Carcinoma of Unknown Primary (CUP)
Cancer Clinical Guidelines

Carcinoma of Unknown Primary EAG on behalf of NCA

Title:	CUP Guidelines
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Introduction

The term “cancer of unknown primary” refers to a condition in which a patient has metastatic malignancy without an identified primary source. This is a very heterogeneous disease in which the type of tumour, the extent of spread, and the outcome of treatment all vary widely.

The term “carcinoma of unknown primary” (CUP) refers to those patients with metastatic malignancy of epithelial, neuroendocrine or undifferentiated lineage whose investigation and management is considered within the scope of this guideline.

Patients with tumours of non-epithelial lineage (melanoma, sarcoma, lymphoma, germ-cell) form a distinct and important minority, since subsequent management can often be satisfactorily undertaken even in the absence of an identifiable primary source. Such patients are not considered in this guideline, since their care is adequately defined in existing guidelines for their specific tumour type.

When a patient presents with metastatic malignancy on clinical examination or by imaging, without an obvious primary site, they can be regarded as having “malignancy of undefined primary origin” (MUO). Although a primary site is subsequently found in a majority, or an uncommon non-epithelial malignancy is diagnosed, some patients will ultimately be diagnosed with “true” carcinoma of unknown primary after extensive testing.

For the purpose of defining optimal management during the various phases from initial presentation to completion of testing, the following definitions have been devised within NICE guideline CG104 and are used throughout this guideline:

Definitions

- Malignancy of undefined primary origin (MUO):
  - *Metastatic malignancy identified on the basis of a limited number of tests, without an obvious primary site, before comprehensive investigation.*

- Provisional carcinoma of unknown primary (provisional CUP):
  - *Metastatic epithelial or neuroendocrine malignancy identified on the basis of histology/cytology, with no primary site detected despite a selected initial screen of investigations, before specialist review and possible further specialised investigations.*

- Confirmed carcinoma of unknown primary (confirmed CUP):
  - *Metastatic epithelial or neuroendocrine malignancy identified on the basis of final histology, with no primary site detected despite a selected initial screen of investigations, specialist review, and further specialised investigations as appropriate.*

Patient Pathways and Northern Cancer Alliance Configuration of CUP services

The referral pathway for patients with MUO or pCUP is as follows:

- Any patient identified by the Emergency Department, hospital Consultants or a site-specific MDT within the hospital, who meets the definition of MUO/pCUP, should be referred without delay to the hospital CUP team.
- In-patient referrals will be reviewed by the CUP team by the end of the following working day. Out-patient referrals will be reviewed by the CUP team within 2 weeks of the date of referral.
- Any patients with MUO referred to a site-specific MDT will be referred on to the CUP MDT without delay.
- All patients with pCUP will be discussed at the next CUP MDT with which the hospital is associated, for any advice on remaining investigations needed to confirm the diagnosis of CUP or establishment of a primary site, any necessary decision regarding suitability for 'active treatment' and any relevant treatment planning decisions.

The configuration of CUP services across the Northern Cancer Alliance is as follows:

CCG Population	Hospital	CUP team	Associated CUP MDT
249,000	Royal Victoria Infirmary	Dr Chris Jones CNS Angela Simpson CNS Nicola Cosford CNS Jacqueline Marsh	Newcastle upon Tyne Hospitals NHS Foundation Trust CUP MDT
	Freeman Hospital		
	Queen Elizabeth Hospital	Dr Jeremy Killen Dr Fiona McDonald Nurse Consultant Lynsey Robson	Queen Elizabeth Hospital CUP MDT
427,000	Sunderland Royal Hospital	Dr John Painter CNS Louise Davison CNS Sue Hedley	Sunderland Royal Hospital CUP MDT
	South Tyneside District Hospital	Dr Anna Porteous CNS Jen Blake	South Tyneside Hospital CUP MDT
519,000	Wansbeck General Hospital	Dr Deepta Churm CNS Dawn Elliott CNS Lyndsey Walton	Northumbria Trust CUP MDT
	North Tyneside General Hospital		

	Northumbria Specialist Emergency Care Hospital		
	Hexham General Hospital		
288,000	University Hospital of North Tees	Dr Richard Thomas CNS K Powell CNS Tracey Nugent	North Tees NHS FT CUP MDT
536,000	University Hospital of North Durham	Dr S Jordan CNS Thelma Rosenvinge CNS Pam Mohan	South Tees NHS FT CUP MDT
	Darlington Memorial Hospital	CNS Catherine Simpson CNS Louise Galley	
275,802	James Cook University Hospital	Dr Sanjana Masinghe CNS Emily Park CNS Judith Curtis	
153,165	Friage Hospital		
318,000	Cumberland Infirmary	Dr Syed Haidar CNS Kerry Miles	Newcastle upon Tyne Hospitals NHS Foundation Trust CUP MDT
	West Cumberland Hospital		

Guidelines for investigation of possible MUO or pCUP

The following investigations should be offered to patients with MUO, as clinically appropriate, guided by the patient's symptoms, and in discussion with the hospital CUP team:

1. Initial investigations

- comprehensive history and physical examination including breast, nodal areas, skin, genital and rectal examination
- holistic assessment of the physical, emotional, practical, psychological and spiritual needs of the patient
- full blood count; urea, electrolytes and creatinine; liver function tests; calcium; urinalysis
- myeloma screen (when there are isolated or multiple lytic bone lesions)
- alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) (particularly in the presence of midline nodal disease)
- prostate-specific antigen (PSA) in men
- CA125 in women with peritoneal malignancy or ascites
- chest X-ray
- computed tomography (CT) scan of the chest, abdomen and pelvis, including head and neck if clinically appropriate
- testicular ultrasound in men with presentations compatible with germ-cell tumours
- upper or lower gastrointestinal (GI) endoscopy **only** where the symptoms, histology or radiology suggest a GI primary tumour
- biopsy and standard histological examination, with immunohistochemistry; consider obtaining a tissue sample by ascitic tap, paracentesis or laparoscopy for histological examination in patients with MUO who present with ascites. **Note: in patients with apparent solitary metastasis, inappropriate biopsy of the lesion may make radical treatment ineffective – the patient must be discussed in the site-specific MDT appropriate to the location of the lesion before a biopsy is recommended.**

Note: tumour markers should not be measured during diagnosis except for:

- AFP and hCG in patients with presentations compatible with germ-cell tumours (particularly those with mediastinal and/or retroperitoneal masses and in young men)
- AFP in patients with presentations compatible with hepatocellular cancer

- PSA in men
- CA125 in women with presentations compatible with ovarian cancer (carefully interpret the results because of limited test specificity)

2. Further investigations for presentations of CUP which may benefit from radical, potentially curative treatment

Certain presentations of CUP may potentially be curable through radical surgery or radiotherapy, and will be referred after discussion with the hospital CUP team to the appropriate site-specific MDT without delay:

- Squamous carcinoma involving upper or mid neck nodes
  - will be referred to the Head & Neck MDT
  - consider ENT panendoscopy
  - consider positron emission tomography-computed tomography (PET-CT) for patients with provisional CUP presenting with cervical lymphadenopathy with no primary tumour identified on ENT panendoscopy if radical treatment is an option.
  - may be amenable to radical surgery/radiotherapy

- Adenocarcinoma involving axillary nodes
  - will be referred to the Breast MDT
  - consider mammography, breast ultrasound or breast MRI
  - may be amenable to radical surgery and adjuvant chemotherapy/radiotherapy

- Squamous carcinoma involving inguinal nodes
  - will be referred to the gynae-oncology, uro-oncology or anal cancer MDTs as clinically indicated
  - may be amenable to radical surgery

- A solitary apparent metastasis
  - must be referred to the site-specific MDT most appropriate to the location of that metastasis before biopsy is performed
  - consider positron emission tomography-computed tomography (PET-CT) for patients with solitary or oligo-metastatic disease if radical treatment is an option
  - may be amenable to radical surgery

3. Management of presentations of CUP which have a poor prognosis

- Brain metastases as the only apparent sign of malignancy
  - will be referred to the neuro-oncology MDT for evaluation and treatment
  - important to exclude primary cerebral tumours which can masquerade as metastases, and more treatable primaries with a high response rate to systemic therapy

- Multiple metastases including brain involvement
  - patients with confirmed CUP involving the brain in addition to other sites have a very poor prognosis.

- there is no evidence that any treatment offers improved survival and there is limited evidence of improvement in neurological symptoms with surgery and/or whole brain radiotherapy.
- the management of this group of patients generally involves providing symptomatic care and in some patients providing palliative cranial irradiation.
- the more aggressive approach of combining whole brain radiotherapy and systemic chemotherapy is offered to selected group of patients after careful consideration and discussion about factors such as the poor median survival, or limited efficacy of chemotherapy because of the “blood-brain barrier”.

Guidelines on the systemic therapy of treatable syndromes of CUP

The following chemotherapy regimes will be considered for treatable syndromes within the CUP spectrum, according to the Network guidelines (figure 1). Patients will also be offered clinical trials where this is appropriate.

- poorly differentiated carcinoma with a midline distribution
  - will be discussed with the uro-oncology/germ cell MDT
  - consider cisplatin-based chemotherapy (BEP/EP)

- women with predominantly peritoneal adenocarcinoma
  - will be discussed with the gynaecology MDT
  - consider carboplatin +/- paclitaxel chemotherapy

- women with adenocarcinoma involving axillary nodes
  - will be discussed with the breast cancer MDT
  - consider FEC or FEC-T chemotherapy

- squamous cell carcinoma of lymph nodes in the neck
  - will be discussed with the Head & Neck MDT
  - consider cisplatin-based chemotherapy +/- radiotherapy

- poorly differentiated neuroendocrine carcinoma
  - will be discussed with the NET MDT
  - consider carboplatin + etoposide chemotherapy

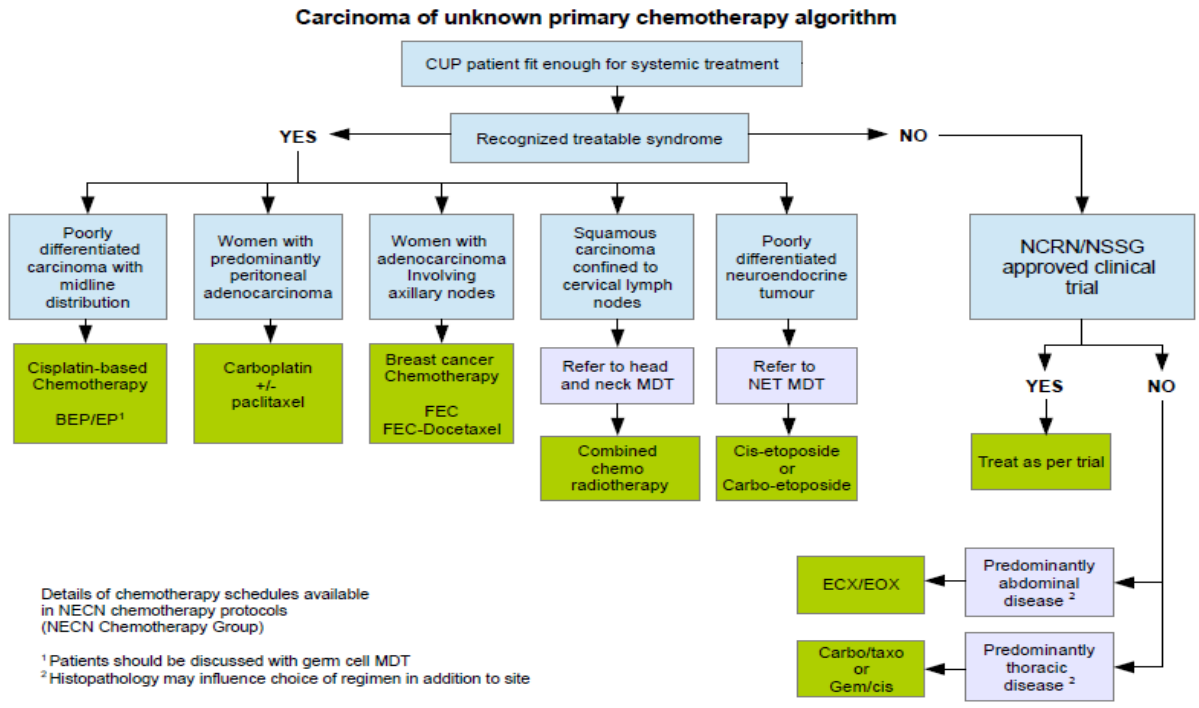

Figure 1: Network algorithm for systemic treatment of CUP