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Descriptive epidemiology of cancer of unknown primary site in Scotland, 1961–2010

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ABSTRACT

Background: Cancers of unknown primary site (CUP) pose problems for diagnosis, treatment, and accurate prediction of prognosis. However, there are limited published data describing the epidemiology of this disease entity. Our aim was to describe the epidemiology of CUP in Scotland.
Methods: Anonymised data, covering the period 1961–2010, were extracted from the Scottish Cancer Registry database, based on the following ICD-10 diagnostic codes: C26.0, C26.8, C26.9, C39, and C76–C80. Age-standardised incidence rates were calculated by direct standardisation to the World Standard Population. Estimates of observed survival were calculated by the Kaplan–Meier method.
Results: Between 1961 and 2010, there were 50,941 registrations of CUP, representing 3.9% of all registrations of invasive cancers. Age-standardised rates increased to a peak in the early to mid-1990s, followed by a steeper decrease in rates. During 2001–2010, age-standardised rates of CUP were higher in the most compared with the least deprived fifth of the population. Observed survival was marginally higher in patients diagnosed during 2001–2010 (median 5.6 weeks) compared with those diagnosed in the previous two decades. During the most recent decade, survival decreased with age at diagnosis, and was higher in patients with squamous cell carcinoma and with lymph node metastases.
Conclusion: Patterns of CUP in Scotland are largely consistent with those reported from the few other countries that have published data. However, in comparing studies, it is important to note that there is heterogeneity in terms of definition of CUP, as well as calendar period of diagnosis or death. Variation in the definition of CUP between different epidemiological studies suggests that there would be merit in seeking international agreement on guidelines for the registration of CUP as well as a standard grouping of diagnostic codes for analysis.

1. Introduction

Cancer of unknown primary site (CUP) is a heterogenous group of cancers with, it has been argued, a distinct biology [1]. Estimates of the incidence of CUP depend crucially on how it is defined. In recent population-based studies, CUP has been estimated to account for around 2–4% of cancers depending on definition, population, and period of diagnosis [2–9]. However, estimates of the proportion of CUP in some developing countries can exceed 10% [10].

Since cancer management depends considerably on knowledge of the primary site of origin of the tumour, the absence of this information poses particular challenges for diagnosis, therapy and accurate prediction of prognosis.

The purpose of the present study is to describe the epidemiology of CUP in Scotland, which has a population of approximately five million.

2. Methods

2.1. Definition of cancer of unknown primary site

CUP is widely defined as "histologically confirmed metastatic cancer for which clinicians are unable to identify a primary tumour after a standard diagnostic approach" [1]. However, since this

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definition excludes, for example, cancers that are not microscopically verified, it is almost certain to under-estimate the population burden of disease. There does not appear to be an internationally accepted definition of CUP in terms of diagnostic codes. At one extreme, the National Institute for Health and Clinical Excellence, sponsored by the Department of Health in England, provides quite a restricted definition of CUP (or more accurately, *carcinoma* of unknown primary), based on the following codes from the tenth revision of the International Statistical Classification of Diseases and Related Problems (ICD-10) [11]: C77 (Secondary and unspecified malignant neoplasm of lymph nodes), C78 (Secondary malignant neoplasm of respiratory and digestive organs), C79 (Secondary malignant neoplasm of other and unspecified sites), and C80 (Malignant neoplasm, without specification of site) [12]. In contrast, the International Agency for Research on Cancer (IARC) has identified a category labelled as "Other and unspecified" for the monograph, Cancer Incidence in Five Continents, which includes additionally 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), C48 (Malignant neoplasm of retroperitoneum and peritoneum, excluding mesothelioma and Kaposi's sarcoma), and C76 (Malignant neoplasm of other and ill-defined sites), but excludes C77–C79, which would usually be re-coded to C80 for the purposes of this publication [10]. In volumes V and VI of this monograph, an equivalent category (but excluding retroperitoneum and peritoneum) was labelled "Primary Site Uncertain". Recent population-based epidemiological studies specifically about CUP have used varying ranges of diagnostic codes including ICD-10 C39, C76, C80, [9] ICD-O(3) C80, [5,8] ICD-9 195.1–195.3, 196, 197.0–197.3, 197.6–197.7, 198.2–198.5, 199, [13] ICD-9 195–199, [14] ICD-9 196–199, [15] ICD-7 199, [6,16] and ICD-9 196–199 [3,4]. Muir applied a broader range of diagnostic codes, more in line with IARC, including ICD-O(1) 165, 195, 199, plus non-lympho-haematopoietic neoplasms of 169.0–169.1, 169.3–169.9, and 196 (Appendix 1) [2].

In fact, the National Institute for Health and Clinical Excellence guideline makes distinctions between three diagnostic entities: (1) Malignancy of undefined primary origin (MUO), defined as metastatic malignancy identified on the basis of a limited number of tests, without an obvious primary site, before comprehensive investigation; (2) Provisional carcinoma of unknown primary origin (provisional CUP), defined as metastatic epithelial or neuro-endocrine malignancy identified on the basis of histology or cytology, with no primary site detected despite a selected initial screen of investigations, before specialist review and possible further specialised investigations; and (3) Confirmed carcinoma of unknown primary origin (confirmed CUP), defined as metastatic epithelial or neuro-endocrine malignancy identified on the basis of final histology, with no primary site detected despite a selected initial screen of investigations, specialist review, and further specialised investigations as appropriate [12]. In practice, even if these three categories were more precisely defined, it is not always possible to make these distinctions in population-based cancer registry data because of limited information on the extent and nature of diagnostic investigations.

In the interests of being inclusive and providing a realistic estimate of the overall burden of CUP in the Scottish population, we decided to select the following ICD-10 codes: C26, C39, C76–C80. However, we excluded the code C26.1, which refers specifically to primary malignant neoplasms of the spleen (for example, angiosarcomas), and not to metastatic disease of the spleen which should be coded as C78.8. In fact, only 13 cases were coded to C26.1 during the period 1961–2010. We did not restrict our analysis to histologically confirmed disease or to carcinomas.

2.2. Data

Anonymised incidence data for the period 1961–2010 were extracted from the Scottish Cancer Registry (SCR). SCR is a population-based registry, which receives electronic data from multiple sources, including acute hospital discharge records, pathology records, and death records. It is believed to hold data of comparatively high quality, including basic information on primary treatment [10,17,18]. We used the audit trail within the cancer registry database to assess the stability of diagnostic data relating to CUP from 2005 to 2010 with follow-up to 14th January 2013. Stability was assessed on the basis of the frequency of subsequent alterations to diagnostic coding as a result of new information becoming available. Mid-year population estimates and mortality data were obtained from the General Register Office for Scotland (now part of National Records of Scotland). Death records are linked to SCR records by computerised probability matching, enabling analysis of survival [19]. Estimates based on clerical checking suggest that rates of false positive and false negative linkages are maintained below 1% [20]. Follow-up for survival was to 31st December 2011. Emigrations of patients registered with cancer from Scotland to other UK countries are notified to the cancer registry by the National Health Service Central Register (NHSCR), allowing censoring or exclusion of these individuals from survival analyses. We used the Scottish Index of Multiple Deprivation (SIMD) 2006 as a postcode-referenced, small area indicator of socio-economic position [21].

For the purpose of analysis, we defined the following anatomic sub-sites: metastatic disease of lymph nodes (ICD-10 C77), lung (C78.0), pleura (C78.2), retroperitoneum/peritoneum (C78.6), liver (C78.7), brain/cerebral meninges (C79.3), bone/bone marrow (C79.5), and multiple metastatic sites (C80); and "Other" (remaining ICD-10 codes within the range C26.0, C26.8, C26.9, C39, C76–C80). Similarly, we defined histological sub-types as follows: not microscopically verified; adenocarcinoma (ICD-O morphology codes 8140–8384, 8400–8403, 8408–8551, 8560, 8570–8574, 8576, 9014–9015, 9110); squamous cell carcinoma (8051–8078, 8083–8084, 8123–8124); and "Other morphologies" (all remaining ICD-O M-codes).

2.3. Statistical methods

Age-standardised incidence rates were calculated by direct standardisation to the World Standard Population [22]. In relation to analysis of incidence rates across socio-economic categories, 95% confidence intervals for the rates were calculated based on the gamma distribution [23]. Poisson regression was used to test for a trend in incidence rates across deprivation categories. Estimates of observed survival were calculated by the Kaplan–Meier method [24], using *SPSS* version 21. The statistical significance of differences in survival was assessed using the log-rank test.

3. Results

Between 1961 and 2010, there were 50,941 registrations of CUP, representing 3.9% of all registrations of invasive cancers. While the numbers of registrations of all invasive cancers increased over successive decades, the numbers of registrations of CUP decreased in the most recent decade (Table 1). The number and percentage of CUP registrations has been consistently higher in females, but the percentage has decreased in both sexes in the most recent two decades. Between 2001 and 2010, CUP was the sixth most common incident cancer, accounting for 3.2% of all cancer registrations, after non-melanoma skin, lung, breast, colorectal and prostate cancer. During the same period, it was