

Evidence Discussion – Carcinoma of Unknown Primary Site (ONC-31.7)

Carcinoma of unknown primary site (CUP) is defined as carcinoma found in a lymph node or in an organ known not to be the primary for that cell type (e.g., adenocarcinoma arising in the brain or in a neck lymph node). This guideline also applies to a pathologic fracture that is clearly due to metastatic neoplastic disease in an individual without a previous cancer history.

Individuals with suspected unknown primary based on only suspicious lytic bone lesions should be considered for serum protein electrophoresis (SPEP); urine protein electrophoresis (UPEP) and serum free light chains prior to consideration of extensive imaging.

CUP generally occurs in older adults, the majority 6-75 years, and accounts for 2-9% of all tumors. Median survival is poor, at 3-10 months. 20% of patients fall into a more favorable risk group with median survival >1 year, and imaging may help identify this group (Kramer 2022, Stevenson 2024). The primary step in workup of CUP, before advanced imaging, is a detailed history and physical examination including pelvic and rectal exams and laboratory tests, including basic CBC/Chemistries/LFTS but also tumor markers, immunohistochemistry, and PSA (for men over 40). Endoscopy should also be considered if pathology suggests a GI primary. CT of the chest, abdomen and pelvis with contrast is supported for all individuals where primary site is not suggested on physical and lab evaluation, in alignment with NCCN and the European Society of Medical Oncology (ESMO) (Stevenson 2024, Kramer 2022). CT neck may be included if cervical or supraclavicular involvement, as well as CT or MRI for other symptomatic sites or abnormal sites on physical, with the choice of modality driven by body site of interest. If the site of carcinoma is a bone lesion that is not consistent with multiple myeloma, a bone scan should be added to the workup. Morphology on bone scan can help determine the primary site, where lytic lesions are most suggestive of myeloma, renal cell, GI and melanoma, and blastic lesions most commonly occur with prostate cancer and GI carcinoid. Other morphologic features such as location and expansile nature can also help guide workup and treatment toward a particular primary site. (Piccioli 2015). PET/CT has not been shown to be superior to bone scan for this purpose, and in fact may be less sensitive than bone scan for lesions <1cm (Piccioli 2015, Stevenson 2024).

It is essential that female patients have a diagnostic (not screening), mammogram and full pelvic exam. If pathology is consistent with breast cancer from axillary node or other metastatic site, but mammogram is inconclusive, a bilateral breast MRI with and without contrast is supported, as MRI may identify the breast as the primary site in approximately half of the patients presenting with axillary adenocarcinoma metastases (Buchanan 2005, Stevenson 2024). If a primary site is still not found, CT neck, chest, abdomen and pelvis are supported.

EviCore guidelines align with the NCCN and support PET-CT can be used as a problem-solving tool to look for a primary site of disease when the studies described above still do not reveal a primary site (Stevenson 2024). PET is of intermediate specificity in this setting and large randomized trials are lacking (Stevenson 2024). A meta-analysis on the use of PET/CT in patients with CUP found that primary tumors were detected in 37% of 433 patients across 11 studies, with pooled sensitivity and specificity of 84% (Kwee 2009, Stevenson 2024). In addition, if CT scans reveal oligometastatic disease and definitive curative therapy is planned, the

absence of other sites of disease may be confirmed with PET-CT to prevent over- or under-treatment (Kramer 2022, Stevenson 2024).

Subsequent imaging and surveillance should follow the eviCore guideline for each primary site, once a likely primary has been established. EviCore guidelines align with the NCCN, which states follow-up should be with history and physical with subsequent diagnostic testing based on symptoms. In 20-50% of patients, the primary site remains unidentified even after postmortem examination, thus continued imaging is low-yield and may contribute to the significant distress associated with the uncertainty of this condition (Kramer 2022, Stevenson 2024). There is no data-driven algorithm for imaging surveillance when the primary site of disease remains undiscovered (Stevenson 2024).

References

1. Stevenson MM, Kohutek Z, Phay J . Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Occult Primary (Cancer of Unknown Primary [CUP] Version 2.2024-April 29,2024. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) . All rights reserved. Accessed [June 13,2024]. To view the most recent and complete version of the guideline, go online to NCCN.org
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