

# Understanding and managing cancer of unknown primary

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## Abstract

As a nurse, it is important to understand, and to be able to meet, the informational needs of patients and their family caregivers. Comprehensive information can help to reduce the fear of a challenging diagnosis. In the case of cancer of unknown primary (CUP) it may be helpful to understand some of what is unknown as well as what is known of this phenomenon, which represents some 5% of cancer diagnoses (Pentheroudakis et al, 2007b). Drawing on the literature, this article focuses on definitions, characterization, categorization and treatment of CUP.

**Key words:** Cancer of unknown primary ■ Carcinoma ■ Cancer biology ■ Oncology ■ Patient support

Cancer of unknown primary (CUP) is a challenging diagnosis for the patient and the clinician. There is a lack of information available regarding CUP and as a result patients are receiving confused explanations from oncologists about their CUP diagnosis (Boylard and Davis, 2008). Any cancer diagnosis is frightening for patients and their family and friends. Not to know where the cancer has originated in the body compounds this fear.

It often falls to nurses to try and make sense of CUP and communicate information appropriately to patients and their families. This article aims to contextualize what is known and what is unknown about CUP, where possible balancing theory with practice. In an under-researched area, where the majority of the literature is related to chemotherapy trial data, it is also helpful to consider what may be known; in other words the emerging thinking that may improve the situation for patients and medical practitioners.

## Cancer of unknown primary

### Prevalence

Owing to the problems of classification, and the lack of consensus on terminology and treatment, there is no definitive figure for CUP incidence in the UK. Estimates range between 3% and 10% of cancer diagnoses (Bridgewater et al, 2008). Shaw et al (2007) identified 3.7% CUP referrals in 1 year at a cancer centre in Wales.

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Taking a universal view, Pavlidis (2007) states that 'Cancer of unknown primary (CUP) ... represents one of the ten most frequent cancers and the fourth commonest cause of cancer death'.

## Defining CUP

The National Comprehensive Cancer Network (NCCN) (2008) states that 'Occult primary tumors or cancers of unknown primary (CUP) are defined as histologically proven metastatic malignant tumors whose primary site cannot be identified during pretreatment evaluation'. This is given more detail by van de Wouw et al (2003), who describe it as 'A biopsy-proven metastasis of a malignancy in the absence of an identifiable primary site after a complete history and physical examination [has] been carried out, along with basic laboratory studies, chest X-ray and additional directed studies ...'.

Even at this point it is important to recognize some of the difficulties of defining CUP. CUP is an umbrella term for heterogeneous clinical presentations associated with hidden (occult) primary cancers for which there is no consensus on terminology. The phenomenon, in its broadest definition, is referred to using different terminology such as metastatic malignancy of unknown origin, occult primary malignancy and tumour of unknown origin. The different terms, in part, reflect the heterogeneity of both presentation and possible site but also the lack of agreement and established practice regarding CUP and its classification.

In reality, the most significant clinical problems lie with carcinoma of unknown primary as, unlike melanoma or sarcoma, determining the primary site is fundamental for effective treatment.

A further problem is that CUP, using the definitions above in their broadest sense, reflects a continuum from those patients who have an 'uncertain' primary, where the primary tumour's lineage is eventually determined through specialized pathological study, to those that are truly 'unknown' where the primary is never conclusively identified. At some point those who are identified initially as CUP patients may be re-classified with an identified cancer. It is also important to recognize that some patients may be treated for a 'known' primary for pragmatic reasons, such as to give comfort to the patient and his or her family, even though the primary is not diagnosed with certainty.

## Diagnosis

The most important step in diagnosis of CUP is usually the biopsy, because this allows a general categorization of

carcinoma, sarcoma, lymphoma or melanoma from cells that are too poorly differentiated to reveal a primary source. In the case of carcinoma, further distinctions can be made (e.g. neuroendocrine and adenocarcinoma) from the biopsy. Based on the site(s) of the cancer spread, supplemented by the initial evidence, including physical examination, history and perhaps X-ray, the oncologist will then judge which further tests are likely to be most useful, such as tumour markers, positron emission tomography-computed tomography (PET-CT) and mammogram. There are no standard tests.

### Survival rates

The lack of universally recognized definitions of CUP is highlighted when trying to assess survival rates. For example, Baron-Hay and Tattersall (2001) recorded a survival median of 4–11 months with a 6% 5-year survival rate. What is not made clear in relation to survival rates is the definition used for CUP and the figures may well represent those with an uncertain primary. Life expectancy statistics in the literature vary considerably depending on the sub type of CUP, the performance status of the patient and the effectiveness of chemotherapeutic agents.

### Metastatic characteristics and investigation

Generally accepted characteristics of CUP tumours are that they stay small or regress after migrating through the body to find a 'sanctuary site' where they can thrive and confuse the immune system (see *Box 1* for a summary of reasons why the primary site may be hidden).

A cancer patient presenting with a metastatic lesion is likely to undergo a biopsy to allow the pathologist to try and determine the origin of the cancer. It is important to remember that when tumour cells spread or metastasize, the secondary or metastatic tumour cells are those of the original tumour (whether it can be found or not, every secondary tumour will have a primary tumour and certain secondary tumours tend to come from certain primary tumours). This is significant because effective cancer therapeutics seek to target the original, ancestral cells. Depending on the patient's level of fitness he or she then faces further tests to try and identify the primary tumour. If the primary tumour cannot be found the treatment is essentially palliative.

The scope of the investigatory process should not be underestimated. Shaw et al (2007) report that even within a single subtype patients 'underwent a total of 19 different investigations before any treatment [was] given'. Bridgewater et al (2008) see persistent investigation in search of the primary as often being 'time consuming and expensive yet futile'.

The tension between what is possible and what is desirable in relation to medical interventions may well become evident at this point, and patients may have different views to their loved ones requiring sensitively presented information and guidance from healthcare professionals.

There is some consensus in the literature that CUP patients present with unusual metastatic patterns in more organs than those with known primary tumours. There is less consensus regarding presentation sites. According to van de Wouw et al (2003) 'a relatively high number of

### Box 1. Reasons why the primary site may be hidden

- The primary tumour may have disappeared spontaneously because the patient's immune system may have destroyed the primary tumour, but not the secondaries.
- The secondaries may have grown and spread very quickly, while the primary is still too small to be seen on X-rays or scans.
- The primary tumour may be impossible to see on X-rays or scans because it is hidden by several larger secondaries that have grown close to it.
- It is thought that sometimes tumours of the lining of the digestive system may be passed out of the body through the bowel.

From: Cancerbackup (2008)

metastases are found in the kidneys, adrenal gland, skin and heart when compared with expected sites of metastases'. Shaw et al (2007) found the most common sub groups to be 'CUP-liver/multiple sites (25%), CUP-bone (21%) and CUP-brain (16%)'.

In terms of detection, Pavlidis et al (2003) note that 'the most frequently detected primaries are carcinomas hidden in the lung or pancreas'. van de Wouw et al (2003) report that in patients where the primary tumour was found during autopsy, it is revealed as a small asymptomatic tumour 'often localized in the lung or pancreas'. This view is not supported fully when compared with data from molecular investigation using genetic profiling (Pentheroudakis et al, 2007a).

### Categorization

Treatment options will be based on the metastatic pattern and the evidence that can be determined from histopathological analysis, which will allow discrimination by a particular CUP sub set. There is no universal agreement on this level of categorization or further levels. Taking the University of California, San Francisco classification and incidence, which is most recently referenced to Dowell (2003), the classification (and incidence) is given as (*Box 2*):

- Adenocarcinoma (60%)
- Poorly differentiated (35%)
- Squamous cell carcinoma (5%).

Findings by Yakushiji et al (2006), who retrospectively reviewed 86 CUP patients in a cancer hospital in Japan, show that the above figures are reasonably consistent in practice. Yakushiji et al (2006) reported incidences of adenocarcinoma at 71%, poorly differentiated carcinoma at 21%, and squamous cell carcinoma at 5%.

Other sources include neuroendocrine carcinoma as a rare CUP category, and Greco et al (2004) include a 'poorly differentiated neoplasm' where the pathologist cannot differentiate a general category of neoplasm, for example carcinoma, lymphoma, melanoma and sarcoma, but they maintain that 'few remain without a defined lineage after specialized pathologic study' (Greco et al, 2004).

Greco et al (2004) report, in relation to adenocarcinoma of unknown primary (ACUP) – the most frequent form of CUP – that the primary site becomes obvious in only 15–20% of patients during their lifetime – with 70–80% of patients having the primary site detected at autopsy.

## Box 2. Cancer of unknown primary categories

- Adenocarcinoma – sometimes referred to as adenocarcinoma of unknown primary. ‘Adeno’ refers to a gland and carcinoma is any cancer that arises from epithelial cells. This is a form of cancer that can arise in most internal organs.
- Poorly differentiated cancer – anaplastic tumours are poorly differentiated, meaning that their cells do not resemble normal cells.
- Squamous cell cancer – this is a form of cancer that may occur in many different organs, including the skin, mouth, oesophagus, lungs, and cervix.

CUP occurs equally in men and women and tends to affect older people ‘usually in the sixth decade of life’ (NCCN, 2008). This is supported by Shaw et al (2007), who recorded 166 CUP cases in a single UK cancer centre in a 12-month period: ‘One hundred and sixty-six patients were recorded to have a diagnosis of CUP, representing 3.7% of all referrals to the cancer centre. The median age of patients was 68 years (range 32–94 years), and 52.0% were women’. It is significant to note that while CUP is seen usually as a phenomenon affecting older people it is possible for it to affect younger people as shown in the age range in this study.

### Treatment

Oncologists may attempt one or more therapeutic regimen for CUP. Treatment will depend on the patient’s resilience and may include surgery, radiotherapy, chemotherapy, hormone therapy or a combination. In the case of the study by Shaw et al (2007), 47 (28.0%) patients received radiotherapy, 30 (18.0%) received chemotherapy and 58 (35.0%) patients received supportive care alone.

In terms of chemotherapy – the most likely treatment for a CUP patient – the histopathological clues may encourage a particular combination of therapy. Sometimes the clinician will resort to empirical chemotherapy (based on observation and experience), which according to Pavlidis et al (2003) ‘... benefits some of the patients who do not fit into any favourable sub-set, and should be considered in patients with a good performance status’. Bridgewater et al (2008), on the other hand, discourage physicians from the temptation to guess.

Pavlidis (2007) provides a summary to this section in his note stating that: ‘In general, chemotherapy [for the majority of CUP patients in unfavourable groups] offers poor results although several platinum or taxane/platinum regimens have reported to produce better responses as compared to old combinations... best supportive care should be recommended’. These rather dispiriting views on the effectiveness of chemotherapy reinforce the value of a palliative care programme identified early in the patient pathway and not left as a last resort.

### The patients’ perspective

Patients may want to have more information about their cancer to enable them to understand prognostic information and the treatment options available. Relatives will almost certainly want more information to enable them to support

their loved ones, and to know what to expect so that they can plan their lives. Most patients will have never heard of CUP. It can seem incomprehensible in our scientific age that a primary tumour is invisible and that there are no clearly defined treatment paths.

Boyland and Davis (2008) identify a number of themes in relation to patients responses to a CUP diagnosis. In their limited study of 10 patients it is shown that CUP patients find it extremely difficult to adjust to the diagnosis, in part, because healthcare professionals – the experts – are unable to explain the phenomenon and treat them (Boyland and Davis, 2008). This situation can be exacerbated by the good intentions of the NHS system. It is the intention of the NHS for all cancer patients and their carers to have access to medical and nursing specialists. But if a patient does not have a site-specific cancer he or she may fall into a gap for continuity and coordination, emotional and psychological support.

In the Boyland and Davis (2008) study the way each patient was handled with information by the oncologist appeared to vary. One oncologist was reported to have explained that ‘... only the secondaries could be treated, so recurrence was inevitable (despite having chemotherapy)’. This was in contrast to ‘some oncologists who emphasize that chemotherapy reaches the primary as well as the secondaries’ (Boyland and Davis, 2008). Understandably this variability adds to the bewilderment and distress of a cancer diagnosis. The distress is compounded for patients unable to explain their cancer to others. Tellingly, there is the suggestion in the research that those who choose to accept a provisional diagnosis gain reassurance from a known course of treatment (Boyland and Davis, 2008).

All those in the study by Boyland and Davis (2008) raised the issue of the number of investigations they faced which proved nugatory.

### Emerging thinking

Significant though it is to encourage hope in advanced cancer patients (McClement and Chochinov, 2008), this is something of a challenge with regard to patients with confirmed CUP.

The treatment and management of CUP has been tarnished with the nihilistic view, from some medical professionals, that nothing can be done; and sometimes, a more defensible, utilitarian view that health economics do not justify research and expensive treatment. Such views will not bring hope or encouragement to those who have CUP.

In 2008, the CUP landscape is starting to change with some hope for patients. A number of avenues may prove fruitful, individually or collectively:

- Improvements in medical imaging technology, which may help reveal the primary tumour for those with uncertain primaries
- Improved treatment for CUP and other metastatic, late-stage, diseases through:
  - The development of specific therapies targeted at cancer stem cells
  - Anti-angiogenic therapies (CUP seemingly having a highly active angiogenic profile)
  - The development of epidermal growth factor receptor inhibitors.

- Improved management and treatment pathways with consistent evidence-based guidance for clinicians (National Institute for Health and Clinical Excellence have started work on clinical guidelines for CUP, which are due to enter service in England, Wales and Northern Ireland in 2010)
- Better diagnostic markers to enable the assignment of metastases to likely sites of origin from pathological samples. (While this is supported by Dennis et al (2005), Shaw et al (2007) believe that because of the heterogeneous nature of CUP ‘a pathologically validated role for tumour markers will probably remain elusive ...’.)

With knowledge of CUP biology comes increased capabilities for treatment and a likelihood of greater survival. But, there is very little known about CUP biology. The traditional focus has been on the study of CUP in relation to its anatomical position. In the 21st century, researching the biology of the CUP phenomenon is likely to offer improved therapeutic options and may prove CUP to be an as yet unrecognized cancer.

### CUP biology

Claims that are made about CUP biology are based on limited studies and are inconclusive. Pavlidis (2007), for example, notes reports of abnormalities of the short arm of chromosome 1(1p). But as van de Wouw et al (2003) recognize, such karyotypic abnormalities are found in many metastatic solid tumours. Similarly, the finding of aneuploidy in 70% of unknown primary tumours, quoted by Pavlidis (2007), and the frequency of certain oncogenes and p53 is not shown with any evidence to be different to known primary tumours.

Greco et al (2004) believe that improved treatment for CUP ‘... will probably follow advances in the understanding of the biology and treatment of non-small cell lung cancer, pancreatic cancer, and the other gastrointestinal cancers because many insensitive carcinomas either arise from these occult primary sites or share a common biology’. The key question facing those who are concerned to investigate CUP is whether it is a group of metastatic tumours with unidentified primaries, or whether CUP has a specific biological entity of its own?

van de Wouw et al (2003) advanced the hypothesis that CUP may form a specific biological entity in 2003 but no consensus exists. If CUP is an as yet uncharacterized metastatic disease, its identification will put an end to chasing the primary tumour and allow specific therapy to be developed. Pentheroudakis et al (2007b) believes that ‘if [this hypothesis] proves right, the term “primary metastatic disease” would be better suited to describe the true nature of CUP’.

Until this hypothesis is proven or disproven, the focus for treatment remains based on the accepted theory that CUP is a clinical presentation of metastases in patients in whom the primary tumour cannot be detected. At some point, genetic profiling is likely to unlock the mysteries of CUP and it can help with diagnosis now.

### Genetic profiling

Gene expression profiling seeks to identify the genetic signature or the fingerprints of the cancer to detect the

specific tumour lineages of the malignant cells involved (each tumour maintains some traces of its genetic signature during metastasis). While this is unlikely to result in a cure for true CUP patients, tests available now (but not available presently on the NHS) can, depending on the confidence level of the result, bring the relief of knowing the origin of the cancer and help target the therapeutic regimen more effectively.

Bridgewater et al (2008) undertook a study of 21 patients in the North London Cancer Network, whose tumours were investigated with gene expression microarray analysis. The cohort showed a significant increase in survival, against predicted survival, following changed treatment resulting from identification. Bridgewater et al (2008) suggest that ‘the primary site can be predicted in the majority of patients and propose that overall investigative costs for CUP patients could be reduced using genetic profiling of the tumour’.

Further studies are needed to support such findings but there are an increasing number of oncologists and researchers such as Pentheroudakis et al (2007a), who see genetic profiling as the light at the end of the CUP tunnel.

### Conclusion

CUP is a little known and little understood phenomenon. A CUP diagnosis covers a wide range of clinical presentations and histology. It is usually characterized by unpredictable metastasis, often to more than one site, and poor outcomes.

A number of hypotheses exist about the phenomenon, such as the primary tumour metastasizes early and stays small, the primary enjoys particularly fast or slow growth and the metastatic process somehow inhibits the growth of the primary tumour.

Because of the heterogeneous nature of the cancer there will be many treatment options but there is no consensus on optimal management of CUP in UK cancer centres. In the absence of a focal point or clinical lead for CUP within the cancer centre, and until national guidelines are published, the management and treatment of CUP is likely to be variable.

For patients and loved ones a CUP diagnosis, where the primary consistently defies discovery, is particularly distressing. Patients and carers may feel excluded by the lack of information available to them and this brings into focus the need for sensitive information handling. Nurses play a vital role in supporting the patient and carers with appropriate information. Patients and their families need information from those who understand what is known and unknown about CUP to enable individuals to cope with CUP diagnosis.

CUP will remain a problematic diagnosis in the absence of evidence. It is likely to remain an enigma until genetic profiling unlocks the secret of the CUP tumour. BJN

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## KEY POINTS

- It is important to recognize the heterogeneous nature of cancer of unknown primary (CUP) and differentiate between uncertain, unconfirmed and truly unknown primary sites.
- Although cancer treatment in the UK is starting to move away from highly toxic therapies towards more specific interventions that impact on a particular gene or the way cancer progresses, there is a lack of research into the molecular characterization of cells associated with CUP.
- Genetic profiling may prove to be a way of reducing investigations for CUP patients and determining effective treatment that extends life for those with a favourable performance status.
- Research is needed to establish whether CUP has a specific biological entity (an as yet unknown cancer) or is the manifestation of unknown primary tumours with atypical metastatic spread.

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