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# A Carcinomas of Unknown Primary Tends to be Aggressive

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**Abstract**

*Carcinomas of unknown primary (CUP) are a category of serious diseases where secondary cancers are discovered, but thorough testing does not reveal where the original tumor started. These types of cancers make up about 3-5% of all malignant tumors.*

**Keywords:** CUP, Patient, Diagnosis, Metastasis, Health

## 1. Introduction

Cancer often shows itself through symptoms linked to its original location, although sometimes it spreads before the initial tumor can be detected because it is too small [1]. Unlike known primary tumors, carcinomas of unknown primary (CUP) typically include early spread, unpredictable patterns of metastasis, aggressive behavior, and lack of symptoms from the original location. CUP is characterized by the discovery of one or more metastatic tumors without identifying the primary site. Around 5% of all cancers come from an unknown primary source, which equates to approximately 8-20 cases per 100,000 people each year. This form of cancer ranks as the 7th most common and is the 4th leading cause of cancer-related deaths in both men and women. Patients are usually around 60 years old when diagnosed, and half of them have multiple areas affected, while the others may have only one affected area such as the liver, bones, lungs, or lymph nodes.

## 2. Patient

When a person is diagnosed with advanced or metastatic cancer but their history, exams, and imaging do not pinpoint a primary cancer site, it is important to evaluate the patient's overall health, the extent of the disease, additional health issues, and the patient's preferences [2]. Required tests should be performed, but not all patients need a thorough search for the primary cancer site; tests should focus on those that aid in treatment. Specialized tests like endoscopies should only be done if there are reasons based on imaging findings or if there are specific symptoms suggesting a location. In certain situations, for example, if there is a clinical suspicion of germ cell tumors, high-grade lymphomas, or small-cell cancers, or in cases of urgent oncological issues, immediate referrals to oncology or hematology are crucial to start treatment quickly, possibly before all tests are completed. For patients deemed fit for tests and potentially for treatment, a core biopsy from the easiest accessible metastatic site is typically the fastest method to collect tissue for cancer type evaluation. Analyzing tumor characteristics, immunohistochemistry, and molecular pathology is normally enough to determine suitable treatment options. Patients showing signs suggesting a specific type of cancer should be quickly identified and referred to the relevant multidisciplinary or oncology team for further testing and treatment considerations. If the original site remains unknown after thorough investigations, the patient is classified as having a cancer of unknown primary (CUP).

While it is important to recognize patients with CUPs that are highly treatable, some of whom may live for many years or even be cured, it is noted that most CUPs are poorly differentiated cancers or adenocarcinomas that have spread to the liver or multiple other sites in the body. These types of cancer often act in an aggressive manner, making it critical to have early conversations with oncology specialists within a dedicated multidisciplinary team to facilitate investigations and evaluate eligibility for cancer treatments. Although responses to standard systemic cancer treatment tend to be limited, advancements in gene expression testing or molecular tumor profiling are increasingly offering valuable insights into probable tissue origins or potential treatment options, which may enhance the understanding of CUP and lead to improved outcomes. Patients dealing with CUP face the challenge of fighting a cancer

they struggle to comprehend and articulate [3]. Many may refer to their condition as "bone cancer," "liver cancer," or another kind based on where the pain or symptoms are most severe; labeling their illness as CUP often raises questions and uncertainties related to the diagnosis. CUP is not just a highly frustrating diagnosis but also a deadly one, with an average survival time of less than two years.

It is believed that most instances of CUP represent the spread of a carcinoma that has either completely regressed or is too small to be detected with current diagnostic techniques. Pathologists will carry out various tests on the cancer samples to try to trace their origins. If these tests do not reveal the site of origin, patients with CUP should consult their oncologist about the possibility of a genomic analysis (gene testing) to obtain further insights. This advanced testing is generally covered by most insurance plans and is offered by several companies, including Pathwork Diagnostics. Cancers that originate from an unknown primary site are typically addressed with chemotherapy, and sometimes radiation therapy is also included. If the cancer is localized and has not spread throughout the body, some patients may have a chance for a cure, and surgery might be an option. There is a clear need for improved treatments for advanced CUP cases. Researchers are working to understand how CUP develops better, aiming for significant progress against this form of cancer.

## 3. Diagnosis

Patients with CUP usually come in with noticeable symptoms and are more likely to be admitted as emergencies compared to those with known tumor types [4]. In England, around 56% of CUP patients present as first emergency cases. Those arriving through these channels often show symptoms and may have borderline or poor health status, which can ultimately impact their overall prognosis. The diagnostic procedures for CUP patients should entail a comprehensive clinical history that emphasizes symptoms and risk factors. This should be complemented by a meticulous examination of the entire body, including lymph nodes and skin, as well as remote areas like the hairline and the soles of the feet. Additionally, for women, a thorough breast and vaginal examination should be carried out, while men should undergo testicular examinations. When cancer is suspected, a CT scan of the chest, abdomen, and pelvis with contrast should be performed. The aim of additional tests is to identify the type of primary tumor and to recognize cancer types that are easy to treat and possibly curable.

The choice of further imaging tests should be based on the patient's medical history and examination findings, focusing on the signs, symptoms, and the suspected primary tumor. The assessment process and specialized examinations for identifying possible primary diagnoses include mammograms or MRI of the breast for women who have swollen lymph nodes in the armpit; gastrointestinal endoscopy for patients with symptoms or signs suggesting a gastrointestinal primary tumor; and colonoscopy for those with symptoms relating to the lower gastrointestinal tract or concerning lower GI issues. In appropriate cases, serum tumor markers such as CEA for colon cancer, CA19-9 for issues in the liver or pancreas, CA125 for ovarian cancer, PSA for prostate cancer, HCG for germ cell cancers, AFP for both germ cell tumors and liver cancers, Chromogranin-A for neuroendocrine tumors, and a GI hormone profile for neuroendocrine tumors should be utilized. However, these markers differ in specificity and sensitivity and should be understood in the context of the patient's overall clinical situation and imaging and pathology results. Serum tumor markers alone are not definitive for diagnosis, and in cases of carcinoma of unknown primary (CUP), it is common to find several markers elevated at the same time. PET CT scans are used in particular situations in cases of CUP, and research is ongoing to evaluate its use as a standard diagnostic tool.

Currently, PET CT is recommended for patients with single metastatic spots who might consider radical treatment, for patients with specific limited lymph node disease like suspected head and neck squamous cell carcinoma, and for isolated bone metastases where it might help guide biopsy location. When no primary cancer is identified after a specialist review by a CUP multidisciplinary team, a diagnosis of CUP is confirmed. Patients can then be classified as "favorable" or "unfavorable" based on clinical, pathology, and imaging results. For around 20% of patients in the "favorable" category, clinical signs may suggest a possible type of primary tumor, and these individuals should be treated according to that tumor type. Individuals falling into the "unfavorable" CUP group, which makes up around 80% of cases, should be considered for standard systemic cancer treatment if their health allows, or for clinical trials if available. If patients are not fit for treatment due to poor health, they should receive the best supportive care to manage symptoms effectively.

## 4. Metastasis

As a tumor develops and grows, it can sometimes spread to other areas [5]. This process involves tumor cells gaining the ability to move away from their original site and, through various biological and mechanical methods, settling in new locations, where they form secondary tumors. This movement may take place through lymphatic or blood vessels, or by other means. Metastasis is regarded as the deadliest stage in the development of tumors, and due to its widespread nature, it can affect the metabolism and functionality of organs. Metastasis can take place at any stage of tumor development. Initially, it begins with fundamental mutations (the original mutations that lead to tumor growth) and later progresses through subclonal mutations (mutations that arise in particular subgroups of cells within the tumor). Carcinomas that have an unknown primary source are found in 2 to 5% of metastatic cancer cases. This situation arises when the primary tumor is too small to be detected or has spontaneously shrunk after extensive metastasis has occurred. To enable this movement, cancer cells undergo various metabolic changes arising from their highly adaptable nature, allowing them to adjust to new environments. In this context, the process of metastasis includes three overlapping phases: dissemination, dormancy, and colonization. During these stages, cancerous cells navigate a series of steps to invade tissues, survive during their journey, and establish

themselves in different organs. These stages together are referred to as the metastatic process.

## 5. Investigations

The primary step is to rule out any potentially treatable tumors, and then to identify tumor types that correlate with better outcomes due to their responsiveness to therapies. Although thorough investigations are conducted, fewer than 20% of patients have a primary cancer site identified before death; even at autopsy, 70% of cases show an untraceable primary site. The primary sites are most commonly found in the lungs and pancreas, followed by other cancers of the gastrointestinal tract and gynecological systems.

Initial investigations might include:

- A comprehensive medical history and physical check-up
- Complete blood count
- Serum biochemistry and liver function tests
- Serum tumor markers can assist but are often not specific
- Urinalysis and stool tests for hidden blood
- Chest X-ray
- Endoscopy based on symptoms
- Imaging of the chest, abdomen, and pelvis (CT, MR, or PET)
- Plain X-ray imaging in areas of bone pain
- Biopsy for histology (from any affected area)

Patients should be referred early to a multidisciplinary team (MDT) focused on cancers of unknown origin, which can recommend necessary investigations. This will enhance both time and cost efficiency, ensuring that appropriate treatment can begin in a timely manner. A focused diagnostic strategy that prioritizes benefits to patients, aiming to identify those with favorable prognosis features, is the most effective method. Patients might worsen during the investigative period, and a definitive diagnosis of the primary site may not always be possible. Hence, a balanced approach is needed that considers adequate testing to prepare for management while also addressing the treatment of the disease.

## 6. Imaging Tests

- CT scan (Computed tomography)—provides a cross-sectional view of the body. CT scan images show bones, organs, and soft tissues more clearly compared to regular x-ray images.
- MRI scan (Magnetic resonance imaging)—produces images by capturing cross-sectional views from various angles. MRI uses powerful magnets instead of radiation to generate images.
- X-rays—produce shadow-like pictures of certain organs, bones, and tissues. X-rays are typically quick, painless, and do not require special preparation.
- Mammography—low-radiation x-ray images that can aid in detecting breast cancer.
- Nuclear imaging (bone scans, PET scans)—create images based on the different chemical activities in the body instead of their shapes. The specific type of nuclear scan depends on the organ being examined.
- Ultrasound—produces sonogram images by sending high-frequency sound waves through the body. It is used to look for tumors in areas that x-rays cannot detect.

Positron emission tomography (PET) scanning utilizes glucose tagged with fluorescence and the faster metabolism of cancerous tissues to find tumors [7]. The use of PET in the head and neck region has mainly focused on 1. Finding hidden lymph node metastases, 2. Differentiating between malignant growth recurrence and radiation necrosis or other effects from previous treatments, 3. Locating any unidentified primary cancer. The function of PET/CT in diagnosing and staging head and neck cancer patients has been changing. PET/CT integrates detailed anatomical data from CT scans with PET's capability to spot subtle lesions. PET/CT can be significant during the pre-treatment phase by identifying synchronous or metastatic lesions that may alter planned procedures or treatment options. After treatment, PET/CT is known for its high sensitivity and specificity in spotting recurrences, making it highly valuable for cancer monitoring.

## 7. Mammography

1. Performing regular screenings for women without symptoms who are at risk of developing breast cancer
2. Assessing each breast once a potentially treatable breast cancer diagnosis is confirmed, and at scheduled intervals afterward
3. Investigating any suspicious or unclear breast mass or changes
4. Looking for hidden breast cancer in women with metastatic conditions in lymph nodes or other areas with no known primary source
5. Screening women before cosmetic procedures or before biopsies to check for any unknown cancers
6. Keeping track of women who have undergone breast-conserving treatments and radiation after having breast cancer; and
7. Observing the remaining breast in women who have had a mastectomy due to breast cancer.

Calcifications are the most commonly recognized abnormality seen in mammograms. The typical signs linked with breast cancer are clustered pleomorphic microcalcifications. These calcifications are generally found in groups of five to eight, located in a specific section of the breast, and vary in size and shape, often taking on branched or V- or Y-like forms. They might be accompanied by a mammographic mass density, or sometimes just show density without any calcifications. Such density typically has uneven or poorly defined edges and can cause noticeable changes in breast structure, although it might be subtle and hard to identify. Patients with a noticeable or concerning mass found during examination must have a biopsy, regardless of what the mammogram shows. The mammogram should be done before the biopsy to identify any other areas of concern and to check the other breast. Mammography cannot replace biopsy, as it might not show existing cancer, particularly in very dense breast tissue.

## 8. Melanoma

About 2% to 8% of melanoma cases originate from unidentified

primary sites [9]. A significant two-thirds of these patients show regional spread without an obvious primary lesion or a known history of melanoma; the remaining third often has distant spread to locations such as the subcutaneous layers, lungs, and brain. For patients with melanoma from an unknown source, it is essential to search for the primary site by evaluating the entire body's skin and mucosal areas. Previous skin biopsies or skin lesions that have vanished on their own may provide useful information. All pathology slides from previously removed lesions need to be reviewed again. The process for checking for metastasis is the same as that for cases with known primary sites, as will be explained later. After adjusting for tumor stage, melanomas with unknown primary origins have a prognosis that generally matches those with identified primary sites.

## 9. Management

For individuals suffering from an incurable cancer that has spread extensively, the use of combination systemic chemotherapy is the most fitting option . The treatment selection will be based on the best evaluation of the likely original location and the patient's performance status. Radiotherapy is beneficial for certain areas causing pain or discomfort. All treatments are provided with the intent to relieve symptoms and enhance the patient's quality of life. Additionally, treatments should be stopped if the patient is not experiencing any benefits or improvements in their symptoms. In cases of well or moderately differentiated adenocarcinoma of an unknown origin, 90% of patients show a low response to chemotherapy. Those in this group tend to have a poor outlook. Patients suspected to have ovarian or peritoneal primary sites may respond effectively to proper chemotherapy; 40% can achieve complete remission, and 20% may experience an extended period without disease. Individuals with axillary lymph node metastasis can be treated as if they have breast cancer and might require a modified radical mastectomy.

Around 30% of patients with carcinoma of unknown primary origin have poorly differentiated carcinoma or adenocarcinoma. These patients typically have a low response to systemic chemotherapy, leading to unfavorable outcomes and shorter survival rates. Such patients are usually younger, with a median age of 40 years, and experience rapid symptom progression. Commonly affected areas include lymph nodes, the mediastinum, and the retroperitoneum. Although there are rare instances of excellent responses and improved survival, no known factors can predict these favorable outcomes in these patients. For patients with a single metastatic site, surgical removal and radiotherapy should be considered. This approach can lead to significant stretches of time without disease in certain patients. In male patients with osteoblastic bone metastasis, empirical hormonal treatment should be considered similar to that for prostate cancer, irrespective of the serum PSA level.

## 10. Conclusion

A carcinoma of unknown origin is a condition resulting from cancer that has spread from another area of the body, but the original tumor site remains unknown. Thanks to advancements in diagnostic testing, instances of carcinomas with an unknown primary are declining. In four out of five cases initially recognized as such, further diagnostic evaluations eventually identify a specific tumor type. Carcinomas of unknown primary origin often present as aggressive cancers that tend to metastasize to multiple locations before diagnosis.

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