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Metastatic Cancer of Unknown Primary: Workup

Effective Date: April 2024

Cancer Care Alberta

Clinical Practice Guideline SPEC-001 – Version 1
www.ahs.ca/guru

Background

Cancer of unknown primary (CUP) is defined as a heterogeneous group of tumours that present initially with metastasis, and in which a properly standardized diagnostic work-up cannot identify the original site of the malignancy[1, 2]. It accounts for 2-9% of cancer diagnoses, is the eighth most frequent cancer diagnosis, and occurs most commonly between the ages of 60 and 75 years[2-4]. A review of 884 CUP patients in 12 autopsy studies reported that the most common underlying occult primary tumours are of lung, pancreas, and hepatobiliary tree origin[5]. The prognosis is favourable in only 15-20% of cases where tumours are more chemosensitive; favourable prognosis is associated with poorly differentiated midline carcinomas, peritoneal papillary adenocarcinomas in women, metastatic adenocarcinoma involving the axillary lymph nodes only, metastatic squamous cell carcinoma in the cervical lymph nodes, single-node metastases, poorly differentiated neuroendocrine carcinoma, resectable tumours, and germ cell tumours[6, 7]. The remainder have a poor prognosis with a median survival of only approximately 4 months. This larger latter group includes most of those who present with either an impaired performance status or elevated serum LDH level[6, 7]. Aggressive treatments for these poor prognosis patients usually result in more harm than benefit. Therefore, the initial clinical assessment of patients should be directed only at identifying the extent of the disease and tumour subtypes in which a specific therapy may improve the patient's symptoms and prognosis.

Guideline Questions

1. What is the recommended diagnostic evaluation strategy for patients who may have cancer of unknown primary?
2. What is the recommended strategy for tumour biopsy and pathological evaluation for patients who may have cancer of unknown primary?

Search Strategy

The PubMed and TRIP Medical databases were searched from January 2012 to August 2021 with a combination of the following search terms: cancer of unknown primary, unknown primary cancer, PRUNK cancer, diagnosis, diagnosis pathway, diagnosis protocol, and diagnosis guidelines, resulting in 63 citations. In addition, two searches conducted by the Alberta Health Services Knowledge Resource Service (KRS) addressing "colonoscopy and gastroscopy for unknown primary cancer" and "cancer of unknown primary diagnosis delays compared to other cancer types" yielded an additional 19 citations. A total of 16 citations were deemed relevant after inclusion/exclusion criteria were applied, and the overall strength of the evidence was evaluated against the Evidence-Based Medicine Pyramid of Evidence and the Mixed Methods Appraisal Tool, modified to include the CASP Checklist for Systematic Reviews. Online resources from oncology-based health organizations and guideline developers were also systematically searched, and 6 relevant guidelines and pathways were considered in the development of our recommendations. Evidence tables are available upon request.

Target Population

The following recommendations apply to adult patients with suspected metastatic cancer of unknown primary.

Recommendations

The following recommendations are based on low levels of evidence (Level III, IV, or V) since it is not feasible or ethical to conduct randomized clinical trials in this patient population. The recommendations below are all strongly recommended (Level A) unless otherwise stated.

Evaluation of Patients with Metastatic Cancer of Unknown Primary

1. It is imperative that the decision-making process regarding diagnostic test and treatment be done in discussion with and collaboratively with the patient and, if they choose, those close to them. It is not a single discussion; patient goals and priorities for care may need to be revisited throughout the diagnostic and treatment process, and then only perform investigations if[8, 9]:
    a) The patient or their proxy understands the potential benefits and risks of investigations and is prepared to accept treatment
    b) The patient or their proxy understands why the investigations are being carried out
    c) The benefits for treatment would outweigh the risks, and treatment is consistent with patient goals and values
    d) The results are likely to affect a curative or palliative oncologic treatment (explain to patient and caregivers if further investigation will not alter treatment options) or other supportive care decisions that would impact the person's quality of life

First Diagnostic Phase Evaluation

2. The aim of this phase is to perform the most appropriate investigations efficiently to identify one of the following[8]:
    a) an easily identifiable primary site
    b) non-epithelial malignancy, which can be treated regardless of the primary site (e.g., lymphoma, myeloma, other hematological malignancies, melanoma, sarcoma, and germ-cell tumours)
    c) metastatic epithelial or neuro-endocrine malignancy without an identifiable site (CUP).

3. The medical history should include special attention to previous cancers, biopsies or removed lesions, spontaneously regressing lesions, previous imaging tests, tobacco smoking, alcohol consumption, and family cancer history[4, 7].

4. The physical examination should include examination of the skin (for lesions consistent with melanoma), head and neck region, lymph nodes (for lymphoma or accessible sites for biopsy), genitourinary with attention to prostate exam, rectal exam, breast, and pelvic examination[4, 7].

5. Routine laboratory tests include complete blood count with differential white cell count, electrolytes, creatinine, albumin, calcium, liver function tests, LDH, and basic urinalysis. Also consider serum protein electrophoresis (myeloma screen) for patients with lytic bone lesions and no obvious primary[6, 7].

6. Serum tumour markers should not be tested routinely, except in the following cases[1, 6].
    a) Men with bone metastases: prostate-specific antigen (PSA)
    b) Men with midline disease/brain metastases: serum alpha-fetoprotein (AFP) and human chorionic gonadotrophin (β-HCG; presentations compatible with germ-cell tumours)
    c) Patients with liver only disease: AFP

7. Diagnostic imaging studies should include a contrast-enhanced CT scan of the chest, abdomen, and pelvis in all patients. If there are cervical lymphadenopathies, this should be accompanied by a CT scan of the neck[4, 6, 7].

8. Patterns of disease requiring URGENT specific action include[1, 8, 10]:
    a) Spinal cord compression requires urgent hospitalization and referral to neurosurgery
    b) Superior vena cava obstruction requires urgent hospitalization and referral to thoracic surgery
    c) Brain metastasis, if associated with confusion/seizures/loss of consciousness – requires urgent hospitalization and referral to neurosurgery/RO

9. Consider a different cancer diagnosis pathway that may be more appropriate:
    a) Lymphoma Diagnosis Program for patients presenting with multiple enlarged nodal masses
    Lymph Node Assessment Primary Care Pathway (albertahealthservices.ca)
    b) Head & Neck Cancer Diagnosis Pathway for patients presenting with oral lesions or isolated cervical nodes
    Provincial Head & Neck Cancer Diagnosis & Referral Pathway (albertahealthservices.ca)

Tumour Biopsy and Pathological Evaluation

In addition to the above clinical assessment and basic testing, the most important step in evaluating potential CUP patients is to obtain an adequate biopsy for pathological evaluation. The sample should be obtained using a procedure that provides as much tissue as possible but is not highly invasive for the patient.[4] The following recommendations are for samples obtained during an interventional radiology (IR) procedure. There may be circumstances where IR is not feasible due to location and can be referred to another service (i.e., Endoscopic Ultrasound or Surgery). The limitation of this would be smaller gauge core needles (19-21) which may result in less tissue for pathological evaluation.

10. Core needle biopsy is recommended over fine needle aspirate to ensure enough tissue is procured[6]. Core biopsy recommendations include[9]:
    a) Needle gauge: 14 (preferred) to 16 (use the largest needle that can be performed safely in order to obtain largest amount of tissue possible)
    b) Biopsy size: Recommended minimum total sample length of 3 cm (3 x 1cm biopsy cores)

11. There is no standard recommended immunohistochemistry panel as cases vary clinically; the NCCN guidelines have helpful information for pathologists.

12. If the primary site cannot be identified using histological and immunochemistry, and the oncologist has access to specific targeted therapies, discuss with pathologist about identifying specific actionable targets, including[7]:
    a) MMR immunochemistry to identify MMR-deficient tumours
    b) Immunohistochemistry, FISH or NGS to assess mutations with available targeted therapies

13. The entire specimen should be put directly into formalin and sent to the lab. Deliver as soon as possible to the Anatomical Pathology lab along with the Anatomical Pathology Requisition (for sites not live on EPIC). For sites live on EPIC, order surgical pathology through EPIC and then deliver as soon as possible to the Anatomical Pathology lab.

Targeted Second Phase Investigation

14. It is important to provide appropriate information about CUP, potential treatment and palliative care options, emotional and psychological support, while engaging in discussion with the patient and/or their proxy about their goals and priorities of care, and then only perform investigations if[9, 11]:
    a) The benefits for treatment would outweigh the risks, and treatment is consistent with patient goals and values
    b) The results are likely to affect a curative or palliative oncologic treatment (explain to patient and caregivers if further investigation will not alter treatment options) or other supportive care decisions that would impact the person's quality of life
    c) The patient or their proxy understands why the investigations are being carried out
    d) The patient or their proxy understands the potential benefits and risks of investigations and treatment and is prepared to accept treatment

15. Endoscopy should not be routinely employed, because it rarely detects the primary tumour in asymptomatic patients, and false positive results can cause confusion. Gastroscopy or colonoscopy should be considered only if suspicion of abdominal symptoms exist, the patient has blood in their stool, imaging is suggestive of a tumour present in the GI tract, or a tumour biopsy revealed a suspicious immunohistochemistry result[2, 4, 6].

16. Other diagnostic procedures should be based on clinical assessment and interpretation of the histological sample obtained by biopsy, including[6]:
    - PET: recommended only for patients with single metastases
    - Refer to Head & Neck cancer diagnosis pathway for patients with cervical lymphadenopathies due to squamous cell carcinoma or cervical lymph node involvement
    - Mammography: in women with adenocarcinoma
    - Refer to breast tumour team: if adenocarcinoma with negative mammogram and metastasis to unilateral axillary lymph nodes for further investigation and treatment options
    - Bronchoscopy: in case of radiological findings such as hilar or mediastinal lymph node involvement, and pulmonary symptoms
    - Testicular ultrasound: men with retroperitoneal or mediastinal mass presentations compatible with germ-cell tumors
    - Gynecological ultrasound: if pelvic or peritoneal metastases CK7+ on the biopsy tissue
    - Octreotide scan and plasma chromogranin A level or PET CT Ga 68 Dotatate: if neuroendocrine tumour CUP

Favourable and Unfavourable Prognosis Subgroups

17. Prognostically favourable subgroups for surgical intervention include[2, 12]:
    - Peritoneal carcinomatosis of a papillary adenocarcinoma in women: median 15-42 month survival
    - Axillary lymph node metastasis of adenocarcinoma in women: 72% 5-year survival
    - Cervical lymph node metastasis of squamous cell: 40-60% 5-year survival
    - Inguinal lymph node metastasis: 37.5% 5-year survival

Patterns of Disease Requiring Specific Action

18. Patterns of disease that require specific action include[7, 8]:
    a) Men with bone metastases and elevated PSA – referral to GU medical oncologist
    b) Women with axillary nodes – referral to breast surgeon and medical oncologist
    c) Women with peritoneal disease – referral to gynecological oncologist, unless histology suggests non-gynecology origin
    d) Solitary liver lesion – referral to hepatobiliary surgeon
    e) Squamous cell carcinoma of neck nodes – referral to head and neck (ENT) surgeon/ tumour group
    f) Isolated brain metastasis – referral to neurosurgery / radiation oncology

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Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Health Services Cancer Strategic Clinical Network (SCN), external participants identified by the Working Group Lead, and methodologists from the Cancer SCN and the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial Tumour Teams who were not involved in the guideline's development, including surgical oncologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2024.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2028. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AFP, alpha-feto protein; β-HCG, serum chorionic gonadotropin; CUP, cancer of unknown primary; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence in situ hybridization; IR, interventional radiology; KRS, knowledge resource service; LDH, lactate dehydrogenase; MMR, mismatch repair; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NGS, next generation sequencing; PET, positron emission tomography; PSA, prostate specific antigen; RO, radiation oncologist.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Tumour Teams and the Alberta Health Services Cancer Strategic Clinical Network (SCN) and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Funding Source

Financial support for the development of Cancer Care Alberta's evidence-based clinical practice guidelines and supporting materials comes from the Cancer Care Alberta operating budget; no outside commercial funding was received to support the development of this document.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the *Outpatient Cancer Drug Benefit Program Master List*.

Conflict of Interest Statements

Shelly Allenby has nothing to disclose.

Xanthoula Kostaras has nothing to disclose.

Dr. Douglas Stewart* reports: grants or contracts from Alberta Health, Alberta Health Services and the Canadian Partnership Against Cancer Corp; consulting fees from Hoffmann LaRoche, SeaGen Canada, Novartis, Gilead, AbbVie and Exact Sciences Canada outside the submitted work.

Rachel Vanderploeg has nothing to disclose.

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Citation

Allenby S, Kostaras X, Stewart D (lead), Vanderploeg R. Cancer Care Alberta, Alberta Health Services (2024). Clinical Practice Guideline on Metastatic Cancer of Unknown Primary: Workup. Accessed [Month, Year]. Available from: www.ahs.ca/guru