Cancer of Unknown Primary: A Rare Disease?

Poster presentation for ***NCIN/UKACR Cancer Outcomes Conference***
14-15 June 2012, Birmingham

John Symons

Cancer of Unknown Primary (CUP) Foundation

INTRODUCTION

Each year in the UK more than 10,000 persons die with a significant, but largely unrecognised, public health problem: Cancer of Unknown Primary (CUP). Few people, outside the medical profession, know that it is possible to have cancer without the primary site being identifiable. Few within the medical profession have any knowledge of this complex and heterogeneous disease. Consequently, CUP is often referred to as a "rare" disease. But is such a 'label' accurate or helpful?

Methodology. Review of national and international published data related to CUP supplemented by empirical research.

WHAT CONSTITUTES CUP?

CUP does not have a discrete classification within the International Classification of Disease (ICD) nomenclature. The ICD codes, which capture registrations of CUP in the UK, are usually ICD-10 C77 to C80. See Table 1.

Most international classifications include C76 (*Malignant neoplasm of other and ill-defined sites*). Some countries, such as Australia, include C26 (*Malignant neoplasm of other and ill-defined digestive organs*), C39 (*Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs*), as well as C76 – 80 within their CUP designation.

Table 1 : UK CUP Incidence by ICD code C77-C80:

ICD Code:	2009	2008
C77: Secondary and unspecified malignant neoplasm of lymph nodes	**972**	854
C78: Secondary malignant neoplasm of respiratory and digestive organs	**3,163**	3,388
C79: Secondary malignant neoplasm of other sites	**1,230**	2,189
C80: Malignant neoplasm without specification of site	**5,105**	4,321
Total (C77-80)	**10,470**	**10,752**

Source: CRUK 2012

UK CUP - ANALYSIS

CUP, with 10,472 deaths (7% of cancer mortality), was the 5th commonest cause of cancer *mortality* in the UK in 2010. This ranking is based on C77-80, but adding C26 (3,155 deaths), C39 (16 deaths), C76 (578 deaths) would increase the total to 14,221 ranking CUP mortality significantly higher than that of Breast cancer.

Since the mid 1990s, age standardised rates for the UK show a decline in CUP *incidence* (C77-80) of some 40%, with an absolute decline of some 30% in the numbers of cases. Whilst absolute cases in women are higher than men this is reversed by age standardisation. CUP incidence exceeds 'all cancers' in people over 75 but age standardisation of 'total persons' masks the absolute burden of CUP in those in younger age groups such as those under 25 and between 25-49.

Representing CUP accurately is problematic. Research amongst UK Registries in 2011 *(Binysh, Osborne & Symons, 2011)* indicated that there was a lack of clarity and consistency with CUP. Hospital Episode Statistics (HES) data input from MDTs were inconsistent. Variability existed between MDTs in terms of the precision of the diagnosis recorded. Anecdotal evidence suggests that CUP patients reviewed at MDTs are often classified as having a probable primary tumour which corresponds to the site-specialty of the MDT; and MDTs have different thresholds for attributing a site-specific diagnosis.

Using the NICE 2010 designations, the data that are captured are likely to be recording patients with provisional CUP (pCUP) or confirmed CUP (cCUP). Some patients with an initial presentation of Malignancy of Undefined primary Origin (MUO), and pCUP patients, may subsequently have their primary site determined. These changes may not be captured in records.

Notwithstanding the welcome decline in CUP incidence in the UK, it remains a very challenging clinical condition. Few people who are diagnosed with CUP survive more than a year. Table 3 shows mortality exceeding incidence in the past 11 years. Possible explanations include inaccurate recording of death (unchangeable on a death certificate); and/or a retrospective attempt by Registries to allocate a primary site *post mortem* based on patient records. The latter explanation, based on anecdotal evidence, has the potential to distort validity and create inconsistencies. Such 'CUP denial' masks the true burden of the disease which impacts on research and patient experience.

Table 2. UK CUP Mortality with AS rates/ 100,000 (C77-C80): 2010

		England	Scotland	Wales	N. Ireland	UK
Male	**Deaths**	**4,023**	**362**	**307**	**123**	**4,815**
	AS Rate	11.5	10.5	13.6	12.1	11.6
Female	**Deaths**	**4,702**	**451**	**359**	**145**	**5,657**
	AS Rate	10	9.2	11.9	9.8	10.1
Persons	**Deaths**	**8,725**	**813**	**666**	**268**	**10,472**
	AS Rate	10.7	9.7	12.5	10.8	10.7

Source: CRUK 2012

Table 3: UK (ICD-10 C77-80)

	Incidence		*Mortality*	
Year	No. of new cases	Rate* per 100,000	No. of deaths	Rate* per 100,000
1996	15,838	20.4	15,024	19.4
1998	14,972	19.0	15,259	19.3
2000	14,013	17.3	14,559	18
2002	13,428	16.1	14,058	16.7
2004	12,640	14.8	13,288	15.4
2006	11,566	13.1	12,267	13.7
2008	10,752	11.9	11,228	12.0
**Age-standardised to the European Population.* Source: NCIN				
2009	10,470	11.5	10,793	11.3
2010	NYK		10,472	10.7

Source: CRUK 2012

Table 4: CUP Incidence as a % of all cancers by country: ICD10 codes C26, C39, C76-80

	Male	Female
Europe		
Austria	1.3	2
Belarus	2.5	1.7
Belgium	2.7	3.2
Bulgaria	4.7	3.6
Croatia	3.4	3.5
Czech Rep	2.4	2.8
Denmark	3.7	3.9
Estonia	2.6	2.1
Finland	2.2	3.4
France	2.9	3
Germany	2.5	3
Iceland	1.9	3.1
Ireland	3.6	4.4
Italy	1.9	2.4
Latvia	2.6	2.0
Lithuania	2.5	2.1
Malta	4	4.3
Norway	2.8	3.9
Poland	4.7	4.6
Portugal	2.8	2.7
Russia	1.8	1.7
Serbia	2.6	2.6
Slovak Rep	2.3	2.5
Slovenia	1.3	1.6
Spain	3.3	3.9
Sweden	3.8	5.2
Switzerland	2.1	2.5
NL	4.5	4.6
UK	4.5	5.3
Oceania		
Australia	3.7	4.1
French Polynesia	4.5	4
New Zealand	3.4	4.2
Hawaii	2.1	2.1
Africa		
Algeria	3	2.6
Egypt	6.1	5.5
Tunisia	3.5	3.9
Uganda	4.1	3.3
Zimbabwe	2.3	2.4
America Cent &S		
Argentina	4.7	3.2
Brazil	3.8	4
Chile	5.9	6.4
Columbia	6.1	6.3
Costa Rica	4.6	4.1
Ecuador	2.8	3.5
Martinique	1.6	2.7
Peru	2.6	2.8
America North		
Canada	2.7	3.3
USA	2.5	3
Asia		
Bahrain	4.7	2.5
China	2.1	2.3
Cyprus	2.1	1.9
India	8.2	5.5
Israel	3.5	3.9
Japan	1.2	1.6
Korea	2.1	2.2
Kuwait	4.8	3.2
Malaysia	7.2	5.4
Oman	5.5	5.7
Pakistan	10.5	6.4
Philippines	5.2	4
Singapore	2.7	2.2
Thailand	9.4	6.7
Turkey	3.2	3

Source: Extracted from WHO (IARC) Vol ix. 2007

DISCUSSION

Is CUP rare? CUP might be categorised as rare on the basis that it has been a neglected disease, unfamiliar to the majority of clinicians, who are challenged by the diagnosis. The European Commission on Public Health defines rare diseases as "life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them…" (EU)

Numerically, rarity is interpreted differently in the USA (incidence of less than 200,000 in the whole population), Europe (incidence of less than 5 per 10,000), and Japan (less than 50,000 patients, or about 1: 2,500). At a meta level, data presented in Tables 1-3 do not support a label of 'rare' for CUP. But at a national level the UK's Department of Health's Cancer Policy Team use a working definition for a rare cancer as: "any cancer other than the four most commonly occurring cancers." (C52, 2012.)

Table 4 might indicate that CUP is rarer in some parts of the world than others. But the data is of variable quality. For example, Russian incidence is based solely on St Petersburg whilst the authorities in Hawaii distinguish the population in ethnic detail between Chinese, Filipino, Hawaiian, Japanese, and White. The only reliable deduction from Table 4 is that CUP is a worldwide problem.

CUP subtypes are represented by: adenocarcinoma (55-60%), poorly differentiated adenocarcinoma or undifferentiated carcinoma (30%), squamous carcinoma (5-10%) and neuroendocrine carcinoma (5%). (Oien, 2009). Thus subtypes of one disease may be classified as rare when the headline disease is not. It is rare for children to be diagnosed with CUP; but it is not a rare disease for those over 60. In terms of prevalence, the number of people living with CUP supports the term 'rare'.

Does it matter: the key question is whether patients, and patient outcomes, are better served by a rare cancer diagnosis? A rare label can exacerbate inequalities and, for a patient increase psycho-social problems. There are a range of factors associated with this contention from: positivistically–designed clinical studies that discriminate against less common cancers, to the recognition that 5 year life survival from rare cancers is on average significantly worse than common cancers (C52). It does not escape the patient that rare tumours are a challenge to clinical practice and, with regard to CUP, this diagnosis is particularly challenging. When patients are referred to even major cancer centres the experience of oncologists lies very obviously with commoner cancers. The description 'heartsink' can be used to reflect both the patient's and the clinician's reaction to a CUP diagnosis.

CONCLUSION

'Rare' is too broad and variable a term to be an enabler of improving outcomes. In any case, a disease description based on rarity will become increasingly irrelevant as mutations become defined by molecular profile rather than by anatomical origin.

- A disease description defined by numbers is seldom important for patients. It may contribute inadvertently to patient inequalities. Rarity is irrelevant for a cancer patient unless it brings benefits. It is *their* cancer. The concern for CUP patients is to be treated by a clinician with specialist knowledge of *their* disease, and supported by nursing staff who understand this very difficult, 'heartsink', diagnosis

- CUP, at 7% of overall cancer mortality, is not rare. But it is a phenomenon that is poorly understood leading to uncertainty amongst clinicians (ameliorated by the advent of the 2010 NICE Guideline for England and Wales by the physicians who make reference to it) and epidemiologists. This has an impact on the quality of patient care and research

- There has to be a data credibility issue when *mortality* consistently exceeds *incidence* in the UK (Table 3). There is a need to undertake a review that attempts to reconcile and standardise CUP data collection and reporting with regard to:-
  - international norms
  - Registry custom and practice where retrospective, *post mortem,* allocation of site incidence is made from previous, or tentative, primary identification that is not necessarily congruent with the atypical nature of the disease
  - data collection related to the NICE Guideline taxonomy

- CUP incidence in the younger age groups may be masked by age standardisation and a headline decline in the incidence of 'total persons'. Further analysis is needed.

References

Australian Institute of Health and Welfare (AIHW). 2008 . *Cancer in Australia – an overview.* http://www.aihw.gov.au/publication-detail/?id=6442468196&tab=2
Binysh, Kathie. Osborne, Richard. Symons, John. 2011. Capturing cancer of unknown primary (CUP) data: known unknowns or unknown unknowns? Poster for *NCIN Conference* 15-17 June 2011.
C52. 2012. Cancer 52 response to the consultation on the UK Plan for Rare Diseases. May 2012
CRUK. 2012. Latest UK Cancer Incidence and Mortality. http://info.cancerresearchuk.org/cancerstats/mortality/cancerdeaths/
EU. **2012**. Rare cancers. http://www.rarecare.eu/aims/aims.asp
NICE. 2010. Diagnosis and Management of Metastatic malignant disease of unknown primary origin. NICE. July 2010 http://www.nice.org.uk/CG104
Oien, Karin. 2009. Pathologic Evaluation of Unknown Primary Cancer. *Seminars in Oncology* Vol 36 (1). Feb.
WHO. 2007. WHO International Agency for Research on Cancer (IARC) Vol ix. 2007 and International Statistical Classification of Diseases and Related Health Problems 10th Revision Version. ICD – 10 codes. http://apps.who.int/classifications/apps/icd/icd10online/

Acknowledgements. The author would like to thank Catherine Thomson of CRUK for her help with data sourcing. *Any errors, or opinions expressed, in this poster are those of the author.*

CUP Foundation, The Follies, Brightwalton, Newbury, RG20 7BZ

www.cupfoundjo.org
john@cupfoundjo.org