120e Carcinoma of Unknown Primary

Gauri R. Varadhachary, James L. Abbruzzese

Carcinoma of unknown primary (CUP) is a biopsy-proven malignancy for which the anatomic site of origin remains unidentified after an intensive search. CUP is one of the 10 most frequently diagnosed cancers worldwide, accounting for 3–5% of all cancers. Most investigators limit CUP to epithelial cancers and do not include lymphomas, metastatic melanomas, and metastatic sarcomas because these cancers have specific histology- and stage-based treatments that guide management.

The emergence of sophisticated imaging, robust immunohistochemistry (IHC), and genomic and proteomic tools has challenged the "unknown" designation. Additionally, effective targeted therapies in several cancers have moved the paradigm from empiricism to considering a personalized approach to CUP management. The reasons cancers present as CUP remain unclear. One hypothesis is that the primary tumor either regresses after seeding the metastasis or remains so small that it is not detected. It is possible that CUP falls on the continuum of cancer presentation where the primary has been contained or eliminated by the natural body defenses. Alternatively, CUP may represent a specific malignant event that results in an increase in metastatic spread or survival relative to the primary. Whether the CUP metastases truly define a clone that is genetically and phenotypically unique to this diagnosis remains to be determined.

CUP BIOLOGY

Studies looking for unique signature abnormalities in CUP tumors have not been positive. Abnormalities in chromosomes 1 and 12 and other complex cytogenetic abnormalities have been reported. Aneuploidy has been described in 70% of CUP patients with metastatic adenocarcinoma or undifferentiated carcinoma. The overexpression of various genes, including *Ras*, *bcl-2* (40%), *her-2* (11%), and *p53* (26–53%), has been studied in CUP samples, but they have no effect on response to therapy or survival. The extent of angiogenesis in CUP relative to that in metastases from known primaries has also been evaluated, but no consistent findings have emerged. Using the Sequenom (SQM) Massarray platform, a study in consecutive CUP patients showed that the overall mutational rate was surprisingly low (18%). No "new" low-frequency mutations were found using a panel of mutations involving the P13K/AKT pathway, MEK pathway, receptors, and downstream effectors. Nevertheless, it is possible that newer "deep sequencing" techniques in select patients may yield consistent abnormalities.

CLINICAL EVALUATION

Initial CUP evaluation has two goals: search for the primary tumor based on pathologic evaluation of the metastases and determine the extent of disease. Obtaining a thorough medical history from CUP patients is essential, including paying particular attention to previous surgeries, removed lesions, and family medical history to assess potential hereditary cancers. Adequate physical examination, including a digital rectal examination in men and breast and pelvic examinations in women, should be performed based on clinical presentation.

Role of Serum Tumor Markers and Cytogenetics Most tumor markers, including CEA, CA-125, CA 19-9, and CA 15-3, when elevated, are nonspecific and not helpful in determining the primary tumor site. Men who present with adenocarcinoma and osteoblastic metastasis should undergo a prostate-specific antigen (PSA) test. In patients with undifferentiated or poorly differentiated carcinoma (especially with a midline tumor), elevated β-human chorionic gonadotropin (β-hCG) and α fetoprotein (AFP) levels suggest the possibility of an extragonadal germ cell (testicular) tumor. With the availability of IHC, cytogenetic studies are rarely needed.

Role of Imaging Studies In the absence of contraindications, a baseline IV contrast computed tomography (CT) scan of the chest, abdomen, and pelvis is the standard of care. This helps to search for the primary tumor, evaluate the extent of disease, and select the most accessible biopsy site. Older studies suggested that the primary tumor site is detected in 20–35% of patients who undergo a CT scan of the abdomen and pelvis, although by current definition, these patients do not have CUP. These studies also suggest a latent primary tumor prevalence of 20%; with more sophisticated imaging, this has decreased to ≤5% today.

Mammography should be performed in all women who present with metastatic adenocarcinoma, especially in those with adenocarcinoma and isolated axillary lymphadenopathy. Magnetic resonance imaging (MRI) of the breast is a follow-up modality in patients with axillary adenopathy and suspected occult primary breast carcinoma following a negative mammography and ultrasound. The results of these imaging modalities can influence surgical management; a negative breast MRI result predicts a low tumor yield at mastectomy.

A conventional workup for a squamous cell carcinoma and cervical CUP (neck lymphadenopathy with no known primary tumor) includes a CT scan or MRI and invasive studies, including indirect and direct laryngoscopy, bronchoscopy, and upper endoscopy. Ipsilateral (or bilateral) staging tonsillectomy has been recommended for these patients. 18-Fluorodeoxyglucose positron emission tomography (18-FDG-PET) scans are useful in this patient population and may help guide the biopsy; determine the extent of disease; facilitate the appropriate treatment, including planning radiation fields; and help with disease surveillance. A smaller radiation field encompassing the primary (when found) and metastatic adenopathy decreases the risk of chronic xerostomia. Several studies have evaluated the utility of PET in patients with squamous cervical CUP, and head and neck primary tumors were identified in ~21–30%.

The diagnostic contribution of PET to the evaluation of other CUP (outside of the neck adenopathy indication) remains controversial and is not routinely recommended. PET-CT can be helpful for patients who are candidates for surgical intervention for solitary metastatic disease because the presence of disease outside the primary site may affect surgical planning.

Invasive studies, including upper endoscopy, colonoscopy, and bronchoscopy, should be limited to symptomatic patients or those with laboratory, imaging, or pathologic abnormalities that suggest that these techniques will result in a high yield in finding a primary cancer.

Role of Pathologic Studies A detailed pathologic examination of the most accessible biopsied tissue specimen is mandatory in CUP patients. Pathologic evaluation typically consists of hematoxylin and eosin stains and immunohistochemical tests.

LIGHT MICROSCOPY EVALUATION Adequate tissue obtained preferably by excisional biopsy or core-needle biopsy (instead of only a fine-needle aspiration) is stained with hematoxylin and eosin and subjected to light microscopic examination. On light microscopy, 60–65% of CUP is adenocarcinoma, and 5% is squamous cell carcinoma. The remaining 30–35% is poorly differentiated adenocarcinoma, poorly differentiated carcinoma, or poorly differentiated neoplasm. A small percentage of lesions are diagnosed as neuroendocrine cancers (2%), mixed tumors (adenosquamous or sarcomatoid carcinomas), or undifferentiated neoplasms (Table 120e-1).

TABLE 120e-1 MAJOR HISTOLOGIES IN CARCINOMA OF UNKNOWN PRIMARY

Histology	Proportion, %
Well to moderately differentiated adenocarcinoma	60
Squamous cell cancer	5
Poorly differentiated adenocarcinoma, poorly differentiated carcinoma	30
Neuroendocrine	2
Undifferentiated malignancy	3