PATIENTS WITH METASTATIC CANCER OF UNKNOWN PRIMARY SITE: DIAGNOSTIC WORKUP AND THERAPEUTIC MANAGEMENT

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Abstract
Metastatic Cancer of Unknown Primary site (CUP) accounts for about 4% of all cancer patients and is therefore one of the 10 most frequent cancer diagnoses in man. It is defined as biopsy-confirmed malignancy for which the site of origin is not identified by routine workup. It is believed that CUP represents a heterogeneous group of malignancies that have a presumably, specific biology with clinical characteristics of rapid progression and random atypical metastases. The diagnostic work-up could be variable. Certain clinicopathological CUP entities are considered as favorable subsets responding to systemic platinum-based chemotherapy or managed by locoregional treatment. These subsets have a better prognosis than the average median survival time of four months in patients who belong to the non-favorable subsets.

Introduction and incidence
Several terms have been used to describe the condition of unknown primary tumours: these includes: Cancer of Unknown Primary (CUP) site, Unknown Primary Tumours (UPTs), Occult Primary Tumours, Carcinoma of Unknown Primary, Tumour of Unknown (Unidentified) Origin, and Metastases of Unknown (Tumours) Origin. The most widely used terms are the CUP and UPTs.

CUP is the seventh to eighth most frequently occurring cancer in the world and the fourth commonest cause of cancer death in both males and females.

The routine workup usually includes a complete history and physical examination, chest x-ray, digital rectal examination and test for stool occult blood. Women should undergo breast and pelvic examination, and men should have a complete prostate and testicular examination.

The scenario of CUP poses diagnostic and therapeutic problems, which could cause an unsettling situation to both the patient and relatives from one side and the treating doctor from the other side. It is difficult to determine the appropriate treatment without knowing the primary, because current cancer treatment has been based on the identification of the primary tumour. Also it remains controversial whether the prognosis in CUP improves when the primary tumour is identified by intensive diagnostic search.

In 30% of all patients no primary tumour is identified. The primary site becomes obvious in only 25% of patients during their lifetime. The primary lesion can be identified in only 30% to 82% of cases at autopsy. The most common sites of origin are the lung (30%) and the pancreas (20%). Furthermore, primary tumours are
regularly found in the large bowel, the kidney, and the breast\(^5\).

CUP are diagnosed more often in men than in women (ratio 5:4). In unselected series the median age at diagnosis is about 65 years, with only 10% of the patients younger than 50 years. The liver, lung, bone, and lymph nodes are the commonest sites of metastases. In 30% of patients multiple metastases are present at the time of diagnosis\(^5\).

**Explanation of unknown primary**

It was thought that the inability to detect the primary tumour has two possible explanations\(^6\). The first hypothesis is that the primary has involuted and is not detectable when the metastases become evident. Although this is not a common phenomenon, spontaneous tumour regression has been described in several tumours\(^7\). The second explanation is that the phenotype and genotype of the primary tumour behaves with metastatic ability rather than with local tumour growth\(^8\). It seems that these tumours do not undergo type 1 progression (from a premalignant lesion to malignant), but are malignant at the onset of the disease (type 2 progression). The main difference, however, from other type 2 progressors is that they do not form a primary site and do not follow any predictable pattern of metastatic spread\(^8\).

The primaries, when identified, are small and asymptomatic in the majority of patients. Clinical manifestations are the short medical history, typically less than three months, and a rapid progression of the disease\(^2\).

In the majority of patients, metastases are found at different sites. The unpredictable metastatic patterns refer to the differences in the incidence of metastatic sites at diagnosis between known and unknown primary cancers. For example, lung cancer presenting as CUP involves the bones in 4%, while presenting as a known primary bone metastases in 30%-50%. Similarly pancreatic cancer presenting as CUP has 4-fold higher incidence to affect bones, whereas prostatic cancer has 3-fold less incidence compared with known primaries\(^10\). Similar unpredictable patterns can be seen in splanchnic metastatic sites\(^5\).

**Determination of site of primary**

An exhaustive series of studies to identify the primary is not warranted, because it usually adds little information to aid in the diagnosis and expand the expenses. Besides the majority of these patients will have a limited response to therapy, and therefore a limited survival. However, a complete history and thorough physical examination including the breast, rectal and pelvic examination must be undertaken. The standard laboratory tests are expected to be performed. Additional tests are only indicated in patients who have clinical features, which might give some guidance to the primary.

**Pathologic evaluation**

**Light microscopy:** The initial diagnosis of malignant cancer is reached by simple microscopic evaluation using standard stains. CUP are categorized into four major types: (a) well differentiated or moderately differentiated adenocarcinoma, (b) undifferentiated or poorly differentiated adenocarcinoma, (c) squamous cell carcinoma and (d) undifferentiated neoplasm\(^10,11\). Approximately half of the patients will be diagnosed with metastatic adenocarcinoma, 30% will have undifferentiated or poorly differentiated carcinomas and 5% will have undifferentiated neoplasms\(^10,11\). With modern immunohistopathology, most of the tumours in the latter group may be categorized to poorly differentiated carcinomas, neuro-endocrine tumours, lymphomas, germ cell tumours,
melanomas, sarcomas and embryonal malignancies.\textsuperscript{11}

**Immunohistochemistry:**
Immunoperoxidase antibodies are directed at cell components or products, which can include enzymes (e.g., prostatic acid phosphatase, and neuron-specific enolases); tissue components (e.g., keratin, vimentin); hormones or their receptors (e.g., oestrogen); and oncofoetal antigens (e.g., CEA). Another benefit of using immunoperoxidase staining is the ability to use formalin-fixed specimens to perform these tests without taking another biopsy.\textsuperscript{11,12}

**Electron microscopy:** Although is a powerful tool for visualizing cellular organelles and demonstrating subcellular structures electron microscopy is not widely available, is relatively expensive and the special fixation requirements have limited its practical use. Electron microscopy should be considered in the evaluation of poorly differentiated neoplasms in young patients, particularly when immunoperoxidase stains are inconclusive. It may prove useful in distinguishing lymphoma from carcinoma, adenocarcinoma from squamous cell carcinoma, and in identifying neuroendocrine tumours, melanomas or poorly differentiated sarcomas.\textsuperscript{11}

**Molecular cytogenetics:** Genetic analysis often demonstrates multiple complex abnormalities and therefore it is limited in determining a diagnosis. In addition the use of conventional or molecular cytogenetics in identifying the origin of the primary tumour is limited because only a few tumour-specific chromosomal abnormalities have been identified.\textsuperscript{10} However, occasionally it may prove useful as shown in a single report of group of young men with poorly differentiated carcinoma of unknown primary and the clinical features of an extragonadal germ cell tumour. Molecular genetic analysis showed the i(12p) abnormality in 25% of the cases. Those patients were then treated with cisplatin-based chemotherapy and were noted to have a significant response with an improvement in survival when compared to historical controls.\textsuperscript{13}

**Tumour markers:** Although most markers lack adequate specificity in determining the site of the primary, their use with the clinical information and pathologic findings may prove to be helpful in the diagnosis of the primary.\textsuperscript{6} However, an elevation in a mere event is not diagnostic and does not predict response to treatment.

**The role of radiology**

**Conventional radiology:** Based on autopsy studies chest X-ray interpretation was able to differentiate between primary and secondary malignancy in the lungs in only one-third of the cases. Barium enema study is of very limited value.\textsuperscript{14}

**Computed Tomography:** CT Scan of the abdomen and pelvis found to be useful in detecting the primary site in 30%-35% of cases. In contrast CT Scan of the chest has limited value but might be useful in patients with abnormalities in the chest X-ray, or to assess the mediastinum or it might provide guidance in selecting an optimal site for a biopsy.\textsuperscript{15}

**The role of breast imaging**

Mammography might be indicated in women with metastatic adenocarcinoma involving the axillary lymph nodes but its sensitivity was found to be around 20%\textsuperscript{16}. It was shown that MRI is very sensitive for the detection of breast cancer in patients with high suspicion of a primary breast tumour but there is no palpable mass and both the mammogram and the ultrasound scan were unable to detect the tumour.\textsuperscript{17}

**The role of endoscopy**
Endoscopy might be indicated in patients with CUP. For instance ENT
endoscopy might be useful in cases with isolated cervical lymphadenopathy. Fiberoptic bronchoscopy, gastrointestinal endoscopy, and colposcopy might be found necessary in patients with specific clinical features related to these systems or organs.

**Therapeutic strategy**

According to the clinical presentation and pathological findings two subsets of patients groups with CUP were recognized, favourable or non-favourable groups. These subdivisions of patients are thought to guide the diagnostic approach and therefore to be able to offer optimal therapeutic management. The lines of treatment in patients with CUP may be locoregional and / or systemic, and may have a curative or palliative intent.

Systemic chemotherapy has been the main treatment for patients with CUP for a long time, and it has undergone some refinement. In the 1960s and 1970s, the use of 5-fluorouracil, cyclophosphamide, mitomycin-C, nitroureas and vincristine offered a response rate of less than 10%. In the next decade, although the use of doxorubicin-containing chemotherapy improved the response rate to around 25%, the median survival remained low at 4-6 months. Since platinum became available in 1980s, its use in chemosensitive, favourable subset of patients achieved better responses and survival. Since 1995, the use of taxane (paclitaxel or docetaxel) in combination with a platinum compound has reported some improved treatment option for those patients groups who do not fit into any favourable subsets.

**Favourable groups of patients and their treatment**

**Poorly differentiated carcinoma with midline distribution (extragonadal germ cell syndrome):** These patients should be treated similar to patients with poor prognosis germ cell tumours using platinum-based combination chemotherapy. The overall response rate, complete response rate and long-term disease-free survival were reported to be around 50%, 25%, and 15% respectively.

**Peritoneal carcinomatosis:** In women who present with disseminated peritoneal carcinomatosis, the primary tumour usually originates in the ovary. Occasionally, primary breast or gastrointestinal tumours (especially, gastric or appendiceal carcinomas) may present with this pattern. It is recommended that these patients should be treated similar to patients with stage IIIB ovarian carcinomas. This includes aggressive cytoreduction of all visible disease to less than 1 cm in size and adjuvant cisplatin-based chemotherapy, with or without taxol. It had been reported that 22% of the patients had complete clinical response with a median survival of 19 months and a 26% long-term survival rate.

**Adenocarcinoma involving only axillary lymph nodes:** Men should undergo evaluation for a primary lung cancer. The gastrointestinal and genitourinary carcinomas may be a potential primary. In women the primary is most likely in the breast. Lymph nodes’ positive receptors were found in more than 50% of these cases. In patients with N1 disease (mobile lymph nodes) axillary clearance followed by either simple mastectomy or breast radiotherapy is recommended. In premenopausal women with positive oestrogen receptors, adjuvant chemotherapy followed by tamoxifen is advised. For postmenopausal patients with positive oestrogen receptors tamoxifen is still recommended. No data are available concerning adjuvant chemotherapy in these latter group of patients. In patients with N2 disease (fixed lymph nodes), preoperative neoadjuvant chemotherapy is suggested, and in non-responding tumours or in elderly patients, radical radiotherapy is...
the treatment of choice while tamoxifen should be continued in patients with positive receptors\textsuperscript{1,10,23}.

Squamous cell carcinoma involving the cervical lymph nodes: When the upper or middle cervical lymph nodes are involved a primary tumour in the head and neck should be suspected. After thorough evaluation it was reported that a primary was identified in up to 50\% of these cases\textsuperscript{24}. This evaluation may include CT scan and panendoscopy with biopsies of suspicious areas. Otherwise when no suspicious areas were visualized then biopsies from potential occult primary sites were recommended. These areas include the nasopharynx, base of tongue, pyriform sinus, and tonsil fossa. Treatment options are varied and may involve radical neck dissection, comprehensive radiotherapy, or a combination of both. The 5-year survival rates range from 35\% to 50\%\textsuperscript{25}. Although the role of systemic chemotherapy remains undefined, concurrent chemotherapy seems to be beneficial particularly in patients with an N2 or N3 lymph node disease\textsuperscript{1,10}. Patients with supraclavicular nodal involvement most likely have lung or gastrointestinal primaries and therefore may be investigated and possibly treated accordingly\textsuperscript{6}.

Isolated inguinal lymphadenopathy from squamous cell carcinoma: Inguinal lymph nodes dissection with or without radiotherapy is the recommended treatment for this group of patients\textsuperscript{26}. The role of systemic chemotherapy has not been evaluated\textsuperscript{1,10}.

Poorly differentiated neuroendocrine carcinomas: The recommended treatment of this group of patients is platinum-based or paclitaxel/carboplatin-based chemotherapy\textsuperscript{27}. The reported response rate is 50\%-70\% with 25\% complete response and 10\%-15\% long-term survival\textsuperscript{1,10,27}.

Men with blastic bone metastases and elevated PSA from an adenocarcinoma: This is a rare subset of patients with a debatable treatment. However, it was thought that they should be considered as having metastatic prostatic cancer and treated with hormone therapy\textsuperscript{11}.

Patients with single, small metastasis: A considerable number of these patients benefit from palliative local treatment with either resection and/or radiotherapy\textsuperscript{1,10}.

Metastatic Melanoma: True amelanotic melanoma may constitute 2\% to 15\% of all cases of melanoma\textsuperscript{28}. The primary site may be determined on the basis of a history of a pigmented skin lesion that was excised, abraded, or frozen. Absence of such a history may suggest that the primary is visceral in origin and if it is appropriate the eyes, adrenals, and gastrointestinal tract may need to undergo diagnostic evaluation\textsuperscript{6}. The possible explanations for the unknown primary site are either a complete regression of the primary melanoma or the primary origin may be the lymph nodes\textsuperscript{6}. Regional lymphadenectomy is therefore recommended if the only site of involvement is single regional lymph nodes. This line of treatment resulted in a 5-year survival rate of 30\% to 45\%\textsuperscript{29}. Non-favourable groups of patients and their treatment

Non-favourable subsets of patients with CUP may include cases with poorly differentiated neoplasms, metastatic adenocarcinoma to the liver or other organs, non-papillary malignant (adenocarcinoma) ascites, multiple cerebral metastases (adenocarcinoma or squamous carcinoma), multiple lung/pleural (adenocarcinoam) metastases, and multiple (adenocarcinoma) metastatic bone disease\textsuperscript{1,6,10}. 

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Patients with favourable subsets of CUP who were discussed earlier constitute a minority. Unfortunately most other patients with CUP showed a very poor response to systemic chemotherapy with resultant short survivals. Because of that they are identified as non-favourable subsets. Recently, improved response was achieved and reported by using newer chemotherapeutic agents, namely taxane/platinum regimens, which resulted in longer survival times. However, despite of these encouraging results definitive conclusions are difficult to be drawn due to the heterogeneity of these patients and to the retrospective nature of comparisons. In addition, similar to any other clinical trials accepting patients with advanced cancer, considerable patients’ selection was involved in these studies. Therefore, and in order to make further progress, definitive randomized trials are needed in this group of patients with CUP to confirm the benefit of recent chemotherapeutic regimens and to better define the standard treatment.

**Conculding remarks**

Few malignancies create anxiety similar to that experienced by the cancer of unknown site. At present it has been realized that this group of patients represents a heterogeneous group with varying prognosis. Recent advances in diagnostic technology including laboratory, radiology and pathology have improved clinicians ability to recognize subsets of patients with relatively favourable prognosis. Further improvement in the survival was achieved through the discovery and use of newer chemotherapeutic agents. Most patients with CUP are able to and should enter a treatment trial. For patients who do not fall in the category of favourable subsets, a trial of empirical combination chemotherapy should be considered if their general status is adequate. For those patients who are either very elderly or who do not enjoy good health status symptomatic and palliative treatment is recommended. Ongoing research to identify better understanding of the nature and molecular biology of these tumours and studies to develop focused treatment regimens are essential.

**References**