Reply to Letter to the Editor

THE CHALLENGES OF UNDERSTANDING CANCER OF UNKNOWN PRIMARY (CUP)

K. Hemminki[1,2], M. Riihimäki[1,2], K. Sundquist [2,4] and A. Hemminki [3]

[1]Division of Molecular Genetic Epidemiology, German Cancer Research Centre (DKFZ), 69120 Heidelberg, Germany;

[2]Center for Primary Health Care Research, Lund University, Malmö, Sweden;

[3]Cancer Gene Therapy Group, Transplantation Laboratory & Department of Pathology, Haartman Institute, University of Helsinki, 00290 Helsinki, Finland;

[4]Stanford Prevention Research Center, Stanford University School of Medicine, Palo Alto, California, USA.

Word count: 717.

CONFLICT OF INTEREST

None.

Cancer of unknown primary (CUP) ranks among the most fatal cancers and the apparent survival varies, depending on how the patient population was selected. For example, Greco and Pavlidis cited 9 studies on median survival time for CUP patients; for three cancer registry-based studies, the survival ranged from 2.75 to 4 months and for hospital-based studies it ranged from 3 to 11 months [1]. The median survival in our recent Swedish population-based study was 3 months and 1-year survival was around 20%, in line with population-based data from the Netherlands and the UK (www.nice.ong.uk/cg104) [2,3]. Hospitals, and particularly high-quality referral centers, receive surviving patients, which for CUP may account for substantially less than the initial patient population. Performance score, concomitant disease and age might impact referral. Also, the location of metastases may determine if and where the patient is referred to. For example, brain metastases patient may be referred to a radiation oncology department while a patient with ovarian metastases might be seen by a gynecological oncologist. Thus, not only is the patient clientele in tertiary/quaternary referral centers highly selected with regard to survival but so are the CUP types that underlie the differences in survival and all other measurable outcomes. Unfortunately, much of the CUP literature originates from such biased populations and sporadic readers may fail to catch the implications. Furthermore, the survival kinetics in population-based studies from Sweden and the Netherlands [2,3], with diagnoses based on histological confirmation, show a steep time-dependent monotonous decline, which is normally interpreted as indicating a single or very many indiscernible components, the latter being more likely for CUP. The UK data, cited by National Institute for Health and Clinical Excellence, show survival kinetics like ours (NICE, www.nice.ong.uk/cg104). Such data give no support for 'two distinct patient groups', which Vajdic and coworkers proposed in their letter [4]. In many fatal cancers, in addition to CUP, physical condition varies at diagnosis and frailty is one of the predictors of outcome.

In view of the unrepresentative patient groups in the CUP literature, discussed above, it is a misunderstanding by Vajdic et al that our study would suffer from such bias. We deleted only cases for which there was a specific statement of more than one metastatic site (<3% of all). In our paper, 'unspecified CUP' is included and this is likely to be representing metastatic dissemination at multiple sites, accounting for 32.1% of all cases, in line with 26% in the population-based Dutch data for disseminated cases [2]. Vajdic et al claim that 60% of CUP

2

patients should have metastases at multiple sites, a figure originating from a quaternary referral center on 657 patients studied around 1990. Our study was based on more recent population-based data on 9,306 CUP patients. Moreover, Vajdic et al erroneously cite this figure (60%) to show multiple metastases 'at diagnosis', failing to understand the difference between 'at diagnosis' and 'at referral'. The original paper that they cite uses the proper term.

In the same vein, these authors criticized the accuracy of our diagnostic data on metastatic location. The Swedish Cancer Registry requires double notifications about cancer patients, one from a clinician and the other from a pathologist. Claiming that these two specialists cannot define the location of metastasis shows how far these authors are from clinical reality. Similarly, in relation to autopsies, 'accurately distinguishing between these causes of death is imperative' these authors seem to be unaware that autopsies are performed just for that reason, to establish the cause of death. As an ultimate lesson, Vajdic et al teach us, 3 medical professors and all 4 co-authors trained and practiced in Swedish/Finnish health care and death certificates, that the cause of death studies 'universally' use the underlying cause of death, which, as they point out, 'in Sweden and elsewhere' is defined as the disease that initiated the train of morbid events leading directly to death. The train of thought by Vajdic et al should not have stalled: what initiates the train of morbid events when the initiating primary cancer is unknown? This is why the Swedish death registrar writes down the cause that killed the patient, according to him.

We share the concerns of Vajdic et al that persons not understanding about unrepresentative patient groups and misinterpreting scientific data do harm to the course of CUP patients.

REFERENCES

1.   Greco FA, Pavlidis N. Treatment for patients with unknown primary carcinoma and unfavorable prognostic factors. Semin Oncol 2009;36:65-74.
2.   van de Wouw AJ, Janssen-Heijnen ML, Coebergh JW, Hillen HF. Epidemiology of unknown primary tumours; incidence and population-based survival of 1285 patients in Southeast Netherlands, 1984-1992. Eur J Cancer 2002;38:409-13.

3.   Hemminki K, Bevier M, Hemminki A, Sundquist J. Survival in cancer of unknown primary site: population-based analysis by site and histology. Ann Oncol 2012;23:1854-63.

4.   Vajdic C, Wyld L, Symons J. The challenge of attributing causality in Cancer of Unknown Primary. Int J Cancer 2013;in press.

4