Peninsula and Somerset, Wiltshire, Avon and Gloucestershire (SWAG) Cancer Services

Cancer of Unknown Primary

Clinical Advisory Group

Clinical Guidelines

2025

VERSION CONTROL

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VERSION	DATE ISSUED	SUMMARY OF CHANGE	OWNER'S NAME
Draft 0.1	5th June 2015	First draft	SWAG CUP SSG
Draft 0.2	12th June 2015	Updated GP referral guidelines	Anna Kuchel
1.0	30th June 2015	Finalised	SWAG CUP SSG
1.1	18th February 2016	Extension of revision date to April 2017 and correction of typing error page 5	H Dunderdale
1.2	April 2017	Biennial review	SWAG CUP SSG
1.3	June 2017	Finalised	SWAG CUP SSG
1.4	April 2019	Biennial review	SWAG CUP Clinical Advisory Group (CAG, formerly SSG)
1.5	28th June 2019	Finalised	H Dunderdale
1.6	23rd September 2021	Biennial update	H Dunderdale
1.7	4th October 2021	Amendment of Section 2.1.2, 2.1.3.4, 2.1.3.5, 2.1.3.6, 2.1.4, 2.3.1	T Tillett
1.8	7th June 2022	Amendment of Section 2.1.3.6 to Section 3.0	L Biddlestone
1.9	September 2025	Biennial Review – delayed due to workload pressures	H Dunderdale
2.0	5th November 2025	Addition of Peninsula logo in recognition that the group is now south west wide	H Dunderdale

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Cancer of Unknown Primary CAG Clinical Guidelines Contents

1. Introduction

The following guidelines pertain to the local management of cancer of unknown primary malignancies for the Peninsula and Somerset, Wiltshire, Avon and Gloucestershire (SWAG) Cancer of Unknown Primary Clinical Advisory Group (CAG) at the time of publication. Clinical Guidelines are constantly evolving and clinical teams should search for the most up to date national/international peer reviewed publications.

The CAG refers to the National Institute for Health and Care Excellence (NICE) guidelines 'Diagnosis and Management of Metastatic Malignant Disease of Unknown Primary Origin' (July 2010). The guidance summary is located here (and the references below refer to this): http://www.nice.org.uk/guidance/CG104

The full guidelines including evidence are located here: http://www.nice.org.uk/guidance/cg104/evidence

The two week wait (2WW) referral guidance does not apply to the CUP CAG. This has been agreed by General Practitioners (GPs) and the Clinical Commissioning Groups (CCGs) within the region. The local target is for any CUP referral to be reviewed by a CUP clinician and respond to the patient's GP within 2 working days with a plan for the patient. Inpatient referrals will be reviewed within 1 working day. The date and time of referrals and the date and time of responses will be recorded on the CAG CUP audit data spreadsheets. The CAG will adhere to the National 31 day and 62 day cancer wait targets. Details on how to refer to the CUP MDT are in the CUP Constitution which will also be uploaded to the SWAG website here.

The CAG is committed to offering all eligible patients entry into clinical trials where available. Consent to provide tissue for research purposes will also be sought wherever appropriate.

2. The CAG Agreed Clinical Guidelines for Cancer of Unknown Primary (NS/CUP-17-003)

2.1 Investigation protocols for Malignancy of Unknown Origin (MOU) patients in general

2.1.1 Diagnosis

Diagnosis is divided into two phases for patients presenting with a malignancy of unknown origin. The initial diagnostic phase aims to efficiently perform the most appropriate investigations in order to identify:

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

If further investigation is deemed necessary, a second phase of special investigations may be offered to patients with provisional CUP. If a primary site has still not been identified once these have been completed, a diagnosis of confirmed CUP can be made.

These guidelines aim to define the following:

- The core initial tests for patients in whom clinical investigation is clinically relevant
- The contribution of special tests
- The most appropriate histological assessment of tissue samples
- The most appropriate approach for specific presentations or difficult diagnoses.

2.1.2 The initial diagnostic phase

The following investigations will be offered with MUO, as clinically appropriate, being guided by the patient's symptoms:

- A comprehensive history and physical examination including breast, nodal areas, skin, genital, rectal and pelvic examination
- Full blood count, urea, electrolytes and creatinine, liver function tests, calcium, lactate dehydrogenase
- Urinalysis if clinically appropriate
- Myeloma screen if bone only disease
- Symptom directed endoscopy
- Computed tomography (CT) scan of the chest, abdomen and pelvis
- Prostate-specific antigen (PSA) in men
- Cancer antigen 125 (CA125) in women with peritoneal malignancy or ascites
- Alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) (particularly in the presence of midline nodal disease
- Testicular ultrasound in men with presentations compatible with germ-cell tumours
- Biopsy and standard histological examination, with immunohistochemistry where necessary, to distinguish carcinoma from other malignant diagnoses.

2.1.3 The second diagnostic phase – special investigations

2.1.3.1 Tumour markers

Tumour markers will not be measured during diagnosis except for:

- 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 (including those with inguinal node, chest, pleural, peritoneal or retroperitoneal presentations). The results will be interpreted carefully due to the limited test specificity.

2.1.3.2 Upper and lower gastrointestinal endoscopy

An upper or lower gastrointestinal (GI) endoscopy will not be performed in patients with MUO unless the symptoms, histology or radiology suggests a GI tumour.

2.1.3.3 Mammography

A mammography will not be routinely offered to women presenting with MUO unless clinical or pathological features are compatible with breast cancer.

2.1.3.4 Breast imaging

Patients with adenocarcinoma involving the axillary nodes will be referred to a breast cancer MDT for evaluation and treatment. If no breast primary tumour is identified after standard breast investigations, consider dynamic contrast- enhanced breast magnetic resonance imaging (MRI) to identify lesions suitable for targeted biopsy. There should be a low threshold for breast imaging, mammogram or MRI, for patients with metastatic cancer which could be in keeping with a pattern of breast cancer. Please consider this in male as well as female patients.

2.1.3.5 Positron emission tomography-computed tomography

Positron emission tomography-computed tomography (18F-FDG PET- CT) will be offered to patients with provisional CUP presenting with cervical lymphadenopathy with no primary tumour identified on ear, nose and throat panendoscopy if radical treatment is considered to be an option.

PET Positron emission tomography- computed tomography (18F-FDG PET-CT) scans should be offered to all patients with CUP who are being considered for radical treatment options such as patients with cervical lymphadenopathy with no Head and Neck primary seen, as agreed by the CUP MDT team or site specific MDT team considering the radical treatment.

2.1.4 When investigations should cease

Investigations will not be undertaken to identify the primary site of origin of the malignancy for patients who are unfit for treatment

Investigations will only be undertaken 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.

It will be explained to patients and carers that further investigations will not alter treatment options. Appropriate emotional and psychological support, information about CUP, treatment options and palliative care will be provided.

2.1.5 Selecting optimal treatment

Prognostic factors, in particular performance status, presence of liver metastases, lactate dehydrogenase levels and serum albumin, will be taken into account when making decisions about further diagnostic investigations and treatment.

The patient's prognostic factors will be discussed with the patient and their relatives or carers, if appropriate, to help them make informed decisions about treatment.

The patient's prognostic factors will be included in decision aids and other information for patients and their relatives or carers about treatment options

2.2 Presentations that may benefit from radical treatment

2.2.1 Squamous cell carcinoma involving upper- or mid-neck nodes

Patients presenting with upper- or mid-neck squamous cell carcinoma and an unidentified primary tumour will be referred to a head and neck MDT for evaluation and treatment.

2.2.2 Adenocarcinoma involving the axillary nodes

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

2.2.3 Squamous cell carcinoma involving the inguinal nodes

Patients with squamous cell carcinoma confined to the inguinal nodes will be referred to a specialist surgeon in an appropriate MDT to consider treatment with curative intent.

Patients with operable disease will be offered either:

- superficial lymphadenectomy and consider post-lymphadenectomy radiotherapy (for patients with risk factors for residual disease, for example multiple involved nodes or extracapsular spread) **or**
- simple excision of clinically involved nodes, followed by radiotherapy.

2.2.4 Solitary metastases

A tumour will not be investigated 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. An apparent metastasis could be an unusual primary tumour.

Patients with a solitary tumour in the liver, brain, bone, skin or lung will be referred to the appropriate site specific MDT to consider radical local treatment.

2.3 Presentations with a poor prognosis

2.3.1 Multiple metastases including brain involvement

Patients presenting with apparent brain metastases as the only sign of malignant disease after initial and special investigations will be referred to a neuro-oncology MDT for evaluation and treatment.

Chemotherapy will only be for patients with brain metastases of unknown primary origin as part of a controlled clinical trial.

Given the poor prognosis of patients with multiple brain metastases, strong consideration will be given to Best Supportive Care for patients with multiple brain metastases from a Cancer of Unknown Primary site.

Patients with brain metastases of unknown primary origin and their carers will be informed that there is no evidence that any treatment offers improved survival and there is limited evidence of improvement in neurological symptoms with surgery and/or whole brain radiotherapy.

3.0 Histopathology and cytopathology

The Royal College of Pathologists document “Dataset for histopathological reporting of cancer of unknown primary (CUP) and malignancy of unknown origin (MUO)” 2018 sets out the pathological approach to exclusion or diagnosis of CUP/MUO using clinical context, morphology, immunohistochemistry and other techniques including molecular analysis. This is a useful document with an algorithmic approach to diagnosis including helpful tables of appropriate immunohistochemical panels that may be used for potential CUP/MUO cases.

The dataset for histopathological reporting of cancer of unknown primary (CUP) and malignancy of unknown primary origin (MUO) can be found here.

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