Malignancy of Unknown Primary

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Introduction

A malignancy or cancer of unknown primary (CUP) is a histologically proven metastatic malignancy where a site of origin cannot be identified, despite comprehensive workup. Generally, cancer of unknown primary is divided into five main categories [1]:

- Adenocarcinoma
- Squamous cell carcinoma
- Carcinoma not otherwise specified (NOS) or poorly differentiated carcinoma
- Neuroendocrine tumor
- Poorly differentiated malignant neoplasm (may include melanoma, sarcoma, lymphoma, germ cell tumor, thyroid cancer)

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Table 15.1 Histology-based survival outcomes [3]

Histology	Proportion of CUPs (%)	Median survival (months)	12-month survival (%)
Adenocarcinoma	60	2	15
Squamous cell carcinoma	5	15	53
Carcinoma NOS/poorly differentiated carcinoma	29	2	15
Neuroendocrine	1	11	48

Epidemiology

Cancer of unknown primary makes up 3–5% of all malignancies; however, the incidence is decreasing [2, 3]. In 20–50% of patients, the primary tumor is never identified, even after the completion of postmortem evaluation [4]. When a primary is identified, the most common sites are lung (27%) and pancreas (24%), followed by other hepatobiliary sites (8%) and kidney (8%) [5].

Unknown primaries are slightly more common in females (52% of CUPs); however, squamous cell carcinomas with unknown primary sites are more commonly diagnosed in men (67% are male) [3]. In general, prognosis is poor, with median survival of 3–9 months [6]. Histologic diagnosis will impact the survival, with longer survival seen in neuroendocrine tumors and squamous cell carcinomas, while shorter survival is seen in adenocarcinoma and carcinoma not otherwise specified (NOS) (Table 15.1).

Diagnostic Workup

Although the majority of patients have poor outcomes, the goal of investigations is to try and identify the primary tumor site, to identify favorable subgroups that may benefit from directed therapy, and avoid unnecessary investigations or delays [7]. At any point in the workup, if the site of the primary is identified, the treatment algorithm (Table 15.2) should be redirected to that tumor type.

Pathologic Assessment

When obtaining tissue for diagnosis, core biopsies are preferred over fine-needle aspirated (FNA) biopsies to allow pathologic assessment [1]. The exception is in head and neck nodes where FNA is acceptable [8]. It is critical to give the pathologist the full clinical picture and inform them of investigations to date to guide testing including immunohistochemistry (IHC). IHC can predict a primary site in 35–40% [1].

Initial stains that help determine the cell line of origin are listed here [9, 10]:

Epithelial: PanKeratin, CAM5.2, AE1, AE3
Squamous cell carcinoma: CK5/6, p63/p40

Table 15.2 Basic workup, special test, and invasive procedures required to assess the site of primary tumor

Basic workup[a]	Special tests	Invasive procedures
Indicated in all patients with CUP	Should be guided by pathology and clinical presentation	Not recommended for initial workup Should be guided by pathology and clinical presentation
Complete history and physical exam: include complete skin exam including the perineum, scalp, head and neck, breast and pelvic exam Review any prior biopsies, prior regressing lesions CBC, chemistry CT chest, abdomen, and Pelvis Urine cytology, urinalysis Mammogram (female) *Core biopsy with pathology review and appropriate immunohistochemistry (IHC)*	Breast MRI and ultrasound – in a female with isolated axillary nodes and negative mammogram PET CT – SCC metastases in the neck, can also be considered in a single metastasis to rule out other occult disease [7] Bone scan if bone metastases Gynecology oncology consult if female with pelvic disease Serum tumor markers[b]	Gastroscopy and colonoscopy if liver metastases, or symptoms CT enteroclysis or capsule endoscopy if small bowel primary is suspected Cystoscopy: for retroperitoneal nodes and suspicious urine cytology Triple endoscopy for isolated neck nodes (laryngoscopy, esophagoscopy, nasopharyngoscopy)

[a]Primary only considered "unknown" if basic workup fails to identify primary site
[b]Tumor marker ordering should not be empiric but suggested by clinical picture. Consider AFP, PSA, beta-hCG, chromogranin A, CEA, Ca125, CA 19-9, thyroglobulin

Table 15.3 Common epithelial tumor sites based on staining patterns of CK7 and CK20 [9]

CK7+/CK20+	*CK7-/CK20+*
Upper gastrointestinal adenocarcinoma Pancreatic ductal adenocarcinoma Urothelial	Colorectal Merkel cell
CK7+/CK20-	*CK7-/CK20-*
Breast Ovarian Pulmonary adenocarcinoma Endometrial and endocervical adenocarcinoma Thyroid Salivary gland adenocarcinoma	Prostate Hepatocellular Renal cell Adrenal cortical Squamous cell Carcinoma (including lung)

Melanoma: S100, SOX10
Lymphoma: LCA, CD20, CD3
Germ cell tumor: OCT 3/4, SALL4
Mesothelial: WT1, calretinin, mesothelin, D2-40
Sarcoma: vimentin, actin, desmin S100, c-kit

If an epithelial marker is determined, CK7 and CK20 status help determine the site of origin (Table 15.3). Further stains can help assess for a primary site (Table 15.4).

Table 15.4 Common tumor-specific antibodies [11]

Carcinoma	Antibody	Sensitivity	Specificity	Other cancers
Breast	GATA3 GCDFP-15	+++ +	++ ++	TCC, salivary, skin Salivary, sweat gl.
CRC	CDX2	+++	+++	Gastric, pancreas
Lung-adeno	TTF-1	+++	+++	Thyroid, NE
GYN	PAX8	++++	++	Thyroid, RCC
Serous Ovarian	WT1	++++	+++	Mesothelioma
RCC	PAX8	++	++	GYN, thyroid
TCC, squamous	P63 p40	++++ ++++	++++ ++++	Thymoma, salivary, NE, trophoblastic
Prostate	PSA	++++	++++	
Thyroid	Tg	+++	++++	

Adapted from Kandalaft and Gown [11]
TCC transitional cell carcinoma, *NE* neuroendocrine, *RCC* renal cell carcinoma, *GYN* gynecologic malignancy

Molecular Testing

When the basic workup, targeted investigations, and IHC are still unable to localize the likely site of the primary, molecular profiling may be attempted. Gene expression profiling (GEP) has been used to identify gene expression patterns of tumor subtypes and helps to identify the primary site. There are many commercial tests available. Studies have compared GEP with site-specific therapy to empiric treatment [12, 13]. A randomized prospective study found that identifying the tissue of origin has not led to improved survival; however, it may allow better prognostication for patients by identifying tumor types that are more likely to respond to treatment [13]. Given that they have not shown improved survival, guidelines are not recommending the use of these tests as the standard of care [14]. Next-generation sequencing may be able to identify targetable mutations; however, similar to gene expression profiling, the impact on outcomes has not been defined and it is not routinely recommended [14].

When there is a suspected tissue of origin based on pathology or pattern of disease, molecular tests may be useful in directing treatment. For example, a patient with a likely diagnosis of lung cancer should have EGFR, ALK, and ROS1 mutation testing. Similarly, KRAS and MSI testing should be performed for colorectal cancer. PDL1 testing should be considered for lung, urothelial, and renal cell cancers.

Special Considerations in Workup

Neck Mass

A mass in the neck is a common presentation for a head and neck primary and has a unique workup.

Following CT scans of the head and neck, FDG-PET scan should be obtained in order to identify a primary site. If there is no primary identified, fiberoptic examination of the nasopharynx, oropharynx, hypopharynx, and larynx should be performed as an examination under anesthesia [15]. If histology is squamous cell, Human Papilloma Virus (HPV) and Epstein Barr Virus (EBV) testing should be performed on the biopsy. HPV positivity is often correlated with a tonsil or base of tongue primary [16]. Selective biopsies should be taken depending on the nodal location. Deep tonsillar biopsies or ipsilateral tonsillectomy should be performed at the time of examination under anesthesia as the base of tongue and tonsils will harbor the majority of primary tumors [8, 17, 18].

Adenocarcinoma in the neck should trigger an evaluation for a thyroid primary with thyroglobulin and calcitonin levels. Nodes in levels IV and V should be a signal of a possible infraclavicular primary tumor.

If no primary is identified, treatment is determined by histology and location of the metastatic nodes.

Neuroendocrine Tumors (NET)

Forty to fifty percent of patients with NETs will present with metastatic disease, often in lymph nodes and the liver, and rarely in the bone. In 13% of patients presenting with metastatic disease, the primary tumor location is unknown. The most common site of the primary in these cases will be the small intestine or the lung [19]. Many other tumor types can have neuroendocrine differentiation and should be considered in the differential when pathology suggests neuroendocrine features (Table 15.5). IHC suggestive of a neuroendocrine tumor includes epithelial stains, synaptophysin, chromogranin, and CD56 [1].

Identifying the primary site is important for definitive management, particularly when the metastatic disease is resectable. Radiologic evaluation may include CT chest, abdomen and pelvis, capsule endoscopy, functional imaging (Octreotide Scan or ^{68}Ga-DOTATOC PET-CT) and upper and lower endoscopy [19, 20]. It is important to distinguish the primary site if possible as some systemic treatment decisions are dictated by the site of the primary tumor [19]

Pathologic grade (determined by Ki67 and mitoses) can guide a management plan.

Table 15.5 Tumors that have neuroendocrine differentiation

Indolent	Aggressive
Well-differentiated neuroendocrine tumor	Small-cell and large-cell neuroendocrine lung cancers
Well-differentiated pancreatic NET	High-grade NET
Medullary thyroid cancer	Extra-pulmonary small-cell carcinoma
Paraganglioma	Merkel cell carcinoma
Pheochromocytoma	Neuroblastoma

Table 15.6 Favorable and unfavorable presentations of CUP [1, 21–24]

Favorable presentation	Unfavorable presentation
Adenocarcinoma in a female with axillary lymph node disease	Adenocarcinoma
Female with peritoneal papillary adenocarcinoma	More than two metastatic sites
Squamous cell carcinoma nodes in the neck or inguinal region	Liver metastases
Poorly differentiated carcinoma in a young male with mediastinal or retroperitoneal (midline) disease (features of germ cell tumors)	Poor performance status (ECOG > 2)
Colorectal cancer IHC profile (CDX2+, CK20+, CK7−)	Elevated LDH
Neuroendocrine features	Low albumin
Isolated resectable metastasis	Non-papillary peritoneal adenocarcinoma
Men with skeletal-only metastases	

Management of CUP

Commonly, patients with CUP are classified as having a favorable or unfavorable presentation (Table 15.6). Patients with favorable presentations make up to 15–20% of patients with CUP and they tend to present with good performance status and clinical features that suggest a specific tumor subtype that has appropriate treatment. Treatment in these patients can often offer reasonable oncologic outcomes. The remaining 80–85% of patients present with unfavorable features and tend to have poor prognosis [21].

Approach to Patients with Favorable Subtypes

Recognition of favorable subtypes is essential as many patients in this category can be approached with curative intent. The following is a list of favorable presentations and how they are approached:

Isolated or single site of metastasis

- Consideration should be given to surgical resection if technically possible. Definitive radiation can be considered if applicable.
- Consideration can be given to PET scan to consider other occult disease prior to surgical resection.
- If it is a retroperitoneal mass, evaluate whether histology is consistent with germ cell tumor [14].
  - If it is a non-germ cell histology, surgical excision can be considered.

Female with papillary adenocarcinoma in the peritoneal cavity

- Should be treated like a stage III ovarian cancer. Cytoreduction followed by platinum-based systemic chemotherapy can achieve complete response and prolonged disease-free intervals in some patients [23]
- If serous histology, BRCA testing should be performed.

Axillary mass in a female

- With negative mammogram, MRI, and ultrasound and pathology suggestive of a breast primary, it can be approached as stage II or III breast cancer [14]. The absence of a radiologically evident primary in the breast does not rule out the breast as the primary site.
  - Prognosis is similar to stage II/III breast cancer.
- Hormone receptor (ER, PR) and HER2 status should be evaluated.
- The breast can be treated with mastectomy or whole breast irradiation.
- Management of the axilla should follow principles of management for breast cancer presenting with clinical node involvement.
- In a male presenting with axillary adenocarcinoma, axillary dissection is recommended.

Young males (<40) with mediastinal or retroperitoneal poorly differentiated carcinoma

- Can be approached as germ cell tumors.
- Serum AFP, beta-hCG, and testicular ultrasound should be ordered [21].
- Treatment often consists of systemic therapy (etoposide, cisplatin ± bleomycin) [25].

Inguinal adenopathy [14]

- If squamous cell carcinoma:
  - Investigations should be directed at a pelvic or anal primary
  - Nodal dissection followed by radiation can be performed for patients with no primary identified
- If adenocarcinoma is isolated to a single lymph node basin:
  - Can be treated with therapeutic nodal dissection ± adjuvant radiation

Isolated liver metastases

- If no primary is identified, and patient is fit, resection should be considered if technically feasible
  - Pathology should be assessed for possible intra-hepatic cholangiocarcinoma

Colorectal cancer IHC profile

- Investigated with upper and lower endoscopy [21]
- Managed as a stage IV colon cancer with systemic therapy and consideration of resection in appropriate patients

Male with skeletal metastases
- Serum PSA should be ordered
- Even without evidence of prostate disease, a trial of hormonal therapy and bisphosphonates can be considered [21]

Neck mass
- Squamous cell carcinoma: can be definitively treated with neck dissection, radiation therapy, or chemoradiation. In patients that undergo neck dissection, consideration for adjuvant radiation should be given [15].
- Adenocarcinoma: If no thyroid primary is identified, nodes in levels I-III can be treated with neck dissection with parotidectomy followed by radiation.

Neuroendocrine features
- Both low-grade and high-grade neuroendocrine tumors are considered favorable.
- Low-grade tumors tend to be indolent and may be amenable to surgery or to somatostatin analogues.
- High-grade tumors, often called "small cell" neuroendocrine carcinomas, can show good responses to systemic chemotherapy [1, 26].

Approach to Patients with Unfavorable Prognosis CUP

It is essential to identify favorable presentations such as patients benefit from specific, multidisciplinary treatment approaches. Patients who present with unfavorable prognosis CUP typically receive empiric systemic therapy [1].

When deciding on the optimal systemic therapy regimen, clinical presentation, pathology including IHC, and molecular tests all need to be considered. If a putative primary is suggested, then the patient should be treated accordingly.

Patients with CUP tend to have disease that is not very responsive to chemotherapy. Some of the poor outcomes are thought to be related to chromosomal instability in CUP tumors, which results in atypical behavior and chemoresistance [27]. Despite poor outcomes, in those with adequate performance status, chemotherapy should be considered.

When choosing chemotherapy regimens, drugs that are often selected are those that are included in multiple common regimens, such as taxanes and platinum-based drugs, with hopes of broad efficacy. In phase II studies and small randomized studies, no single superior chemotherapy regimen has been identified, and response rates are generally in the range of 10–65%. A meta-analysis by Golfinopoulos et al. [28] could not identify a single regimen to recommend. This analysis attempted to formally exclude favorable prognosis subtypes when possible; however, the heterogeneity in this population makes it difficult to study. Based on current evidence, recommended regimens should include a platinum, a taxane, or both [14]. Commonly used regimens include carboplatinum/paclitaxel, gemcitabine/cisplatinum, carboplatinum/paclitaxel/etoposide, and cisplatinum/paclitaxel/5-FU (used for SCC) [14].

Landmark Trials

- As CUP patients are heterogeneous and often have advanced disease or poor performance status, prospective studies are challenging to perform. Current practice guidelines are based on multiple small trials; no landmark trials exist in this field [14].

Referral to Multidisciplinary Case Conference

- All patients without an identified primary tumor should be reviewed in a multidisciplinary case conference before considering surgical excision.

Referral to Medical Oncology

- All patients with unknown primary tumors should be seen by medical oncologists.

Referral to Radiation Oncology

- Adjuvant therapy after therapeutic lymph node dissection
- Definitive management of some squamous cell carcinomas
- Palliative treatment of symptomatic metastases

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