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Cancer of unknown primary site

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Cancer of unknown primary site accounts for 3–9% of all patients seen in tertiary cancer centres.[1] The most common sites of presentation (excluding head and neck) are shown in Table 1.[2] The composition of the patient population has changed over the years with the evolution of clinical investigations, the three main aims of which (as with all cancers) are to:

- define the histology
- identify the primary site
- determine the degree of spread.

Identification of the site of origin of the cancer is central to management and understanding of the likely prognosis and treatment possibilities. However, the extent of investigation needs to be tailored to the patient's likely prognosis and prospects for treatment. Exhaustive investigation of poor performance status patients with cancers of unknown primary site is often counterproductive because of the diminishing likelihood of identifying a primary site, the increasing expense of continuing investigation and discomfort to the patient with limited life expectancy.[1,3,4] Even after post-mortem examination the primary site will remain unknown in approximately 15–20%.[5]

Table 1. The most common sites of presentation of cancer where the primary is unknown.[2] Reproduced with permission of the American Cancer Society.

Site of presentation	%
Lymph nodes	30
Bone	15–28
Other abdominal sites	15
Liver	9–31
Lung and pleura	8–12
Central nervous system	8
Skin	8
Adrenal	6

Histology

The histological groups are listed in Table 2.[6]

Adenocarcinoma

The most common histological type is adenocarcinoma, comprising 50–60% of patients in all series. Immunohistochemical tumour markers and molecular genetics allow a more precise diagnosis. A panel of histochemical and genetic markers is increasingly helpful in identifying likely primary sites including:[7-10]

- thyroid transcription factor-1 for lung cancer
- CK7 and CK20 cytokeratins, and CdX to differentiate between gastrointestinal (GI), gynaecological and breast origin
- oestrogen receptor and progesterone receptor for breast and endometrium
- prostate specific antigen (PSA) for prostate.

Table 2. Histological groups of cancers with unknown primary. Data adapted from Reference 6.

Histological group	%
Main malignancies:	
Adenocarcinoma	50–60
Poorly differentiated tumours	35
Squamous carcinoma	5
Other malignancies include:	
Lymphoma	6
Germ cell	1
Melanoma, sarcoma, neuroendocrine	1

Poorly differentiated cancers

Poorly differentiated cancers can be the most treatable, and chemotherapy-curable. Leukocyte common antigen-positive lymphoma is found in 6% and atypical germ cell tumours bearing alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG) or $I_{12}P$ mutation in 1%.[11] Serum tumour markers, however, are of low specificity and do not contribute to initial diagnosis though they may support the subsequent management of the known tumour.

Squamous carcinoma

The usual presentation of squamous carcinoma is with cervical lymphadenopathy, although rarely inguinal lymphadenopathy may be the first sign of disease originating in the anus, vulva, or penis.

Investigation of cancer of unknown primary

The likely incidence and treatment options available following diagnosis need to be considered in defining the plan of investigation. Post-mortem examination reported in early series identified a primary site in 82–84%.[3,5] The most common primary sites identified are shown in Table 3.

Table 3. The most common primary sites identified at post-mortem.[3,5]

Primary site	%
Lung	17–28
Pancreas	11–27
Colorectal	4–6
Renal	3–7
Liver	3–6
Gastric	3–5
Prostate	2–3
Ovary	2
Thyroid	1–3
Adrenal	1–3
Breast	1
Parotid	<1

Radiological investigation

Historically, computed tomography (CT) has proved to be the most successful technique for identifying the primary site in patients presenting with adenocarcinoma of unknown origin, showing up to 35–40% of all primary cancers discovered by clinical follow-up,[1–3,6,12] including 70% of lung cancers, 86% of pancreatic cancers, but fewer at other sites.

Magnetic resonance imaging (MRI) has proved particularly advantageous in the pelvis and in identifying occult breast cancers.[13,14]

Positron emission tomography

The role of fluorodeoxyglucose (FDG)-positron emission tomography (PET) and PET-CT to detect occult primary carcinomas outside the head and neck region has been reviewed recently.[15] On average, using this method a potential primary site was identified in 41% of patients (range 24–71%), but confirmation from histology at biopsy or post-mortem was achieved in only half the cases. Lung was the detected primary site in 59%, but there was a 58% false-positive rate of detection of putative lower GI tract primaries.

Clinical management was changed as a result of PET scanning in 24–35%, mostly through the choice of chemotherapy agents for lung or pancreatic cancers, but in 12% treatment was directed to breast or prostatic primaries of a usually better prognosis. Further metastases were found in 37% but disease could be localised for appropriate resection in 14%.

Treatment and prognosis for cancer of unknown primary

Investigation of patients presenting with metastatic adenocarcinoma should aim to identify those primary tumours with the greatest treatment potential, including breast, ovary and prostate. However, the most frequent primary diagnosis is non-small-cell lung cancer or pancreatic cancer. There are specific chemotherapy choices even for these traditionally less treatable cancers and other adenocarcinomas from the GI tract that present as cancer of unknown primary in good prognosis patients (see below) that can provide good quality palliation for 6–12 months.

Prognosis

The overall median survival for all patients with cancers of unknown primary site varies from 12–22 weeks.[1,16] Within this is a group with a better prognosis, defined by:

- disease in limited nodal sites or single site of metastasis
- performance status 0–2
- weight loss less than 10%
- absence of liver metastases on CT scan.

Key Points

Lung and pancreas are the most common sites of origin for cancer of unknown primary (CUP)

Prognostic factors are limited nodal or single visceral sites, good performance status, weight loss <10%, absenced liver metastases

Breast, ovary and prostate are the more treatable origins of adenocarcinoma of unknown primary (ACUP)

Non-Hodgkin's lymphoma and germ cell tumours are rare but curable causes of poorly differentiated CUP

Occult head and neck primary squamous cancer are a curable cause of CUP in cervical lymph nodes

KEY WORDS: adenocarcinoma of unknown primary, cancer of unknown primary, investigation, prognosis, treatment

In some series, patients with normal serum albumin and lactate dehydrogenase (LDH) have a median survival of 15 months compared with three months for those in the poor prognosis group.[17,18]

Common clinical scenarios with treatment implications for cancer of unknown primary

1 A primary breast cancer may be found in 40–70% of women presenting with isolated axillary lymph node metastases. MRI is a valuable adjunct to mammography and ultrasound in their examination. The prognosis with breast cancer endocrine and chemotherapy as for known and breast conservation is similar to that of other women with stage II breast cancer, with a median survival of five years.[14,19]

2 Women presenting with peritoneal carcinomatosis, in particular those with papillary serous carcinoma, have a prognosis following platinum chemotherapy similar to that of stage III ovarian carcinoma, with a median survival of 17–23 months.[20]

3 Men with an elevated serum or tumour biopsy PSA and often bone metastases have a clinical course similar to those presenting with prostatic cancer. Response to androgen deprivation is approximately 70% and median survival 24–36 months.[21] However, for most patients presenting with bone metastases, investigation with CT scan of chest, abdomen and pelvis is likely to reveal a primary source in the lung (24%), prostate (17%) or breast or gynaecological organs (16%).[22]

4 Patients commonly present with liver metastases discovered incidentally or symptomatically. Chemotherapy directed at tumours of GI origin can result in a median survival of seven months, depending upon performance status and serum LDH levels.[23]

5 Multiple small-volume lung metastases due to thyroid carcinoma is a rare clinical situation, but response to treatment with radioiodine can be achieved in a high proportion of patients if the tumour is shown to be metabolically active.

6 Patients presenting with central nervous system disease from an unknown primary have a poor prognosis, irrespective of whether or not the primary is identified, with a median survival of five months. The good prognostic factors are age below 65, good performance status, lack of symptoms and other systemic metastases, and treatment with surgery and radiotherapy. Treatment with short-course radiotherapy in five fractions is as effective as longer courses.[24]

If after all efforts the primary site has not been identified, palliative chemotherapy treatment with combination chemotherapy such as carboplatin, gemcitabine and capecitabine can achieve responses in 20–40% of selected patients who have a good prognosis, with median survivals of 9–10 months and 5–10% surviving to five years.[25]

Poorly differentiated carcinoma of unknown primary site (with or without features of adenocarcinoma)

There is a distinctive subgroup of patients with poorly differentiated carcinoma or adenocarcinoma of unknown primary site in whom the clinical characteristics differ from patients with well differentiated adenocarcinoma. The median age of this group is younger, they have a history of rapid progression of symptoms (<30 days) and tumour growth, and may express the germ cell tumour markers AFP or hCG. Lymph nodes within the mediastinum and retroperitoneum are more often infiltrated than in patients with well-differentiated adenocarcinoma. It is important to identify this subset of patients as they may include a high proportion of germ cell tumours that may be more responsive to chemotherapy and potentially curable.[26–28]

Squamous carcinoma of cervical or supraclavicular nodes

Most malignant lymph node masses in the neck are metastatic, arising from primary head and neck tumours in 85%.[29] However, primary lung cancer should be suspected when the lower cervical or supraclavicular lymph nodes are involved. Most primary sites are identified at routine clinical examination, with a further 16% detected at panendoscopy and 4% by CT scan. This last group usually comprises lung cancer presenting with enlarged nodes in the lower cervical region.

There is no identifiable primary site in 3–9%. The addition of FDG-PET can detect the primary in 22–33% of patients negative by all other investigations. FDG-PET scans had the highest sensitivity (69%) and negative predictive value (87%) but lower specificity when compared with CT and MRI. However, FDG-PET cannot replace the need for careful endoscopy which found lesions overlooked by PET in 16% in one series.[30,31]

The prognosis for patients identified as having head and neck primary tumours has improved with modern surgery and chemoradiotherapy. There is a 62–67% five-year survival, varying from 80% for N1 disease with surgery alone to 56% for N3 with surgery plus chemoradiotherapy.[32,33]

Melanoma of unknown primary

The management of patients presenting with lymphadenopathy due to metastatic melanoma is primarily surgical. They should be staged by PET-CT scan if the disease is clinically confined to a resectable nodal basin in order to exclude distant metastases. The prognosis following lymphadenectomy can be excellent, with 55–58% five-year and 13.75-year median overall survival. The management of isolated deposits of metastatic melanoma in other sites such as lung is also primarily surgical.[34,35]

Conclusions

Patients presenting with metastatic cancer of unknown primary origin need expert assessment clinically, histologically and

radiologically to assign the likely tissue of origin and prognosis, from which a logical process of investigation and treatment can be developed.

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