Optimal care pathway for people with cancer of unknown primary

Specific cancer of unknown primary (CUP) subsets have been identified based on histopathological and clinical manifestations. Patients in the specific CUP subset have a favourable prognosis and pattern of disease similar to known cancer types, while the remaining patients are considered within the non-specific subset of CUP.

Step 1: Prevention and early detection

**Risk factors:** As the primary cancer site is not known for people with CUP, it is difficult to identify risk factors. General cancer risk factors include increasing age, male gender, family history, smoking, alcohol, excess body fat, inadequate physical activity, lower socioeconomic status, Aboriginal and Torres Strait Islander people and infrequent GP consultations.

**Prevention:** The causes of CUP are not fully understood, and there is currently no clear prevention strategy.

Step 2: Presentation, initial investigations and referral

Early recognition of CUP is important so that specialist assessment and management is not delayed and futile investigations are avoided.

**Signs and symptoms:** Patients often present to their general or primary medical practitioner with heterogeneous, non-specific symptoms and abnormal test results demonstrating very likely metastatic malignancy but without a clear primary site.

**General/primary practitioner investigations:**
- A thorough medical history and physical examination
- Routine blood tests
- A CT of the chest and abdomen/pelvis
- A biopsy
- Additional investigations as indicated based on the specific presentation.

Patients with CUP may present with poorly controlled symptoms. Symptomatic care must be provided in parallel with the investigation process.

**Referral:** Patients with a disease pattern suggesting a specific CUP subset should be referred to a relevant disease-specific oncology team. Patients with non-specific CUP should be referred to an oncologist with adequate experience in managing acute patients with CUP or a general medical oncology service. The specialist appointment should take place within two weeks of the initial GP referral.

**Communication – lead clinician**
- GPs play an important role in coordinating care for patients with CUP, including assisting with side effects and offering support.
- Provide the patient with information that clearly describes their referral details.

Step 3: Diagnosis, staging and treatment planning

**Diagnosis:** After a thorough medical history and examination, diagnostic workup for patients with metastatic disease should include all of the following investigations to confirm a diagnosis of CUP:
- Basic blood and biochemical analyses
- Contrast-enhanced CT
- Adequate tissue sample from one site of disease for histopathology and immunohistochemistry.

Additional investigations should be carried out for identified CUP subsets.

Investigations should be completed within two weeks of specialist review.

**Staging:** There is no definitive staging classification used for patients with CUP; however, disease can be classified as localized or disseminated disease.

**Treatment planning:** Patients in the specific-CUP subset should be discussed at the multidisciplinary team meetings of the most closely related tumour stream. Patients in the non-specific CUP subset should be referred to a CUP-specific oncology service or the general medical oncology service.

**Research and clinical trials:** Consider enrolment where available and appropriate.

**Communication**
- The lead clinician should:
  - Discuss a timeframe for diagnosis and treatment with the patient/carer
  - Provide appropriate information or refer to support services as required.

1 Lead clinician – the clinician who is responsible for managing patient care.

The lead clinician may change over time depending on the stage of the care pathway and where care is being provided.
Step 4
Treatment: Establish intent of treatment:
• curative
• anti-cancer therapy to improve quality of life and/or longevity without expectation of cure
• symptom palliation.

Step 5
Care after initial treatment and recovery
Treatment options: Treatment should be individualised according to the clinicopathological subset and the suspected primary site. Patients in the specific-CUP subset who have good-prognosis CUP should be treated the same as patients with equivalent known primary tumours with metastatic disease. For patients with a non-specific subset of CUP, but who have a favourable prognosis, a two-drug chemotherapy regimen should be considered. CUP patients identified in the poor-prognosis non-specific group can be considered for treatment with low-toxicity, palliative, chemotherapy regimens and/or best supportive care.

Step 6
Managing recurrent or progressive disease
With the low rates of curable CUP and the majority of patients palliated, it is likely that their current symptoms will worsen progressively, and this should be managed following discussions with palliative care specialists. The supportive care needs, palliative care referral, increased support within the community and GP involvement of these patients are particularly important and should be reassessed.

Step 7
End-of-life care
Palliative care: Palliative care interventions should be considered for all patients diagnosed with CUP. Ensure that an advance care plan is in place.

Communication – The lead clinician should:
• be open about the prognosis and discuss palliative care options with the patient/carer
• initiate specialist palliative care during the diagnostic stage
• establish transition plans to ensure the patient’s needs and goals are addressed in the appropriate environment.

Follow-up care
There is no evidence that follow-up investigations of asymptomatic patients with non-specific CUP affects the outcome. Patients in the specific-CUP subgroup should be followed up as per disease-specific guidelines. Specific examinations should be undertaken as clinically indicated.

Communication
The lead clinician should ensure regular, timely, two-way communication with the patient’s GP because GPs play an important role in coordinating care for patients with CUP.