Cancers of unknown primary

Background

Cancers of unknown primary are a heterogeneous group of tumours which first present with metastases and not the primary. Initial investigations do not identify the primary site of cancer at the time of diagnosis. The occult primary is eventually found to be of colorectal, lung, liver or pancreas origin in the majority of cases (Krämer et al, 2008). Lung, liver and bone are common sites for metastatic disease. Cancers of unknown primary are often rapidly progressive, with 30% of cases presenting with multiple metastases at diagnosis and 57% presenting as an emergency (National Cancer Registration and Analysis Service, 2010). However, there are favourable subsets that can have an excellent response and prognosis with specific treatment.

Epidemiology

More than 9000 new cases of cancers of unknown primary are registered every year in the UK, which accounts for around 2% of all new cases of cancers, and 6% of all cancer-related deaths. Cancers of unknown primary is the fifth most common cause of cancer death in the UK (Cancer Research UK, 2016). There is a slight female predominance and the median age at diagnosis is 65 years. Only 5% of cases occur in those aged under 50 years (National Cancer Registration and Analysis Service, 2010).

Work-up

The term cancers of unknown primary in practice may cover patients referred where absolutely no work-up or assessment has been done, patients who are too unwell to be investigated or patients where investigations eventually identify the primary. However, a true case of cancer of unknown primary means that, despite thorough investigations, the primary site of cancer cannot be determined.

Patients should only be investigated if:

1. The result is likely to affect the treatment decision
2. The patient understands why the investigations are being carried out, and their risks and benefits
3. The patient is prepared and fit enough to accept treatment.

Initial assessment

All patients will need a detailed history including the presenting complaint, occupational, family and smoking history (*Table 1*). The patient's performance status (Oken et al, 1982) (*Table 2*) and comorbidities should also be taken into account.

A general physical examination should be done, including the respiratory and abdominal system as these are the two most common sites of primary cancer. Further examination may depend on the patient's current symptoms and signs, and the

Table 1. Occupational cancers

Occupation	Exposure	Cancer association
Hairdressers, barbers, textile industry workers	Benzidine, beta-napthylamine, 4-aminobiphenyl	Bladder
Metal working, rubber, plastics and textile industry workers	Asbestos, wood dust, paint fumes	Larynx
Plastic manufacturing	Arsenic, vinyl chloride, aflatoxins	Liver
Plumber, electrician, mining, railroad and construction industries	Asbestos	Mesothelioma
Textile and baking industry, flour milling, carpenters	Mustard gas, nickel dust, chromium dust, leather dust, wood dust, radium	Nasal cavity and sinus
Iron and steel foundry work, welding, rubber manufacturing, paving and roofing	Radon, second-hand smoke, asbestos, arsenic, cadmium, chromium compounds	Lung

From American Cancer Society (2016)

Table 2. Performance status

	World Health Organization or Eastern Cooperative Oncology Group performance status
0	Fully active, able to carry out pre-disease activities without restriction
1	Restricted in strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of limited self-care, confined to bed or chair for more than 50% of waking hours
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair
5	Death

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clinician's index of suspicion of the likely primary site. Consider examination of the oropharynx, ear, nose and throat, breasts, gynaecological system, testes, rectum and a full skin survey.

Investigations

Blood tests

Basic blood tests such as a full blood count, kidney function, liver function and bone profile should be done as part of the initial assessment. These can help guide suitability of further investigations and management.

Computed tomography

Initial imaging should include a chest X-ray and a computed tomography of the chest, abdomen and pelvis with intravenous contrast. With a cancer of unknown primary, the computed tomography scan will not identify the site of the primary origin of cancer but may help guide further targeted investigations.

Tumour markers

Tumour markers (Pavlidis and Pentheroudakis, 2012) are useful in measuring response to cancer treatment (*Table 3*). Requesting a panel of tumour markers is not recommended for diagnosis as these are low in sensitivity and specificity. If subsequent investigations point towards a particular primary, then the specific tumour marker level if raised can strengthen the case for an ultimate diagnosis.

Positron emission tomography–computed tomography

Positron emission tomography–computed tomography scans can identify areas of high glucose metabolism using a biologically active radioactive tracer, fluorodeoxyglucose (^{18}FDG), which is a glucose analogue. Areas of high ^{18}FDG uptake relate to areas of high metabolic activity which can be indicative of a malignant process and can therefore point to a specific primary site that may not be apparent on the initial computed tomography staging scan. Positron emission tomography–computed tomography scans are useful in identifying small primary tumours in the head and neck region, and the extent of disease in patients who present with metastatic cervical nodal squamous cell carcinoma, especially if radical treatment is being considered (National Institute for Health and Care Excellence, 2016).

> "A biopsy is needed to confirm cancer, and the histology can then be classified into that of epithelial ... or non-epithelial origin."

However, increased ^{18}FDG uptake can also be seen in other conditions such as inflammation, infection or some benign conditions (e.g. sarcoidosis). A positron emission tomography–computed tomography scan is therefore not always conclusive and should be used in conjunction with other investigations to determine the likely site of the primary cancer.

Magnetic resonance imaging

Magnetic resonance imaging provides clearer soft tissue definition than computed tomography and is useful in identifying small primary tumours in the head and neck region, breast, liver and pelvis, which may not be as easily visualized on computed tomography. It is recommended that bilateral breast magnetic resonance imaging should be carried out in patients who present with isolated adenocarcinoma of the axillary nodes as up to 70% of cases of occult primary breast cancers can be identified this way (Pavlidis and Pentheroudakis, 2012).

Oesophago-gastroduodenoscopy and colonoscopy

Upper and lower gastrointestinal tract malignancies do not always present with symptoms relating to the primary cancer. Oesophago-gastroduodenoscopy and colonoscopy should be considered in patients with iron-deficiency anaemia and suspicious pattern of metastatic spread (i.e. liver metastases and/or left supraclavicular fossa lymphadenopathy). Tumours can be seen endoscopically and biopsies should be taken at the same time.

Others

Mammogram, ultrasound of the testes, and nasopharynx endoscopy are other common targeted investigations to consider depending on the patient's history, signs, symptoms and computed tomography findings (*Table 4*).

Histology and immunohistochemistry

A biopsy is needed to confirm cancer, and the histology can then be classified into that of epithelial origin (carcinomas) or non-epithelial origin (sarcoma, melanoma, lymphoma, germ cell or haematological malignancies). In general a 'true' metastatic cancer of unknown primary will be a carcinoma.

First, using light microscopy with haematoxylin and eosin staining on the tissue biopsy, most cancers of unknown primary can be classified into adenocarcinoma (60%), squamous cell carcinoma (5%), neuroendocrine or mixed histology (30%) (Oien and Denis, 2012).

Immunohistochemical markers are then used to help determine the primary site of cancer origin. These markers are usually peroxidase-labeled antibodies against specific subtypes of cytokeratin (CK) intermediate filaments, which have different levels of expression in different cell types and cancers. The most commonly used CK stains in cancers of unknown primary are CK7 and CK20.

Table 3. Common tumour markers

Cancer	Tumour marker
Germ cell tumours	Alpha-feta protein, beta human chorionic gonadotropin
Liver cancer	Alpha-feta protein
Pancreatic cancer	Carbohydrate antigen 19-9
Colorectal cancer	Carcinoembryonic antigen
Prostate cancer	Prostate-specific antigen
Ovary and primary peritoneal	Cancer antigen 125
Breast cancer	Cancer antigen 15-3 (not widely used)

Table 4. Examination and investigations based on presenting findings

Sign, symptom or computed tomography findings	Examine	Further investigations to consider	Possible primary site
Cervical lymphadenopathy	Head and neck	Nasopharynx endoscopy, magnetic resonance imaging head and neck, positron emission tomography-computed tomography scan	Head and neck squamous cell carcinoma
Left supraclavicular lymphadenopathy (Virchow's node)	Abdomen	Oesophago-gastroduodenoscopy, colonoscopy	Gastrointestinal carcinoma
Inguinal lymphadenopathy	Genital (vulva, vaginal, penis), anal and rectal, lymphoreticular system	Examination under anaesthesia of genital or anal region, colonoscopy	Vulva squamous cell carcinoma, penile squamous cell carcinoma, anal squamous cell carcinoma, low rectal adenocarcinoma, lymphoma
Supraclavicular and axillary lymphadenopathy	Breast	Mammogram, magnetic resonance imaging breasts	Breast invasive ductal or lobular carcinoma
Mediastinal mass, retroperitoneal mass	Testes, lymphoreticular system	Ultrasound testes, germ cell tumour markers, thyroid function tests and thyroglobulin, positron emission tomography-computed tomography	Germ cell tumours, lymphoma (Hodgkin's or non-Hodgkin's), thymoma, thyroid
Peritoneal or omentum deposits	Lung, abdomen, gynaecological	Transvaginal ultrasound	Ovarian, primary peritoneal
Lytic bone lesions	Depends on symptomatic site	Urine and serum electrophoresis, urine Bence Jones protein, skeletal survey	Myeloma, renal cell, melanoma, non-small-cell lung cancer, thyroid
Sclerotic bone lesions	Prostate (rectal examination)	Prostate-specific antigen level, bone scan, magnetic resonance imaging pelvis	Prostate adenocarcinoma

Additional markers can be used to differentiate cancers within these groups. These include CEA (colorectal), TTF-1 (thyroid, lung adenocarcinoma or mesothelioma), ER and PR (breast), PSA (prostate), urothelin (urothelial), WT-1 (ovary), Hep Par-1 (liver and biliary/pancreas), chromogranin and CD56 (neuroendocrine) and many others.

It is important to note that no immunohistochemical test is 100% specific, for instance, prostate-specific antigen may be positive in a patient with salivary gland cancer. Therefore the patient's history and imaging results should be taken into context when evaluating the immunohistochemical test results.

Favourable *vs* unfavourable prognosis subsets and treatment

Favourable prognosis subset

Around 15–20% of patients belong to a subset that carries a more favourable prognosis (Pavlidis and Pentheroudakis, 2012). These patients should be discussed at the multidisciplinary meeting and be selected for specific oncological treatment as they tend to have cancers that respond well. Treatment can often achieve excellent long-term control or in some cases even cure the cancer.

Patients with a favourable prognosis include those who present with:

- Isolated cervical (non-supraclavicular fossa) nodal metastases with squamous cell carcinoma histology – they may have a primary tumour site in the head and neck region. This can be treated with radical intent and options include radiotherapy with concurrent chemotherapy, or a neck dissection and/or adjuvant radiotherapy (National Institute for Health and Care Excellence, 2016).
- Isolated axillary nodal metastases with adenocarcinoma histology – they may have a breast primary tumour. A mastectomy and axillary lymph node clearance should be performed and depending on the final histology (which should include the ER and HER2 status), adjuvant chemotherapy, hormonal therapy and/or radiotherapy may be recommended (Pavlidis and Pentheroudakis, 2012).
- Single site metastasis especially of the liver, bone, skin or lung. These patients may in fact have an unusual primary tumour or have oligometastatic disease, so should be considered for definitive surgery and/or radiotherapy. Stereotactic ablative radiotherapy is a radiotherapy technique that allows very high radiation doses to be delivered precisely to a tumour – it is increasingly being used for patients with oligometastatic disease as there is some evidence that it improves survival (Palma et al, 2018).

The specific management of other favourable subsets is listed in *Table 5*.

Unfavourable prognosis subsets

Unfortunately, most patients present with widely disseminated disease and fall into an unfavourable prognosis subset. These include patients with:

- Adenocarcinoma with multiple liver metastases
- Non-papillary malignant ascites
- Multiple cerebral metastases (adenocarcinoma or squamous cell)
- Adenocarcinoma with multiple lung and pleural metastases
- Adenocarcinoma with multiple bone metastases.

Within this group, patients with good performance status (<1) and normal lactate dehydrogenase level have a better outcome than those with poor performance status (>2) and raised lactate dehydrogenase level (Fizazi et al, 2015).

Palliative chemotherapy

Depending on the histology and likely primary site of origin, combination chemotherapy can be considered in patients with a good performance status. However, there is a lack of evidence regarding the benefit of palliative chemotherapy. Observational studies suggest better overall survival in patients treated with chemotherapy *vs* supportive care only (Lofts et al, 1999; Shaw et al, 2007), but this may be because patients who receive chemotherapy tend to be fitter (Seve et al, 2006). A wide variety of chemotherapy regimens have been used in practice, with studies suggesting higher response rates with platinum-based chemotherapy (Culine et al, 2002).

Common chemotherapy combinations include:

- Epirubicin, cisplatin and capecitabine (or 5-fluorouracil)
- Platinum (e.g carboplatin) and taxane (e.g. paclitaxel).

The CUPISCO trial (https://clinicaltrials.gov/ct2/show/NCT03498521), which is currently recruiting in the UK, is an international phase II trial looking at using genomic profiling and comparing targeted therapies, immunotherapy and platinum-based chemotherapy.

> **“Depending on the histology and likely primary site of origin, combination chemotherapy can be considered in patients with a good performance status.”**

Palliative radiotherapy

Radiotherapy can be helpful in improving local symptoms, i.e. pain from bone or soft tissue metastases and haemoptysis in lung metastases. In addition it has a role in preserving neurological function in ambulatory patients with metastatic spinal cord compression (Prewett and Venkitaraman, 2010). In the palliative setting, radiotherapy is given in a small number of sessions, often ranging from 1 day to 2 weeks, depending on the anatomical site of treatment and the patient's performance status. Common palliative radiotherapy schedules include treatment with 8 Gray in one fraction (single day treatment) or 20 Gray in five fractions (over 5 days). It is generally a well-tolerated treatment with minimal side effects and can be a good treatment option for symptomatic patients with poor performance status.

Prognosis

The 1-year survival is approximately 20% (Kramer et al, 2008). However, many patients have a poor performance status as a result of the underlying disseminated cancer and will not be well enough to receive chemotherapy. Patients with extensive metastatic disease and an unknown primary often have a much poorer prognosis. In one study, patients with performance status more than 1 and liver metastases had a median survival of 2.4 months, compared to a median survival of 10.8 months in patients with performance status 0 or 1 without liver metastases (Culine et al, 2002).

Patients in the favourable subset who have responded to treatment have outcomes similar to those of patients with metastatic tumours from a known primary site. For instance, patients with serous papillary adenocarcinoma of the peritoneal cavity managed similarly to patients who have stage III and IV ovarian cancer have a median survival of approximately 36 months (Pavlidis and Pentheroudakis, 2012).

Table 5. Favourable subset and treatment

Histology	Site	Potential primary site	Treatment
Neuroendocrine tumour – poorly differentiated	Any	Any	Chemotherapy (platinum+etoposide)
Neuroendocrine tumour – well differentiated	Any	Any	Somatostatin analogues, sunitinib
Serous papillary adenocarcinoma	Peritoneum (in women)	Ovarian	
Primary peritoneum	Surgical debulking and chemotherapy (platinum+taxane)		
Adenocarcinoma	Isolated axillary lymph nodes	Breast	Surgery and consider adjuvant systemic treatment and radiotherapy
Squamous cell carcinoma	Isolated non-supraclavicular cervical lymph nodes	Head and neck	Primary chemoradiotherapy or surgery +/-radiotherapy
Squamous cell carcinoma	Isolated inguinal nodes	Genital or anorectal	Surgery +/- radiotherapy
Adenocarcinoma	Men with blastic bone metastases and raised prostate-specific antigen level	Prostate	Luteinising hormone-releasing hormone analogues
Other or unknown	Young men with tumours of predominant midline distribution (mediastinum and retroperitoneum)	Germ cell	Chemotherapy (bleomycin, etoposide and cisplatin)
Any	Single metastatic site	Any	Surgery +/- radiotherapy

KEY POINTS

- Cancers of unknown primary present with metastases and initial investigations do not reveal the primary site.
- Direct further investigations depending on the presenting features of the cancer and the likely potential primary site.
- Patients who belong to a favourable subset can have good outcomes from specific treatments.
- Early referral to the oncology and palliative care team is important to guide suitability of further investigations and treatment.

Conclusions

Cancer of unknown primary is a general term used to describe metastatic cancers without an obvious primary origin. Many patients have disseminated disease and are very unwell at presentation. Consider seeking advice from the oncology team to assess the appropriateness of further investigations, to direct investigations, and to identify patients with a favourable prognosis who will benefit from specific treatment. Early input from the palliative care team is essential as in the majority of cases patients are not fit for treatment and require palliation of symptoms. **BJHM**

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