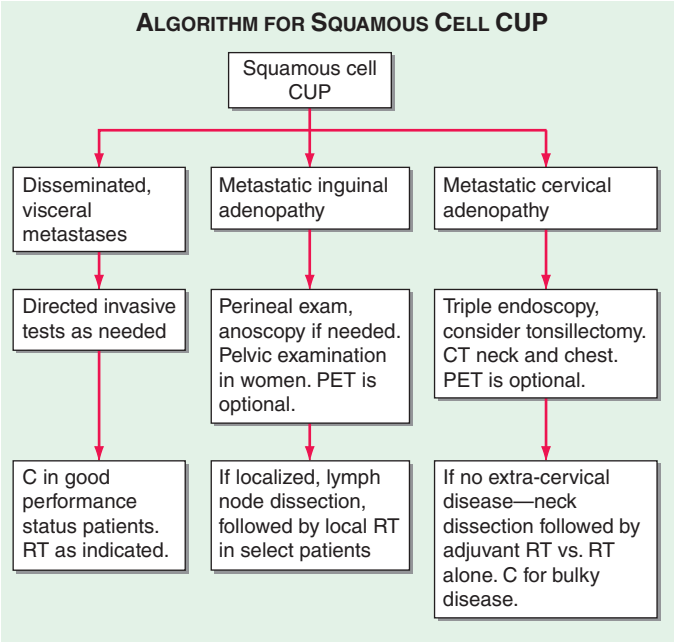


**FIGURE 120e-3 Treatment algorithm for squamous cell carcinoma of unknown primary (CUP).** C, chemotherapy; CT, computed tomography; PET, positron emission tomography; RT, radiation.

retrospective study of 258 women with peritoneal carcinomatosis who had undergone cytoreductive surgery and chemotherapy, 22% of patients had a complete response to chemotherapy; the median survival duration was 18 months (range 11–24 months). However, not all peritoneal carcinomatosis in women is PPSC. Careful pathologic evaluation can help diagnose a colon cancer profile (CDX-2+, CK-20+, CK7–) or a pancreaticobiliary cancer or even a mislabeled peritoneal mesothelioma (calretinin positive).

### POORLY DIFFERENTIATED CARCINOMA WITH MIDLINE ADENOPATHY

Men with poorly differentiated or undifferentiated carcinoma that presents as a midline adenopathy should be evaluated for extragonadal germ cell malignancy. If diagnosed and treated as such, they often experience a good response to treatment with platinum-based combination chemotherapy. Response rates of >50% have been noted, and long-term survival rates of 10–15% long have been reported. Older patients (especially smokers) who present with mediastinal adenopathy are more likely to have a lung or head-and-neck cancer profile.

### NEUROENDOCRINE CARCINOMA

Low-grade neuroendocrine carcinoma often has an indolent course, and treatment decisions are based on symptoms and tumor bulk. Urine 5-HIAA and serum chromogranin may be elevated and can be followed as markers. Often the patient is treated with somatostatin analogues alone for hormone-related symptoms (diarrhea, flushing, nausea). Specific local therapies or systemic therapy would only be indicated if the patient is symptomatic with local pain secondary to significant growth of the metastasis or the hormone-related symptoms are not controlled with endocrine therapy. Patients with high-grade neuroendocrine carcinoma are treated as having small-cell lung cancer and are responsive to chemotherapy; 20–25% show a complete response, and up to 10% patients survive more than 5 years.

### SQUAMOUS CELL CARCINOMA PRESENTING AS NECK ADENOPATHY

Patients with early-stage squamous cell carcinoma involving the cervical lymph nodes are candidates for node dissection and radiation therapy, which can result in long-term survival. The role of chemotherapy in these patients is undefined, although chemoradiation therapy or induction chemotherapy is often used and is beneficial in bulky N2/N3 lymph node disease.

### SOLITARY METASTATIC SITE

Patients with solitary metastases can also experience good treatment outcomes. Some patients who present with locoregional disease are candidates for aggressive trimodality management; both prolonged disease-free interval and occasionally cure are possible.

### MEN WITH BLASTIC SKELETAL METASTASES AND ELEVATED PSA

Blastic bone-only metastasis is a rare presentation, and elevated serum PSA or tumor staining with PSA may provide confirmatory evidence of prostate cancer in these patients. Those with elevated levels are candidates for hormonal therapy for prostate cancer, although it is important to rule out other primary tumors (lung most common).

### MANAGEMENT OF DISSEMINATED CUP

Patients who present with liver, brain, and adrenal metastatic disease usually have a poor prognosis. Patients with nonserous papillary primary peritoneal carcinomatosis can have a large differential diagnosis, which is mainly of gastrointestinal profile and includes gastric, appendiceal, colon, and pancreaticobiliary profiles.

Traditionally, platinum-based combination chemotherapy regimens have been used to treat CUP. Several broadly used regimens have been studied in the last two decades; these include paclitaxel-carboplatin, gemcitabine-cisplatin, gemcitabine-oxaliplatin, and irinotecan and fluoropyrimidine-based therapies. These chemotherapeutic agents used as empiric regimens have shown a response rate of 25–40%, and their use obtains median survival times of 6–13 months.

Outside of favorable subsets, there is a small group of patients with a "definitive" IHC. These patients usually have a single diagnosis based on their clinicopathologic presentation and are often treated for the putative primary tumor. This does not guarantee a response, although it increases the probability of response when select drugs are chosen from a class of drugs known to work in that cancer type. Patients who do not fall into those categories are candidates for broad-spectrum platinum-based regimens, clinical trials, and additional trial-based genomic and proteomic tests. Today, we do not have effective drugs for several CUP cancer profiles, and treatments overlap for some cancers. However, as novel therapies are developed for additional known cancers, tissue of origin and assessment of molecular features of the tumor will be important and might direct more selective treatment.

## SUMMARY

Patients with CUP should undergo a directed diagnostic search for the primary tumor on the basis of clinical and pathologic data. Subsets of patients have prognostically favorable disease, as defined by clinical or histologic criteria, and may substantially benefit from aggressive treatment and expect prolonged survival. However, for most patients who present with advanced CUP, the prognosis remains poor with early resistance to available cytotoxic therapy. The current focus has shifted away from empirical chemotherapeutic trials to understanding the metastatic phenotype, tissue of origin profiling, and evaluating molecular targets in CUP patients.