Poorly Differentiated Cancer of Unknown Primary Site

Poorly differentiated cancers are usually more aggressive than well-differentiated cancers, and metastatic poorly differentiated adenocarcinoma has a poor prognosis; however, some patients with poorly differentiated CUP that is not definitively an adenocarcinoma may have specific treatment options. In particular, young men with predominantly midline poorly differentiated carcinoma, such as those with large retroperitoneal or mediastinal lymphadenopathy, should be carefully evaluated for the possibility of a germ cell tumor. Serum α-fetoprotein and β-human chorionic gonadotropin levels should be measured, and a testicular examination and ultrasonography should be performed. Even if these evaluations have negative findings, an unrecognized germ cell tumor may still exist, and these patients should be treated for this possibility with a platinum-based chemotherapy regimen.

Patients with poorly differentiated neuroendocrine tumors also warrant careful consideration. These tumors frequently both metastasize like small cell lung cancers and respond similarly to platinum-based chemotherapy.

Isolated Regional Lymphadenopathy

Women found to have adenocarcinoma in isolated axillary lymphadenopathy have a more favorable CUP prognosis. These patients should be presumptively considered to have locoregional breast cancer. If mammography is unrevealing, breast MRI should be performed. If the MRI scan is negative, the patient is still assumed to have a presumptive stage II breast cancer. Given the inability to identify the primary, a mastectomy or whole breast radiation therapy is recommended. These patients should all receive adjuvant treatment consistent with a stage II breast cancer diagnosis. Patients with isolated or dominant cervical lymphadenopathy should undergo full endoscopic examination of the upper aerodigestive tract to evaluate for a head and neck primary. Even if a primary is not identified, treatment along a head and neck paradigm with chemotherapy and radiation therapy is often appropriate. In particular, patients with high cervical lymphadenopathy with squamous cell cancer occasionally achieve cure. Supraclavicular lymphadenopathy or adenocarcinoma makes a head and neck primary far less likely, and therapy is less efficacious.

Isolated inguinal lymphadenopathy should prompt anoscopy and careful examination of the perineal and genital regions. Even in the absence of a defined primary tumor, definitive resection or irradiation to inguinal or other isolated solitary or regional lymph nodes may provide long-term tumor control and cures in rare circumstances.

Peritoneal Carcinomatosis in Women

Women who have adenocarcinoma with abdominal carcinomatosis and ascites should be presumptively treated for ovarian cancer, including initial cytoreductive surgery and ovarian cancer chemotherapy regimens.

KEY POINTS

- Patients with cancer of unknown primary who have poorly differentiated carcinoma predominantly in the midline, such as those with large retroperitoneal or mediastinal lymphadenopathy, are likely to have a germ cell tumor and should be treated for that possibility with platinum-based chemotherapy.
- Women with a cancer of unknown primary who have axillary lymphadenopathy and a negative breast MRI scan should be treated for presumptive stage II breast cancer.
- Women with adenocarcinoma with abdominal carcinomatosis and ascites should be treated for presumptive ovarian cancer.
- Patients with isolated or dominant cervical lymphadenopathy and cancer of unknown primary should be treated along a head and neck cancer paradigm with chemotherapy and radiation therapy.

Nonfavorable Subgroups of Cancer of Unknown Primary Site

Therapy for CUP that does not fall into one of the favorable subgroups is empirically directed with chemotherapy and radiation therapy based on the pattern of presentation. CUP presenting above the diaphragm should be evaluated and managed as metastatic lung cancer. CUP that is predominantly below the diaphragm should be managed as gastrointestinal cancer.

Chronic medical comorbidities and patient performance status greatly influence the range of treatment options. As with other solid tumors, patients with several comorbidities and poor performance status are far less likely to benefit from aggressive chemotherapy and are far more likely to experience serious or life-threatening toxicity. Palliative and hospice care should be considered in such patients.

KEY POINTS

- Therapy for cancer of unknown primary that does not fall into one of the favorable subgroups should be managed based on pattern of presentation; cancer presenting above the diaphragm should be treated as metastatic lung cancer, and cancer presenting below the diaphragm should be treated as gastrointestinal cancer.
- Palliative or hospice care is appropriate for patients with an unfavorable subtype of cancer of unknown primary site who have comorbidities and poor performance status.

HVC

Melanoma

Melanoma has been steadily increasing in incidence worldwide, with risk related to sun exposure. Most melanomas begin in and present with cutaneous disease, but they can also

begin in mucosal and ocular sites. About half of cutaneous melanomas arise in preexisting nevi, but many begin in apparently normal skin. Melanoma can also present in nodal or visceral sites without a known cutaneous or mucosal primary. Only 10% of patients with melanoma have a familial history, and mutations in certain genes, such as *CDKN2A*, have been identified in some families. Ocular melanoma is the most common cancer of the eye, and these melanomas have a distinct biology and behavior.

Advances in systemic therapy during the past decade have resulted in significant improvements in survival for patients with metastatic melanoma. These advances include the use of molecular therapy targeted at specific gene mutations and immunotherapy, including the use of immune checkpoint inhibitors.

Treatment of Melanoma

Melanoma has the potential to behave quite aggressively, but it is a highly curable disease when detected and treated early with a wide local excision. For localized melanomas, prognosis is related to the depth of invasion by Breslow depth. A high mitotic rate, lymphovascular invasion, and the presence of ulceration are poor prognostic signs. Surgical resection margins for melanomas do not have to be excessive: 1-cm margins are acceptable for lesions that are less than 1 mm in thickness. Patients with melanomas between 1 mm and 2 mm in thickness should be resected with a 2-cm margin provided that a skin graft is not required for closure. A 1- to 2-cm margin may be selected if wound closure is not feasible without creating a cosmetic deformity or impairing function. Patients with lesions that are greater than 2 mm in thickness should be resected with 2-cm margins. Patients with early-stage disease can be assessed clinically and do not need radiographic staging (for example, CT and PET).

As the depth of invasion increases, the risk of nodal and ultimately distant metastasis increases. Nodal metastases are uncommon in thin melanomas, and nodes are typically not assessed if the melanoma has a Breslow depth of less than 0.8 mm and is without ulceration. Assessing for lymph node metastasis with lymphatic mapping and sentinel lymph node biopsy is often recommended for intermediate and thicker melanomas. Even if the sentinel node is positive, a completion lymph node dissection is no longer routinely performed, as there is no improvement in survival. Patients with positive sentinel lymph node biopsies (stage III) may be followed by clinical examination and serial ultrasounds of the nodal basin involved to detect nodal recurrences. These patients are also eligible for adjuvant systemic treatment.

Systemic therapies for metastatic disease have advanced significantly over the past decade. Conventional cytotoxic chemotherapy has little role in current management. Although interferon and interleukin-2 have some activity in the adjuvant and metastatic setting, respectively, the current focus is on targeted therapy for patients with specific gene mutations and on the use of immune checkpoint inhibitors of programmed cell death transmembrane proteins.

Approximately one half of melanomas harbor a *BRAF* gene mutation (most commonly V600E), and another 20% have an MEK or *NRAS* mutation; all of these mutations activate the mitogen-activated protein kinase pathway. Melanomas with *BRAF* V600E or V600K may respond to oral therapy with the available *BRAF*/MEK inhibitor combinations (dabrafenib/trametinib; vemurafenib/cobimetinib; encorafenib/binimetinib). Combining *BRAF* inhibitors with MEK inhibitors improves the rate and duration of response over *BRAF* inhibitors alone.

In addition to the efficacy of *BRAF* inhibitors, the use of immune checkpoint inhibitors has revolutionized the therapy and prognosis of patients with metastatic melanoma. Cellular immunity is based on T cells recognizing peptide fragments expressed on the surface of antigen-presenting cells when bound to histocompatibility complex molecules. Cytotoxic T-lymphocyte-associated protein 4 is a potent down-regulator of this process. The antibody against cytotoxic T-lymphocyte-associated protein 4, ipilimumab, can result in dramatic tumor response, albeit in a small percentage of patients. Tumor response is independent of *BRAF* status.

Nivolumab and pembrolizumab are both anti-programmed cell death protein 1 antibodies that can result in significant melanoma response rates with sometimes durable response and dramatic survival improvement. Ipilimumab alone has a relatively low response rate (20%) and is associated with considerable toxicity, with various immune-related adverse effects that can include rash, colitis, hepatitis, pneumonitis, myocarditis, and endocrine insufficiency syndromes. Similar adverse effects can occur with nivolumab and pembrolizumab but are less frequent, and these antibodies are associated with a higher response rate (30%-40%). Combining ipilimumab with nivolumab improves response rates compared with either ipilimumab or nivolumab alone but results in significantly more immune-related toxicities. This immunotherapy combination is effective whether or not the patient has *BRAF*-mutated melanoma. Durable benefit in terms of survival is possible in a substantial fraction of patients with metastatic melanoma treated with checkpoint inhibitors.

In addition to their use in metastatic disease, immune checkpoint inhibitors and *BRAF*/MEK inhibitors (in patients with the *BRAF* mutation) have shown survival benefits in the adjuvant setting in patients with resected stage III (nodal) disease.

Although prophylactic lymphadenectomies or completion node dissections for those with positive sentinel nodes have not definitively shown an overall survival benefit, node dissections can be curative in 20% to 50% of patients who present with or develop regional nodal disease. For some patients with distant metastatic disease, surgery may still play a significant role. Melanoma can present with solitary or oligometastatic disease amenable to resection that is curable in some

patients. Following metastasectomy, data would support the use of adjuvant systemic therapy to improve overall outcome.

KEY POINTS

- Melanoma is a highly curable disease when detected and treated early with a wide local excision.
- Nodal metastases are uncommon in thin melanomas (Breslow depth less than 0.8 mm) and need not be assessed.
- More than one half of patients have melanoma that harbors a *BRAF* mutation, which may respond to the *BRAF* inhibitors combined with MEK inhibitors.
- The use of immune checkpoint inhibitors has shown significant improvements in survival for patients with regional nodal and metastatic melanoma.

HVC

Follow-up

All patients should be encouraged to perform skin self-examinations as well as receive regular skin evaluations by a dermatologist for life every 6 months. Patients with early-stage melanoma need not undergo routine blood testing or imaging studies in the absence of signs or symptoms.

Oncologic Urgencies and Emergencies

Structural Urgencies and Emergencies

Superior Vena Cava Syndrome

Obstruction of the superior vena cava (SVC), or SVC syndrome, is usually caused by malignancies with large mediastinal masses. Lung cancer accounts for almost 75% of cases of SVC syndrome, with lymphoma and metastatic disease each causing approximately 10%; rarer tumors, such as germ cell tumor, thymoma, or mesothelioma, account for the remainder.

Patients typically present with edema of the head, neck, and arms, often with cyanosis, plethora, and distended cutaneous collateral vessels. They may have headache, cough, dyspnea, hoarseness, or syncope. The severity of symptoms depends on the degree of narrowing of the SVC and the speed of onset, with slower development allowing venous collaterals to develop. Most patients do not require emergency intervention, and deaths due to SVC syndrome are rare. A chest CT scan with intravenous contrast usually confirms the diagnosis (**Figure 10**).

Management is based on the severity of symptoms and the underlying malignancy. In patients requiring immediate treatment of respiratory distress, an SVC stent can be placed without tissue diagnosis. For most patients, a tissue diagnosis is obtained, with treatment directed by the type of cancer. Options for obtaining diagnostic tissue include mediastinoscopy, bronchoscopy,

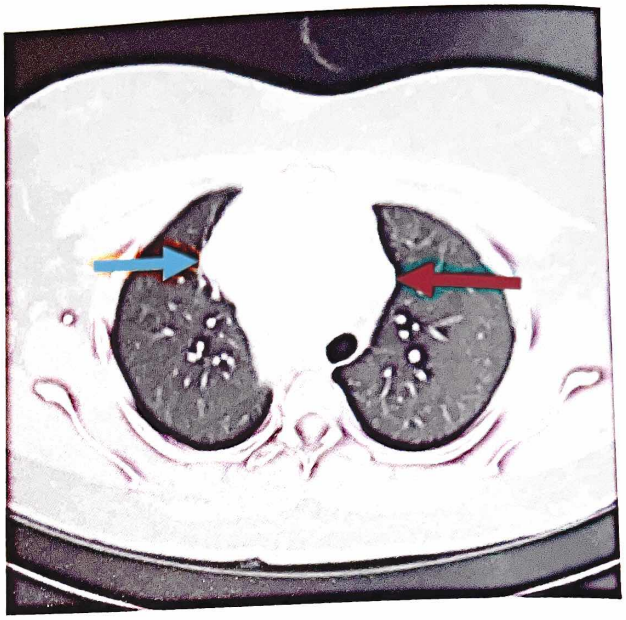

FIGURE 10. Superior vena cava (SVC) syndrome often presents on chest CT scan with bronchial obstruction due to mediastinal mass (*blue arrow*) and SVC compression (*red arrow*).

thoracentesis (if a pleural effusion is present), or biopsy of a peripheral area of lymphadenopathy. Complication rates of these procedures are usually low.

Cancers that are highly responsive to chemotherapy, such as small cell lung cancer, lymphoma, and germ cell cancers, are treated with initial chemotherapy. Non–small cell lung cancer may be treated with initial chemotherapy, radiation therapy, or both. Initial surgery may be required in thymoma and mesothelioma. Although glucocorticoids and loop diuretics are often used, there is no clear evidence of their effectiveness. If thrombosis is present, anticoagulation should be added.

Treatment of curable malignancies should not be compromised by the presence of SVC syndrome, as prognosis is not otherwise altered.

KEY POINTS

- Most patients with superior vena cava syndrome do not require emergency intervention; a tissue diagnosis should be obtained first with treatment directed by the type of cancer.
- Presentation with superior vena cava syndrome does not worsen prognosis in patients who present with otherwise treatable malignancies.

Venous Thromboembolism

Cancer and cancer treatment are risk factors for venous thromboembolism (deep venous thrombosis and pulmonary embolism). Symptoms such as calf discomfort, pleuritic chest pain, or shortness of breath should prompt evaluation of deep venous thrombosis/ pulmonary embolism (see Hematology).