaxel 175mg/ m^2 day1	21d
Carboplatin & Etoposide	• Carboplatin AUC 5 day 1 • Etoposide 100mg/ m^2 day 1 • Etoposide PO 200mg/ m^2 day 2+3 or Etoposide IV 100mg/ m^2 day 2+3	21d
Cisplatin & Gemcitabine	• Cisplatin 100mg/m^2 day 1 • Gemcitabine 1250mg/m^2 day 1 & 8	21d
Gemcitabine & Carboplatin	• Carboplatin AUC 5 day 1 • Gemcitabine 1000mg/m^2 day 1 & 8	21d
ECX	• Epirubicin 50mg/m^2 day 1 • Cisplatin 60mg/m^2 day 1 • Capecitabine 625mg/m^2 po bd continuously	21d
EOX	• Epirubicin 50mg/m^2 day 1 • Oxaliplatin 130mg/m^2 day 1 • Capecitabine 625mg/m^2 po bd continuously	21d
Paclitaxel Weekly	• Paclitaxel 60mg/ m^2-100mg/ m^2 depending on performance status day 1, 8 & 15	21d

Peninsula Cancer Alliance

Appendix 1: Example of a Peninsula MUO/CUP Pathway



For Individual pathways, please contact:

North Devon Healthcare NHS Trust: ndht.aosnorthdevon@nhs.net

Royal Devon & Exeter NHS Foundation Trust: rde-tr.AosExeter@nhs.net

Torbay & South Devon NHS Foundation Trust: sdhct.Aos@nhs.net

University Hospitals Plymouth NHS Trust: plh-tr.AOSUHP@nhs.net

Royal Cornwall Hospitals NHS Trust: rcht.aos@nhs.net

Appendix 2: MUO/CUP Pathway – Initial Diagnostic Process

MUO/CUP Pathway; Initial Management & Diagnostic Pathway		
Please ensure early referral to acute oncology for advice and support		
Consider	Will investigations alter outcome? Is the patient of sufficient performance status to receive treatment? Does the patient want treatment?	
Initial Assessment & Diagnostic Phase		
Observations	Temperature, pulse, blood pressure, respiration rate, O2 Saturations. EWS	
History	Include onset and rate of change of symptoms. Include previous history of cancer, smoking & occupational history	
Examination	Complete clinical examination. Include breast, testicular, skin, nodal areas, PV & PR	
Laboratory	All patients	FBC, U&E's, Creatinine, LFT, Calcium, LDH
	Men; midline disease/brain mets	Serum αFP & βHCG
	Women; peritoneal or pelvic disease	Ca125
	Men; bone mets	PSA
	Liver only disease	Serum αFP
	Bone only disease	Myeloma screen (serum free light chains, protein electrophoresis & urinary bence jones)
	Effusions	Send at least 300mls for cytology, microbiology & protein
OTHER TUMOUR MARKERS ARE UNHELPFUL IN PRIMARY DIAGNOSIS		
Imaging	CT Thorax, Abdomen & Pelvis Other investigations only as indicated by signs & symptoms (includes endoscopies)	
Pathology	Patients with a solitary liver lesion should be referred directly to the local hepatobiliary team ***before*** biopsy All other patients, biopsy (trucut if possible)	

Further Management:

If clinical, radiological or pathological findings suggest a specific cancer primary site, refer to the relevant MDT.

Otherwise, refer to unknown primary team on :

Appendix 3: Performance Status

WHO PERFORMANCE STATUS	
0	Able to carry out normal activities without restriction
1	Restricted in physically strenuous activity, but ambulatory & able to carry out light work e.g. housework, office work
2	Ambulatory & capable of all self-care but unable to carry out any work activities. Up & about for more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair for more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair

References

National Institute for Health & Clinical Excellence (Jan 2010) Clinical Guideline 104; "*Diagnosis and Management of Metastatic Malignant disease of Unknown Primary Origin"*. [Accessed Online 22/01/2018): available at: https://www.nice.org.uk/guidance/cg104/resources/metastatic-malignant-disease-of-unknown-primary-origin-in-adults-diagnosis-and-management-pdf-35109328970437

Fizazi K, Greco F.A *et* al, (2011) ESMO Clinical Practice Guidelines: "*Cancer of Unknown Primary Site*". Ann Oncol; **22** (suppl 6): vi64-v168.

Acknowledgements

We acknowledge the Midlands Acute Oncology Nurses Forum and The Shrewsbury and Telford Hospital NHS Trust for sharing their documents with us.

-END-