Adenocarcinoma of unknown primary site

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INTRODUCTION

Cancer of unknown primary site (CUP) is diagnosed in patients who have metastatic cancer, but have no anatomic primary site identified by a comprehensive initial evaluation [1]. Within this category, cancers from many primary sites with varying biology are represented. Improved diagnostic methods including molecular cancer classifier assays (MCCAs) and immunohistochemical (IHC) staining allow the site of tumor origin to be predicted in most patients with CUP. However, the anatomic primary site is usually not detected during the clinical course, so CUP patients remain a clinically distinct group. (See "Overview of the classification and management of cancers of unknown primary site".)

Adenocarcinomas of unknown primary site comprise approximately 70 percent of CUPs. In autopsy series, although these cancers may arise from a wide variety of primary sites, the most frequently identified sites are lung, pancreas, hepatobiliary tree, and kidney, together accounting for approximately two-thirds of cases [2]. Adenocarcinomas of the breast and prostate are identified infrequently at autopsy, despite being the most common cancers in women and men, respectively. In 20 to 30 percent of patients, no primary site can be identified. However, it seems likely that very small primaries that would require multiple sections for microscopic identification may be missed at autopsy. Large autopsy series include patients who were not evaluated with modern imaging such as computed
tomography (CT) and positron emission tomography (PET), and therefore published data may not accurately reflect the current patient population with adenocarcinoma of unknown primary site.

In patients with adenocarcinomas of unknown primary site, the focus is on identifying specific subsets in which disease-oriented therapy may be more effective than empiric therapy; this is based on a combination of clinical features, IHC results, and MCCA results.

The diagnosis and management of patients with adenocarcinoma of unknown primary site are reviewed here.

The diagnosis and management of the other CUPs are discussed separately:

- (See "Overview of the classification and management of cancers of unknown primary site").
- (See "Poorly differentiated cancer from an unknown primary site").
- (See "Head and neck squamous cell carcinoma of unknown primary").
- (See "Neuroendocrine neoplasms of unknown primary site").
- (See "Squamous cell carcinoma of unknown primary site").
- (See "Axillary node metastases with occult primary breast cancer").

CLINICAL PRESENTATION AND COURSE

The incidence of adenocarcinoma of unknown primary site increases with age. The clinical presentation is determined by the sites of metastatic tumor involvement, which are frequently multiple and often include the liver, lungs, lymph nodes, and bones. Many patients with adenocarcinoma of unknown primary site have widespread metastases and poor performance status at diagnosis. The outlook for most of these patients is poor, although this is influenced by the type of adenocarcinoma, sites of metastases, and extent of tumor burden.

In an analysis of almost 19,000 patients with cancers of unknown primary site (CUPs; 70 percent with adenocarcinoma) from the Swedish Cancer Registry from 1987 to 2008, the median survival for those with adenocarcinoma was three months, with a 17 percent one-year survival rate [3]. Another analysis from this cancer registry found that there was an improvement over time in overall survival (OS) in patients with adenocarcinoma (median OS
of approximately six months for periods 2001 to 2008 versus four months for 1987 to 1993) [4].

However, small subsets of patients have a more favorable outlook, and initial evaluation should attempt to identify these patients. Additional diagnostic tests including improved immunohistochemical (IHC) stains and molecular cancer classifier assays (MCCAs) have improved the identification of the site of tumor origin, and improved the prognosis of selected patients when treated with site-specific therapy. Empiric chemotherapy also results in modest survival improvement (median survival, 9 to 11 months) for patients with good performance status. (See 'Initial evaluation of the tumor specimen' below and 'Specific patient subgroups' below and 'Approach to patients not included in specific subgroups' below.)

**INITIAL CLINICAL EVALUATION**

Initial studies for a patient with cancer of unknown primary site (CUP) should focus on determining the extent of metastatic disease, as well as identifying those patients whose tumors were likely to have arisen in a treatable primary site.

At a minimum, this initial evaluation should include a thorough history and physical examination, complete blood count, urinalysis, basic serum chemistries, and computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. In men, assessment should incorporate a prostate examination and measurement of serum prostate-specific antigen. In women, the evaluation should include a pelvic examination and mammography. Breast MRI should be performed in the setting of a negative mammogram in women with adenocarcinoma involving the axillary lymph nodes. (See 'Women with axillary lymph node metastases' below.)

Positron emission tomography (PET) is an additional standard diagnostic staging procedure that may be useful in certain presentations. In a number of retrospective series, PET identified a primary site in approximately 40 percent of patients [5,6]. However, in the single existing prospective study, PET was not superior compared with CT [7]. Therefore, the use of PET should be restricted to the evaluation of patients with specific clinical presentations (eg, squamous carcinoma in cervical lymph nodes or those with a single metastasis).
Exhaustive imaging and endoscopic testing should not be performed, since these studies rarely detect the primary site in the asymptomatic patient, and confusion can result from false-positive results. Instead, the presence of specific signs or symptoms, or specific findings on biopsy, should guide the choice of additional studies. Colonoscopy should be performed in patients with intra-abdominal metastases who have a cytokeratin (CK)20-positive/CK7-negative immunohistochemical (IHC) staining pattern, a positive caudal-type homeobox transcription factor (CDX)-2 IHC stain, or a gene expression profile predictive of colorectal cancer. (See 'Initial evaluation of the tumor specimen' below.)

Commonly measured serum tumor markers (carcinoembryonic antigen [CEA], cancer antigen [CA] 19-9, CA 15-3, CA 125) are generally not useful as diagnostic or prognostic tests. However, they are commonly elevated and may be useful in following the response to therapy.

INITIAL EVALUATION OF THE TUMOR SPECIMEN

Cancer of unknown primary site (CUP) is, by definition, a metastatic tumor for which pretreatment evaluation does not reveal an anatomic primary site [1]. In cases of suspected CUP, a biopsy of the most accessible site should be performed, preferably using a core needle or excisional biopsy to obtain sufficient tissue for all necessary studies. Adenocarcinoma can usually be distinguished from other histologies by light microscopic examination. Immunohistochemistry (IHC) and additional studies should be guided by the tumor histology, as described below. Treatment should then proceed based on results of these assessments (algorithm 1).

Light microscopy — The diagnosis of adenocarcinoma is usually based on the identification of glandular structures that are formed by the neoplastic cells. These features are shared by all adenocarcinomas, and the site of the primary tumor usually cannot be determined by light microscopy. Although certain morphologic features can be associated with a particular tumor type (eg, papillary features with ovarian cancer and signet ring cells with gastric cancer), they generally are not sufficiently specific to provide a definitive diagnosis.

Special considerations for poorly differentiated adenocarcinoma — The diagnosis of poorly differentiated adenocarcinoma is usually made when only minimal glandular formation is seen on histologic examination or in tumors that lack glandular differentiation
but stain positively for mucin. Adenocarcinoma, poorly differentiated adenocarcinoma, and poorly differentiated carcinoma are histologic diagnoses that represent a spectrum of tumor differentiation rather than well-demarcated entities. Different pathologists may use somewhat different criteria for each of these diagnoses.

The light microscopic diagnosis of poorly differentiated adenocarcinoma should be interpreted with caution, since some of these patients have a distinctive tumor biology and responsiveness to systemic chemotherapy. For this reason, evaluation and treatment of patients with poorly differentiated adenocarcinoma of unknown primary site should follow the guidelines outlined for poorly differentiated carcinoma of unknown primary site, including the use of IHC staining, a molecular cancer classifier assay (MCCA), and electron microscopy (if necessary) to identify potentially chemotherapy-responsive cancer and rule out other tumor types such as hematologic malignancies, sarcomas, neuroendocrine carcinomas, or germ cell tumors. (See "Poorly differentiated cancer from an unknown primary site", section on 'Diagnostic evaluation'.)

Immunohistochemistry — In most instances, IHC is successful in defining the tumor lineage of poorly differentiated neoplasms (table 1). However, IHC allows the determination of the tissue of origin in only a minority of adenocarcinomas of unknown primary site [8]. In part, this is due to the atypical staining patterns present in many adenocarcinomas. However, selection of the appropriate IHC stains is also problematic. It is not possible to do all the IHC stains listed in the table (table 2) due to limitations of available tissue and expense; rather, the pathologist must select stains based on suggestive histologic or clinical findings [9].

In evaluating a CUP, most pathologists start with a panel of four IHC stains that form the basis of several potentially diagnostic patterns (cytokeratin [CK]7, CK20, thyroid transcription factor-1 [TTF-1], caudal-type homeobox transcription factor [CDX]-2) to narrow the diagnostic possibilities, and add stains based on histology, clinical presentation, and results of the initial IHC panel [8]. With this approach, results are strongly suggestive of a single cancer type in only 33 percent of CUP patients [10]. Even in these patients, clinicians have hesitated to use the IHC predictions to guide site-specific treatment, since the pathology reports are often somewhat equivocal, with phrases like "consistent with" or "favor," rather than a firm diagnosis.
In a few situations, IHC provides strong evidence regarding the primary site (table 1 and table 2) [11]:

- Positive staining for prostate-specific antigen is quite specific for prostate cancer and should be included in the evaluation of men with adenocarcinoma of unknown primary site.

- Positive staining for thyroglobulin in concert with TTF-1 is relatively specific for thyroid cancer.

- Positive staining for CDX-2, or the combination of CK20-positive/CK7-negative, is highly suggestive of colorectal cancer [12].

- Positive staining for CK7 and TTF-1, with negative staining for CK20, is highly suggestive of lung adenocarcinoma.

- Positive staining for CK7, gross cystic fluid protein 15, and GATA-binding protein 3 (GATA3) is highly suggestive of breast adenocarcinoma.

- Positive staining for renal cell carcinoma (RCC, also called renal cell carcinoma marker [RCC-Ma]) and paired box gene 8 (PAX8), with negative staining for CK20 is highly suggestive of RCC.

- Positive staining for CK7, Wilms tumor 1 (WT-1), and PAX8 is highly suggestive of ovarian adenocarcinoma.

- Positive staining for octamer-binding transcription factor (OCT)4 and placental alkaline phosphatase is highly suggestive of germ cell carcinoma.

The pattern of staining with the cytokeratins CK20 and CK7 may be helpful in narrowing the diagnostic spectrum (table 3 and table 2). CK20 is a low molecular weight cytokeratin that is normally expressed in the lower gastrointestinal tract, urothelium, and in Merkel cells [12]. CK7 is expressed by cancers of the lung, ovary, endometrium, and breast, but not in cancers of the lower gastrointestinal tract. The CK20-positive/CK7-negative combination is the most specific, particularly if the CDX-2 stain is also positive, and allows a strong prediction of colorectal cancer in patients with compatible clinical and histologic features. In a study of 93 autopsy cases of adenocarcinoma of unknown primary site involving the liver, a CK20-positive/CK7-negative pattern correctly predicted a colorectal primary in 17 of 21
cases (81 percent) [12]. Other CK20/CK7 combinations were not specific enough for confident identification of a primary site.

None of these IHC results have been prospectively evaluated for accuracy in identifying the primary site in patients with CUP. Likewise, no studies have adequately addressed the question of whether treatment based on these IHC "diagnoses" improves the outcome for these patients. However, the increasing availability of the MCCA has provided an opportunity to evaluate the accuracy of IHC predictions and to determine whether they can be used to guide treatment.

Further evaluation — After initial clinical and pathologic evaluation, 15 to 20 percent of patients with adenocarcinoma of unknown primary site fit into one of several specific subgroups, and require further, focused evaluation and specific treatment (see 'Specific patient subgroups' below). The remaining 80 to 85 percent of patients do not fit into these specific subgroups (although some have a primary site suggested by IHC). In these patients, the tissue of origin can usually be identified using an MCCA, and opportunities for targeted therapy can be suggested by comprehensive molecular profiling. (See 'Molecular cancer classifier assays' below and 'Comprehensive molecular profiling' below.)

SPECIFIC PATIENT SUBGROUPS

The group of patients with adenocarcinoma of unknown primary site contains several clinically defined subgroups for which specific therapy is available. All patients who fit into one of these subgroups after the clinical and pathologic evaluations have been completed should receive specific therapy.

Women with peritoneal carcinomatosis — In women, adenocarcinoma causing diffuse peritoneal involvement without an obvious primary tumor usually originates in the ovary or in extraovarian tissues with similar histogenesis. Disease-directed therapy can result in a relatively favorable outlook in these patients compared with adenocarcinoma of unknown primary site of nonovarian origin. (See "First-line chemotherapy for advanced (stage III or IV) epithelial ovarian, fallopian tubal, and peritoneal cancer".)

- Pathology and pathogenesis — In some cases, these tumors arise from the peritoneal surface or fallopian tubes, which share a common histogenesis with ovarian tissues. Many have morphologic features that are typical for epithelial ovarian carcinoma, such
as papillary configuration or psammoma bodies. In such cases, this syndrome has been termed serous carcinoma of the peritoneum or multifocal extraovarian serous carcinoma. However, some patients may present with a poorly differentiated adenocarcinoma that does not exhibit a papillary configuration (analogous to poorly differentiated epithelial ovarian carcinomas); they should be approached similarly to those with typical serous histology. Both immunohistochemistry (IHC) and molecular cancer classifier assays (MCCAs) often corroborate this diagnosis. (See "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Histopathology", section on 'Microscopic pathology'.)

Primary peritoneal carcinoma may share a common biology with ovarian carcinoma, a concept that is supported by the following observations:

- Women at high risk for ovarian cancer may also develop primary peritoneal carcinoma. For example, these cancers occur more commonly in women with breast cancer susceptibility gene 1 (BRCA1) mutations and occasionally in women from families at high risk for ovarian cancer who have undergone prophylactic oophorectomy. (See "Risk-reducing salpingo-oophorectomy in women at high risk of epithelial ovarian and fallopian tube cancer" and "Screening for ovarian cancer").

- The clinical features of primary peritoneal carcinomas are often typical of advanced ovarian cancer, with tumor involvement limited to the peritoneal surfaces and elevated serum concentrations of cancer antigen 125. (See "Screening for ovarian cancer").

- **Management** – Management of women with peritoneal carcinomatosis of unknown primary site may include a multimodality approach that includes surgical debulking and systemic chemotherapy:
  
  - Surgical cytoreduction should be considered in patients with bulky disease. In patients with epithelial ovarian cancer, debulking may provide the best chance for long-term remission, although the optimal timing is controversial [13]. (See "Cancer of the ovary, fallopian tube, and peritoneum: Surgical cytoreduction").

  - Patients with peritoneal carcinomatosis of unknown primary site often respond well to chemotherapy regimens that are effective in the treatment of advanced epithelial ovarian cancer. Several studies have documented high initial response rates
similar to those seen in patients with advanced ovarian carcinoma [14-18]. (See "First-line chemotherapy for advanced (stage III or IV) epithelial ovarian, fallopian tubal, and peritoneal cancer").

Women with axillary lymph node metastases — Breast cancer should be suspected in women (and, rarely, in men) who have an adenocarcinoma of unknown primary site and axillary lymphadenopathy. Multiple series have demonstrated that women presenting with axillary lymphadenopathy have a much better prognosis than those with adenocarcinoma of other unknown primary sites. (See "Axillary node metastases with occult primary breast cancer", section on 'Initial diagnostic workup' and "Axillary node metastases with occult primary breast cancer", section on 'Prognosis'.)

To support a diagnosis of breast cancer, IHC staining (for estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 [HER2], and other breast cancer-specific markers such as GATA-binding protein 3 [GATA3] and gross cystic duct fluid protein 15) and/or an MCCA should be obtained on the biopsy material in such patients. In addition to physical examination of both breasts, mammography is indicated to search for the primary site. A clinically occult breast cancer will be found in approximately one-third of cases. Bilateral breast magnetic resonance imaging (MRI) is indicated if mammography is negative; an occult breast cancer may be found in approximately 75 percent of such cases. (See "Axillary node metastases with occult primary breast cancer", section on 'Breast MRI'.)

If a focal lesion is identified, further diagnostic evaluation should follow standard guidelines for suspected breast cancer. (See "Diagnostic evaluation of women with suspected breast cancer" and "Clinical features, diagnosis, and staging of newly diagnosed breast cancer").

Women with adenocarcinoma or poorly differentiated carcinoma in axillary nodes, compatible IHC staining or MCCA results, and no metastatic sites other than the axillary lymph nodes may have potentially curable breast cancer. These patients are treated according to guidelines for stage II breast cancer. (See "Axillary node metastases with occult primary breast cancer", section on 'Locoregional treatment' and "Overview of the treatment of newly diagnosed, non-metastatic breast cancer").

However if metastatic sites in addition to axillary lymph nodes are present, such patients may have metastatic breast cancer. These women should receive a trial of systemic therapy according to guidelines for the treatment of metastatic breast cancer. (See "Axillary node
metastases with occult primary breast cancer", section on 'Metastatic disease' and "Systemic treatment for metastatic breast cancer: General principles'.

**Men with skeletal metastases or elevated prostate-specific antigen —** When bone metastases are the first manifestation of metastatic adenocarcinoma, the most common primary tumor sites are the lung, prostate, and less often, liver, kidney, thyroid, and colon [19].

Metastatic prostate cancer should be suspected in men with adenocarcinoma predominantly involving bone, particularly if the metastases are blastic or sclerotic. Elevated serum levels of prostate-specific antigen (PSA) or tumor staining with PSA provides confirmatory evidence of prostate cancer, and such patients should be treated using guidelines for metastatic prostate cancer. Occasional patients have a significantly elevated serum PSA or tumor staining for PSA, but a clinical presentation that is atypical for prostate cancer (eg, metastases to the lung or mediastinal or upper abdominal lymph nodes, without concomitant involvement of bone or pelvic lymph nodes) [20,21]. Such patients, in the absence of data supporting another primary, should also be considered for treatment for metastatic prostate cancer. (See "Bone metastases in advanced prostate cancer: Clinical manifestations and diagnosis".)

Metastatic prostate cancer is amenable to treatment with a range of therapies that differ from those used for metastatic adenocarcinoma of other primary sites; therefore, identification of these patients is important in guiding appropriate therapy. (See "Overview of the treatment of disseminated castration-sensitive prostate cancer".)

**Patients with a colon cancer profile —** Current approaches to systemic treatment for patients with metastatic colorectal cancer have resulted in a substantial improvement in overall survival compared with earlier regimens. (See "Systemic chemotherapy for nonoperable metastatic colorectal cancer: Treatment recommendations".)

Accurate recognition of patients with adenocarcinoma of unknown primary site who are likely to respond to similar treatments is therefore increasingly important. A "colon cancer profile" has been described and includes:

- Predominant metastatic sites in the liver and/or peritoneum
- Adenocarcinoma with histology typical of gastrointestinal origin
Typical IHC staining pattern including cytokeratin (CK)20-positive/CK7-negative or CDX-2-positive

Patients with this profile respond well to chemotherapy with contemporary regimens developed for patients with metastatic colorectal carcinoma (eg, FOLFOX/bevacizumab) [22,23].

Increasing evidence also supports the use of site-specific treatment in cancer of unknown primary site (CUP) patients who have a colorectal tissue of origin identified by MCCA. In two retrospective series, CUP patients who had a colorectal site of origin predicted by MCCA and received standard regimens for advanced colon cancer had median survival >20 months [24,25]. In both series, approximately 45 percent of patients predicted to have colorectal cancer by MCCA had atypical IHC staining, and would not have been identified by standard pathologic evaluation. Although prospective data are needed, the survival documented in these retrospective studies, which is similar to patients with advanced colon cancer, suggests accurate identification by molecular profiling.

Adenocarcinoma of unknown primary in a single site — In occasional patients, only a single metastatic lesion is identified after a complete staging evaluation. Such single lesions have been described in a variety of sites including lymph nodes, brain, lung, adrenal gland, liver, and bone. The possibility of an unusual primary site (eg, apocrine, eccrine, or sebaceous carcinoma) mimicking a metastatic lesion should be considered, but can usually be excluded on the basis of clinical or pathologic features.

In most of these patients, other metastatic sites become evident within a relatively short time. A positron emission tomography (PET) scan may be helpful to rule out additional unrecognized sites of metastatic disease prior to definitive local therapy [26]. (See ‘Initial clinical evaluation’ above.)

If no evidence of additional disease is found, resection of the solitary lesion should be considered. If resection is not feasible because of the location of the metastatic lesion, definitive local radiation therapy should be administered. Local treatment sometimes results in long disease-free intervals.

The benefit of surgical resection of more than one metastatic lesion in patients with CUP is not well documented. Since this approach is recommended in highly selected patients with
several tumor types (eg, renal carcinoma, colon cancer with liver metastases, non-small cell lung cancer), it may also be reasonable in occasional patients with CUP.

In some instances (eg, after resection of a solitary brain metastasis), local radiation therapy may also be appropriate to maximize the chance of local control [27,28]. (See "Overview of the treatment of brain metastases".)

The role of adjuvant chemotherapy in this setting is undefined. However, a primary site can now be predicted in many of these patients using IHC and MCCA. Adjuvant therapy is reasonable to consider if indicated in the management of the tumor type predicted. When a primary site cannot be predicted, empiric chemotherapy may be useful in patients with poorly differentiated carcinoma. (See 'Empiric chemotherapy' below.)

**APPROACH TO PATIENTS NOT INCLUDED IN SPECIFIC SUBGROUPS**

A majority of patients (80 to 85 percent) with adenocarcinoma of unknown primary site do not fit into any of the clinical subgroups outlined above. These patients have traditionally received empiric chemotherapy with regimens designed to have efficacy in a broad spectrum of cancer types. However, the role of molecular cancer classifier assays (MCCAs) and comprehensive molecular profiling in the treatment of these patients is evolving.

Patients are encouraged to enroll in clinical trials, where available, since the cancer of unknown primary site (CUP) population continues to have a poor prognosis with standard treatments. (See 'Molecular cancer classifier assays' below and 'Comprehensive molecular profiling' below and 'Empiric chemotherapy' below.)

Local therapy may be appropriate if only a single focus of disease is identified. (See 'Adenocarcinoma of unknown primary in a single site' above.)

**Choice of treatment approach** — For patients who do not fit into any of the clinical subgroups outlined above and do not have an immunohistochemistry (IHC) profile highly suggesting the primary site, we perform an MCCA to classify CUPs based on primary tumor sites and identify those patients with tumors that are either sensitive or resistant to standard treatment approaches.

**Molecular cancer classifier assays** — MCCAs can accurately identify the tissue of origin and subsequently guide site-specific therapy in patients with CUP. The diagnostic
efficacy of MCCAs is based on distinct gene expression profiles present in different normal body tissues. When cancers arise from normal tissues, the distinct gene expression profiles are usually retained, at least in part, by the neoplastic cells, allowing identification of the tumor site of origin (eg, primary site). Several MCCAs, using either reverse transcription polymerase chain reaction (RT-PCR) or gene microarray technology, are commercially available and provide results with a clinical turnaround time of approximately one to two weeks [29-31]. Based on clinical validation studies, MCCAs can correctly identify the primary site in 85 to 95 percent of metastatic cancers from various known primary sites [29-31] and in the large majority of CUP [10,11,32,33].

MCCA-directed site-specific therapy has been compared with empiric chemotherapy, with mixed results. Some data have suggested improved overall survival for site-specific treatment relative to empiric chemotherapy, particularly in those with "treatment-sensitive" tumor types, where site-specific therapy is quite effective [34,35], which includes approximately one-third of patients with CUP.

In contrast, randomized studies have demonstrated similar outcomes between the two treatment approaches [34,36]. In these studies, the majority of patients had "treatment-resistant" tumor types, where site-specific therapy is relatively ineffective. Therefore, further randomized studies are needed to evaluate the benefit of site-specific treatment versus empiric chemotherapy, specifically in those with treatment-sensitive tumor types. Defining treatment-sensitive tumor types may evolve over time with the use of easily accessible molecular testing, more precise delineation of CUP subsets, and continued improvements of treatment efficacy in many types of advanced cancer. (See 'Cancers with predicted treatment sensitivity' below and 'Cancers with predicted treatment resistance or no primary site identified' below.)

**Cancers with predicted treatment sensitivity** — In patients with potentially treatment-sensitive tumor types detected by IHC and/or MCCA (eg, kidney cancer, colorectal cancer, non-small cell lung cancer [NSCLC], breast cancer, melanoma, ovarian cancer, bladder cancer, and others), we use site-specific therapy, which includes (1) use of site-specific first-line and subsequent-line chemotherapy, (2) molecular testing for specific molecular alterations pertinent to the specific tumor type (eg, human epidermal growth factor receptor 2 [HER2] testing for breast cancer), with targeted therapy for appropriate subsets, and (3) use of immunotherapy if indicated for the tumor type identified.
Comprehensive molecular profiling may also be offered to select patients to identify actionable molecular alterations, a technique also used to identify active therapies in those with treatment-resistant tumors. Support for these recommendations is not yet considered definitive by the National Comprehensive Cancer Network (NCCN). (See 'Comprehensive molecular profiling' below.)

Several attempts have been made to improve treatment outcome in CUP by using site-specific therapy, guided by MCCA predictions. Site-specific treatment and empiric chemotherapy have been directly compared in two randomized trials:

- In a phase III trial (GEFCAPI 04), 243 treatment-naive patients with CUP were randomly assigned to receive either empiric chemotherapy with gemcitabine plus cisplatin or site-specific treatment directed by MCCA results [34]. Among a subset of 60 patients with cancer types considered unlikely to respond to empiric gemcitabine plus cisplatin and thus more likely to respond to site-specific treatment (eg, kidney, colorectal, sarcoma, liver, neuroendocrine, breast, melanoma, salivary gland), 37 received site-specific treatment whereas 23 received empiric chemotherapy. In this small cohort, the one- and two-year overall survival (OS) rates favored patients receiving site-specific therapies (one-year OS 39 versus 30 percent; two-year OS 24 versus 10 percent). For the entire group of 243 patients, median overall survival (10 versus 10.7 months; hazard ratio [HR] 0.92, 95% CI 0.69-1.23) and progression-free survival (PFS; 5.3 versus 4.6 months; HR 0.95, 95% CI 0.72-1.25) were comparable between empiric chemotherapy and site-specific therapy.

- In a smaller, randomized phase II trial, 101 CUP patients were randomized to receive either empiric paclitaxel/carboplatin or site-specific therapy directed by an MCCA [36]. In this group, only 17 patients (17 percent) had carcinomas predicted by MCCA to be sensitive to treatment. Overall survival (9.8 versus 12.5 months) and PFS (5.1 versus 4.8 months) were similar between the two treatment groups. However, the study results were potentially biased by the inclusion of patients with lymphoma (26 patients [20 percent]), which is typically detected on standard pathologic examination; inclusion of these patients in a study designed to evaluate those with CUP suggests problems either with the standard pathology or with the MCCA.

Retrospective, observational studies suggest that site-specific treatment improves outcome in specific tumor types, including colorectal cancer, renal cancer, and poorly differentiated
neoplasms [11,24,25,37-39]. For example, in a large prospective nonrandomized phase II trial, 194 CUP patients received site-specific therapy based on MCCA predictions (CancerTYPE ID) [35]. Median OS for the entire group was 12.5 months, which is longer than the OS observed with empiric chemotherapy in separate studies (median 9 to 11 months). In addition, patients with potentially responsive tumor types did better with site-specific treatment than did those with less responsive types (median 13.4 versus 7.6 months).

Cancers with predicted treatment resistance or no primary site identified — In patients predicted to have a tumor type relatively resistant to treatment as detected by IHC and/or MCCA (eg, pancreatic, biliary, gastric, liver cancer, and others) or those in whom no primary tumor site is identified, empiric chemotherapy provides treatment results equivalent to site-specific therapy, although both approaches have relatively poor efficacy. Several two-drug empiric combinations are reasonable choices for initial therapy, such as paclitaxel plus carboplatin, gemcitabine plus cisplatin (or carboplatin), and gemcitabine plus irinotecan. (See 'Empiric chemotherapy' below.)

With the evolution of newer cancer therapies, however, empiric chemotherapy has become less effective in the diverse CUP population. Treatment now differs markedly based on the site of tumor origin and often involves the identification of defined molecular targets, none of which are included in the empiric chemotherapy regimens for CUP. As a result, there is developing interest in using other molecular profiling techniques to identify and offer therapy directed at the tumor of origin in patients with CUP. (See 'Comprehensive molecular profiling' below.)

As an example, patients with advanced NSCLC are treated using checkpoint inhibitor immunotherapy (alone or in combination with chemotherapy) as well as therapies targeting molecular alterations in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and c-ROS oncogene 1 (ROS1). Prior to these newer therapies, most were initially treated with paclitaxel/platinum, a commonly used CUP regimen [40,41]. Similar situations exist in the treatment of other cancer sites including advanced colorectal, kidney, breast, and gastric cancers. Further details on the specific treatment of these cancers are discussed separately. (See "Personalized, genotype-directed therapy for advanced non-small cell lung cancer" and "Systemic chemotherapy for metastatic colorectal cancer: General principles" and "Immunotherapy of renal cell carcinoma" and "Systemic treatment
for metastatic breast cancer: General principles" and "Initial systemic therapy for locally advanced unresectable and metastatic esophageal and gastric cancer").

**Comprehensive molecular profiling** — We offer comprehensive molecular profiling of CUP. Molecular alterations predictive of activity of targeted agents or immunotherapy are present in a sizable minority of these patients. Such treatment should be offered, either as first-line, when other treatment options are unlikely to be beneficial, or as subsequent treatment.

Comprehensive molecular profiling involves assaying a broad group of genes for the purpose of identifying potentially actionable oncogenic molecular alterations (e.g., HER2, EGFR, BRAF, others), which in one study, were identified in approximately 20 percent of patients with CUP [42].

Comprehensive molecular profiling therefore differs from an MCCA, which measures differential expressions of normal genes to enable identification of a tissue of origin. Similar to MCCAs, data suggest comprehensive molecular profiling using a next-generation sequencing (NGS) panel may also be able to predict tissue of origin, but further clinical validation is necessary [43].

Data supporting the use of comprehensive molecular profiling are rapidly evolving. Increased use of comprehensive profiling has allowed for the evaluation of established targeted agents in a wide variety of cancer types that are rare or have a low incidence of the critical molecular alterations. As expected, active targeted agents have efficacy across a variety of tumor types, as long as the critical molecular alteration is present [44,45]. Examples include BRAF, EGFR, HER2, TRK, high microsatellite instability (MSI-H), and high tumor mutational burden (TMB). However, activity of the same targeted agent can vary widely in different tumor types, for reasons that are incompletely understood [46,47]. (See "Tissue-agnostic cancer therapy: DNA mismatch repair deficiency and response to immune checkpoint blockade in solid tumors" and "TRK fusion-positive cancers and TRK inhibitor therapy").

Available evidence suggests that comprehensive molecular profiling of patients with CUP could identify a substantial number of potentially actionable molecular abnormalities. To date, most comprehensive molecular profiling studies in CUP have been performed on tissue biopsies, but blood-based liquid biopsies (circulating tumor DNA) are becoming important and may eventually replace tissue testing [48].
• In a group of 200 CUP patients (125 with adenocarcinoma, 75 with carcinoma), 38 patients (18 percent) had molecular alterations for which targeted agents are approved in other indications (HER2, BRAF, EGFR, ALK, rearranged during transfection proto-oncogene [RET], breast cancer susceptibility gene [BRCA], R0S1) [42]. The rare TRK mutation (not assessed in this group of CUP patients) is another tumor-agnostic targetable alteration responsive to currently available treatment [49]. At present, the efficacy of targeted therapy in patients with CUP is documented only by a few case reports [50-55], so the impact of these actionable mutations on treatment cannot be fully assessed.

• Comprehensive molecular profiling may also identify patients with CUP who may benefit from immune checkpoint inhibitors. While the use of immune checkpoint inhibitors is largely untested in patients with CUP, the efficacy of these agents seems likely. Cancer types known to be responsive to these agents (lung, urothelial, renal) are well represented in the CUP population. Molecular alterations predictive of response to immune checkpoint inhibitors, including MSI-H, high TMB, and programmed cell death ligand 1 (PD-L1) amplification or overexpression [56-58], have been identified in CUP [59-61]. High TMB (≥20 mutations/mb) is relatively common in CUP, occurring in 8 percent of adenocarcinomas, 11 percent of carcinomas, and 23 percent of squamous carcinomas [59]. PD-L1 is also overexpressed in CUP patients; staining in tumor-infiltrating lymphocytes was seen in 63 percent, and staining of cancer cells was observed in 21 percent of CUP patients [60]. MSI-H and PD-L1 amplification are less common (1 to 2 percent) [61]. (See "Principles of cancer immunotherapy".)

Although comprehensive molecular profiling identifies an actionable molecular alteration in a sizable minority of CUP patients, optimal use of these data in guiding therapy may also require additional information, including identification of the likely primary site. Few targeted drugs are recommended for first-line, single-agent treatment in any solid tumor type. Combination chemotherapy continues to play an integral role in the treatment of many cancers. One would not recommend the same chemotherapy for patients with breast versus colon cancer, nor would one treat patients with either of these cancer types with first-line, single-agent, targeted therapy. Likewise, initial treatment with BRAF-targeted therapy would be inappropriate in a patient with a BRAF V600E mutation if the primary site was known to be colorectal.
Empiric chemotherapy — Empiric chemotherapy has historically been the standard initial therapy for patients with CUP and still remains part of the treatment approach in these patients. However, for those who have actionable targets identified on comprehensive molecular profiling, incorporation of targeted therapy or immunotherapy (either as single agents or in combination with chemotherapy) may be offered. (See 'Comprehensive molecular profiling' above.)

Patients with poor performance status are much less likely to benefit from chemotherapy, and optimal management in these patients may be limited to supportive measures.

Choice of chemotherapy

- **Initial therapy** — Several two-drug combinations have similar activity and are reasonable choices for initial therapy. These combinations include paclitaxel plus carboplatin, gemcitabine plus cisplatin (or carboplatin), and gemcitabine plus irinotecan [33,62-65]. These regimens produce response rates of 25 to 45 percent, with a median OS ranging between approximately 7 and 10 months.

As an example, a combined analysis of five single-arm phase II trials included a total of 396 treatment-naïve patients with CUP treated with empiric chemotherapy. Using this approach, the combined objective response rate (ORR) was 30 percent, median PFS was nine months, and two-year OS was 19 percent [33].

- **Subsequent therapy** — A few subsequent-line empiric regimens have been evaluated in phase II trials, usually following initial therapy with taxane/platinum combinations [66-68]. Modest activity was seen with oxaliplatin/capecitabine (ORR 19 percent; median OS 9.7 months) [66], gemcitabine/irinotecan (ORR 10 percent; median OS 4.5 months) [68], and bevacizumab/erlotinib (ORR 10 percent; median OS 7.4 months) [67]. There are limited data to support the benefit for single agent chemotherapy.

Prognostic factors — Retrospective analyses have identified clinical and pathologic features that are associated with a favorable response to treatment using empiric chemotherapy in patients with CUP [69-75]. Many of these features are related to tumor grade or extent of disease and are prognostic factors for many types of advanced cancer.

These include the following:

-
Tumor location in lymph nodes or soft tissue. Patients with involvement of the liver or bones have a relatively poor prognosis.

- Fewer sites of metastatic disease.
- Female sex.
- Poorly differentiated carcinoma histology.
- Good performance status.
- Normal serum lactate dehydrogenase (LDH) level.
- Normal serum albumin.
- Normal lymphocyte count.

In one prognostic factor analysis that included 150 patients with CUP who were seen at a single institution over a 10-year period, the performance status and serum LDH could be used to separate patients into good- and poor-risk categories. The median survival durations for good- and poor-risk patients were 11.7 and 3.9 months, and one-year survival rates were 45 and 11 percent, respectively [74].

A multivariate analysis of prognostic factors based on a series of 317 consecutive patients found that a normal serum albumin and the absence of liver metastases identified a favorable subset of patients (median survival 371 days, versus 103 days in patients with a low serum albumin and/or liver metastases) [75]. In the same report, the favorable prognosis associated with the combination of a normal serum albumin and the absence of liver metastases was validated in a second cohort of 124 patients with CUP.

Prognostic factors have not been studied in patients receiving site-specific therapy, and they may differ from those recognized in previous studies. In addition, it is likely that molecular tumor prognostic factors of greater clinical value will be identified (eg, actionable mutations, alterations predicting response to immune checkpoint inhibitors). (See 'Cancers with predicted treatment sensitivity' above.)

**SUMMARY AND RECOMMENDATIONS**

- Cancer of unknown primary site (CUP) is diagnosed in patients who have metastatic cancer but have no anatomic primary site identified by a comprehensive initial evaluation. CUPs account for 4 to 5 percent of all invasive cancers. Adenocarcinomas of unknown primary site comprise approximately 70 percent of CUPs. (See 'Introduction' above.)
• Initial evaluation should include a history and physical examination, complete blood count, urinalysis, basic serum chemistries, and computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. In men, assessment should incorporate a prostate examination and measurement of serum prostate-specific antigen (PSA). In women, the evaluation should include a pelvic examination and mammography. Additional evaluation may be warranted based on the findings of clinical and pathologic assessment. (See 'Initial clinical evaluation' above.)

• Histologic characteristics of a biopsy specimen usually allow for classification of the lineage of a CUP (ie, carcinoma versus sarcoma, lymphoma, melanoma). Histologic examination cannot distinguish among various adenocarcinomas, but immunohistochemical (IHC) staining strongly suggests the primary site in approximately one-third of patients.

• Patients with adenocarcinoma of unknown primary site should be evaluated to determine whether their clinical features and pathology classify them as belonging to any of the following subsets for which individualized therapy is appropriate (algorithm 1):

  • Women with adenocarcinoma of unknown primary and peritoneal carcinomatosis and consistent pathology should be treated like those with ovarian carcinoma. This approach may include both surgical debulking and systemic chemotherapy. (See 'Women with peritoneal carcinomatosis' above and "First-line chemotherapy for advanced (stage III or IV) epithelial ovarian, fallopian tubal, and peritoneal cancer" and "Cancer of the ovary, fallopian tube, and peritoneum: Surgical cytoreduction".)

  • Women presenting with adenocarcinoma of unknown primary and axillary lymphadenopathy should be treated as if they have primary breast cancer, as long as the pathology and clinical presentation are consistent with that diagnosis. (See 'Women with axillary lymph node metastases' above and "Axillary node metastases with occult primary breast cancer".)

  • Men with metastatic adenocarcinoma and elevated serum levels of PSA and/or tumor staining with PSA should be treated for advanced prostate cancer. (See 'Men with skeletal metastases or elevated prostate-specific antigen' above and "Overview of the treatment of disseminated castration-sensitive prostate cancer".)
• Patients who present with a colon cancer profile (ie, predominant metastatic sites in the liver and/or peritoneum, an adenocarcinoma with histology typical of gastrointestinal origin, and typical immunohistochemical staining pattern [cytokeratin (CK) 20 positive/CK7 negative, or caudal-type homeobox transcription factor (CDX)-2 positive]) should be treated as if they have metastatic colorectal cancer. Treatment for colorectal cancer should also be considered for patients with a colorectal tissue of origin predicted by a molecular cancer classifier assay (MCCA). (See 'Patients with a colon cancer profile' above and "Systemic chemotherapy for nonoperable metastatic colorectal cancer: Treatment recommendations".)

• Patients with a single metastatic focus of adenocarcinoma who do not fit any of the patterns above should be carefully evaluated to exclude any other sites of disease involvement. If no other site of disease involvement can be identified, we offer definitive local therapy, consisting of either surgical resection or radiation therapy. Although most patients will develop disseminated disease relatively rapidly, this approach is associated with prolonged survival in some cases. (See 'Adenocarcinoma of unknown primary in a single site' above.)

• In patients who do not fit into a specific subset, we attempt to identify the site of origin using an MCCA or IHC stains to identify the primary site of the CUP, and classify it as either sensitive or resistant to standard treatment approaches (algorithm 1). (See 'Approach to patients not included in specific subgroups' above and 'Molecular cancer classifier assays' above.)

• In patients predicted to have potentially treatment-sensitive tumor types by IHC and/or MCCA (eg, kidney cancer, colorectal cancer, non-small cell lung cancer [NSCLC], breast cancer, melanoma, ovarian cancer, bladder cancer, and others), we use site-specific therapy, which includes (1) use of site-specific first-line and subsequent-line chemotherapy, (2) molecular testing for specific molecular alterations pertinent to the specific tumor type (eg, human epidermal growth factor receptor 2 [HER2] testing for breast cancer), with targeted therapy for appropriate subsets, and (3) use of immunotherapy if indicated for the tumor type identified. The support for these recommendations is not yet considered definitive by the National Comprehensive Cancer Network (NCCN). (See 'Choice of treatment approach' above and 'Cancers with predicted treatment sensitivity' above.)
• In patients predicted to have a treatment-resistant tumor type by IHC and/or MCCA (e.g., pancreatic, biliary, gastric, liver cancer, and others) or who do not have a specific tumor type identified, empiric chemotherapy provides treatment results equivalent to site-specific therapy (both treatments relatively poor). Several two-drug empiric combinations are reasonable choices for initial therapy, such as paclitaxel plus carboplatin, gemcitabine plus cisplatin (or carboplatin), and gemcitabine plus irinotecan. (See 'Approach to patients not included in specific subgroups' above and 'Cancers with predicted treatment resistance or no primary site identified' above.)

We also offer comprehensive molecular profiling of CUP. Molecular alterations predictive of activity of targeted agents or immunotherapy are present in a sizable minority of these patients. Such treatment should be offered, either as first-line, when other treatment options are unlikely to be beneficial, or as subsequent treatment. (See 'Comprehensive molecular profiling' above.)

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REFERENCES


GRAPHICS

Treatment of patients with cancer of unknown primary site

Clinical presentation

Initial clinical, pathologic evaluation

Additional focused clinical, IHC studies based on initial results

No primary site found

Anatomic primary site located

Specific treatable subgroup

No treatable subgroup identified

Specific treatment for subgroup

Molecular cancer classifier assay

Site-specific treatment

Treatment-sensitive cancer type

Treatment-resistant cancer type or no tissue of origin predicted

Additional testing if necessary for the specific cancer type (may include molecular testing of biopsy, tumor markers)

Consider comprehensive molecular profiling of tumor

Site-specific therapy or clinical trial

Consider comprehensive molecular profiling of tumor

Empiric chemotherapy, site-specific therapy, or clinical trial

IHC: immunohistochemistry.

## Characteristic immunohistochemical staining patterns for undifferentiated neoplasms

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Cytokeratin</th>
<th>EMA</th>
<th>LCA</th>
<th>S-100</th>
<th>Desmin/vimentin*</th>
<th>OCT 4/HCG/ AFP/ PLAP*</th>
<th>Chromogranin/ synaptophysin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>S</td>
<td>-</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>Melanoma</td>
<td>- R</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>-</td>
<td>S</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>-</td>
<td>- R</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>- R</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

EMA: epithelial membrane antigen; LCA: leukocyte common antigen; S-100: S-100 protein; HCG: human chorionic gonadotrophin; AFP: alpha-fetoprotein; PLAP: placental leukocyte alkaline phosphatase; +: positive; -: negative; S: sometimes positive; R: rare positive cells.

* Positive for one or more of these markers.

### Immunohistochemical and histochemical stains useful in the differential diagnosis of various carcinomas

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Immunohistochemical staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma</td>
<td>Positive: Pan keratin, AE 1/3, CAM 5.2, OSCAR, EMA</td>
</tr>
<tr>
<td></td>
<td>Negative: CD 45</td>
</tr>
<tr>
<td></td>
<td>Variable: CK 7, CK 20, S-100, vimentin</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>Positive: CK 20, CDX-2</td>
</tr>
<tr>
<td></td>
<td>Negative: CK 7</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Positive: TTF-1, napsin A, CK 7, mucicarmin, PAS-D</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>Positive: p 40, p 63, CK 5/6, desmoglein</td>
</tr>
<tr>
<td></td>
<td>Negative: CK 7 (usually)</td>
</tr>
<tr>
<td>Small-cell carcinoma</td>
<td>Positive: TTF-1, high proliferative rate (Ki-67, MIB-1)</td>
</tr>
<tr>
<td></td>
<td>Variable: Chromogranin, synaptophysin</td>
</tr>
<tr>
<td>Neuroendocrine carcinoma</td>
<td>Positive: Chromogranin, synaptophysin, epithelial stains</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>Positive: HCG, AFP, Oct4 transcription factor, placental alkaline phosphatase, epithelial stains</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Positive: Hep par 1, CEA, AFP, glypican 3</td>
</tr>
<tr>
<td></td>
<td>Negative: CK 7, CK 20</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>Positive: Pan keratin, CAM 5.2, Pax-8, CK 7, vimentin, RCC, CD 10</td>
</tr>
<tr>
<td></td>
<td>Negative: CK 20, CEA</td>
</tr>
<tr>
<td>Prostate carcinoma</td>
<td>Positive: PSA, prostatic acid phosphatase</td>
</tr>
<tr>
<td></td>
<td>Negative: CK 7, 20</td>
</tr>
<tr>
<td>Pancreas carcinoma</td>
<td>Positive: CA 19-9, CK 7, CDX-2, CK 17</td>
</tr>
<tr>
<td></td>
<td>Variable: CK 20</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>Positive: ER, PR, Her-2-neu, CK 7, gross cystic fluid protein 15, epithelial stains, GATA 3, mammaglobin</td>
</tr>
<tr>
<td></td>
<td>Negative: CK 20</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>Positive: CK 7, WT-1, Pax-8, ER</td>
</tr>
<tr>
<td></td>
<td>Negative: CK 20, CDX-2</td>
</tr>
</tbody>
</table>

EMA: epithelial membrane antigen; CD: luster of differentiation; CK: cytokeratin; S-100: S-100 protein; CDX: caudal-type homeobox transcription factor 2; TTF-1: thyroid transcription factor-1; PAS-D: Periodic Acid Schiff with diastase predigestion; NSE: neuron-specific enolase; HCG: human chorionic gonadotropin; AFP: alphafetoprotein; Hep par: hepatocyte paraffin 1 monoclonal antibody; CEA: carcinoembryonic antigen; Pax: paired box gene; RCC: renal cell carcinoma; PSA: prostatic specific antigen; CA: carbohydrate antigen 19-9; ER: estrogen receptor; PR: progesterone receptor; WT-1: Wilms tumor-1 protein.

**References:**


2. Pelosi G, Rossi G, Bianchi F, et al. Immunohistochemistry by means of widely agreed-upon markers (cytokeratins 5/6 and 7, p63, thyroid transcription factor-1, and vimentin) on small biopsies of non-small...

Graphic 56518 Version 12.0
### Differential diagnosis of unknown primary cancers based upon immunostaining for cytokeratin (CK) 7 and 20

<table>
<thead>
<tr>
<th>CK7+ CK20+</th>
<th>CK7+ CK20-</th>
<th>CK7- CK20+</th>
<th>CK7- CK20-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelial tumors</td>
<td>Non-small cell lung cancer</td>
<td>Colorectal cancer</td>
<td>Hepatocellular cancer</td>
</tr>
<tr>
<td>Mucinous ovarian cancer</td>
<td>Small cell lung cancer</td>
<td>Merkel cell cancer</td>
<td>Renal cell cancer</td>
</tr>
<tr>
<td>Pancreatic or biliary cancer</td>
<td>Breast cancer</td>
<td>Endometrial cancer</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Nonmucinous ovarian cancer</td>
<td></td>
<td></td>
<td>Squamous cell lung cancer</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td></td>
<td></td>
<td>Head and neck cancer</td>
</tr>
<tr>
<td>Squamous cancer of cervix</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic or biliary cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CK: cytokeratin; +: positive; -: negative.


Graphic 58475 Version 4.0

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