promise of substantially increasing this yield. Gene expression profiles are most commonly generated using quantitative reverse transcriptase polymerase chain reaction (RT-PCR) or DNA microarray.

Neural network programs have been used to develop predictive algorithms from the gene expression profiles. Typically, a training set of gene profiles from known cancers (preferably from metastatic sites) is used to train the software. The program can then be used to predict the putative origin of a test tumor and presumably of true CUP. Comprehensive gene expression databases that have become available for common malignancies may also be useful in CUP. These approaches have been effective in testing against known primary cancers and their metastases.

mRNA- or microRNA-based tissue of origin molecular profiling assays have been studied in prospective and retrospective CUP trials. Most of the CUP studies have evaluated assay *performance*, although the challenge with validating the accuracy of an assay for CUP is that, by definition, the primary cancer diagnosis cannot be verified. Thus, current estimates of tissue of origin test accuracy have relied on indirect metrics including comparison with IHC, clinical presentation, and appearance of latent primaries. Using these measures, the assays suggest a plausible primary in ~70% of patients studied. The only outcomes-based study is a single-arm study reporting a median survival of 12.5 months for patients who received assay-directed site-specific therapy. Firm conclusions of therapeutic impact cannot be drawn from this study given the nonrandomized design, statistical biases, confounding variables including use of subsequent lines of (empiric) therapy, and the heterogeneity of the CUP cancers. Additional studies are needed to better understand the clinical influence of tissue of origin profiling tools and how these assays complement IHC and help guide therapy.

TREATMENT CARCINOMA OF UNKNOWN PRIMARY

GENERAL CONSIDERATIONS

The treatment of CUP continues to evolve, albeit slowly. The median survival duration of most patients with disseminated CUP is ~6–10 months. Systemic chemotherapy is the primary treatment modality in most patients with disseminated disease, but the careful integration of surgery, radiation therapy, and even periods of observation is important in the overall management of this condition **(Figs. 120e-2 and 120e-3)**. Prognostic factors include performance status, site and number of metastases, response to chemotherapy, and serum lactate dehydrogenase (LDH) levels. Culine and colleagues developed a prognostic model using performance status and serum LDH levels, which allowed the assignment of patients into two subgroups with divergent outcomes. Future prospective trials using this prognostic model are warranted. Clinically, some CUP diagnoses fall into a favorable prognostic subset. Others, including those with disseminated CUP, do not and have a more unfavorable prognosis.

TREATMENT OF FAVORABLE CUP SUBSETS

Women with Isolated Axillary Adenopathy Women with isolated axillary adenopathy with adenocarcinoma or carcinoma are usually treated for stage II or III breast cancer based on pathologic findings. These patients should undergo a breast MRI if mammogram and ultrasound are negative. Radiation therapy to the ipsilateral breast is indicated if the breast MRI is positive. Chemotherapy and/or hormonal therapy are indicated based on patient's age (premenopausal or postmenopausal), nodal disease bulk, and hormone receptor status **(Chap. 108)**. It is important to verify that the pathology suggests a breast cancer profile (morphology, immunohistochemical breast markers including estrogen receptor, mammoglobin, GCDFP-15, HER-2 gene expression) before embarking on a breast cancer therapeutic program.

WOMEN WITH PERITONEAL CARCINOMATOSIS

The term *primary peritoneal papillary serous carcinoma* (PPSC) has been used to describe CUP with carcinomatosis with the pathologic and laboratory (elevated CA-125 antigen) characteristics of ovarian cancer but no ovarian primary tumor identified on transvaginal sonography or laparotomy. Studies suggest that ovarian cancer and PPSC, which are both of müllerian origin, have similar gene expression profiles. Similar to patients with ovarian cancer, patients with PPSC are candidates for cytoreductive surgery, followed by adjuvant taxane- and platinum-based chemotherapy. In one

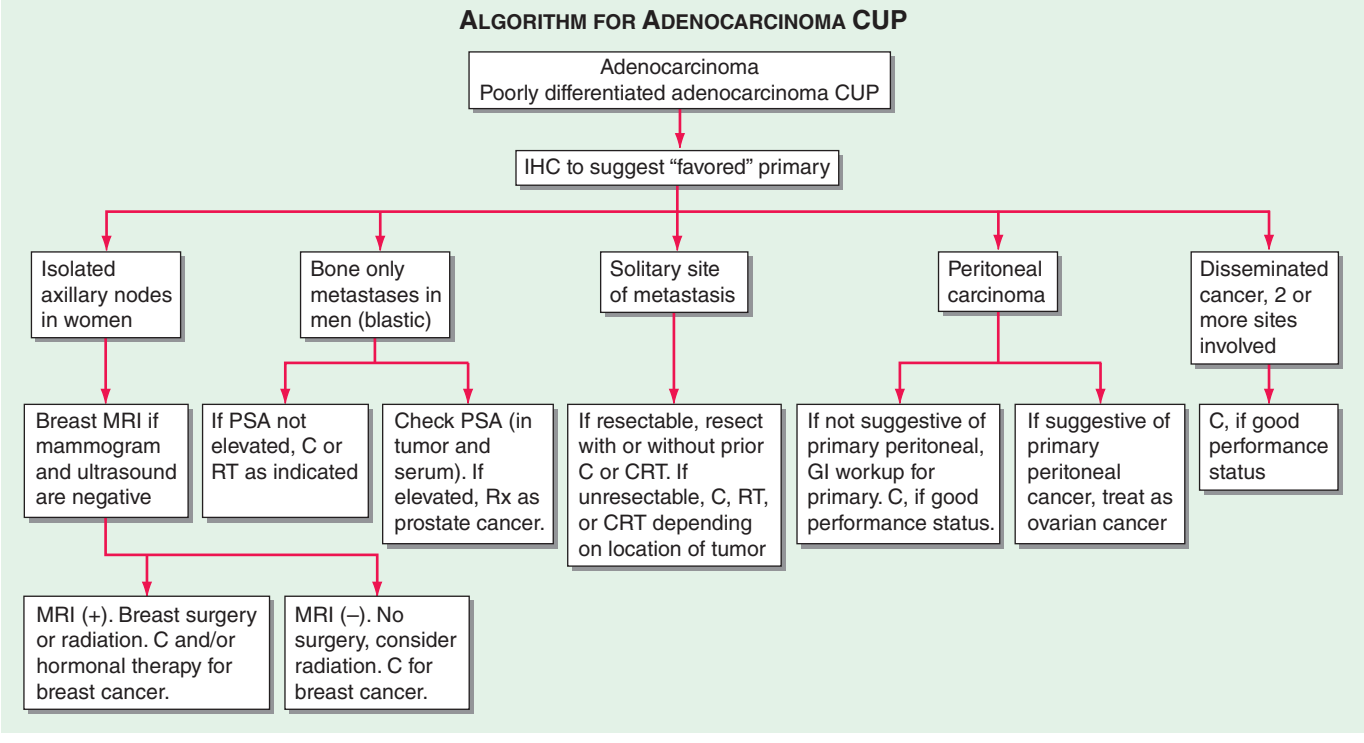

FIGURE 120e-2 Treatment algorithm for adenocarcinoma and poorly differentiated adenocarcinoma of unknown primary (CUP). C, chemotherapy; CRT, chemoradiation; GI, gastrointestinal; IHC, immunohistochemistry; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; RT, radiation.