Cancer of Unknown Primary 2011 – Where Do We Go Now?

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Cancer of unknown primary (CUP) has fascinated and frustrated oncologists for decades. Since the earliest reports, and particularly the tantalising possibility of major benefits from treatment in a minority of patients [1], attempts to characterise CUP and improve outcomes have slowly developed. Progress has been hampered, however, by a lack of concerted large-scale approaches to therapeutic studies, and fundamentally by the lack of agreed definitions and biological understanding of the clinical problem. Furthermore, the continued 'orphan' status of CUP has denied this sizeable group of patients with poor prognosis access to modern services, e.g. multi-disciplinary team (MDT) management and clinical nurse specialist support, adding to the disadvantages they and their carers suffer.

This pessimistic overview of the plight of CUP patients may seem surprising, coming so soon after an important milestone - the publication in mid-2010 of the NICE guideline on management of metastatic malignant disease of unknown primary origin [2]. However, an understanding of the limitations of the NICE guideline development process, and recognition of the barriers to implementation of the resulting output, both give cause for concern. Nevertheless, appreciation of these limitations can act as a call to arms for those wishing to achieve meaningful progress in 2011 and beyond.

The heterogeneous, ill-defined, and poorly researched nature of CUP means that evidence-based statements about clinical management developed during the NICE appraisal process must necessarily be limited in their force of expression and impact. A greater strength of the recent guideline is its explicit recommendations about service configuration for newly diagnosed CUP patients, but major uncertainties, particularly about epidemiology and funding, have inevitably acted as a brake on the introduction of desired, and manifestly necessary, services.

This article therefore asks the question "where do we go now in improving care for CUP patients?" In view of the recent guideline, and the current clinical, scientific and financial climate, practical recommendations will be made, which can be translated into useful and rapid progress, avoiding the otherwise glacial pace of change that will result if the momentum initially provided by NICE is lost.

Defining CUP

One major problem for those considering how to develop and deliver services for CUP is that the condition has previously been poorly defined. A fundamental difference between CUP and other well-characterised malignancies is that a diagnosis of CUP means different things at different times to different people.

A new operational definition (Table 1) was devised for the NICE guideline that takes account of the continuum of diagnosis in CUP, which ranges from the patient who presents with obvious metastatic malignancy without an immediately identifiable origin (but who may very well be found to harbour an obvious primary after basic investigation) and the 'hard-core', 'classic' or 'true' CUP patient. Uniform application of these definitions is a basic requirement if services for CUP patients are to be rationally devised.

Table 1: New Nice definitions

- Malignancy of undefined primary origin (MUO).
  - Metastatic malignancy identified on the basis of a limited number of tests, prior to comprehensive investigation.
- Provisional carcinoma of unknown primary (pCUP).
  - Metastatic epithelial or neuro-endocrine malignancy identified on the basis of histology / cytology, with no primary detected despite an initial screen of investigations, prior to specialist review and possible further specialised investigations.
- Confirmed carcinoma of unknown primary (cCUP).
  - Metastatic epithelial or neuro-endocrine malignancy identified on the basis of definitive histology, with no primary detected despite a selected screen of investigations, specialist review, and completion of further appropriate specialised tests.

Measuring CUP

The lack of a generally agreed definition of CUP has limited the ability to obtain accurate data about incidence and outcomes for this group of patients. Regrettably, this has often led to their complete omission from commonly used and official statistics, such as those published by Cancer Research UK [3], the Office for National Statistics [4], and NCIN [5]. Using the best available data, based on codes to which CUP patients are commonly allocated (Table 2), it is reasonable to claim that there are 11,000 deaths annually in England and Wales caused by cancer without an identified primary site [6]. This exceeds the number of patients who die from breast cancer each year [7].

Table 2: ICD-10 Codes applied to CUP

- C77 Secondary and unspecified malignant neoplasm of lymph nodes.
- C78 Secondary malignant neoplasm, respiratory and digestive systems.
- C79 Secondary malignant neoplasm of other sites.
- C80 Malignant neoplasm without specification of site. Includes cancer, carcinoma, carcinomatosis, generalised cancer or malignancy, malignancy, multiple cancer, malignant cachexia and primary site unknown.

It is possible to compile and present meaningful epidemiological data about CUP. The Australian Institute of Health and Welfare has published comprehensive data, filling the gaps seen in UK reports [8]. CUP is in the top 10 incidence list of cancers for both men and women, and is the 5th most common cause of cancer mortality, accounting for 6% of all cancer deaths. An increasing incidence is forecast.

Steps to resolve this deficiency in the UK were proposed in the NICE guideline. Adequate data collection, through a refined coding system modified on the basis of new definitions, is a high priority, and work is in progress with NCIN to improve the current situation. The establishment of network site-specific groups for CUP will ensure better quality epidemiological data.

It is important to recognise that the incidence of MUO is vastly greater than the incidence of confirmed CUP, and it is expected that developments in provision of acute oncology services, mandated by explicit cancer measures, will ensure high quality data about this entity is obtained, allowing meaningful service planning to meet the needs of this large and currently disenfranchised group.

Initial management of MUO

Having recognised the shortcomings in current care for those presenting with MUO, a holistic approach to delivering a high quality service for this neglected group can be proposed, based on – and in some areas improving on – existing practices for site-specific cancers.

The requirements for optimal initial management of MUO are:

- Rapid identification
- Rapid assessment by an expert team
- Rapid, appropriate, expert-led investigation, with multi-disciplinary review
- Concurrent holistic support

Existing services for newly-diagnosed cancer patients provide excellent care when the organ of origin of a tumour is known. Rapid initial assessment in the relevant clinic, protocol-led investigation, specialist nurse support, and multi-disciplinary management are well organised in modern oncology practice. Problems arise, however, when patients present with metastatic malignancy without an identified primary site. Although many cases fortuitously enter the appropriate diagnostic portal at the first referral (for instance, patients with anaemia who are referred to gastroenterology and are subsequently found to have gastric or bowel cancer), there are many instances in which either the 'suspected cancer' referral sends a patient to an inappropriate team, or a diagnosis of cancer is not initially considered.

Four new measures can improve this inefficient and distressing situation.

First, revision of existing guidelines for the referral of suspected cancer [9] to cover MUO cases is urgently required. Plans for such a review are in progress [10].

Table 3: The CUP Team

The NICE CUP Guideline recommends that every hospital with a cancer centre or unit should establish a CUP team, and ensure that patients have access to the team when MUO is diagnosed. The team should consist of an oncologist, a palliative care physician and a CUP specialist nurse or key worker as a minimum. One member of the CUP team should be designated as Lead Clinician, with responsibilities that include ensuring effective multi-disciplinary working and provision of adequate support for the broad functions of the team [11].

Second, introduction of 'CUP Teams' (Table 3) will permit rapid access to necessary expertise and support at the earliest point in the diagnostic pathway, both speeding the process and, equally importantly, avoiding inappropriate, overly extensive, and wasteful investigation when ultimately no benefit will accrue.

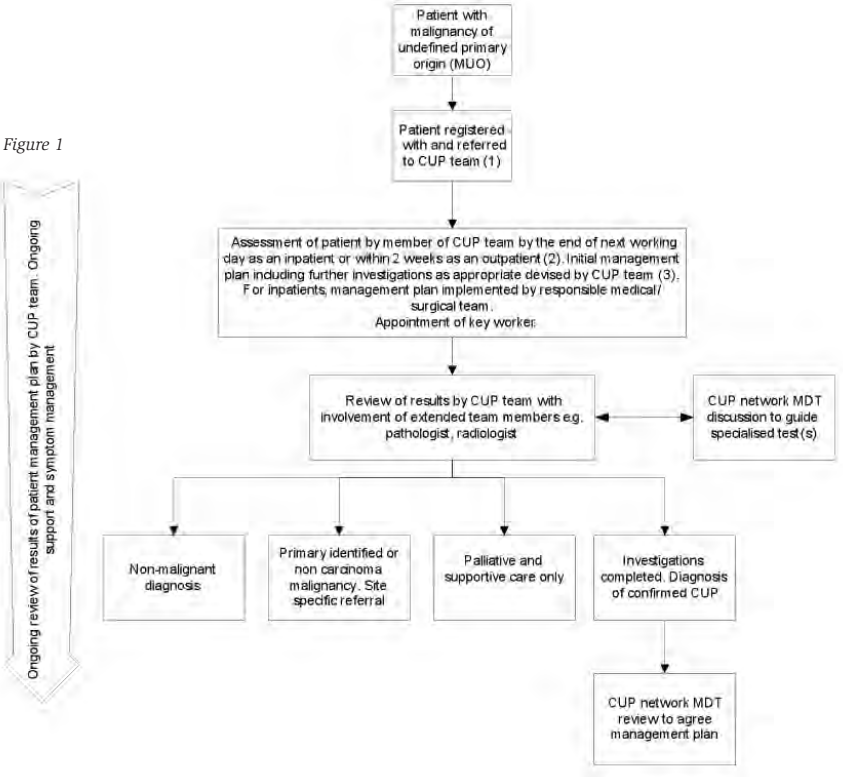
Some steps towards earlier oncology involvement in MUO have already been taken as part of national acute oncology initiatives arising from the NCAG report [12]. Publication of the final peer review measures is imminent, but full implementation based on appointment of new staff will be challenging in the current financial climate.

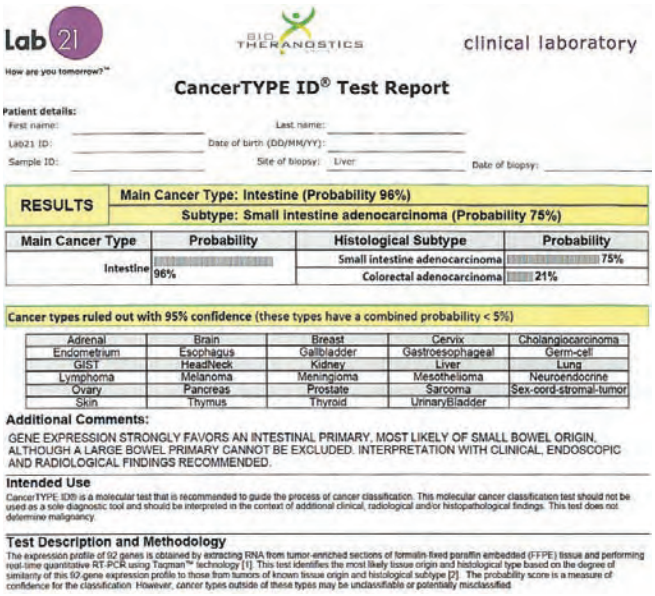
The third component of a better approach to initial management of MUO / CUP is to develop new ways of decision making. Having established a system for early identification and rapid assessment, it is desirable to harness the best components of MDT working without the disadvantages, such as delays caused by the standard weekly meeting cycle and the inefficiency arising from requiring all members of a team to be present when individuals only contribute for a short period. A solution suitable for MUO management is to conduct "oligo-disciplinary" discussions, more frequently, only involving relevant specialists for the minimum time necessary, using new technology. Online meeting solutions provide highly efficient communications and decision making [13], and this approach is already being applied where logistic difficulties, such as excessive travel, make conventional MDT meetings impractical. A dynamic virtual oligo-disciplinary team is being developed at Dorset Cancer Centre to specifically meet the recommendations in the NICE guideline for the real-time management of MUO/CUP patients. Uniquely, this approach is designed to access the opinions of multiple specialists in medical oncology to overcome the drawback of limited discussion inherent in conventional trust- or network-based MDT meetings, when usually only a single participant has relevant expertise in the area under review. A similar system for managing care for all patients with advanced or recurrent site-specific cancer (who are rarely re-discussed in MDT meetings) would be a logical future development.

Finally, initial care of the newly presenting MUO patient must be improved by the provision of adequate information and support at the earliest opportunity, in an expert manner. Patients without a site-specific diagnosis face the usual distress associated with metastatic cancer, but are additionally traumatised by the uncertainty associated with the "unknown primary" label, and the lack of specialist care. Early involvement of a key worker, ongoing explanation of the diagnostic process, specific tailored information, and access to relevant support agencies [14, 15], will all contribute to improved quality of care and of life.

Full implementation of these organisational measures will contribute significantly to changing outcomes in Cancer of Unknown Primary. An overview of this strategy is shown in Figure 1.

Figure 1





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CancerTYPE ID® Test Report

Patient details:
First name: Last name:
Lab21 ID: Date of birth (DD/MM/YY):
Sample ID: Site of biopsy: Liver Date of biopsy:

RESULTS
Main Cancer Type: Intestine (Probability 96%)
Subtype: Small intestine adenocarcinoma (Probability 75%)

Main Cancer Type	Probability	Histological Subtype	Probability
Intestine	96%	Small intestine adenocarcinoma	75%
		Colorectal adenocarcinoma	21%

Cancer types ruled out with 95% confidence (these types have a combined probability < 5%)

Adrenal	Brain	Breast	Cervix	Cholangiocarcinoma
Endometrium	Esophagus	Gallbladder	Gastroesophageal	Germ-cell
GIST	Headneck	Kidney	Liver	Lung
Lymphoma	Melanoma	Meningioma	Mesothelioma	Neuroendocrine
Ovary	Pancreas	Prostate	Sarcoma	Sex-cord-stromal-tumor
Skin	Thymus	Thyroid	UrinaryBladder	

Additional Comments:
GENE EXPRESSION STRONGLY FAVORS AN INTESTINAL PRIMARY, MOST LIKELY OF SMALL BOWEL ORIGIN, ALTHOUGH A LARGE BOWEL PRIMARY CANNOT BE EXCLUDED. INTERPRETATION WITH CLINICAL, ENDOSCOPIC AND RADIOLOGICAL FINDINGS RECOMMENDED.

Intended Use
CancerTYPE ID® is a molecular test that is recommended to guide the process of cancer classification. This molecular cancer classification test should not be used as a sole diagnostic tool and should be interpreted in the context of additional clinical, radiological and/or histopathological findings. This test does not determine malignancy.

Test Description and Methodology
The expression profile of 92 genes is obtained by extracting RNA from tumor-enriched sections of formalin-fixed paraffin embedded (FFPE) tissue and performing real-time quantitative RT-PCR using Taqman™ technology [1]. This test identifies the most likely tissue origin and histological type based on the degree of similarity of this 92-gene expression profile to those from tumors of known tissue origin and histological subtype [2]. The probability score is a measure of confidence for the classification. However, cancer types outside of these types may be unclassifiable or potentially misclassified.

Figure 2 – Gene expression-based profiling
Based on the principle that different tumour types have characteristic RNA profiles, various techniques (c-DNA microarrays, oligonucleotide microarrays, quantitative RT-PCR, and Serial Analysis of Gene Expression) have been used to perform gene expression-based profiling (GEBP) in CUP. The output from such investigations is a report comparing the CUP sample with a known tumour panel, and a statement of the likely homology (putative organ of origin). GEBP shows high accuracy when tested with blinded samples from known tissues.

The benefit of GEBP in guiding specific investigations or defining treatment has not been proven in formal studies comparing it with standard approaches, but anecdotal evidence supports its use to complement existing decision making processes.

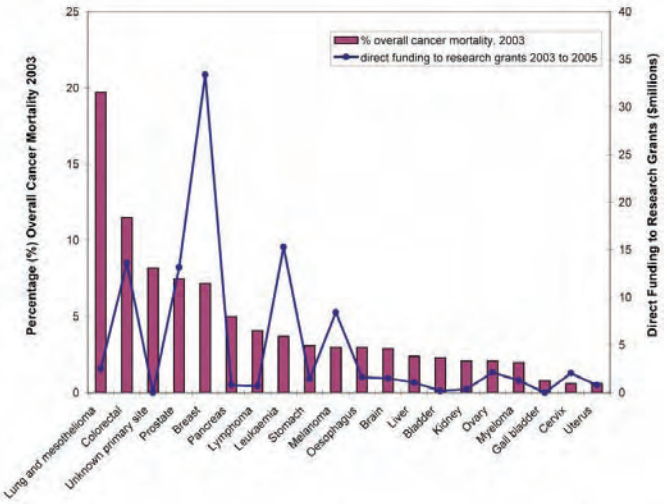

Figure 3 - Research expenditure by disease type
Direct funding to tumour site-specific cancer research projects in Australia 2003-5 compared with the top 20 tumours by overall mortality (23). Despite the large disease burden of CUP, research funding is negligible.

New diagnostic strategies for MUO/CUP

Several expert groups have defined the optimal nature and extent of standard investigations needed when investigating metastatic malignancy of undefined origin [2, 16, 17]. The role of two new approaches, PET scanning and gene-expression based profiling (GEBP – see Figure 2) was examined by NICE in 2010. The absence of high quality data demonstrating major advantages in terms of efficacy or cost-effectiveness from these recently introduced approaches led to recommendations that routine use was unsupportable. Anecdotal evidence does, however, suggest that the additional information gained, combined with the outcomes from conventional tests, aids decision making.

Future studies to investigate the impact of either PET or GEBP on survival in CUP are unlikely to achieve positive results. The likelihood of uncovering large numbers of highly treatable conditions is low. When the prognosis for metastatic carcinoma is uniformly poor, as a result of the limited efficacy of available treatment, minor refinements in diagnosis (for instance discriminating between pancreatic cancer and lung cancer) will also fail to make a meaningful impact on survival, and hence the added expense of sophisticated extra investigations is unlikely to translate into a cost effectiveness benefit.

Altering the diagnostic strategy, by performing a relatively expensive but highly informative test at initial presentation, may result in measurable benefits in terms of shortening the overall process along with consequent cost saving. In the current era, when CUP patients endure up to 19 separate investigations without any useful outcome in the majority [20], it is likely that there are avoidable costs in standard practice. Investigations on such new strategies based on GEBP are under consideration.

Treatment of CUP in 2011 and beyond

Regrettably, the number of cases of confirmed CUP that fall into the category of 'extragonadal germ cell tumour', and are hence potentially curable, is vanishingly small. The majority simply behave like relatively chemo-resistant metastatic epithelial tumours that have a poor prognosis. Evidence for unique biology that both underlies the presentation without an obvious source and also offers specific therapeutic options is currently very limited [21]. Undoubtedly, patients with CUP will benefit from better characterisation of their tumours, allowing 'personalised' therapy with newer agents, in the same way as is proposed for those with other common cancers [22].

Research into all aspects of CUP has long been a neglected area, and the shortcomings are highlighted when expenditure is compared with the size of the clinical problem [23] (Figure 3). Important new studies, such as CUP-ONE [24], which aims to correlate clinical outcomes with molecular parameters will serve to both improve outcomes for patients and increase the profile of this neglected syndrome.

n the short term however, the greatest benefit for CUP patients will derive from ensuring they begin to receive standard high quality cancer care, delivered by experts, supported by the panoply of services and support already available to those with site-specific disease. In this regard, the 2010 NICE guidance and the related Peer Review Cancer Measures offer a robust and invaluable template for better treatment in 2011 and beyond. ■

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