Cancer of Unknown Primary Site: Evolving Understanding and Management of Patients

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Abstract: Cancer of unknown primary site is a common clinicopathologic syndrome representing a very heterogeneous group of patients with metastatic cancers and clinically undetectable primary tumor sites. The standard treatment for these patients for the last 15 years has been empiric "broad-spectrum" chemotherapy. In recent years, improved immunocytochemistry and the emergence of gene expression profiling have provided the diagnostic tools necessary to accurately define the tissue of origin in the majority of patients. Recent data have confirmed the ability of molecular profiling assays to complement standard pathologic diagnosis, and a large prospective study has documented a survival improvement for patients treated with site-specific therapy directed by the molecular assay diagnoses of their tissues of origin compared to empiric chemotherapy. The clinicopathologic evaluation of patients is now more standardized. The era of empiric chemotherapy administered to all patients is coming to an end, and customized therapies are favored. The management of patients has evolved with the ability to confidently define the tissue of origin. Further delineation of the molecular aberrations in advanced solid tumors, regardless of the primary tumor site, signals a more precise and perhaps more effective therapy for each patient.

Keywords
Cancer of unknown primary site, site-directed therapy, molecular profiling, immunohistochemistry, gene expression profiling

Introduction

Cancer of unknown primary site (CUP) is not a single entity, but rather a common clinical syndrome that represents many types of cancers. Patients are considered to have CUP if no primary site is identified after standard clinical and pathological evaluation. CUP accounts for approximately 3–4% of all advanced cancers in the United States diagnosed annually.[1] In autopsy series, primary tumor sites have been documented in roughly 75% of CUP patients.[2] The majority of CUP patients have carcinoma, with adenocarcinoma as the most common histology. Although the biology of CUP remains

an enigma, most patients have a small primary tumor that can metastasize, and the metastases grow while the primary tumor usually remains small.

The spectrum of patients with suspected CUP continues to evolve with the emergence of new and improved diagnostic technologies. There is no universal agreement regarding the diagnostic tests required for all patients at the time of clinical presentation. The large majority of biopsies from these patients reveal carcinomas and, rarely, other lineages are eventually diagnosed (eg, lymphoma, sarcoma, and melanoma). This review will discuss the evolving changes in the understanding and management of CUP.

Emerging Role of Immunohistochemistry (IHC) and Gene Expression Profiling

More precise IHC marker stains[3] and gene expression/molecular profiling assays have led to improvements in the evaluation of tumors. [4,5] Over the past 10–15 years, improvements have also been made in the treatment of many known advanced solid tumors. Standard treatment now offers extended survival in patients with advanced cancers of the colon, lung, ovary, breast, stomach, kidney, gallbladder, and others. Therefore, the identification of the tissue of origin in CUP is now more important than it was in the past. The stakes are higher now than they were a decade ago and are likely to be even higher in the future, since many CUP patients will have better outcomes if treated with site-specific regimens that are known to be effective for their particular tumor type.

Advancements in properly diagnosing the occult primary cancer or tissue of origin have occurred with the use of panels of IHC stains and molecular profiling assays. However, several drawbacks are associated with the IHC stains. In order to perform these tests accurately and in a reproducible manner, technical expertise is required. Proper interpretation requires an experienced pathologist, and any of these stains can yield false-positive and false-negative results. Although there is no universal consensus regarding which IHC stains should be obtained on the initial biopsy, the chosen stains should be based on the clinical findings, histologic diagnosis, and knowledge of the common occult tumors presenting as CUP with relatively diagnostic IHC profiles. Screening with multiple IHC stains is expensive, frequently exhausts the biopsy specimen, and does not tend to be more revealing than a rational and measured step-wise approach. Although several IHC staining patterns or profiles are highly suggestive of particular primary tumor types, there remains substantial variability. For example, the absence of TTF-1 or CDX-2 positivity in a minority of lung and colon adenocarcinoma, respectively, is well recognized. There are likely many subsets within each category of specific carcinomas. For example, IHC in breast cancer may include positive, negative, or mixed staining for estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2). Additional details regarding IHC and CUP will be discussed later.

Molecular profiling assays have emerged from microarray technology that was invented approximately 15 years ago. Several assays are commercially available in the United States.[5] The usefulness of molecular assays in CUP has been difficult to prove, but substantial data now validate the relative accuracy of these tests in predicting the tissue of origin.[6-13] Molecular assays have improved outcome for CUP patients who were consequently able to receive site-specific or customized therapy, rather than the standard empiric therapy.[14]

As demonstrated by several correlative methods in CUP,[13] the accuracy of the molecular profile assay (Cancer TYPE ID, bioTheranostics; real-time reverse transcription polymerase chain reaction [RT-PCR]) in predicting the tissue of origin is approximately 80%. This accuracy is similar to that shown in known advanced primary cancers.[5,10-12] Considerable data now support the utility of molecular assays to complement standard pathology by providing the diagnosis of the tissue of origin in some patients when there is uncertainty based upon IHC staining.

Recently, my colleagues and I conducted a large prospective study in CUP that examined the outcomes or survival of patients treated with site-specific or customized therapies, based upon the molecular assay diagnosis.[14] In 98% of tumors with successful assays, a single tissue of origin was predicted. A total of 194 patients received site-specific treatment; the median survival was 12.5 months, compared to the expected survival of approximately 9 months for CUP patients receiving empiric, "one-size-fits-all" therapy.[1] Furthermore, the survival of 115 patients with molecular diagnoses of more responsive tumors (colorectal, breast, ovary, kidney, prostate, bladder, non–small cell lung, germ cell, poorly differentiated neuroendocrine tumor, lymphoma, and small cell lung) versus the survival of 79 patients with less responsive tumors (biliary tract, pancreas, gastroesophageal, liver, melanoma, sarcoma, cervix, carcinoid, endometrium, mesothelioma, skin, thyroid, head and neck, and adrenal) was significantly longer (13.4 months vs 7.4 months, respectively; P=.04). The following are examples of survival with individual, molecularly-diagnosed tumor types: biliary tract, 6.8 months; pancreas, 8.2 months; ovarian, 29.6 months; breast, greater than 24 months (not yet reached). These data support a survival advantage in CUP when patients receive site-directed therapy based on the molecular diagnosis, rather than the administration of empiric standard regimens to all patients. When consid-

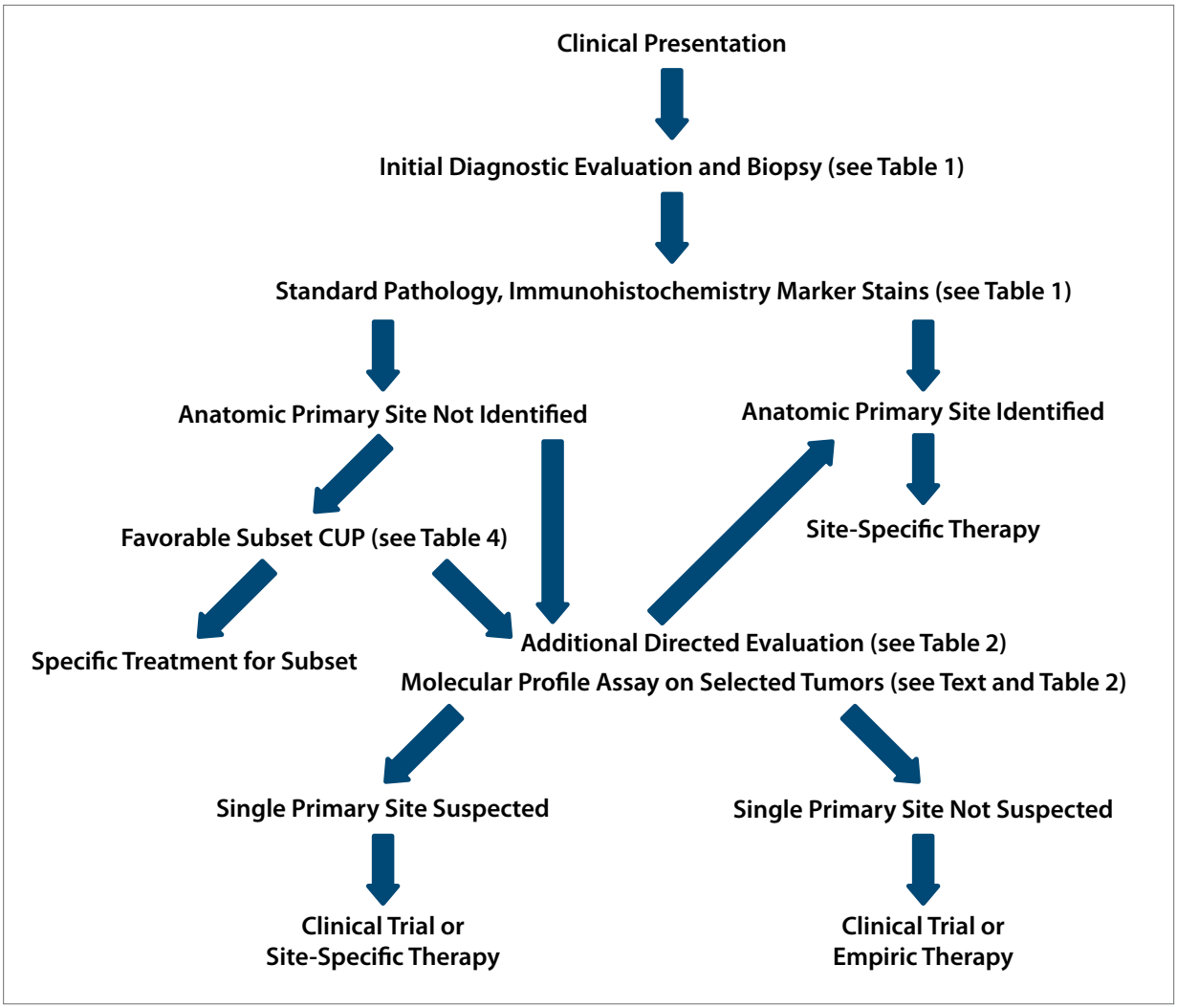

Figure 1. Evaluation of patients with possible cancer of unknown primary site (CUP).

ering the fact that many CUP patients have tumor types that are relatively unresponsive to any chemotherapy, the results of this large prospective trial are noteworthy.

The aggregate data from several studies,[6-9,14-17] both retrospective and prospective, now make a compelling argument that gene expression profiling of the biopsy specimen in CUP patients will provide a relatively accurate tissue of origin diagnosis and customized or site-specific therapy directed by the molecular assay diagnosis results in an improved outcome compared to empiric chemotherapy. The probability of accurately determining the tissue of origin is enhanced even further when considering all of the clinicopathologic findings in concert with the molecular assay result. The ability to diagnose the likely tissue of origin in most CUP cases has substantially changed the management for the majority of these patients.

Current Evaluation and Management

A diagnostic approach to patients with possible CUP is illustrated in Figure 1. A biopsy should be performed (incisional, excisional, or core biopsy preferred) before embarking on a more extensive evaluation. The clinicopathologic findings may suggest additional clinical and/or specialized pathology testing. The initial diagnostic evaluation recommended is listed in Table 1. Positron emission tomography (PET) scanning can be included in this initial evaluation of CUP, but supporting data regarding primary site detection in large numbers of patients are lacking. Squamous cell carcinoma involving cervical lymph nodes is an exception; in a large number of these patients, the primary site is identified by PET scan in the head and neck region.[1] Several additional tests may be suggested by the clinical findings and pathology in an attempt to find the primary

Table 1. Initial Diagnostic Evaluation in CUP Patients

☐ Complete history, including detailed review of systems
☐ Complete physical examination
☐ CBC, CMP, LDH, UA
☐ CT scans of chest, abdomen, pelvis
☐ PET scan in select patients
☐ Mammography in women
☐ Serum PSA in men
☐ Pathology, including screening IHC marker stains on carcinomas (CK7, CK20, TTF-1, CDX-2)
☐ Further clinical and pathologic evaluation based on clues from history, physical examination, laboratory testing, medical imaging, and specialized pathology (Table 2)

CBC=complete blood count; CMP=complete metabolic profile; CT=computed tomography; CUP=cancer of unknown primary site; IHC=immunohistochemistry; LDH=lactate dehydrogenase; PET=positron emission tomography; PSA=prostate-specific antigen; UA=urinalysis.

site or correctly establish the tissue of origin. Although no single algorithm has been uniformly accepted, Table 2 lists additional types of supplemental directed evaluation, based on several clinicopathologic features. Atypical sites of metastasis are not unusual in CUP, as proven by necropsy series, in which the primary tumor site is identified. For example, occult pancreatic primaries initially metastasize to bones and/or lungs more frequently than what is expected from known pancreatic carcinoma; prostate carcinoma seems to initially spread to nodes and/or lungs more often than to bones. However, the majority of occult primary tumors spread to regional nodes and to other well-established sites similar to their counterparts with known primary cancers. Although the sites of metastasis are not specific enough to definitely identify the tissue of origin, they do aid in narrowing the possibilities in some patients. Examples include colorectal to liver/peritoneal cavity; lung to mediastinal/hilar nodes/bone/brain; ovary to peritoneal cavity; breast to nodes/liver/bone/skin/lung; and kidney to nodes/bone/lung. Therefore, the sites of metastasis do suggest which occult primaries may be present and help to determine which additional IHC staining to perform. Any clues should be investigated further. For example, patients with occult blood in the stool should undergo esophagogastrodudenoscopy and colonoscopy. In patients presenting with isolated axillary adenopathy, magnetic resonance imaging (MRI) of the breasts should be obtained, even if mammography is unrevealing. In patients with large liver lesions and no other detectable metastasis, serum alpha-fetoprotein (AFP) is indicated.

New and evolving diagnostic technology helps to facilitate a more personalized therapy for each patient. However, the clinical context (including sex, specific historic details, sites of metastasis, laboratory and medical imaging findings, and histopathology) sets the stage for further evaluation, and should be used in concert with IHC stains and, when necessary, a molecular profiling assay. In the initial diagnostic evaluation (Table 1), screening IHC stains should be performed on all carcinomas, to include CK7, CK20, TTF-1, and CDX-2. The IHC profiles for some lung (adenocarcinoma/large cell) and colorectal carcinomas are relatively specific, and these carcinomas represent common occult primary sites in CUP. For patients whose tumors fit a classic colorectal IHC profile (CK7-, CK20+, CDX-2+), colonoscopy should be performed. In those with an adenocarcinoma/large cell non–small cell lung cancer profile (CK7+, CK20-, TTF-1+), bronchoscopy should be considered. Several IHC staining profiles are now believed to suggest a single primary tumor site (Table 3).[3] However, even if these occult primaries are present, not all stains will reveal the expected positivity or negativity in the tumor cells of all patients. Furthermore, it is not practical or feasible to perform all possible IHC stains on every biopsy specimen. As previously mentioned, initial clinicopathologic findings should guide further possible testing in each patient, including other imaging tests, additional IHC stains, and, in selected patients without a single likely tissue of origin diagnosis, a molecular profile assay. Oncologists and pathologists need to communicate regarding the clinical features and histopathologic findings. Pathologists play a vital role in deciding which additional specialized studies are indicated. In many instances, the clinical setting suggests which additional IHC stains may be useful, and IHC staining patterns may suggest further specific clinical testing. A stepwise evaluation begins with the initial diagnostic evaluation of the patient within a particular clinical context.

The diagnosis of CUP is made if an anatomic primary tumor site is not detectable. The IHC findings and/or molecular profiling results may establish the tissue of origin or primary site, but patients should still be considered within the clinicopathologic syndrome of CUP. However, it is now appropriate to identify those patients who have a tumor with IHC and/or molecular profiles that strongly suggest a single primary site as CUP-colorectal, CUP–non-small cell lung, CUP-breast, etc. Customized or site-specific treatment regimens are reasonable in these patients, as recent data show that their overall survival is improved by such tailored therapeutic approaches.[14] If further investigation verifies survival that is similar to their counterparts with advanced known primary carcinomas, these patients may be included as subsets of those same known advanced primary cancers.

Over the past 3 decades, considerable clinicopathologic data have established several "favorable subsets"

Table 2. Additional Evaluation of Specific Patient Subsets Defined by Initial Diagnostic Evaluation

Results of Initial Evaluation	Additional Evaluation	
	Clinical	IHC Staining
Features of colon cancer (liver/peritoneal metastases; CK20+/CK7-, CDX2+)	Colonoscopy	–
Features of lung cancer (hilar/mediastinal adenopathy; TTF-1+)	Bronchoscopy	–
Mediastinal/retroperitoneal mass	Testicular ultrasound; serum HCG, AFP	PLAP, OCT4; FISH for i(12p)
Women with features of ovarian cancer (pelvic/peritoneal metastases; CK7+)	Pelvic/intravaginal ultrasound	WT-1
Women with features of breast cancer (axillary nodes, bone, lung, liver metastases, CK7+)	Breast MRI	ER, GCDFP-15, HER2, or FISH
Predominant liver metastases (CK7-, CK20-)	Serum AFP	Hepar-1
Poorly differentiated carcinoma, with or without clear cell features	Serum AFP if Hepar-1+; octreotide scan if neuroendocrine stains +	Chromogranin, synaptophysin, RCC, Hepar-1, HMB-45
Any histology without a single site of origin predicted by IHC	Obtain a molecular profile assay on biopsy specimen	

AFP=alpha-fetoprotein; ER=estrogen receptor; FISH=fluorescence in situ hybridization; GCDFP=gross cystic disease fluid protein; Hepar-1=hepatocyte paraffin-1; HER2= human epidermal growth factor receptor 2; HCG=human chorionic gonadotropin; IHC=immunohistochemistry; MRI=magnetic resonance imaging; PLAP=placental alkaline phosphatase; RCC=renal cell carcinoma.

(Table 4) of CUP patients (20% of all CUP) who have an improved prognosis with specific therapies[1] compared to the majority of patients (80%) with unfavorable prognostic features. Patients who are not defined in a favorable subset have a relatively poor prognosis, despite the use of empiric chemotherapy (combinations of broad-spectrum antineoplastic agents), which has been the standard treatment for approximately 15 years. While the overall long-term survival has improved (40% at 1 year, 20% at 2 years, and 10% at 3 years and beyond), the median survival has remained at approximately 9 months.[18,19] It has become clear that the administration of empiric therapeutic regimens to all patients is no longer appropriate.

Improvements in systemic therapy have occurred in the past decade for many patients with advanced carcinomas (including non–small cell lung, breast, ovary, esophagus, stomach, renal, bladder/renal, pelvis/ureter, prostate, colon, rectal, uterine cervix, anal canal, liver, melanoma, and head and neck). Several targeted drugs are now also indicated for many of these patients. In advanced colorectal carcinomas, the median survival has increased from 8 months to nearly 2 years. There are now recognized subsets of breast cancer (HER2-amplified) and non–small cell lung cancer (EGFR mutation, anaplastic lymphoma kinase [ALK] translocation, and R0S1 mutation) that respond well to targeted agents.

According to a first-generation gene expression–based classifier for 6 specific cancer types plus other undesignated types, identifying a small subset of patients with CUP having a colorectal-like gene expression pro-

Table 3. IHC Marker Staining Profiles Supportive of a Single Primary Site in CUP*

Colorectal	CK7-, CK20+, CDX-2+
Lung, adenocarcinoma/ large cell	CK7+, CK20-, TTF-1+
Lung-Neuroendocrine (small cell/large cell)	Chromogranin+, synaptophysin +, TTF-1+
Breast	CK7+, ER+, GCDFP-2+ and/or mammoglobulin+
Ovary	CK7+, ER+, WT-1+
Prostate	CK7-, CK20-, PSA+
Renal	RCC+ and/or PAX8+, Vimentin+, CD10+
Liver	Hepar-1+, CD10+, CD13+
Melanoma	S100+, Melan-A+, HMB-45+
Germ cell	PLAP+ and/or OCT4+
Thyroid (follicular/papillary)	TTF-1+, Thyroglobulin+
Adrenal	Alpha-inhibin+, melan-A (A103)+

*When the above IHC profiles are present in an appropriate clinical context, CUP should be designated as CUP-colorectal profile, CUP–non-small cell profile, CUP breast profile, etc. In patients without a single diagnosis by IHC, a molecular profile assay should be obtained.

CUP=cancer of unknown primary; IHC=immunohistochemical.

Table 4. Favorable Subsets Identified by Clinical and Pathologic Features

Histology	Clinical Subset	Therapy	Prognosis
Adenocarcinoma	Women, peritoneal carcinomatosis (usually serous)	Treat as stage III ovarian cancer	Survival improved
	Women, axillary node involvement	Treat as primary breast cancer	Survival improved
	Men, blastic bone metastases or high serum PSA/tumor PSA staining	Treat as metastatic prostate cancer	Survival improved
	Colon cancer profile (IHC and/or molecular assay)	Treat as metastatic colon cancer	Survival improved
	Single metastasis	Surgical resection and/or radiotherapy ± chemotherapy	Survival improved
Squamous carcinoma	Inguinal adenopathy	Inguinal node dissection, radiation therapy, ± chemotherapy	15–20% 5-year survival
	Cervical adenopathy	Treat as locally advanced head/neck primary	25–40% 5-year survival
Poorly differentiated carcinoma	Extragonadal germ cell syndrome	Treat as poor prognosis germ cell tumor	10–20% cured
Neuroendocrine carcinoma	Low grade	Treat as advanced carcinoid/islet cell tumor	Indolent biology/long survival
	Aggressive (small cell/large cell poorly differentiated)	Treat like extensive-stage small cell lung cancer	High response rate/ survival improved

IHC=immunohistochemical; PSA=prostate-specific antigen.

Table 5. Changing Clinical Landscape of Cancer of Unknown Primary Site

	1999	2012
Immunohistochemistry	Few "specific" markers, not helpful in most patients	Several "specific" markers used in panels, helpful in several patients
Molecular profiling	Not developed/available	Helpful in many patients Complements immunohistochemistry
Single primary site suspected based on all data	Occasionally Mainly favorable subsets	Usually
Empiric systemic treatment	Most patients	Small minority of patients
Systemic treatment for common solid tumors	Useful for a few types	Useful for many types and improving
Clinical trials	Few available	Few available

file predicted responses to treatment similar to those of known colon cancer patients.[7,20-22] When treated with empiric paclitaxel and carboplatin, these patients had low response rates and poor survival. This subset may be recognized by IHC marker stains[20] or molecular profiling assays,[7,21,22] and the prognosis is considerably better when site-directed therapy is chosen over empiric chemotherapy. The CUP-colorectal subset appears to be an example of colorectal carcinoma presenting as CUP, and the prognosis appears similar to that of advanced colorectal cancer with appropriate therapy. The ability to accurately and frequently predict the primary site in CUP is reshaping the field and producing a new paradigm of patient management.

In renal and hepatocellular carcinoma, targeted drugs improve overall survival, and cytotoxic therapy does not tend to be useful. The use of chemotherapy and/or targeted drugs has also improved survival for patients with colorectal cancer, select subsets of non–small cell lung cancer, melanoma, and breast carcinomas. The use of customized therapy for the specific type of carcinoma is much more important now than it was a decade ago. Therefore, the identification of the tissue of origin in CUP is also more important. The era of empiric-based chemotherapy

regimens for CUP is drawing to a conclusion in favor of site-specific treatment based on accurate identification of the tissue of origin. The clinical landscape has evolved rather rapidly in the last several years (Table 5).

Conclusion

The ability to make a specific diagnosis of the occult primary cancer or tissue of origin in CUP patients has greatly improved with the use of panels of IHC stains and molecular profiling assays. Molecular profile assays have been reported to be relatively accurate. A large prospective study of CUP patients who were treated with site-specific therapy based on the molecular assay diagnoses was recently reported. The overall median survival was improved, and various subsets of molecular diagnosed patients had survivals generally similar to their counterparts with known advanced cancer. Survival was significantly superior in those with molecular diagnosed responsive tumor types as compared to those diagnosed with less responsive tumor types.

As site-specific and molecular targeted therapies continue to improve for patients with several advanced solid tumors, these therapies can immediately be applied to CUP patients, specifically defined by IHC profiles and/or molecular profile assays. Clinical oncology is an evolving and fluid field, and new technology is often slow to be incorporated into clinical practice until data are rather firm. Clinical judgment should be exercised in the use of molecular profile assays in CUP, but this is no different than any other new technology in medicine. Additional clinical trials are needed in order to better define the precise role of molecular diagnosis in CUP and to further document the survival of CUP patients treated with specific regimens based on IHC and molecular profile assay diagnoses. Additional molecular studies may also eventually find CUP-associated abnormalities, which may explain the biology of these cancers and perhaps provide additional clues to improve therapy. Empiric chemotherapy regimens will soon have a role only in a small percentage of CUP patients in whom the tissue of origin remains uncertain. Patients with the more responsive or treatable tumor types will benefit most from discovery of their tissue of origin. A fairly large percentage of patients will not currently benefit from site-directed therapy, since effective therapy for their tumor types is not yet available. Confidence in the molecular diagnosis will allow these patients to receive more effective treatment as the standard therapies for these tumor types improve. In the future, most patients with CUP will be treated with therapy indicated for their specific tumor type or with other molecular targeted agents directed at critical molecular aberrations documented in their tumors, regardless of their primary tissue of origin.

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