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The challenge of attributing causality in Cancer of Unknown Primary

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To the Editor: In a large registry-based study, Hemminki *et al* examined the correlation between the reported metastatic site and the cause of death in patients with a registered diagnosis of histopathologically-verified cancer of unknown primary (CUP).[1] They observed an association between metastasis location and registered site-specific cancer death, and found lung cancer to be the most common cause of site-specific cancer death.

We urge caution before these findings are used to inform clinical practice due to the unrepresentative patient group, misinterpretations of the data, and the largely unfounded clinical conclusions.

There is no recognition by the authors that CUP patients with a histopathological diagnosis registered by population-based cancer registries include two distinct patient groups: those who undergo an "extensive diagnostic work-up" and those with limited diagnostic investigations beyond histopathology due to poor health at presentation.[2] In practice, an oncologist's diagnostic approach is influenced by the site of the metastases in the context of the clinical presentation, and led by the potential benefits of treatment, where the patient is fit for treatment, and the patients' wishes. Further, the authors fail to recognise the atypical nature of the study population. Extensive literature supports the knowledge that confirmed CUP possesses the fundamental characteristics of early dissemination and an unpredictable metastatic pattern.[3] The authors restricted their analysis to CUP patients with one reported metastatic site. Most patients (60%) with CUP present with two or more metastases at diagnosis.[4] Several studies have shown a single, solitary metastasis at diagnosis represents a favourable subgroup potentially amenable to radical treatment.[5] Thus, the diagnostic and treatment pathway for this subgroup of confirmed CUP patients is unique.

In the Hemminki study, the CUP diagnosis and the metastatic location were obtained from the Swedish cancer registry, while the Swedish mortality registry provided the cause of death. Underlying the authors' analysis and interpretation is the assumption that cancer registries are notified about all clinically detected metastatic sites and further that the metastatic lesion sampled for histopathological analysis is the key metastatic lesion. There is no validation of the cancer registry data to ensure that no other metastatic sites were identified by radiological or clinical examination. In clinical practice the metastasis used for histopathological diagnosis is selected on the basis of size and accessibility for biopsy, neither of which is related to its role within the metastatic pathway.

This study relies on the accuracy of the registered cause of death and the authors show unsupported confidence in the validity of this data in patients with a registered diagnosis of CUP. The death data was variously described as the "organ specific cancer which kills the patient, as judged by the death registrar", "the final cause of death", and "the main causes of death". Cause of death studies based on registry data universally use the *underlying cause of death*, which in Sweden[6] and elsewhere according to WHO International Classification of Diseases (ICD) rules[7], is the disease or injury which *initiated* the train of morbid events leading directly to death.

Previous studies show that the *ante* mortem frequency of detecting the primary tumour in CUP patients is around 30%.[8] The Hemminki study argues that the site-specific cause of death can be identified in 67.9% of cases, based on death certification, and it then postulates that this site-specific cause of death is predictive of the site of the primary tumour. This argument is unfounded and incongruous with current knowledge in the area (primary tumours are not identified as they may have regressed, be too small to be detected or have been sloughed off *post*-metastasis). The authors' attempt to validate the postulated link between site-specific cause of death and primary tumour with the use of autopsy data on 67 patients. They describe the cause of death attributed at autopsy as "lung cancer", "ovarian cancer" etc; but it is not clear whether primary lung cancer was histologically confirmed in these cases or that the patient was found at autopsy to have multiple metastases in the lung which led to death. Accurately distinguishing between these causes of death is imperative if the authors wish to show a relationship between a site-specific cause of death and the site of the primary tumour.

It is unclear, in the paper, whether the site-specific cause of death is determined by clinical symptoms, examination findings, new diagnostic evidence or clinical judgement. A death registered as lung cancer may be the result of comprehensive immunohistochemistry, a PET scan showing a single or multiple lung tumour(s) or a patient dying of respiratory failure. Unfortunately, there is no medical-record information presented to validate the basis of the cancer death data. The authors neglect to recognise a plausible alternative explanation for their findings: deaths due to the progression of metastatic lesions, in the absence of a known primary site, may have been wrongly attributed to death from cancer at the metastatic site (instead of CUP). The data presented in Table 2 appear to support such errors in the attribution of the underlying cause of death. For example, 319 (62%) of deaths attributed to liver cancer had a liver metastasis; and 56 (57%) of deaths attributed to peritoneal cancer had a peritoneal metastasis recorded by the registry.

The poor survival statistics shown in this paper reinforce the need for good quality data and research that leads to a better understanding of the biology of CUP and the true burden of the disease. The immediate future rests on the diagnostic pathway where improvements will enable timely diagnosis and improve outcomes for patients with CUP. Molecular profiling has begun to offer clinically important information and has the potential to improve understanding of the genetic lineage of the primary tumour and the drivers of the neoplastic process.[9] This technique also poses a new challenge for the population-based registration of incident cancers and cancer-related deaths where the primary site is not confirmed by traditional means.

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