Impact of Phenol-based Cleaners at Royal Perth Hospital

Cancer of unknown primary site

Epidemiology Branch: June 3, 2011

This document has been prepared to define cancer of unknown primary site, as described in the 'Impact of Phenol-based Cleaners at Royal Perth Hospital' report, provide more detailed information on how they are recorded by the WA Cancer Registry, and an overview of the epidemiology of these cancers.

Definition of cancer in the RPH study

In this study, eligible cancers were confirmed cases of primary neoplasms of types subject to a statutory notification requirement, diagnosed during the study period (1983-2008), and registered with the Western Australian Cancer Registry (WACR) by April 2010. This incorporated malignant, invasive neoplasms ("cancers") included in standard cancer incidence reporting as well as in-situ carcinomas and benign and uncertain behaviour central nervous system (CNS) tumours. Other benign, uncertain behaviour and unconfirmed tumours were excluded as they are not routinely reported to the WACR and do not fit the generally accepted definition of cancer. All primary neoplasms were included; therefore an individual could have second and subsequent primary occurrences of the same or different types of neoplasm.

Observed cancers were defined as eligible primary neoplasms identified from the WACR data and diagnosed after commencement of employment in a Patient Support Services (PSS) position at RPH. The observed cancers could be diagnosed during or after employment ceased in a PSS position at RPH, and each individual could be diagnosed with more than one primary cancer.

Coding for all cancer types is consistent with WACR reporting and is based on the International Classification of Diseases for Oncology 3rd edition (ICDO-3) coding system.

Definition of cancer of unknown primary site in the RPH study

Cancer of unknown primary site in this study is defined as those recorded as an 'unknown primary' in the cancer type variable by the WACR (and meeting the criteria mentioned above).

The WACR defines cancer of unknown primary site as cancer which is diagnosed at the metastatic stage and a pathology test was unable to be completed, or unable to confirm, the location of the primary cancer. This definition is consistent with the International Agency for Research on Cancer (IARC) and International Association of Cancer Registries (IACR), who are recognized international reference bodies for cancer research and registries.

Where possible the morphology of the cancer is also recorded. Some morphological types can be confidently assigned to specific sites even without direct evidence (e.g. clear cell renal cell carcinoma). By international convention, melanoma of unknown primary site is classified as if it arose in the skin. However, even some apparently "specific" types such as osteosarcoma would not be assigned to a site in this way, as they occur in a variety of sites. Cancers of types neoplasm not otherwise specified, squamous and adenocarcinomas can occur in such a wide variety of sites that assignment of the tumour to a particular primary site would require further evidence.

Rigorous checking is performed by the WACR to ensure that cancers recorded as an unknown primary site should not, more accurately, be recorded as another cancer type. This includes checking the registration report, pathology reports, hospital and doctor follow-up, and death certificates. Unfortunately, locating the primary site may be difficult if the patient has not undergone any pathology testing or is deceased. Therefore cancers of unknown primary site are commonly diagnosed by non-microscopic methods. If the primary site is located at a later date then the registry is updated. This process of registration for cancers of unknown primary site is consistent with all other tumours on the WACR. The methods used for selecting cancer records for RPH PSS employees and the Perth metropolitan comparison population were the same.

Cancer of unknown primary site in the RPH study

There were 12 RPH PSS employees diagnosed with a cancer of unknown primary site.

- The morphological subtypes of cancer among these tumours was neoplasm not otherwise specified (ICDO-3 8000) (4), epithelial neoplasms not otherwise specified (8010) (4), non-small cell carcinoma (8046) (2), and adenocarcinomas (2).

- The diagnosis for the 12 cancers of unknown primary site was based on histopathology for four, cytology for four, x-ray, ultrasound and/or MRI for two, clinical for one and unknown for one.

- Of the 12 employees, seven were male and five were female. Three were aged in their 50's at diagnosis, four in their 60's, three in their 70's and two in their 80's. All died within 12 months of their diagnosis, with five passing away within one month of diagnosis.

Epidemiology of cancer of unknown primary site

Cancer of unknown primary site (CUP) is a common, well-recognised and heterogeneous clinical syndrome.[1] It is diagnosed at the metastatic stage, and despite sometime extensive diagnostic work-up, the primary tumour remains unidentified.[2] It is characterised by early dissemination, clinical absence of the primary tumour, unpredictability of metastatic pattern and aggressiveness of the disease itself.[1] In more than 50% of cases there is multiple site involvement, and antemortem detection of primary site is only 20-30%.[1]

Cancers of unknown primary site are one of the ten most commonly diagnosed cancers in developed world.[1] They account for 2.7% of all cancer diagnoses and 5.9% of cancer deaths in Australia[3] and percentages as high as 10% have been found in other countries.[4] In WA, there were 257 people diagnosed, and 159 deaths, from cancer of unknown primary site in 2008.[5] They accounted for 2.3% and 2.7% of all cancers diagnosed in males and females respectively and has them ranked as the 7th and 8th most common.[5] For cancer deaths, they are the 6th most common cause in males and females, and account for 4.0% and 4.8% respectively.[5]

Although the proportion of cancers of unknown primary site is higher in females, the risk of diagnosis is higher in males.[5] The incidence in males is 7.8 per 100,000 person years compared to 5.3 per 100,000 person years in females which is a ratio of 1.5:1.[5] In addition, the risk of cancer of unknown primary site increases with increasing age.[5] The prognosis for patients with cancers of unknown primary site is very poor, with a median survival time of three to four months.[6, 7] Survival to twelve months post-diagnosis is estimated at 20%,[2] and five-year survival 11%.[8] Research into this type of cancer has lagged behind other areas of oncology.[9]

As cancers of unknown primary site are a heterogeneous group of malignancies, there are no obvious aetiological causes or risk factors.[10] However they are typically associated with older people, late diagnoses and in persons with a history of smoking.[7, 9] The incidence of cancer of unknown primary site increases with age[7, 11] with the median age at diagnosis usually reported at around 70 years of age.[2, 6] The proportion of cancers of unknown primary site, of total cancers, is higher in females but males are more likely to be diagnosed and die from the condition.[5, 7, 11, 12] In the Indigenous population, there is a higher proportion of cancer of unknown primary site when compared to the non-Indigenous population.[11] There is also a higher proportion in people born outside Australia and those living in low socio-economic areas, but little difference between those in metropolitan and non-metropolitan areas.[2, 11]

Tobacco smoking is considered a risk factor for cancer of unknown primary site[2] and it is estimated that more than half of patients have a history of smoking.[7, 13] Dietary risk factors associated with stomach and colorectal cancer may also be risk factors for cancers of unknown primary site given they are potential primary sites.[7] A Nordic occupational cancer study found that medical doctors have the lowest risk of cancer of unknown primary site for males and females.[14] The highest risk for males was for tobacco workers (SIR: 1.73, 95%CI: 0.86-3.09), waiters (SIR: 1.49, 95%CI: 1.19-1.84), cooks and stewards (SIR: 1.30, 95%CI: 1.10-1.54), and hairdressers (SIR: 1.28, 95%CI: 1.06-1.54).[14] In females, the highest risk was for “other construction workers” (SIR: 1.45, 95%CI: 1.02-2.00) followed by chemical process workers (SIR: 1.24, 95%CI: 1.04-1.50) and waiters (SIR: 1.14, 95%CI 1.05-1.23).[14]

Cancers of unknown primary site have traditionally been considered as a cross-section of common cancers where the primary site could not been determined. Cancer registries internationally report the incidence and mortality of these cancers and use the classification to monitor the quality of reporting and follow-up of cases.[7, 15] The primary site is commonly thought to be located in the lung, pancreas, breast, prostate, stomach, liver and large bowel.[16-18] Familial clustering has also suggested a link with kidney, colorectal and ovarian cancer.[2] It is well recognised that many primary sites with different morphologies are represented[9] however,

even with extensive investigation (including autopsy) the primary site is only detected in 20-30% of cases.[1]

The site of a primary tumour may remain unknown for several reasons. In some cases further investigations to identify a primary site may not be of any clinical benefit, or may be refused by a patient or their family – most common in the elderly or with other serious illness; some may have rapid progression and die before investigation can be completed; or a primary site may evade identification because the primary tumour remains dormant or has disappeared through mechanisms that can halt tumour growth, apoptosis, senescence and response to the microenvironment.[2] IARC and IACR recognise that the percentage of cases registered with an unknown primary site may be related to the quality of diagnostic information,[15] however these other aspects of medical care may play a large part.

The morphology of a cancer refers to the histological classification and behaviour of the cancer tissue and is determined by the examination of tumour cells. Among cancers of unknown primary site, there are a high proportion of cases with no morphological type known, as many are diagnosed only through clinical or imaging techniques. In addition, there is a high proportion of diagnoses with problems with histological classification as the tumour cells may be difficult to characterise.[12] When the morphological type can be confirmed, approximately 50% are well to moderately differentiated adenocarcinomas, 30% are undifferentiated adenocarcinomas or carcinomas, 15% are squamous cell carcinomas and 5% are undifferentiated neoplasms.[1] Obviously, when there are more cases with limited or no pathology, the level of uncertainty in morphological type increases.

Recently, there has been discussion as to whether some cancers of unknown primary site represent a new type of cancer. A recent report, by the Cancer Institute NSW, showed that cancers of unknown primary site have different characteristics to metastatic disease of a known site.[3] This is similar to previous conclusions that these cancers possibly have a unique clinical behaviour and biological profile.[16, 17] Cancers of unknown primary have been characterised by rapid progression, atypical metastatic spread and multiple metastases that result in lower survival rates than cancers of known primary site of the same stage.[7, 17, 19] Familial clustering has also shown that it is not a randomly occurring metastatic cancer.[2] Unfortunately, at the moment no consensus exists on whether cancers of unknown primary site are a group of tumours missing their primary site or a new type of cancer.[19]

In summary, cancers of unknown primary site are a common diagnosis and occur when the specific organ or tissue of the body where the cancer originated cannot be identified. They are thought to be a cross-section of common cancers that have been diagnosed at an advanced stage however it is possible that some of the cancers within this group are a unique type of cancer. As cancers of unknown primary site are a heterogeneous group of malignancies, there are no obvious aetiological causes or risk factors. Given the range of diagnostic characteristics in those with cancer of unknown primary site in the RPH study, it would seem unlikely that they have a single cause.

References

1. Pavlidis N, Pentheroudakis G. Cancer of unknown primary site: 20 questions to be answered. *Ann Oncol* 2010;21 Suppl 7:vii303-vii7.
2. Hemminki K, Ji J, Sundquist J, et al. Familial risks in cancer of unknown primary: tracking the primary sites. *J Clin Oncol* 2011;29(4):435-40.
3. AIHW, CA (Cancer Australia), AACR (Australasian Association of Cancer Registries). Cancer survival and prevalence in Australia: cancers diagnosed from 1982 to 2004. Canberra: AIHW, 2008.
4. Parkin D, Whelan S, Ferlay J, et al. Cancer Incidence in Five Continents. Vol. VIII. *Scientific Publication No 155*. Lyon, France: IARC, 2002.
5. Threlfall T, Thompson J. Cancer incidence and mortality in Western Australia, 2008. *Statistical Series Number 87*. Perth: Department of Health, Western Australia, 2010.
6. Seve P, Sawyer M, Hanson J, et al. The influence of comorbidities, age, and performance status on the prognosis and treatment of patients with metastatic carcinomas of unknown primary site: a population-based study. *Cancer* 2006;106(9):2058-66.
7. Tracey E, Glass P, Roder D, et al. Unknown Primary Cancer in New South Wales. Sydney: Cancer Institute NSW, 2008.
8. English D, Farrugia H, Thursfield V, et al. Cancer Survival Victoria 2007: Estimates of survival in 2004 (and comparisons with earlier periods). Melbourne: Victorian Cancer Registry, Cancer Epidemiology Centre and Cancer Council Victoria, 2007.
9. Hainsworth J, Greco F. Chapter 136: Neoplasms of Unknown Primary Site. In: Bast R, Kufe D, Pollock R, et al., eds. *Holland-Frei Cancer Medicine, 5th edition*. Hamilton: BC Decker, 2000.
10. Pavlidis N, Fizazi K. Carcinoma of unknown primary (CUP). *Crit Rev Oncol Hematol* 2009;69(3):271-8.
11. Luke C, Koczwara B, Karapetis C, et al. Exploring the epidemiological characteristics of cancers of unknown primary site in an Australian population: implications for research and clinical care. *Aust N Z J Public Health* 2008;32(4):383-9.
12. Muir C. Cancer of unknown primary site. *Cancer* 1995;75(1 Suppl):353-6.
13. Tracey E, Baker D, Chen W, et al. Cancer in New South Wales: Incidence, Morality and Prevalence, 2005. Sydney: Cancer Instistute NSW, 2007.
14. Pukkala E, Martinsen JI, Lynge E, et al. Occupation and cancer - follow-up of 15 million people in five Nordic countries. *Acta Oncol* 2009;48(5):646-790.
15. Parkin D, Chen V, Ferlay J, et al. Comparability and Quality Control in Cancer Registration. *IARC Technical Report No 19*. Lyon: IARC and IACR, 1994.
16. Briasoulis E, Pavlidis N. Cancer of Unknown Primary Origin. *Oncologist* 1997;2(3):142-52.
17. Pavlidis N, Briasoulis E, Hainsworth J, et al. Diagnostic and therapeutic management of cancer of an unknown primary. *Eur J Cancer* 2003;39(14):1990-2005.
18. Pentheroudakis G, Golfinopoulos V, Pavlidis N. Switching benchmarks in cancer of unknown primary: From autopsy to microarray. *Eur J Cancer* 2007;43(14):2026-36.
19. Pentheroudakis G, Briasoulis E, Pavlidis N. Cancer of Unknown Primary Site: Missing Primary or Missing Biology? *Oncologist* 2007;12(4):418-25.