

**MAURIE MARKMAN, MD**

Dr. Markman is chairman of the Department of Hematology/Medical Oncology at the Cleveland Clinic, and an associate editor of the *Cleveland Clinic Journal of Medicine*.

# The dilemma of evaluating and treating cancer of unknown primary site

Cancer of unknown primary site usually has a poor prognosis

In 5% to 10% of cases of cancer, the initial signs, symptoms, and radiographic findings reflect metastases and not the primary lesion, which is not easily found. For example, patients often present with enlarged cancerous lymph nodes in the groin, axilla, or neck; or pain in the right upper quadrant (due to liver metastases).

In such cases, the primary care physician faces several important questions:

## ■ HOW SHOULD THE PATIENT BE EVALUATED?

In general, if a limited evaluation does not reveal the primary cancer site, neither will any further extensive workup. In fact, not even an autopsy discloses this information in as many as 30% of patients whose site of cancer origin could not be identified during life.

Autopsy studies have shown, however, that for patients whose primary cancer sites were not documented during life, the most likely primary site is the pancreas if the manifestations occurred below the diaphragm, or the lung if the manifestations occurred above the diaphragm.

**TABLE 1** lists the elements of a limited workup. Of note, certain primary cancers typically spread to particular sites, and these patterns may help in identifying the most proba-

ble sites of origin (**TABLE 2**).

## ■ HOW AGGRESSIVELY SHOULD ONE SEARCH FOR THE PRIMARY SITE?

There is no evidence that an aggressive search for a primary tumor improves either the prognosis or the quality of life for a patient who has no symptoms related to that site at presentation (eg, lung metastasis from an occult gastrointestinal primary lesion).

The goals of the diagnostic evaluation of a patient with cancer of unknown primary site include:

- To document histologically that cancer is present (eg, by biopsy of a liver mass, biopsy or removal of a “rock hard” axillary, cervical, or inguinal lymph node).
- To find any primary sites that may have important therapeutic implications (see “Exceptions to the rule” below).
- To confirm any abnormalities that need to be treated to prevent immediate harm to the patient, such as a fungating, bleeding, or partially obstructing cancer of the colon or stomach.

## Does the primary site matter?

With several important exceptions (noted below), cancer of unknown primary site carries



TABLE 1

**EVALUATION OF PATIENTS PRESENTING WITH CANCER OF UNKNOWN PRIMARY SITE**

- Detailed history
- Complete physical examination, including rectum, pelvis, and breasts
- Complete blood count, liver-function tests, and serum chemistry profile
- Urinalysis, in particular, looking for occult blood, suggestive of urological primary
- Stool test for occult blood (suggestive of gastrointestinal primary)
- Measurements of serum prostate specific antigen, alpha fetoprotein, beta-human chorionic gonadotropin
- Chest radiograph
- Review of pathology material, special histochemical stains, electron microscopy, hormone receptors

**Treatment aims are to optimize quality of life rather than to prolong survival**

a poor prognosis. Only approximately 25% of patients survive 1 year, and the median life expectancy is less than 6 months from the date of diagnosis. In adenocarcinoma of unknown primary site, one large series noted a life expectancy of only 3 months after diagnosis, and a 1-year survival rate of only 16%. Further, the overall survival rate in cancer of unknown primary site has changed little over the past 20 years.

Of some interest, patients presenting with major manifestations above the diaphragm have a higher survival rate than those with signs and symptoms principally below the diaphragm.

■ **EXCEPTIONS TO THE RULE: WHEN AGGRESSIVE TREATMENT IS WARRANTED**

In a few situations, reasonably aggressive local and regional treatment appears to prolong disease-free survival, even without a histologic diagnosis of the origin of the cancer.

**Squamous cell cancer in a high cervical lymph node**

Patients with squamous cell cancer in a cervical lymph node, with no obvious primary site or other metastases (eg, to the lungs or bone), should be considered to have a primary cancer in the head or neck, and be given aggressive

TABLE 2

**COMMON METASTATIC SITES FOR PRIMARY CANCERS**

Metastatic site	Primary cancer type
Bone	Breast Lung Hodgkin's disease Multiple myeloma (lytic lesions) Prostate (blastic lesions)
Brain	Breast Lung Melanoma Pancreas Prostate
Liver	Breast Gastrointestinal Lung Pancreas
Lung	Breast Gastrointestinal Lung Melanoma Pancreas Sarcomas
Peritoneum (ascites)	Colon Ovary Pancreas Stomach
Pleura (effusions)	Breast Lung Ovary Pancreas
Skin	Breast Kidney Lung Lymphoma Melanoma
Spinal cord	Breast Lung (cervical/thoracic) Lymphoma (thoracic/lumbar) Prostate (lumbar)

local therapy (surgery or radiation with or without chemotherapy).

**Adenocarcinoma in axillary lymph nodes in women**

Women presenting with adenocarcinoma in an axillary lymph node or nodes, but without

evidence of a breast mass, should be treated as if they have breast cancer, with both local (surgery, radiotherapy) and systemic therapy (chemotherapy, hormonal therapy).

### Young men with midline tumors

Recent studies have shown that some young men with cancers of unknown primary site, particularly involving midline structures such as the mediastinum, have unrecognized testicular or extragonadal germ cell tumors.

The serum level of beta-human chorionic gonadotropin or alpha fetoprotein may help in the differential diagnosis in this situation. If either or both of these tumor markers are elevated, the patient should receive chemotherapy for germ cell cancer. Some patients may achieve dramatic and prolonged responses.

### Brain metastases

It is also reasonable to consider moderately aggressive treatment in carefully selected patients presenting with brain metastases without a known primary site. Either surgical resection of a single metastatic lesion, or stereotactic radiosurgery if there are several metastatic foci, can prolong survival in this situation.

## ■ PALLIATIVE TREATMENT

With the exceptions noted above, treatment of cancer of unknown primary site is palliative in intent, aiming to optimize the quality of life rather than to prolong survival. Watchful waiting may be reasonable if the tumor is not causing any symptoms, until symptoms of disease progression appear.

If the differential diagnosis includes several possibilities, it is reasonable to treat for the cancer type most likely to respond to treatment. For example, in a middle-aged woman who presents with malignant ascites, cytologic evidence of adenocarcinoma, and no obvious primary site, the most likely diagnoses are ovarian cancer, primary carcinoma of the peritoneum, and gastrointestinal cancer. The latter hardly ever responds to systemic therapy, but 60% to 80% of patients with ovarian cancer or primary carcinoma of the peritoneum exhibit clinical evidence of tumor regression

and at least short-term palliation of symptoms in response to systemic therapy. This type of patient should therefore receive treatment for these types of cancer.

Other tumor types that are moderately or extremely sensitive to chemotherapy include lymphomas, germ cell tumors, breast cancer, and small-cell cancer of the lung. Both breast and prostate cancers may respond to hormonal therapy.

Local radiation therapy can control pain and prevent complications in bone metastases. Other palliative measures include surgery to stop or prevent bleeding or obstruction, pleural sclerosis to prevent malignant pleural effusions from reaccumulating, and medications to control pain or to treat hypercalcemia. ■

## ■ SUGGESTED READING

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**ADDRESS REPRINT REQUESTS** to Maurie Markman, MD, Department of Hematology/Medical Oncology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.