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Cancers of Unknown Primary

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Et al.

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Summary and Key Points

1. Multi-disciplinary team involvement is essential to the care of patients with Cancers of Unknown Primary (CUP).
2. Most presentations of CUP have a poor prognosis, with median survival of 6-9 months.
3. Similarly, axillary nodal metastasis pathologically consistent with breast cancer and undifferentiated carcinoma in the midline of the thorax in young males have a far better prognosis and are each managed differently with curative intent.

Introduction

Cancers of unknown primary (CUP) are a heterogeneous group of histologically proven metastatic tumors whose primary site can't be determined after a standard diagnostic and pathologic work-up. CUP accounted for 2% of all cancers diagnosed in the United States in 2009 (estimated 31,490 cases).[1] CUP occurs equally in men and women, most frequently in the sixth decade of life. Even with thorough investigation, a primary tumor is found in fewer than 30% of patients who initially present with CUP.[2]

CUP can manifest with an unlimited variety of clinical presentations and have a poor prognosis in most patients. The median survival is 6-9 months.[3] Multiple sites of involvement are observed in more than 50% of patients. The most common sites of involvement include the liver, lungs, bones, and lymph nodes. Although patterns of metastases can suggest clues as to the primary tumor, CUP can metastasize to any site in the body, making the pattern of metastasis alone insufficient to determine the origin. Like most cancers, CUP possesses both favorable and unfavorable prognostic factors (Table 1).[4] For these reasons, a thorough clinical and pathologic evaluation is essential for helping people diagnosed with CUP.

Table 1. Prognostic Factors in Cancers of Unknown Primary

Favorable	
1.	Poorly differentiated carcinoma with midline distribution
2.	Women with papillary adenocarcinoma of the peritoneal cavity
3.	Women with adenocarcinoma only involving axillary lymph nodes
4.	Squamous cell carcinoma involving only cervical or inguinal lymph nodes
5.	Poorly differentiated neuroendocrine tumors
6.	Men with blastic bone metastases and elevated prostate-specific antigen (PSA)
7.	Single, small resectable tumors
Unfavorable	
1.	Male gender
2.	Adenocarcinoma with multivisceral metastases
3.	Non-papillary malignant ascites
4.	Multiple cerebral metastases
5.	Adenocarcinoma with multiple pulmonary or bony metastases

Initial Evaluation

As noted above, CUP is defined by the inability to determine a primary tumor site despite a standard diagnostic and pathologic evaluation. While different clinicians may select different approaches to any individual patient, this section and the following section on the pathologic evaluation of CUP are reasonable examples of standard evaluations.

Initial evaluation of a patient with suspected metastatic cancer involves a complete history and physical examination, including breast, genitourinary, pelvic and rectal examination. Special attention should also be paid to both the individual and family cancer history.

All past biopsies, removed lesions or spontaneously regressing lesions should be reviewed, as should any previous imaging studies. Other important diagnostic tests include laboratory studies (complete blood count, electrolytes, liver function tests, creatinine, calcium and urinalysis); computed tomography (CT) scan of the chest, abdomen and pelvis; and heme-occult stool testing. Endoscopy should be employed as directed by clinical signs and symptoms or other diagnostic findings. Determining whether the malignancy is localized or disseminated is also important for treatment planning. Positron emission tomography (PET) and/or PET-CT scan is frequently used for this aspect of evaluating patients with metastatic disease.

Biopsy is necessary to confirm the presence of malignancy. Core needle biopsy is the preferred method of biopsy, although fine needle aspiration or incisional biopsy, by an experienced surgical oncologist, are also options. Biopsy of the most easily attainable lesion is usually performed. A pathologist should be involved at the time of biopsy to confirm the adequacy of the specimen or to determine the need for more tissue if a biopsy was performed prior to presentation to the oncologist.

Extensive pathologic analysis of the tumor is required to determine the site of the primary tumor. This type of evaluation will identify a primary site in about 30% of patients. Light microscopic examination is usually done first. CUP can be classified into four major subtypes following routine light microscopic evaluation:

I. Well or moderately differentiated adenocarcinoma (60%)
II. Poorly- or undifferentiated adenocarcinoma (30%)
III. Squamous cell carcinoma (5%)
IV. Poorly differentiated malignant neoplasm (5%).[5]

Immunohistochemical (IHC) studies are used to help characterize the poorly- and un- differentiated tumors. For example, carcinomas are usually positive for the anti-cytokeratin antibody CAM5.2 and endomysial antibody (EMA), whereas melanoma is positive for S-100, and lymphomas and leukemias are positive for leucocyte common antigen (LCA). In addition, IHC studies are useful for the pathologic diagnosis of the occult primary tumor. For example, the low molecular weight cytokeratins CK7 and CK20 are the two most common immunostains used to define subsets of carcinomas. CK7 is usually found in tumors of the lung, ovary, endometrium and breast, whereas CK20 is found in lower gastrointestinal, urothelial and Merkel cell carcinomas.[6] Combining the two immunostains can further narrow the differential diagnosis (Table 2).

Table 2. Immunohistochemical Markers for Cell Differentiation and Diagnosis of Occult Primary Tumors

Marker	Association
CAM 5.2	Carcinoma cell differentiation
Endomysial antibody (EMA)	Carcinoma cell differentiation
S-100	Melanoma
Leukocyte common antigen (LCA)	Lymphoma, leukemia
Placental alkaline phosphastase (PLAP)	Seminoma
Cytokeratin 7	Lung, ovary, endometrium, breast, biliary tract, pancreas
Cytokeratin 20	Lower gastrointestinal tract, urothelium
CDX2	Colon, duodenum
Thyroid transcription factor (TTF)	Lung, thyroid
Thryoglobulin	Thyroid (papillary and follicular)
Gross cystic disease fibrous protein-15 (GCDFP-15)	Breast
Uroplakin III	Urothelial
WT1	Epithelioid mesothelioma, serous ovarian carcinoma

Recently, gene expression profiling (GEP) has been used to identify metastatic carcinoma tissue of origin in patients with CUP. Both microarray and reverse transcriptase polymerase chain reaction (RT-PCR) assays have been used. The microarray technique measures the mRNA expression of more than 1,500 genes in the tumor tissue, and then compares the mRNA profile to established RNA tissue profiles. This technique has demonstrated an overall sensitivity of 87.8% and an overall specificity of 99.4%.[7] One RT- PCR assay measures the expression of 10-specific gene markers designed to detect tumor originating from lung, breast, colon, ovary, pancreas and prostate.[8] This assay has an overall accuracy of 78%. While GEP looks promising, at this time prospective clinical trials are necessary to determine whether this approach can be used in choosing treatment options that will significantly improve the outcomes for patients with CUP.

There is some debate as to how much additional evaluation should be performed to search for the primary malignancy beyond the initial tests and pathologic evaluation. Most oncologists agree that it is reasonable to consider additional studies as indicated by the clinical and pathological situation, particularly if there is a chance of discovering a treatable primary such as breast cancer. For example, adenocarcinoma with positive axillary lymph nodes in a woman is highly suggestive of an occult breast primary, and evaluation with a breast MRI would be indicated.

Treatment

Caring for patients with CUP is one of the most challenging situations in oncology. Given the uniqueness of each patient's situation, individualized, multimodality treatment approaches are essential. Involvement of a multi-disciplinary tumor board including medical oncologists, surgical oncologists, radiation oncologists, palliative care physicians, psychologists, pharmacists, social workers, case managers, chaplaincy, or other indicated specialists is particularly helpful.

In a majority of patients, CUP is refractory to systemic chemotherapy and treatment is often only palliative. Establishing realistic goals of care with the patient and family is difficult but necessary, and patients should be informed of the availability of any appropriate clinical trials.

Currently the National Cancer Center Network (NCCN) guidelines for occult primary cancers (their term for CUP) recommend that in patients with disseminated disease, treatment goals should be directed toward symptom control and ensuring the best quality of life. Chemotherapy should be limited to symptomatic patients with a reasonable performance status or asymptomatic patients with aggressive cancer histology. The choice of the regimen should be based on the histologic type of cancer. (Table 3)

Table 3. Common Chemotherapy Regimens for Cancer of Unknown Primary

Adenocarcinoma
Paclitaxel and carboplatin (+/- etoposide)
Docetaxel and carboplatin
Gemcitabine and cisplatin
Gemcitabine and docetaxel
Squamous cell carcinoma
Paclitaxel, cisplatin and 5-flourouracil
Docetaxel, cisplatin and 5-flourouracil

For localized disease, consultation with a surgical oncologist should be obtained to determine a potential therapeutic or palliative role for surgery. Similarly, radiation therapy can be therapeutic and/or palliative in certain situations of localized disease. For patients with unresectable, localized disease not amenable to radiation therapy, local regional treatments such as hepatic artery infusion, chemoembolization, or radiofrequency ablation can be considered. At this time, the recommended follow-up consists of a history and physical examination every three to six months for three years, then yearly, and diagnostic tests as indicated by symptoms.

Unlike other cancers that present with metastatic disease, the uncertainties surrounding the diagnosis of CUP and the grim prognosis can lead to significant psychosocial distress for both the patient and family. Early involvement of a palliative care team and/or oncology-focused psychologist or psychiatrist can beneficially impact the patient and family as well as the entire team of health care providers by facilitating the many difficult transitions that CUP brings to all the lives that it disrupts.[10]

Exceptions

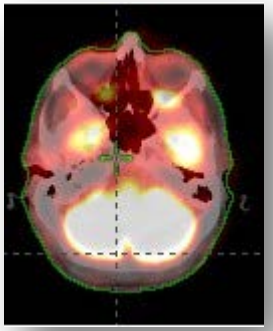
Three conditions, also called carcinoma of unknown primary, should be considered separately, essentially as different diseases, even though they are each labeled carcinoma of unknown primary, because the treatment and the prognosis of each is so different.

Cancer of Unknown Primary in the Neck (SCCUP)

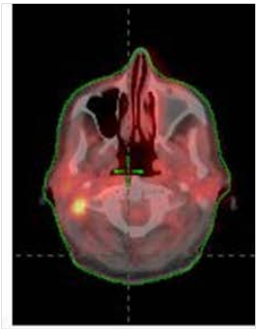
Nodes in the supraclavicular fossa most likely arise from the trunk, and are included in the above discussion. Squamous cell carcinoma (SCCUP) presenting above the clavicles is a different disease, with a far better prognosis, and is managed differently, with curative intent. There is even a separate NCCN guideline for SCCUP. This condition is managed primarily by otolaryngologists and radiation oncologists.[9]

Cancer presenting in the mid to upper neck is most likely to be squamous cell carcinoma arising from the upper airodigestive tract. Patients with palpable nodes in the neck should be referred to qualified oncologic otolaryngologists for workup; no other physician should attempt biopsy. Location of nodes in the neck should direct initial physical examination. Posterior triangle nodes suggest involvement of the nasopharynx. Also, this is the only cancer of unknown primary in which PET scanning has been demonstrated to be effective in helping determine a primary site. It reveals the primary site in about 25% of patients (Figure 1).

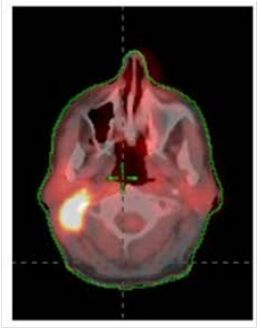
Figure 1. PET/CT Fusion axial images (1a-1d) and sagital and coronal images (1e & 1f) of patient with a PET+ necrotic node on right posterior triangle of the neck. Note entirely negative respiratory mucosa. University of Massachusetts Medical School, Department of Radiation Oncology.



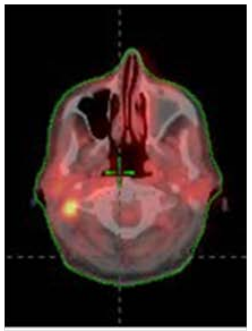
1a. Brain is hot, fusion between CT and PET is not perfect, even though the images were obtained on PET/CT machine.



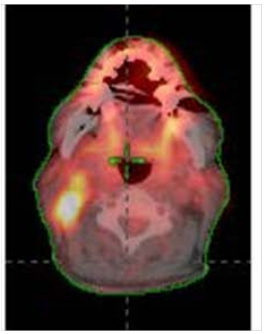
1b. Top of neck node



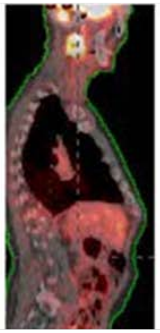
1c. Next cut inferiorly



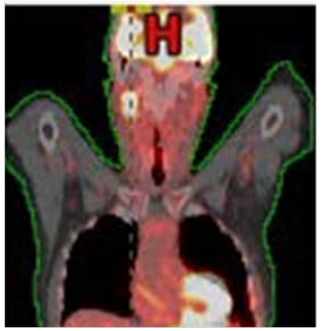
1d. Note dark core, consistent with necrosis



1e. Note dark core, consistent with necrosis



1f. Sagittal view of patient; note necrotic core



1g. Coronal view of patient; again, note necrotic core

The traditional paradigm for work-up of these patients requires panendoscopy with blind biopsies of nasopharynx, tonsils (perhaps with tonsillectomy) and base of tongue. The new paradigm for work- up of SCCUPs involves transoral robotic surgery. This procedure finds a primary malignancy in 70-90 % of patients, as opposed to 25% with the traditional examination under anesthesia and blind biopsies.[11]

If office physical examination, including endoscopy, does not establish a primary site to biopsy, fine needle aspiration of the involved node is strongly preferred to open biopsy. Then panendoscopy, with biopsy of any suspicious lesions, and if none, tonsillectomy and blind biopsies of base of tongue, and nasopharynx are indicated. Pathology of the nodal disease may be revealing; lymphoepitheliomas usually arise in Waldeyer's ring, and HPV infection patients have a better prognosis. And the precise location of the palpable nodal disease helps direct both the search for the primary and radiotherapy planning. For example, posterior triangle nodes are indicative of nasopharyngeal origin, so treatment of the larynx will not benefit the patient.

Management of the neck is the same as for other head and neck squamous cell cancers- surgery +/- radiotherapy to the lymphatic volumes of the neck; but for SCCUP, treatment of most or all of the mucosa of the upper aerodigestive tract is indicated in an attempt to prevent later appearance of the primary. Finding a primary site allows for restriction of radiotherapy treatment volume; completely resecting an early primary may eliminate the need for radiotherapy to the mucosa. In both cases, shrinking the radiotherapy target dramatically decreases the risk of late xerostomia and dysphasia, improving quality of life. Hence, searching for the primary in a SCCUP is worthwhile.

Treatment of the neck depends on the volume of disease. Small volume nodal disease may be managed with neck dissection or radiotherapy alone. Larger volume disease requires bimodality or trimodality therapy (see Principles of Multidisciplinary Management chapter). However, the role of chemotherapy in this disease remains unproven. Volume of tissue which should receive radiotherapy remains controversial; some advocate treatment of the entire upper aerodigestive tract.

Outcome

The NCI website reports 3 year disease free survival rates for SCCUP: 40-50% for N1 disease, 38% for N2 and 26% for N3. Overall survival is significantly better. Patients who develop a head and neck primary tumor after a first course of treatment in this setting have a poorer outcome than those who do not. Unfortunately, many of these patients arrive at the otolaryngologist expecting the same prognosis as the other CUP patients. It is important that all physicians be aware of the difference between this disease and what is explained to in the rest of this chapter.

Poorly differentiated carcinoma in the thoracic midline in a young male

As noted previously in this chapter, most patients with carcinoma of unknown primary have a poor response to chemotherapy. However, in the 1980's, clinical investigators recognized that men with midline, poorly differentiated carcinomas frequently did very well with cisplatin-based chemotherapy12. Although the tumors in these patients may not be recognizable as germ cell tumors, their location and response to chemotherapy is consistent with extra-gonadal germ cell tumors. Gain of the short arm of chromosome 12 (isochromosome 12p; i(12p)) is the most common chromosome abnormality seen in germ cell tumors and has been reported in midline poorly differentiated carcinomas in young men. These cancers may also express beta-human chorionic gonadotropin or alpha-fetoprotein.

Axillary nodal metastases pathologically consistent with breast origin

Occasionally a woman may present with axillary adenopathy without clinical or radiographic evidence of a primary breast cancer. If excision of the suspicious node shows an adenocarcinoma consistent with breast cancer, the tumor cells should also be studied for the presence of the estrogen receptor, progesterone receptor, and HER2. If pathologic and clinical evaluations suggest that the node involvement is likely due to breast cancer, the patient should be treated for breast cancer with appropriate surgery, radiation, hormonal therapy, and chemotherapy. Over half of these patients will enjoy prolonged survival.

Conclusion

Cancers of unknown primary (CUP) are metastatic tumors whose primary site cannot be determined after a standard diagnostic and

pathologic work-up. Most patients have a very poor prognosis, with the exception of the squamous cell carcinoma of the head and neck, axillary metastases pathologically consistent with breast origin, and undifferentiated carcinomas in the thoracic midline in young men, which behave like germ cell tumors. These three conditions should be considered different diseases than the usual carcinomas of unknown primary.

For several years, there has been interest in whether genomic profiling of CUPs may allow identification of the site of origin of tumors, and if that identification would permit therapy targeted at that tumor type. Several laboratories in the United States now offer molecular testing of CUP samples. Whether molecular identification will lead to improved survival must await clinical trials.[13]

Thought Questions

1. How is it biologically possible for a cancer to spread widely throughout the body and yet not be able to identify the primary tumor site? Suggest three hypotheses that could explain this phenomenon.

   Your answer:

Expert Answer

2. The "favorable" prognostic cancers listed in Points 1-6 in Table 1 all share characteristics of specific known cancers. Which cancer does each of these clinical scenarios resemble? Why are they relatively "favorable"?

   Your answer:

Expert Answer

3. Why is squamous cell carcinoma metastatic to cervical lymph nodes considered a different disease from other CUPs?

   Your answer:

Expert Answer

Glossary

Bimodality therapy– Treatment with any two of the three cancer treatment modalities– surgery, radiation therapy and chemotherapy

Chemoembolization- Injection of chemotherapy and occlusive material into the artery feeding a tumor. This exposes the tumor to very high concentrations of chemotherapy and also obstructs arterial blood flow to the cancer and may infarct a cancer.

Core needle biopsy- Removal of a tissue core into a large gauge needle

Fine needle aspiration- Removal of a cellular aspirate from a tissue with a small gauge needle

Gene expression profiling (GEP)- Analysis of mRNA expression of a tissue. Typical GEP will assess thousands of genes at a time.

Hepatic artery infusion- Installation of material (e.g., chemotherapy) directly into the hepatic artery. Note that many cancers involving the liver obtain their principle blood supply from the hepatic artery, not the portal vein.

Immunohistochemical (IHC) studies- Use of monoclonal antibodies directed against specific proteins expressed by cells to identify the presence of such proteins on or in cells.

Incisional biopsy- Removal of tissue through a surgical incision

Light microscopic examination- Review of a tissue specimen by light microscopy.

Multivisceral- Metastases to more than one organ

Radiofrequency ablation- Insertion of a radiofrequency probe into a tumor, followed by microwave heating of the tissue by the probe

Regional treatments- Any treatment directed only at a specific body region. This contrasts with systemic therapies (e.g., drugs) which can reach virtually any part of the body.

Trimodality therapy– Treatment with all three cancer treatment modalities– surgery, radiation therapy and chemotherapy

Waldeyer's ring– A ring of lymphatic tissue surrounding and protecting the upper airway– nasopharynx, lingual tonsils and base of tongue

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