

# Development and implementation of a service for patients with cancer of unknown primary

Gillian Knowles and colleagues report on how the reorganisation of services in Edinburgh decreased time from referral to oncology review, cut length of hospital stay and improved disease management

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\*Acknowledgement: joint last authors for significant contribution to this work

**Date of submission**  
September 6 2013

**Date of acceptance**  
September 26 2013

**Peer review**  
This article has been subject to double-blind review and checked using antiplagiarism software

**Author guidelines**  
cnp.rcnpublishing.com

## Abstract

Metastatic cancer of unknown primary (CUP) is a common, well-recognised yet heterogeneous clinical syndrome. Patients may be disadvantaged during their diagnostic workup because they fall outside established multidisciplinary team pathways.

The authors undertook an audit after introducing a CUP service in 2010 and compared it with a baseline audit to determine whether the new service improved the patient pathway. The baseline audit of medical records consisted of 45 consecutive patients referred to the Edinburgh Cancer Centre over six months in 2007. A repeat audit was performed in 2011 of the first 100 consecutive CUP patients.

After introducing the service, the mean number of days from secondary care review to oncology referral fell from 37 to 17 days, length of hospital stay from 12 to six days, number of blood tests from 16 to eight, and radiological investigations from four to three. Sixty six patients initially presented via inpatient admissions. Referral to palliative care increased from 60 per cent to 77 per cent. Based on these encouraging results, the authors hope to expand the service throughout Lothian.

## Keywords

Acute oncology, metastatic cancer of unknown primary, palliative care, service redesign, supportive care

**METASTATIC CANCER** of unknown primary (CUP) is a common, well-recognised yet heterogeneous clinical syndrome. Patients with CUP often present with aggressive disease and early dissemination in the absence of an identifiable primary tumour despite a diagnostic workup, which includes patient history, examination, and diagnostic tests and investigations.

Cancer of unknown primary represents between 3 per cent and 5 per cent of all malignancies across Europe and the US, and is the fourth most common cause of cancer-related death (Pavlidis and Pentheroudakis 2012). Five-year survival is about 6 per cent (Baron-Hay and Tattersall 2001).

Osborne (2011) describes patients with CUP as a group with 'orphan' status, by which he means a neglected group. They can be disadvantaged during their diagnostic workup as they may present to a number of specialists,

fall outside established multidisciplinary team pathways and rarely have nurse specialist input. In addition, treatment options are limited and there is little evidence to inform management.

Recognition of these shortfalls resulted in publication of the National Institute for Health and Care Excellence (NICE) (2010) clinical guideline on diagnosis and management of metastatic CUP in the UK. The recommendations are aimed primarily at ensuring pathways are put in place to identify treatable subtypes of CUP, so that patients receive prompt and appropriate care.

Equally, in patients where treatment is not appropriate, the guidance aims to prevent overinvestigation and ensure timely symptom and supportive management, thereby providing a high quality service equivalent to that offered to those presenting with site-specific disease.

**Table 1** Route of referral

Hospital admission	<i>n</i> = 66	Outpatient clinics	<i>n</i> = 34
Gastroenterology	4	GP direct to oncology	8
General medicine	32	Ear, nose and throat	1
General surgery	15	Gastroenterology	11
Infectious diseases	2	General medicine	5
Medicine for the elderly	4	Gynaecology	1
Neurology	2	Haematology	3
Neurosurgery	2	Neurosurgery	1
Oncology via accident and emergency	1	Orthopaedics	1
Oncology via GP/radiology	2	Stroke	1
Orthopaedics	1	Vascular surgery	2
Respiratory	1		
Total patients, <i>n</i> = 100			

In response to a national enquiry into chemotherapy-related deaths (National Confidential Enquiry into Patient Outcome and Death 2008), the National Chemotherapy Advisory Group (NCAG) (Department of Health 2010) for England and Wales also made recommendations relevant to CUP patients. NCAG advised that all hospitals with an emergency department should have an 'acute oncology team' to oversee the management of patients presenting with acute chemotherapy toxicities or oncological treatment complications, as well as those presenting as emergencies without a known cancer diagnosis.

Scotland has not embraced the need for acute oncologists in all hospitals, partly due to its unique geography and population dynamics. However, there is recognition of the need to develop safe, robust and effective systems to ensure that unscheduled cancer presentations, including patients with acute chemotherapy toxicities, cancer complications and CUP, are managed optimally across the country.

The UK focus on acute oncology provided an opportunity to review the services offered to patients with CUP in the authors' large cancer centre. A baseline audit of the medical records of 45 consecutive patients referred to the Edinburgh Cancer Centre with CUP over six months in 2007 showed that patients were hospitalised for a mean of 12 days during their diagnostic workup and underwent an average total of 22 diagnostic tests; this included four radiological investigations, 16 laboratory tests, one endoscopy and one biopsy per patient.

There was no single point of contact, no specialist cancer nursing involvement, no consistent multidisciplinary discussion, no investigative or management plan, and no clear avenue for obtaining prompt cancer specialist review or advice. It took, on average, more than a month from secondary care review to referral to oncology, and patients were seen by a number of different cancer specialists and no consistent management plan was followed.

This audit demonstrated that changes could be made to standardise care, streamline the diagnostic pathway, ensure early specialist and supportive care input, and improve patient care and outcomes.

This article describes the developments undertaken in Edinburgh Cancer Centre, NHS Lothian, to improve the service for CUP patients. It also presents a prospective audit of CUP patients presenting to the centre after the introduction of service changes and compares it with the baseline audit of 2007. A primary aim of this work was to determine whether the development and implementation of a new service for patients with CUP in Lothian improved the patient pathway and used resources more efficiently.

### Assessing clinical need

A CUP service was established at the Western General Hospital, one of three hospital sites in NHS Lothian. In part, this was done to scope the extent of clinical need, to help understand how to provide a sustainable CUP service. The main service developments included:

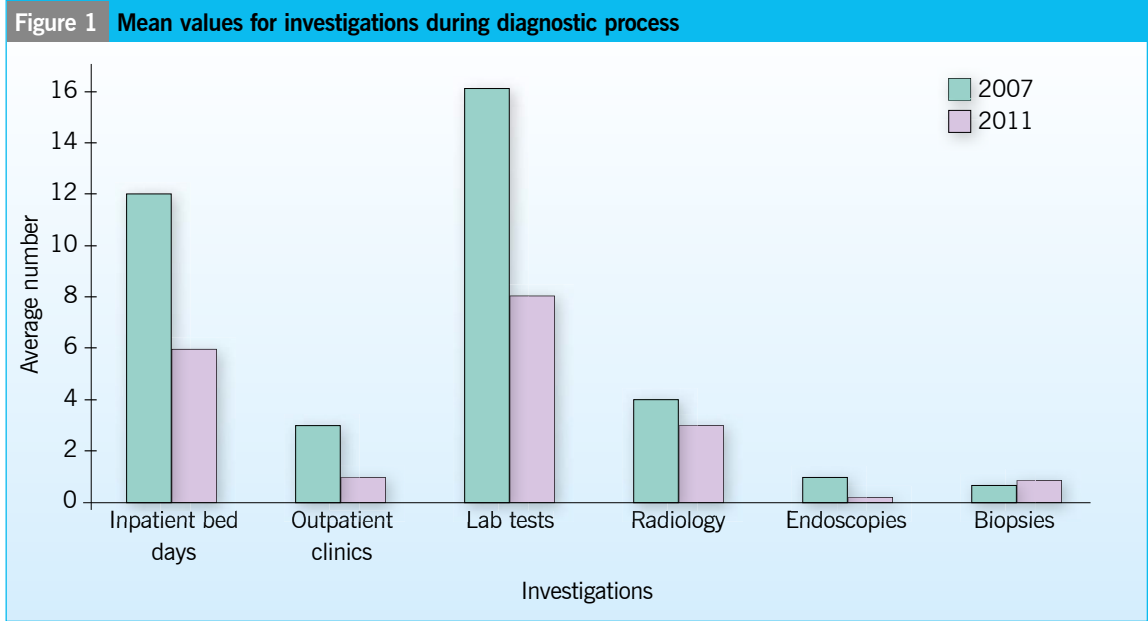
**Table 2 Diagnostic groupings**

Cancer of unknown primary (CUP)	Total (n=73)	'CUP' with cancer site/type identified during CUP team workup	Total (n=27)
<i>Diagnosis by pathology subtype</i>	<i>Pathology for 51</i>	<i>Cancer site and type identified</i>	
Adenocarcinoma	27	Lymphoma	4
Poorly differentiated carcinoma	7	Myeloma	3
Squamous	3	Breast	3
Adenosquamous	2	Pseudomyxoma peritonei	2
Undifferentiated small round cell	1	Pancreas	2
Other cancer	11	Hepatocellular carcinoma	1
<i>Diagnosis by immunophenotyping (where known)</i>	<i>Pathology for 51, 30 of whom had immunopathology</i>	Small bowel carcinoid	1
Colorectal (CK20+/CDX2+/CK7-)	9	Lung	1
Upper gastrointestinal (CK7+/CK20-)	5	Prostate	1
Pancreatobiliary (CK7+/CK20-)	7	<i>Cancer type identified</i>	
Urothelial (CK7+/CK20+/urothelin+)	1	Desmoplastic small round cell tumour	1
Renal (CD10/RCC)	2	Leiomyosarcoma	1
Lung (CK7+/TTF1+/CK20-)	3	Melanoma	2
Ovarian/primary peritoneal CK7+/CA125+/ER+)	3	Neuroendocrine (of which one pancreatic and one high grade)	4
		<i>Non-malignant</i>	
		Haemangioma	1

- Establishing a clinical team consisting of existing staff members who had expressed an interest in CUP and had some capacity in their job plans. The team consists of two medical oncologists, one clinical oncologist and one nurse consultant. Additionally, a radiologist, pathologist and palliative care physician who were interested in contributing to the new service were identified.
- Devising a site policy, diagnostic pathway, guidance for referral to a cancer multidisciplinary team meeting and an investigation pathway for patients with suspected metastatic disease to the brain.
- Creating a dedicated nurse specialist telephone contact point patients can call for advice and support.
- Creating dedicated clinic spaces each week for CUP patients.
- Setting up a weekly CUP multidisciplinary team meeting to review investigations, including pathology and radiology, and discuss treatment, care and complex decisions.
- Establishing a database to audit all referrals, including treatment and outcomes, and consenting for use of tissue for future research.
- Developing treatment protocols/patient information.
- Disseminating information and raising awareness of the service.

### Prospective audit

After development of the CUP service, a prospective audit was performed on the first 100 consecutive patients who presented in 2011. An audit sheet was developed to ensure consistency of data collection, which included:



- Patient characteristics.
- Number of investigations.
- Time spent at different stages of the diagnostic pathway.
- Oncological treatment.
- Referral to palliative care services.

The baseline audit of the medical records of 45 consecutive patients referred to the centre with CUP over a six-month period in 2007 was used as a control group.

All data were entered on an Excel database and analysed descriptively. Data collection was based on the time spent at different stages of the diagnostic pathway and the number of investigations carried out in that period up to the first oncological review. One-tailed independent *t*-test was used to determine significance differences between groups.

### Results

**Referral routes** Of the 100 patients attending in 2011, 66 presented via inpatient admissions, including two who were admitted directly to oncology (Table 1, page 34). Twenty six presented to outpatient clinics in nine specialties and eight were referred to oncology directly by their GP. The most common routes of referral for CUP patients were admission to general medicine or general surgery, or referral to gastroenterology outpatient clinics.

**Diagnosis** All patients were referred to the service as 'CUP' after initial non-specialist investigations and workup. After CUP team workup, diagnosis of a known primary cancer was made in 27 cases (Table 2, page 35), enabling prompt referral of these patients to relevant specialist teams. In 73 patients

the primary cancer remained unknown. A tissue diagnosis was obtained in 51 patients. A biopsy was undertaken only if it was thought that the results would influence subsequent patient management.

After pathological review there were 27 adenocarcinomas in this group. Nine patients had a colorectal immunophenotype.

**Investigations** Figure 1 outlines a comparison of the mean number of inpatient bed days and investigations performed in the workup of patients presenting with CUP. The CUP service substantially reduced length of hospital stays during diagnostic workup (mean six versus 12 days); reduced the number of outpatient attendances (one versus three); and reduced non-essential investigations (eight versus 16 blood tests; three versus four radiology investigations). The CUP service resulted in a slight increase in tissue diagnosis to help inform subsequent management.

**Time to oncology review** Introduction of the CUP service helped ensure more timely review of patients by specialist oncology and palliative care services. The most variable component of the patient pathway is the time in secondary care before referral to oncology. Since introducing a defined point of contact, the mean number of days from secondary care review to oncology referral fell from 37 days in 2007 to 17 days in 2011 ( $P=0.001$ ) (Figure 2).

**Cost** The development of a more efficient diagnostic pathway and early specialist review resulted in an estimated cost saving of £3,169 per patient (Figure 3).

**Impact of early specialist review** Although a smaller proportion of referred patients received oncological treatment in 2011 (50 per cent versus 65 per cent in 2007), all patients received prompt specialist assessment, information and advice with an increased proportion referred to palliative care for symptomatic or terminal care (Figure 4).

## Discussion

The complex pathway referrals for those presenting with advanced CUP has meant that, in many cases, diagnostic workup has been lengthy, resulting in considerable uncertainty and anxiety for patients and their families. Not knowing who to contact for information and support at a time of great uncertainty is a recognised unmet need (Boylund and Davis 2008, Symons 2008). Structuring services for patients presenting with CUP is a first step towards rebalancing perceived inequity of care for this group.

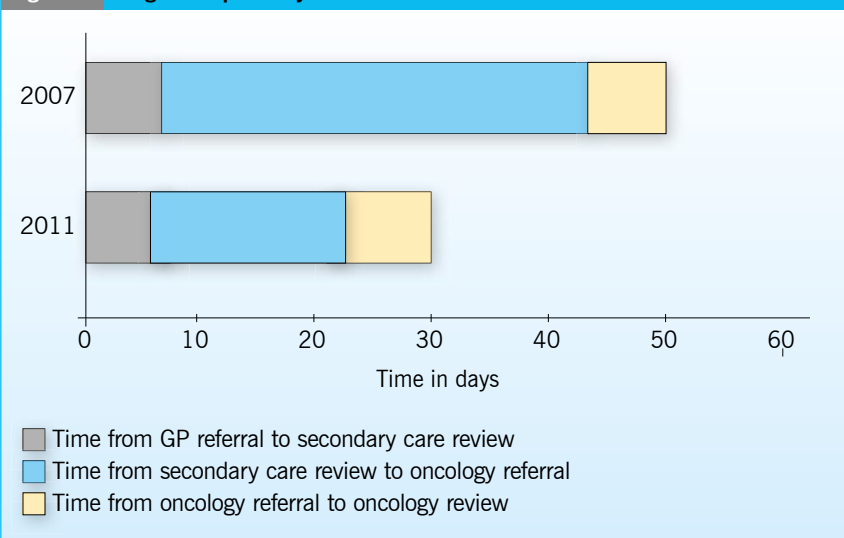
This article has described the process of setting up a CUP service in a cancer centre, with minimal use of additional resources. The audit of patient pathways before and after establishing the CUP service highlights the wide number of specialties involved in diagnosing patients with metastatic CUP. After clinical review and/or review of imaging and pathology in the CUP team, 13 different primary cancer types or 'known primary' malignant diagnosis and one non-malignant diagnosis were made demonstrating the heterogeneous nature of CUP.

The audit of patient pathways before and after establishing the service suggests that it has led to a significant reduction in the time spent by patients in hospital, has reduced the number of non-essential investigations, and helped ensure more rapid review of patients by the specialist oncology team and palliative care services. This has led to substantial efficiency savings for the organisation and improved the cancer journey for many patients. While not a primary objective of this work, anecdotal evidence suggests that developing the service has increased the profile of this neglected patient group.

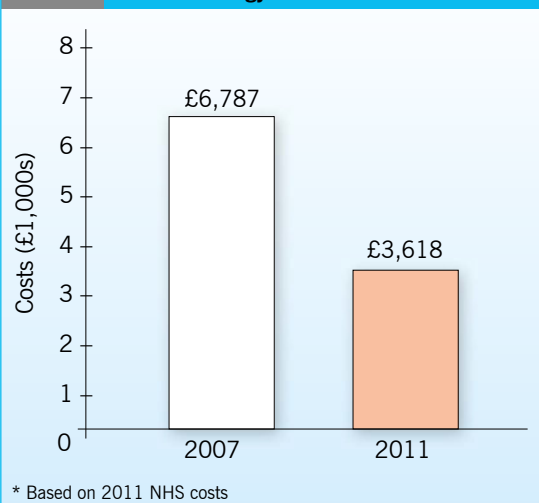
There is no doubt that efficiency savings are sought in the current economic climate, and the audit suggests that streamlining the investigation and review pathway for CUP patients has resulted in significant cost savings. However, at the core of the NICE (2010) recommendations is quality, to ensure timely treatment for patients presenting with treatable phenotypes and good supportive care for those without.

Because CUP is a heterogeneous group of cancers with a distinct biology (Pavlidis and Pentheroudakis 2012), there is a limited evidence base or consensus on best treatment for this patient group. Indeed,

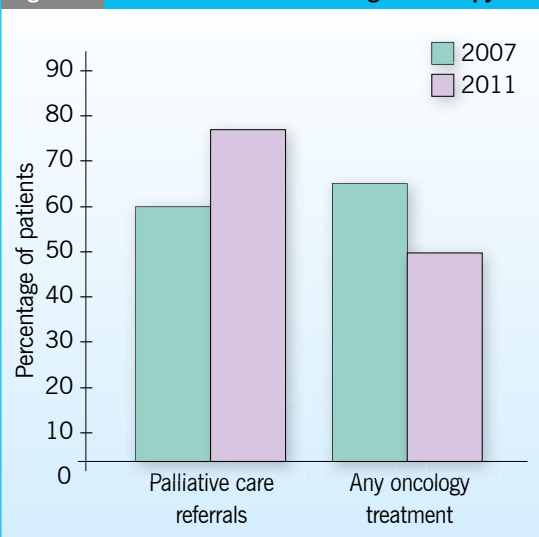
**Figure 2 Diagnostic pathway times**



**Figure 3 Estimated total cost of diagnostic pathway before oncology review\***



**Figure 4 Palliative care and oncological therapy**



despite progress in this area (Varadhachary *et al* 2008, Trivanović *et al* 2009), significant advances are required in molecular profiling, diagnostic markers and targeted therapies before these can be used routinely. In the meantime, identifying patients with more, or less, favourable subsets by prompt clinical assessment and immunohistochemistry remains vital to guide clinical management.

The audit found that, while the overall percentage of people who received oncological treatment fell, 27 patients referred to the service as having CUP were diagnosed as having a known primary cancer or highly treatable phenotype, and so were able to start effective therapy promptly. Additionally, the number of symptomatic patients referred for support or terminal care planning to the palliative care team increased.

These findings suggest that early review by members of a designated multidisciplinary team improved oncological treatment selection and symptom control and support for patients and carers. For patients who have less favourable subsets of CUP adjustment time is limited, and time at home with an early focus on supportive care is crucial. Reducing the amount of time spent in hospital during the diagnostic workup and limiting the number of non-essential investigations, while providing early specialist explanation and information, may result in enhanced quality, if not length, of life for those patients with a short prognosis.

It was not the focus of the audit to gather patient experiences. However, anecdotal evidence suggested that, for many, the uncertainty surrounding a diagnosis of CUP can be difficult. Not only are patients having to adjust to a cancer diagnosis, but

often they have experienced a diagnostic pathway where words such as 'unknown' and 'can't find' are used, leaving them feeling at a disadvantage or that they are in some way receiving suboptimal treatment.

Little has been written about the experiences of individuals presenting with CUP. In one small study by Boyland and Davis (2008), patients found dealing with uncertainty difficult in terms of its unpredictability and the number of investigations required. They wanted a firmer diagnostic label that would allow them to identify with others.

In part, one of the greatest challenges in establishing the CUP service has been how best to 'manage' the uncertainty that surrounds CUP for patients. This management will involve establishing patients' main concerns, health professional education, establishing CUP as a distinct entity in its own right and in some way 'normalising' it as is done for site-specific diseases.

With increasing interest in CUP and gradual reconfiguration of services across the NHS in Scotland and the UK, it is hoped that in the short term progress will bring consistency and high quality cancer care to this group.

## Conclusion

Reconfiguration of local services, initially with minimal extra investment, resulted in improvement in the care pathway of a disparate group of cancer patients, reduction in time to specialist review and management, and cost savings. The authors believe that the results enhanced quality of care and hope they will also improve patient outcomes in future. They plan to use the pathway template to implement a service in other hospitals in NHS Lothian.

## Online archive

For related information, visit our online archive and search using the keywords

**Conflict of interest**  
None declared

## References

Baron-Hay S, Tattersall M (2001) Cancer of unknown primary site. In Souhami R, Tannock I, Hohenberger P *et al* (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.

Department of Health (2010) *Chemotherapy Services in England: Ensuring Quality and Safety*. DH, London.

National Confidential Enquiry into Patient Outcome and Death (2008) *For Better, For Worse? A Review of the Care of Patients Who Died Within 30 Days of Receiving Systemic Anti-Cancer Therapy*. NCEPOD, London.

National Institute for Health and Care Excellence (2010) *Diagnosis and Management of Metastatic Malignant Disease of Unknown Primary Origin*. Clinical guideline 104. NICE, London.

Osborne R (2011) Cancer of unknown primary 2011 - where do we go now? *Oncology News*. 6, 1, 20-22. [tinyurl.com/lvtltfz](http://tinyurl.com/lvtltfz) (Last accessed: October 25 2013.)

Pavlidis N, Pentheroudakis G (2012) Cancer of unknown primary site. *The Lancet*. 379, 9824, 1428-1435.

Symons J (2008) Understanding and managing cancer of unknown primary. *British Journal of Nursing*. 17, 18, 1160-1164.

Trivanović D, Petkovic M, Stimac D (2009) New prognostic index to predict survival in patients with cancer of unknown primary site with unfavourable prognosis. *Clinical Oncology*. 21, 1, 43-48.

Varadhachary G, Raber M, Matamoros A *et al* (2008) Carcinoma of unknown primary with a colon-cancer profile-changing paradigm and emerging definitions. *The Lancet Oncology*. 9, 6, 596-599.

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