

Dilemmas in managing patients with cancer of unknown primary

John Symons and colleagues explore the dilemmas affecting healthcare staff, patients and carers as they try to balance testing with treatment side effects and the consequences of trying to identify a primary tumour that may never be found

Summary

Cancer of unknown primary (CUP) is one of the ten most common cancer diagnoses in the UK. Since publication of the *NHS Cancer Plan* (Department of Health 2000), significant advances have been made in the co-ordination and management of patients with site-specific tumours, with concomitant improvements in patient and carer support. However, despite the prevalence of CUP, and the distress facing patients with no 'label', there is no consensus on optimum pathways and diagnostic testing for the condition. Many patients with CUP face multiple investigations to reveal or exclude the primary site. This article explores the dilemmas affecting healthcare professionals, patients and carers trying to balance optimum testing with treatment side effects and the psychosocial consequences of trying to identify a primary tumour that may never be found.

Keywords

Cancer of unknown primary, diagnostic testing, palliative care

CANCER OF unknown primary (CUP) is an umbrella term for a number of heterogeneous clinical presentations associated with hidden (occult) primary tumours. Van de Wouw *et al* (2003) described CUP 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.'

Problems of classification mean that there is no definitive figure for CUP incidence in the UK. It is generally reported to be about 5 per cent; estimates range between 3 and 10 per cent of all cancer diagnoses (Bridgewater *et al* 2008).

Patients with CUP face a challenging diagnosis and pathway. The challenges are shared by the healthcare professionals caring for those with this poorly understood condition. Until the National Institute for Health and Clinical Excellence (NICE)

guideline for CUP is published in summer 2010, there are no national guidelines for the treatment and management of patients with CUP.

Winston (2009) argued that doctors are losing the ability to assess patients because they rely too much on tests rather than on traditional clinical skills. 'Chasing the primary' through multiple testing is a characteristic of CUP. Particular challenges lie in defining the optimal point to cease diagnostic tests, and discussing the implications effectively with patients and their loved ones. These challenges may fall to consultants, GPs and, often, specialist nurses.

The *NHS Cancer Plan and the New NHS* (Department of Health (DH) 2004) identified the important role that nurses play in cancer care: 'Many clinical nurse specialists working in cancer or palliative care can be considered to have a "case management" role, working with individual patients to enhance their ability to cope with their disease and helping to ensure that their care is well co-ordinated... Nurse specialists in each of these groups have important roles in relation to the provision of information and support to cancer patients. They also have expertise in a specific area, for example, pain control and end of life care, chemotherapy, and knowledge of treatments for specific cancers.'

However, while there are specialist nurses expert in most cancer disease sites, there are no nurses expert in CUP in the UK despite the fact that it is one of the ten most common cancers and, according to Pavlidis (2007), taking a global view, the fourth commonest cause of cancer death.

The aim of this article is to examine the dilemmas facing clinicians and patients, balancing the factors that encourage testing with communicating difficult information that requires traditional clinical skills.

What is cancer of unknown primary?

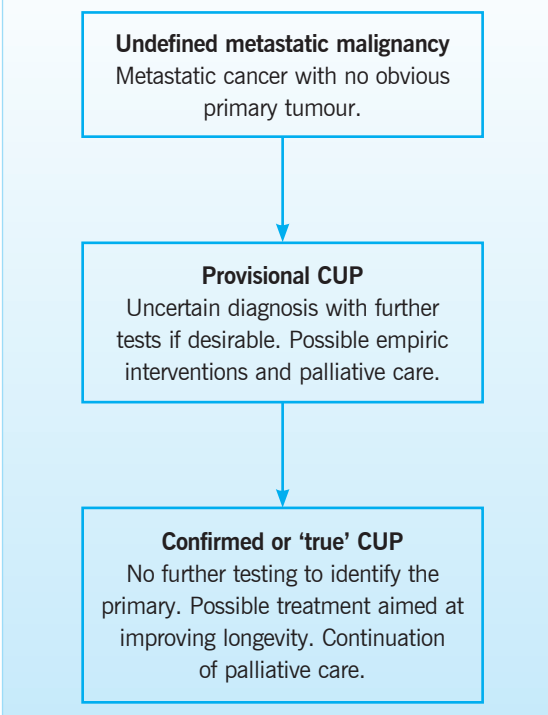
- Cancer of unknown primary (CUP) is hidden cancer. A patient is diagnosed as having metastatic cancer but the origin of the cancer cannot be determined. This makes treatment, based on the site of the primary cancer, extremely difficult. There is some consensus in the literature that CUP patients present with unusual metastatic patterns in more organs than those with known primaries (Symons 2008).
- There are a number of possible reasons why the primary site cannot be found. For example: the immune system may have destroyed the primary after it has spread; the secondary cancers may have grown and spread very quickly while the primary remains too small to be detected on scans. The primary cancer may be obscured by secondary cancers.
- CUP occurs equally in men and women; predominantly, but not exclusively, in people aged over 60 years.
- The most important step in diagnosis is usually biopsy because this allows a general categorisation of carcinoma, sarcoma, lymphoma or melanoma from cells that are too poorly differentiated to reveal a primary source. 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.
- In the case of carcinoma, further distinctions can be made, for example neuroendocrine and adenocarcinoma. Adenocarcinomas are the most common form of CUP. Greco and Hainsworth (2004) report in relation to adenocarcinoma of unknown primary that the primary site becomes obvious in 15 per cent to 20 per cent of patients during their lifetime, with 70-80 per cent of patients having the primary site detected at autopsy.
- It is possible that CUP represents a distinct biological entity rather than a heterogeneous grouping of various cancers in which the primary is difficult to identify (Mackay *et al* 2009).
- Life expectancy statistics in the literature vary considerably, reflecting the type of CUP, performance status and the effectiveness of chemotherapeutic agents. Baron-Hay and Tattersall (2001) record a median of 4-11 months with a 6 per cent five-year survival rate.
- Chemotherapy for the majority of CUP patients in unfavourable groups generally offers poor results (Pavlidis 2007).

The CUP continuum

The National Comprehensive Cancer Network (2008) stated that: 'Occult primary tumors or cancers of unknown primary are defined as histologically proven metastatic malignant tumors whose primary site cannot be identified during pretreatment evaluation.'

There is a continuum from those patients who have an 'uncertain' primary, where the primary tumour's lineage may eventually be determined through specialised pathological study, to those that remain truly 'unknown' where the primary cancer is never conclusively identified, even at post-mortem (Figure 1). The most significant clinical problems lie with carcinomas of unknown primary because, unlike melanoma or sarcoma, determining the primary site is often assumed to be fundamental for effective treatment. However, there is little evidence that

Figure 1 The cancer of unknown primary (CUP) continuum



Box 1 Patients with cancer of unknown primary

- **Group one:** patients who are too ill on presentation for any investigation or treatment; or who choose not to undergo treatment other than palliative care.
- **Group two:** those patients who could benefit significantly from testing that leads to treatment.
- **Group three:** those patients where further testing has no clinical benefit, leaving only generic palliative treatment options.

identifying the primary site affects outcomes even when it changes treatment. Tumour behaviour is likely to be more important than finding the primary site.

In a classification of carcinoma, some patients will fall into sub-sets considered to be more or less likely to respond to treatment based on histology and metastatic presentation. The initial investigating clinician's focus on 'finding the primary' may influence how patients view investigations and treatment throughout their journey. The initial explanation given to patients is likely to affect how they cope with a final diagnosis of CUP and the process of discontinuing investigation. Patients and carers may perceive a confirmed CUP diagnosis as a failure in comparison with, a diagnosis of pancreatic cancer, for example. In reality the outcome is likely to be the same in both cases.

Critical CUP issues

Despite its prevalence, and because CUP is often perceived as a failure of diagnosis rather than a diagnosis in its own right, patients are treated as if they have a rarer cancer. Those who have been diagnosed with a rarer cancer are often a neglected group in their pathway. The provision of supportive care is at times inconsistent, unfocused and poorly co-ordinated (Griffiths 1997, Griffiths *et al* 2007) and the treatments offered are not evidence based. Clinical experience suggests that patients with a disease where no anatomical name can be attributed often receive a worse deal than those who have a rarer cancer with a diagnostic label.

Survival prospects for patients with CUP are generally poor, but variable (Shaw *et al* 2007). Common factors determining outcomes are generally the same as for any other metastatic malignancy. These include: tumour burden, general fitness (performance status), extent of vital organ involvement and function, age and the innate aggressiveness of the tumour. Such is the heterogeneity of CUP that it is unlikely that any two patients will have the same characteristics. Nevertheless, some broad groupings can be constructed to help examine the dilemmas and choices in more depth. Three groups are proposed in Box 1.

Though it is significant to encourage hope in patients with advanced cancer (McClement and Chochinov 2008), this is a challenge in patients with confirmed CUP. Logic would suggest that those in groups one and three in Box 1 receive no (further) investigations aimed at identifying a primary site because they are unfit or unwilling for treatment, or because there is no potential clinical benefit. But clinicians, patients and their loved ones in group three may want 'just one more test'.

The *Cancer Reform Strategy* (DH 2007) stated that patients will have access to high quality treatment at every stage of their cancer journey and that action will be taken to empower patients so they can play as active a role in decisions about their care and treatment as they wish.

The management and support of patients with CUP are perceived as more complex than those with known cancers, yet experience suggests that the patient may receive less support. Factors such as the heterogeneity of this group of patients' presentations and their pathways and inconsistent approaches to the management and treatment of CUP, can lead to inadvertent neglect and suboptimal treatment and care.

Patients with a known cancer are likely to be cared for by a multidisciplinary team (MDT) and benefit from an appointed key worker, usually a

nurse. However, if a patient does not have a site-specific cancer he or she may not get continuity and co-ordination, emotional and psychological support.

The key worker's role in co-ordinating the patient's care includes promoting continuity and ensuring the patient has access to information and advice. Many patients with undefined metastatic malignancy or patients with provisional CUP, where the primary does not rapidly become apparent, can move between MDTs as further tests are undertaken to try to identify the cancer. The result can be that some patients get no action or support when speed of action is vital. There is a need to replicate for patients with CUP the improved communication between professionals, the better continuity and co-ordination of care through all stages and the better advice on treatment that other patients with cancer receive (DH 2000).

Shaw *et al* (2007) identified an average of 19 investigations for each patient with CUP. Boyland and Davis (2008) showed the distress that nugatory investigations cause patients and suggested that investigations should be limited to those that identify the more favourable prognostic subgroups of CUP, which may respond to treatment.

For patients and carers, investigations can be similar to the highs and lows of a roller coaster: they have a stressful experience but can achieve a high thinking that they will be rewarded by an answer. They then drop after finding the test unsuccessful before moving onto another cycle. Such cycles are stressful and often emotionally damaging if patients end up at a lower place than the starting point. This is a particular risk where success is defined in terms of finding a primary leaving many patients set up to fail. The roller coaster ride can also be a feature of treatment regimens.

While it would seem uncontroversial that investigations are valuable only if they lead to improved treatment, there are other complex factors associated with managing patients with CUP. Physicians will be reluctant to end patients' real or perceived chances of identifying the cancer or improving knowledge of the condition that can enhance treatment options. With the best of intentions, clinicians do not like to accept failure and will want to do the best possible.

What is possible may not be desirable or appropriate. In a study of patients with CUP, James

It was difficult to adjust to the diagnosis, in part because healthcare professionals were unable to explain and treat the phenomenon

Box 2 The Kübler-Ross model

- **Denial:** 'This can't be happening to me.' A temporary defence generally replaced with heightened awareness of situations and recognition of the individuals that will be left behind after death.
 - **Anger:** 'Why me? It's not fair!' The individual recognises that denial cannot continue but, because of anger, the person may be difficult to care for.
 - **Bargaining:** 'Just let me live to see my first grandchild.' The third stage involves the hope that the individual can somehow postpone or delay death.
 - **Depression:** 'I'm going to die... What's the point?' The dying person begins to understand the certainty of death. Because of this, the individual may become silent, and disconnect.
 - **Acceptance:** 'I can't fight it, I may as well prepare for it.' This final stage comes with peace and understanding of the death that is approaching.
- (Kübler-Ross 1969)

(2007) found that inappropriate or repetitive testing was common: 'One patient who had requested that he should not be resuscitated had an abdominal computed tomography and an abdominal ultrasound on the same day. Another example was seen where a liver ultrasound showed the liver was almost "entirely replaced by the tumour". It was repeated a few days later when the patient became increasingly jaundiced.'

The distress of a cancer diagnosis is compounded for patients unable to explain their cancer to others. There is a suggestion that those who choose to accept a provisional diagnosis gain reassurance from a known course of treatment (Boyland and Davis 2008). Boyland and Davis (2008) identified a number of themes in relation to patients' responses to a CUP diagnosis, showing that patients with CUP found it difficult to adjust to the diagnosis, in part because healthcare professionals – the 'experts' – were unable to explain the phenomenon and treat them (Boyland and Davis 2008).

In Boyland and Davis's (2008) study the way information was presented to patients by the oncologist appeared to vary. Understandably this variability increases the bewilderment and distress of a cancer diagnosis.

Dilemmas and choices

CUP treatment and management have been tarnished by the nihilistic view of some medical professionals that nothing can be done and sometimes a utilitarian

view that health economics do not justify research and expensive treatment (Symons 2008). As a result, little research has been undertaken to improve the position for future patients with this condition. However, 'doing nothing' in relation to tests and/or anti-cancer treatment may, at some point, be in the individual patient's best interests.

While many patients with CUP will receive a combination of cancer treatment with palliative care, some patients with advanced cancer may reach a point where they face a difficult choice between (continuing) tests and anti-cancer treatment, such as chemotherapy, or opting for palliative care alone with no (further) curative interventions.

The first dilemma lies in defining the optimal point to advise the cessation of diagnostic tests or oncological treatment, balancing individual benefit and psychological needs. The second dilemma concerns how best to communicate the options to patients and carers.

At some point, particularly for those in an unfavourable CUP sub-group, the clinical benefit of further tests offers little return. However, for the fit patient the commitment to exhaust every possible avenue to locate the primary may remain. Even for the most determined patient, there will come a point where testing is distressing as well as nugatory.

Discussing prognostic and predictive dilemmas with patients is a challenge requiring skill and sensitivity. Some patients, particularly those who are using denial, anger or bargaining as coping or adjustment strategies, may want to keep trying, even if there are no medical grounds for continuing. The Kübler-Ross model, summarised in Box 2, describes five discrete coping strategies for those diagnosed with terminal illness.

The dilemma may be hardest for patients who migrate from the category of provisional CUP (Figure 1), where there is hope of survival, to the point where further testing has no clinical benefit, leaving only generic palliative treatment options (group three of Box 1). An added complication is that relatives may encourage the patient to pursue further tests and treatment even if the patient has reached a level of acceptance.

Prognostic factors will inform the clinician's discussion with the patient. The way information is presented by the doctor is likely to influence the patient's decision. Some patients and carers will want more information than others. The authors favour a joint approach where a patient with CUP receives information on the options from an oncologist or specialist and a palliative care physician to provide balanced views. The NICE (2004) guideline on supportive care placed equal priority on palliative

and supportive care alongside diagnosis and treatment.

The explanation might include the distinction between treatment options and their putative benefits versus making the best of remaining life. More specifically:

- An estimation of the clinical benefit from a more accurate diagnosis.
- The limitations of further tests.
- The potential dangers of particular tests.
- The time delays involved that risk incurring a loss of lifetime.

For the patients in this bewildering environment it may help them to balance the pros and cons. Chiew *et al* (2008) developed a seven-step process for patients with advanced cancer to aid decision making (Box 3).

The steps will encourage interaction between patient, carer, doctors and nurses. Once the patient has a list of pros and cons, which may be long or short, weighting can be ascribed to each such as: very important, somewhat important and not important.

The challenge is defining the optimal point to cease diagnostic tests, particularly for a patient with CUP in group three (Box 1) and explaining the implications effectively to the patient. There is a need to recognise that even patients in group three may have a psychological need for a definitive diagnosis that encourages further tests. However, the authors contend that a further test is not the way to resolve this need. Careful

Box 3 Seven-step patient decision aid

- Understand your situation.
- Learn about your treatment options.
- Review the pros and cons of these options.
- Decide how important these pros and cons are to you (see note).
- Do you want more information or discussion with your doctor?
- Decide who should take the decision: you, your doctor or a shared decision involving you, your doctor and family members?
- Are you leaning towards anti-cancer treatment or towards palliative care?

Note: Weighing up the pros and cons might involve considering the pros of chemotherapy, for example, I may live longer, my cancer symptoms may improve and I'm going to fight this because... along with cons, for example, chemotherapy side effects, frequent trips to hospital, no guarantee that the treatment will work and costs.

(Adapted from Chiew *et al* 2008)

One patient who had asked that he should not be resuscitated had a tomography and an ultrasound scan on the same day

communication and explanation by a specialist are more appropriate.

In assessing dilemmas and choices one has to recognise the effect and nuances between espoused, good intentions and actual custom and practice. For example, complex cases of strict time targets may encourage unnecessary over-investigation or a patient with CUP may receive investigations with consent but without fully informed consent.

These are grey areas. It is easier to recognise bad management that may result from a number of interrelated factors such as delays in organising investigations, a reluctance to engage in a difficult conversation and excessive diagnostic evaluation unrelated to clinical benefit or survival.

The general lack of understanding about CUP and the lack of comprehensive evidence-based guidelines do not help clinician or patient to position CUP in a way that fits into a comfortable mental model. Patients suffer emotionally from the current approach to CUP that sees identifying the primary as the diagnostic aim. From a management perspective, an alternative positioning for the patient would be one which accepts metastatic cancer as the diagnosis. Further testing is then logically positioned to determine the optimal treatment of the metastatic cancer. This has parallels with the treatment of other cancers such as breast cancer where the diagnosis is made and communicated with the patient before information about receptor status is available which will have a major effect on treatment and prognosis. This approach is not to deny CUP: it is only in recognising that CUP is not understood that there will be encouragement for research that will determine the true characteristics of this disease leading to directed treatment options.

Conclusion

This article has discussed the balances between testing and treating the patient with CUP. There is little research on the experiences of patients with CUP and there is an urgent need to understand the issues and dilemmas in more detail from patient, carer and clinician perspectives.

'Just one more test' must not be the default position because it is the easiest, rather than the best, option for patient and clinician in the short term. Investigations should only be made where results are likely to affect a decision about treatment.

At the same time the patient should be fully informed of the reason for investigations and understand the potential benefits and burdens of treatment.

There can be no generalisable optimal point to cease testing because no two patients with CUP will be the same. There is a balance to be struck between clinical benefit and individual psychological need. However, futile or protracted investigations are unlikely to be in the patient's best interest, particularly when the likelihood of further clarifying the diagnosis is very low.

Explaining this to patients and loved ones requires sensitivity and skill based on understanding CUP and the particular circumstances of the patient with CUP.

The authors believe the key to the testing dilemma lies in speed of action to ensure appropriate tests early in the provisional CUP pathway under the direction of a CUP-experienced consultant. As the patient moves along the continuum (Figure 1) towards confirmed CUP, the requirement is for appropriate information to be explained to the patient to allow a reasoned judgement to be made between continuing tests and treatment, and palliative care alone (Box 1).

The authors recommend explaining the diagnosis, at an early stage, in relation to metastatic malignancy with the rationale of further tests to clarify treatment options. If this is communicated to the patient as the focus of investigation from the outset, rather than the search for the primary, future decision making may be easier.

Traditional clinical skills are needed to explain to patients and carers when further investigations

Implications for practice

- Cancer of unknown primary (CUP) is not rare: it is one of the ten most common cancer diagnoses but patients with CUP are often less well served than those with rare tumours.
- Inappropriate testing often occurs and can sometimes take priority over provision of expert supportive care.
- Weighing up the options of testing requires traditional skills including effective communication with patients and carers.
- Patients with metastatic malignancy of unidentified origin should have access to specialist palliative care and this should not be delayed until the search for the primary has finished.

Find out more

For further information on the Cancer of Unknown Primary Foundation – Jo's Friends go to www.cupfoundjo.org

will not alter treatment options. In some cases there may be remaining uncertainty, causing psychological morbidity, which in the patient's mind can only adequately be addressed by further tests seeking a possible primary, regardless of the low yield and additional inconvenience. However, falling back on a 'further test' should not be seen as the easy alternative to offering the information and emotional and psychological support that this need clearly expresses.

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References

- Baron-Hay S, Tattersall M** (2001) Cancer of unknown primary site. In Souhami R, Tannock I, Hohenberger P (Eds) *Oxford Textbook of Oncology*. Oxford University Press, Oxford.
- Boyland L, Davis C** (2008) Patients' experiences of carcinoma of unknown primary site: dealing with uncertainty. *Palliative Medicine*. 22, 2, 177-183.
- Bridgewater J, van Laar R, Floore A et al** (2008) Gene expression profiling may improve diagnosis in patients with carcinoma of unknown primary. *British Journal of Cancer*. 98, 8, 1425-1430.
- Chiew K, Shepherd H, Vardy J et al** (2008) Development and evaluation of a decision aid for patients considering first-line chemotherapy for metastatic breast cancer. *Health Expectations: an International Journal of Public Participation in Health Care and Health Policy*. 11, 1, 35-45.
- Department of Health** (2000) *The NHS Cancer Plan: A Plan for Investment, a Plan for Reform*. DH, London.
- Department of Health** (2004) *The NHS Cancer Plan and the New NHS: Providing a Patient-centred Service*. DH, London.
- Department of Health** (2007) *Cancer Reform Strategy*. DH, London.
- Greco F, Hainsworth J** (2004) Cancer of unknown primary site. In De Vita V, Hellmans S, Rosenberg S (Eds) *Cancer: Principles and Practice of Oncology*. Lippincott Williams & Wilkins, Philadelphia PA.
- Griffiths J** (1997) Holistic district nursing: caring for the terminally ill. *British Journal of Community Nursing*. 2, 9, 440-444.
- Griffiths J, Willard C, Burgess A et al** (2007) Meeting the ongoing needs of survivors of rarer cancer. *European Journal of Oncology Nursing*. 11, 5, 434-441.
- James N** (2007) Managing cancer of unknown primary: are we getting it wrong? *Cancer Nursing Practice*. 6, 7, 25-28.
- Kübler-Ross E** (1969) *On Death and Dying*. Tavistock/Routledge, London.
- McClement S, Chochinov H** (2008) Hope in advanced cancer patients. *European Journal of Cancer*. 44, 8, 1169-1174.
- Mackay J, Pithers A, Symons J** (2009) Cancer of unknown primary. The role of genetic signatures and targeted therapy. *MIMS Oncology & Palliative Care*. 3, 3, pages ???? [Q please check details as unable to find it anywhere]
- National Comprehensive Cancer Network** (2008) *Clinical Practice Guidelines in Oncology: Occult Primary*. www.nccn.org/professionals/physician_gls/E_guidelines.asp (Last accessed: September 12 2009.)
- National Institute for Health and Clinical Excellence** (2004) *Improving Supportive and Palliative Care for Adults with Cancer*. NICE, London.
- Pavlidis N** (2007) Forty years experience of treating cancer of unknown primary. *Acta Oncologica*. 46, 5, 592-601.
- Shaw P, Adams R, Jordan C et al** (2007) A clinical review of the investigation and management of carcinoma of unknown primary in a single cancer network. *Clinical Oncology*. 19, 1, 87-95.
- Symons J** (2008) Understanding and managing cancer of unknown primary. *British Journal of Nursing*. 17, 18, 1160-1164.
- Van de Wouw A, Jansen R, Speel E et al** (2003) The unknown biology of the unknown primary tumour: a literature review. *Annals of Oncology*. 14, 2, 191-196.
- Winston R** (2009) *Medicine and Morality*. 4th Annual Dorchester Lecture, Dorchester Abbey, Oxfordshire. June 18.