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Clinical Radiology
The Royal College of Radiologists

Recommendations for cross-sectional imaging in cancer management

Carcinoma of unknown primary origin (CUP)

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Contents

Clinical background

The incidence of carcinoma of unknown primary (CUP) or occult primary origin ranges from 0.5 to 9% of all patients diagnosed with cancer.[1] Identification of the primary lesion largely forms the basis for predicting the expected behaviour and for assigning appropriate therapy of the malignant disease; thus the identification of a primary tumour poses a major challenge. The most common histology is adenocarcinoma (well- to moderately differentiated 50%; undifferentiated 30%), squamous cell cancer (15%) and undifferentiated cancer (5%).[2] There is considerable controversy over the extent of evaluation needed to locate a primary cancer. Guidance published in July 2010 by the National Institute for Health and Care Excellence (NICE) on the diagnosis and management of metastatic malignant disease of unknown primary recommends dividing the diagnostic process into two phases.[3] The initial diagnostic screen aims to define the primary site and/or a specific histological type of tumour, allowing definitive treatment to be planned. The initial diagnostic phase involves investigations, as clinically appropriate, guided by the patient's symptoms and includes comprehensive history and physical examination, routine blood tests, chest X-ray (CXR), myeloma screen (if there are isolated or multiple lytic bone lesions), symptom-directed endoscopy, computed tomography (CT) of the chest, abdomen and pelvis, testicular ultrasound in men with presentations compatible with germ-cell tumours and biopsy with standard histological examination. Specific tumour markers are indicated in various settings such as CA125 in women with peritoneal malignancy or ascites, prostate-specific antigen (PSA) in men with presentations compatible with prostate cancer. More detail on this aspect is beyond the scope of this chapter but interested readers are directed to the NICE guidelines, which provide further information.[3]

At the completion of a broad screen of initial investigations, several groups can be identified, subdivided according to pathological diagnosis. The subsets include:

- Metastatic epithelial or neuroendocrine malignancy, primary revealed during screening investigations
- Lymphoma and other haematological malignancies
- Metastatic melanoma
- Sarcoma
- Metastatic germ-cell tumour
- Metastatic epithelial or neuroendocrine malignancy, no primary revealed during screening investigations.

A second phase of more specific investigations is appropriate in some patients.

Who should be imaged?

All patients with suspected or diagnosed carcinoma in whom the origin of the primary tumour is unknown. If initial diagnostic tests (chest X-ray, CT +/- endoscopy in symptomatic patients) fail to identify a primary tumour, special investigations should be considered if the results are likely to affect a treatment decision.

Staging objectives

- To identify the full extent of disease and guide the selection of the optimal site for biopsy.
- To identify the site of the primary tumour in order to assign the appropriate therapy.
- To determine potentially favourable subsets of patients with highly treatable malignancies.

The appropriate use of imaging is dependent principally on distribution and histology of known disease. The distribution of disease can provide clues to the likelihood of the primary site being above or below the diaphragm. Lung metastases are twice as common in primary sites ultimately found to be above the diaphragm. Liver metastases are more common from primary disease below the diaphragm. When evaluating patients, it is important to remember that the pattern of metastatic spread of a cancer presenting as an occult lesion can be significantly different from that which would be expected from the usual presentation. For example, bone metastases are approximately three times more common in pancreatic cancer presenting as occult lesions, but for lung cancer bone metastases are about ten times less common.

Staging

Metastatic squamous carcinoma of the neck

Most patients presenting with metastatic squamous cancer to the neck will present with cervical lymphadenopathy and 85% will have a squamous cell cancer of the aero-digestive tract.[4] For these patients, either a contrast-enhanced CT or magnetic resonance imaging (MRI) scan and panendoscopy are required to identify the primary tumour. CT should also include the chest as occult primary lung cancer may also present with metastatic nodal disease in the neck. When a metastatic squamous tumour is found within neck lymph nodes, and routine imaging, panendoscopy and biopsy are all negative (~5% of head and neck cancers present in this way), a fluorodeoxyglucose positron emission tomography-CT (^{18}FDG PET-CT) scan is indicated for locating the primary tumour.[5] Asymmetric uptake of ^{18}FDG on PET-CT of the tonsils should be considered with suspicion.

Values of CT dose index ($CTDI_{vol}$) should normally be below the relevant national reference dose for the region of scan and patient group (see Appendix and chapter on risks of radiation exposure for the patient).

Metastatic adenocarcinoma of unknown primary origin

Initial imaging should consist of a chest X-ray and CT scan of the chest, abdomen and pelvis in most patients. This will be expected to result in the detection of a primary site in 30–35% of patients.[6] Male patients with a presentation compatible with a germ-cell tumour should undergo testicular ultrasound. In 15–25% of patients, the primary site cannot be identified even at post-mortem examination.[7] In patients with negative cross-sectional imaging, upper and/or lower gastrointestinal (GI) tract endoscopy should be considered if symptoms, histology or radiology suggest a GI primary tumour. Patients with adenocarcinoma involving the axillary nodes should be referred to a breast cancer multidisciplinary team (MDT) for evaluation and treatment. If no breast primary tumour is identified after standard breast investigations (breast examination, mammography and ultrasound), dynamic contrast-enhanced breast MRI should be considered to identify lesions suitable for targeted biopsy. ^{18}FDG PET-CT should only be considered in patients with provisional CUP with extra-cervical presentations after discussion with the CUP team or CUP network MDT. There is a developing evidence base for using ^{18}FDG PET-CT in CUP diagnosis, with some evidence

for change of management although no improvement in outcome. Further research is needed to determine whether the identification of a primary tumour site with ^{18}FDG PET-CT modifies treatment and improves patient survival and quality of life, and to determine whether the use of ^{18}FDG PET-CT early in the CUP management pathway reduces the number of investigations that the patient is subjected to.

CT

- Oral administration of 1 litre of water or iodinated contrast medium. Choice of acquisition according to local preference,[8] options include:
  - *Biphasic arterial ± venous acquisition:*
    - 100–150 ml intravenous iodinated contrast medium injected at 3–4 ml/sec
    - Multidetector computed tomography (MDCT) is commenced at 20–25 seconds (chest) and 70–80 seconds (abdomen and pelvis) post-injection
  - *Single acquisition with a monophasic injection (venous phase):*
    - Contrast volume: 70–100 ml (0.1 ml/kg) with 30–40 ml saline chaser at 3 ml/s
    - Portal venous acquisition: 60–80 sec after contrast injection
  - *Single acquisition with a biphasic injection or split bolus:*
    - 65–80 ml contrast media at 2.5 ml/s
    - 15–40 ml contrast media and 30–50 ml saline chaser at 2.5–3 ml/s starting 40 sec after contrast injection
    - Venous acquisition: 60–80 sec after contrast injection
- Using MDCT, slice thickness will depend on scanner capability. In general, sections are acquired at 1.25–2.5 mm and reformatted at 5 mm for viewing.

Values of $CTDI_{vol}$ should normally be below the relevant national reference dose for the region of scan and patient group (see Appendix and chapter on risks of radiation exposure for the patient).

Bronchoscopy and video-assisted thoracoscopic surgery (VATS)

When percutaneous biopsy is unsuitable or inappropriate for intrapulmonary nodules of metastatic origin, flexible bronchoscopy with biopsy, brushings and washings should be considered even when there is no evidence of endobronchial or central nodal disease on imaging. VATS exploration should only be considered after a negative bronchoscopic procedure.

Follow-up

Follow-up is conducted to assess response to chemotherapy and is, therefore, performed at a frequency to correspond with the chemotherapy regimens.

Conclusions

In patients presenting with metastatic malignant disease of unknown primary, initial diagnostic tests including chest X-ray, CT and targeted biopsy will be sufficient for guiding optimal treatment in the majority of patients. Additional specialised investigations are only indicated in selected patients. Endoscopy should be reserved for symptomatic patients. Mammography and breast MRI are only indicated in patients with suspected breast cancer negative on conventional work-up. PET-CT is of value in patients with cervical nodal disease but has variable accuracy elsewhere. Bronchoscopy can be of value in patients with pulmonary metastases of unknown origin. Further evidence on the cost-effectiveness and impact on patient survival of these specialised tests is awaited.

References

1. van de Wouw AJ, Janssen-Heijnen ML, Coebergh JW, Hillen HF. Epidemiology of unknown primary tumours: incidence and population-based survival of 1285 patients in Southeast Netherlands, 1984–1992. *Eur J Cancer* 2002; **38**: 409–413.
2. Daugaard G. Unknown primary tumours. *Cancer Treatment Rev* 1994; **20**: 119–147.
3. National Institute for Health and Care Excellence. *Metastatic malignant disease of unknown primary origin. Clinical Guideline 104*. London: NICE, 2010.
4. Jereczek-Fossa BA, Jassem J, Orecchia R. Cervical lymph node metastases of squamous cell carcinoma from an unknown primary. *Cancer Treat Rev* 2004; **30**: 153–164.
5. Royal College of Physicians and The Royal College of Radiologists. *Evidence-based indications for the use of PET-CT in the United Kingdom 2013*. London: Royal College of Physicians, 2013.
6. McMillan JH, Levine E, Stephens RH. Computed tomography in the evaluation of metastatic adenocarcinoma from an unknown primary site. A retrospective study. *Radiology* 1982; **143**: 143–146.
7. Stewart JF, Tattersall MHN, Woods RL, Fox RM. Unknown primary adenocarcinoma: incidence of overinvestigation and natural history. *Br Med J* 1979; **1**: 1530–1533.
8. Rastogi S, Singh R, Borse R *et al*. Use of multiphase CT protocols in 18 countries: appropriateness and radiation doses. *Can Assoc Radio J 2020*; **Jan 27**: 846537119888390. [Online ahead of print].

Authored by Professor Andrew Scarsbrook, St James's University Hospital, Leeds

Appendix 1
Dataset (to be updated with dates through patient's follow-up)

Patient identification
Location of primary
Date of primary diagnosis
Pathological stage
Lymph node involvement (including date of diagnosis)
If lymph node +ve: anatomical location
Method of detection
Metastatic sites (including date of diagnosis)
Imaging tests utilised
Enrolment into clinical trial (details)

The Royal College of Radiologists
63 Lincoln's Inn Fields
London WC2A 3JW

+44 (0)20 7405 1282
enquiries@rcr.ac.uk
www.rcr.ac.uk
@RCRadiologists

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