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UK Acute Oncology Society

Standard of Care (SoC) for Malignancy of Undefined Origin (MUO)

A UKAOS recommendations

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Purpose and Context	3
Definitions	4
• Non-Specific Symptoms (NSS) Patient	4
• Malignancy of Undefined Origin (MUO)	4
• Cancer of Unknown Primary (CUP)	4
Core Service Requirements for MUO Patients	5
• Key principles	5
• Core components of MUO service	5
• Multidisciplinary Team (MDT)	5
• MDT representation (stage -dependent)	5
• Outpatient review	6
• Consultant clinical ownership	6
• Clinical Nurse Specialist (CNS) / Advanced Practitioner (AP)	6
• Best supportive care (BSC)	6
• Clinical examination	7
• Initial assessment	7
• Investigations	7
○ Imaging	7
○ Blood tests	7
○ Additional diagnostic testing	7
Patients with a Previous History of Cancer	8
• Initial considerations	8
• Multidisciplinary review	8
• Ongoing responsibility	8
Bone and Brain Lesions	9
• Bone lesions	9
○ Initial assessment and investigation	9
○ Risk of complications	9
○ Tissue diagnosis and specialty input	9
• Brain lesions	9
○ Initial investigation and referral	9
○ Urgent escalation	9
○ Tissue diagnosis and MDT discussion	10
○ Ongoing management responsibility	10
Haematological Malignancy Considerations	11
• Initial action	11
• Transfer of responsibility	11
• Managing diagnostic uncertainty	11
Follow-up, Safety Netting, and Patient Advice	12
• Follow-up	12
• Safety netting	12
• Discharge and advice	13
Governance and Quality Assurance	14
References	15

This Standard of Care outlines the minimum requirements for identifying, investigating, managing, and following up patients with **Malignancy of Undefined Origin (MUO)**. It aims to ensure timely diagnosis, appropriate escalation, clear clinical ownership, and equitable access to specialist services.

Recognising that there is existing guidance, this SoC has been constructed by a range of experts to provide best practice clinical guidance. It builds on existing national guidelines but incorporates the lived experience of those involved in managing these patients. The intent is to supplement rather than replace existing local or national documents.

Non-Specific Symptoms (NSS) Patient

An NSS patient is an adult referred with **non-localising, persistent and/or unexplained symptoms** that may be suggestive of cancer but do not indicate a clear primary site, including (but not limited to):

- Unexplained weight loss
- Persistent fatigue
- Appetite loss
- Unexplained pain
- Abnormal blood tests (e.g. raised inflammatory markers)
- General Practitioner 'gut feeling'

These patients are managed via NSS pathways to support early diagnosis and timely exclusion of cancer.

Malignancy of Undefined Origin (MUO)

MUO usually represents an **interim diagnostic category**, not a final diagnosis often based on imaging or anatomical abnormalities of likely cancer. In some patients in whom further invasive investigations such as biopsy will not alter management, this may be a final diagnosis.

Cancer of Unknown Primary (CUP)

Confirmed CUP is a **final diagnosis** that represents a heterogeneous group of metastatic malignancies (2–5% of all cancers) where the primary site remains unidentifiable despite a standardized diagnostic workup.

Core Service Requirements for MUO Patients

Key principles

A specialised multidisciplinary approach is required to manage the 'diagnostic uncertainty' of MUO patients. A team approach is essential to reduce diagnostic delays and avoid inefficient management of patients being bounced between site-specific specialists. The primary goal is to govern a tiered diagnostic process that identifies treatable primary sites while preventing unnecessary or excessive investigation. All investigation and management decisions should be timely to meet current national timed clinical pathway standards.

All patients with MUO must have access to the following services: Malignancy of Undefined Origin (MUO)

MUO usually represents an interim diagnostic category, not a final diagnosis often based on imaging or anatomical abnormalities of likely cancer. In some patients in whom further invasive investigations such as biopsy will not alter management, this may be a final diagnosis.

Core component of MUO service

1. Primary and secondary care referral pathway
2. Key worker
3. AHP (e.g. dietetics, physiotherapy, occupational therapy, speech and language therapy, psychology)
4. Admin support, including documentation to primary care
5. Rapid Diagnostic Assessment
6. Multidisciplinary Team (MDT) input
7. Pathology and Diagnostic Support
8. Standardised Clinical Pathways
9. Patient-Centred Care
10. Timeliness and Coordination of Care

11. Transition of Care
12. Data Collection, Audit and Quality Improvement
13. Governance and Education

Multi-Disciplinary Team (MDT)

Patients should be discussed in an MDT appropriate to their stage in the diagnostic pathway where this is considered clinically necessary (e.g. MUO or CUP MDT, tumour-specific MDT, or Acute Oncology MDT).

A formal standalone MUO MDT is not mandated; local pathways may utilise existing MDT structures.

Not all patients require full MDT discussion; however, MDT review should always remain available for complex cases, diagnostic uncertainty, or where treatment and/or best supportive care decisions require multidisciplinary input.

An Advanced Practitioner or CNS should review the patient and discuss with the responsible clinical consultant to:

1. Assess fitness for further investigation and/or treatment
2. Clarify patient wishes regarding further diagnostics or treatment
3. Determine whether MDT discussion is required

At all stages, a named responsible clinician must be clearly identified.

MDT Representation (Stage-Dependent)

The MDT structure should remain flexible and proportionate to local resources while ensuring safe, coordinated, and patient-centred decision-making. MDT composition should reflect the patient's position in the pathway:

Early MUO / Diagnostic Phase (e.g. NSS/RDC or inpatient setting):

Core Service Requirements for MUO Patients

1. Physician / responsible consultant
2. Radiology
3. Acute Oncology / MUO clinical expertise
4. CNS or Advanced Practitioner

Later Stage / Confirmed CUP or Tissue Diagnosis Available:

1. Oncology
2. Radiology
3. Pathology
4. Acute Oncology / MUO clinical expertise
5. CNS / Key Worker

Palliative Care (where available) MDT outcomes should define:

- o Working diagnosis
- o Diagnostic plan
- o Interim management
- o Clinical ownership
- o Ongoing management plan/treatment plan

Outpatient Review

- Patients should be reviewed in a timely outpatient clinic (ideally within 2-4 weeks) or equivalent acute oncology setting if there is no suitable outpatient clinic.
- Review preferably should be face-to-face; virtual review should be considered according to patients' needs.
- Results, decisions, and next steps must be clearly communicated to the patients, referring clinicians and GP through appropriate clinical documentation.
- It is important to address symptoms, prognosis and advanced care planning needs as appropriate

Consultant Clinical Ownership

Each MUO patient should have a named responsible consultant (noting this person might change throughout pathway) in conjunction with AOS service input, responsible for:

- o Diagnostic coordination
- o Decision-making
- o Communication with the patient and primary care
- o Recognising and managing symptoms

Responsibility must not be ambiguous or fragmented across services

3.5 Clinical Nurse Specialist (CNS) / Advanced Practitioner (AP)

All MUO patients should be referred to appropriate MUO team, accessing a **CNS or AP** with expertise in:

4. Cancer pathways
5. Symptom management
6. Patient communication and support

CNS/AP acts as a key worker for patients and carers.

Best Supportive Care (BSC)

Early assessment of **supportive and palliative needs** is essential.

Best supportive care must run **in parallel with diagnostics**, not be delayed until diagnosis completion. Referral to Specialist Palliative Care should be considered where:

1. Prognosis is poor
2. Symptom burden is high
3. Treatment intent is uncertain or non-curative

Core Service Requirements for MUO Patients

Clinical Examination and Assessment

Initial Clinical Assessment

Offer a face-to-face assessment, guided by the patient's presenting symptoms and clinical concerns.

Perform a comprehensive physical examination, as clinically indicated. This may include:

1. Breast examination
2. Digital rectal examination (PR)
3. Pelvic examination (PV)
4. Skin examination
5. Perform urinalysis (particularly to identify microscopic haematuria).

Assess and document performance status and/or clinical frailty score.

Explore and document the patient's understanding, concerns, and expectations.

Investigations

Imaging

Arrange imaging in accordance with national and regional guidance. Imaging is essential to locate the primary tumour, define the extent of metastatic spread (staging), and guide treatment planning.

Offer:

1. Chest X-ray
2. Contrast-enhanced CT of the chest, abdomen, and pelvis as baseline imaging, unless contraindicated.
3. Consider to add CT neck in the presence of lymphadenopathy above the diaphragm

Consider targeted imaging following multidisciplinary team (MDT) discussion (for example, PET-CT or MRI), where clinically indicated.

Ensure imaging requests are coordinated by secondary care.

Ensure that interval or surveillance imaging remains the responsibility of the secondary care team and is not delegated to primary care.

Blood Tests

Offer the following investigations, guided by clinical presentation:

1. Full blood count; urea, electrolytes and creatinine; liver function tests; calcium; lactate dehydrogenase (even if previously normal)
2. PSA
3. Myeloma screen (when there are isolated or multiple lytic bone lesions)
4. Cancer antigen 125 (CA125) in women with peritoneal malignancy or ascite.
5. Alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) (particularly in the presence of midline nodal disease)
6. Urinalysis

Consider additional tumour markers and blood tests based on symptoms and distribution of disease (for example, CA19-9, CEA, CA15-3).

Additional Diagnostic Testing

Consider further investigations to identify a possible primary malignancy, where clinically indicated. For example:

1. FIT test (if iron-deficiency anaemia and/or gastrointestinal symptoms are present)
2. Biopsy and standard histological examination, with immunohistochemistry where necessary, to distinguish carcinoma from other malignant diagnoses.
3. Testicular ultrasound in men with presentation compatible with germ-cell tumours
4. Symptom-directed endoscopy (upper or lower gastrointestinal; luminal or virtual capsule as appropriate to patient's status)

Patients with a Previous History of Cancer

Initial Considerations

Ensure that a previous cancer diagnosis is clearly documented and that relevant prior records are obtained.

Ensure review of:

1. Previous histology
2. Prior imaging
3. Stage at diagnosis
4. Treatments received
5. Disease-free interval

Multidisciplinary Review

Offer urgent multidisciplinary team (MDT) discussion where there is diagnostic uncertainty regarding recurrence versus new primary malignancy.

Refer directly to the appropriate site-specific MDT where the clinical presentation and pattern of disease are typical for metastatic recurrence of a known primary cancer.

Do not routinely refer to the MUO pathway where the timing, distribution and clinical features are consistent with relapse of a previously treated malignancy, unless there are atypical features.

Refer to the MUO pathway where:

1. The pattern of disease is atypical for recurrence, or
2. Histology is discordant with the previous primary, or
3. The diagnosis remains uncertain following initial review.

Ongoing Responsibility

Ensure that patients with confirmed or clinically typical relapse are managed under the appropriate site-specific MDT.

Ensure that patients remain under the MUO pathway where diagnostic uncertainty persists or where a new primary cancer is suspected.

Bone Lesions

Initial Assessment and Investigation

Suspect malignancy in patients presenting with unexplained bone lesions, particularly where there is persistent pain, pathological fracture, or known history of cancer.

Offer urgent imaging, as clinically indicated. This may include:

- Contrast enhanced MRI (particularly if spinal involvement is suspected)
- Bone scan, where appropriate

Offer full staging with contrast-enhanced CT of the neck, chest, abdomen and pelvis (CTNTAP) if clinically appropriate, unless already performed.

Offer the following blood tests:

- PSA
- Myeloma screen (IGs, EP strip, SFLCs)

Ensure early oncology involvement in all patients with suspected malignant bone disease.

Risk of Complications

Assess immediately for risk of:

- Pathological fracture
- Metastatic spinal cord compression (MSCC)

Initiate urgent referral and management where complications are suspected. This may include:

- Same-day oncology review
- Consideration of hospital admission
- Urgent MRI (if spinal cord compression suspected)

Liaison with spinal surgery or orthopaedics where prophylactic fixation may be appropriate

Ensure Acute Oncology Team input where complications are suspected or confirmed.

Tissue Diagnosis and Specialty Input

Consider obtaining tissue diagnosis prior to radiotherapy in cases of solitary bone lesions, where subsequent biopsy yield may be reduced following treatment.

Involve Haematology urgently where a haematological malignancy is suspected, including discussion regarding the appropriateness of corticosteroids in cases of suspected MSCC.

Brain Lesions

Initial Investigation and Referral

In patients presenting with incidental brain lesions suspicious for malignancy, after benign causes have been excluded:

- Offer urgent contrast-enhanced MRI of the brain, unless contraindicated.
- Initiate immediate referral to:
 - The MUO Team, and/or
 - Neurosurgery
- Offer contrast-enhanced CT of the neck, chest, abdomen and pelvis (CTNTAP) to assess for extracranial disease if clinically appropriate.

Urgent Escalation

Assess immediately for high-risk neurological symptoms, including:

- New-onset seizures
- Features of raised intracranial pressure
- Rapidly progressive focal neurological deficit

Arrange same-day escalation and specialist assessment where high-risk symptoms are present

Tissue Diagnosis and MDT Discussion

Consider biopsy in cases of isolated brain lesions where no other sites of disease are identified, to support diagnosis and inform therapeutic options.

Refer to the Neuro-oncology MDT for guidance regarding:

- Biopsy
- Surgical resection
- Stereotactic radiosurgery, where appropriate

Ongoing Management Responsibility

Refer back to the relevant site-specific MDT where lesions are confirmed to represent metastases from a known primary malignancy.

Ensure patients remain under the appropriate diagnostic MUO pathway where the primary site is unknown or diagnostic uncertainty persists.

Haematological Malignancy Considerations

Initial Action

Suspect a haematological malignancy where imaging, blood results, or clinical features are suggestive (for example unexplained lymphadenopathy, cytopenias, paraproteinaemia, or lytic bone disease).

Offer urgent referral to Haematology where a haematological malignancy is suspected.

Ensure that MUO pathways do not delay haematology-specific diagnostic investigations, including bone marrow biopsy, specialist blood testing, or haematology-directed imaging.

Transfer of Responsibility

Ensure ongoing clinical responsibility transfers to Haematology once referral has been accepted and it is agreed that a haematological malignancy is the most likely diagnosis.

Ensure clear documentation of handover, including named responsible consultant and agreed diagnostic plan.

Managing Diagnostic Uncertainty

Discuss at MUO/CUP MDT where there is diagnostic uncertainty between solid organ malignancy and haematological malignancy.

Agree the most appropriate lead specialty based on the predominant clinical, radiological, and laboratory findings.

Avoid duplicate or parallel pathways unless clinically justified.

Follow-up, Safety Netting, and Patient Advice

Follow-up

Ensure that a follow-up plan is documented for all patients under the MUO pathway.

Ensure that follow-up plans are:

- Clearly documented in the clinical record
- Time-bound, with defined review dates or investigation timelines
- Communicated to the patient verbally and confirmed in writing
- Communicated in writing to the patient's GP

Ensure that no patient on the MUO pathway is lost to follow-up during the diagnostic evaluation phase.

Safety Netting

Provide all patients with clear safety-netting information. This must include:

- Named contact details (for example CNS, Advanced Practitioner, or service contact)
- Clear written instructions on when and how to seek urgent or routine advice (in and out of normal working hours)

Ensure that responsibility for safety-netting remains with secondary care until formal discharge from the MUO pathway.

Discharge and Advice

Diagnostic Outcomes

Following investigation, patients on the MUO pathway may fall into one of the following categories:

- **Site-specific malignancy identified**

- Ensure referral to the appropriate site-specific MDT.

- Ensure ongoing management transfers to the relevant specialty team.

- **Non-malignant diagnosis identified**

- Ensure appropriate referral or discharge in line with the confirmed diagnosis.
- Communicate findings clearly to the patient and GP.

- **MUO with poor performance status or in line with patient wishes**

- Consider early palliative care involvement, including use of the Gold Standards Framework in primary care to support anticipatory care planning and coordination.
- Ensure management aligns with the patient's goals of care.
- Avoid unnecessary further investigation where it will not alter management.

- **Cancer of Unknown Primary (CUP)**

- Refer to the CUP MDT where metastatic malignancy is confirmed and no primary site is identified following appropriate investigation.
- Ensure ongoing management follows CUP pathway guidance (eg. Referral to palliative care team)

- **Not defined malignancy identified**

Patients with suspected malignancy that has not been definitively diagnosed (e.g., lymphadenopathy or bone lesions) may fall into a group where the disease site is not accessible for biopsy, or where prior biopsy has shown no evidence of malignancy despite ongoing radiological concern. In such cases, follow-up imaging

Follow-up, Safety Netting, and Patient Advice

should be considered, with the intention of performing a biopsy if there is evidence of disease progression.

Discharge to Primary Care

- **Discharge to Primary Care only when:**
 - Malignancy has been excluded, or
 - A clear management plan is established and is appropriate for GP-led oversight.

- **Ensure discharge communication includes:**
 - A summary of investigations performed
 - The confirmed diagnosis or working diagnosis
 - Clear advice regarding re-referral triggers
 - Outstanding actions (if any) and responsible clinician

Governance and Quality Assurance

Ensure all MUO cases are recorded in recognised clinical systems and are auditable.
Monitor compliance with the Faster Diagnosis Standard (FDS).

Undertake regular review of MUO outcomes, including conversion rates, time to diagnosis, and discharge patterns, to inform:

- o Pathway improvement
- o Service planning
- o Education and training

Ensure all patients referred with suspected MUO are managed under the Urgent Suspected Cancer pathway.

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