Reviewer's report

Title: The epidemiology and survival of extrapulmonary small cell carcinoma in South East England, 1970-2004

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Reviewer: Mark Mccarthy

Reviewer's report:

It is welcome to receive the revision of this paper, and I thank the authors for the detailed responses to the first set of referee comments. Redrafting has been substantial (although there does not appear to be new analysis) and the revised emphasis deserves attention. I recommend, however, some further tuning to for the paper to achieve the high standard it seeks.

* Major Compulsory Revisions

1. To consider the concept that both EPSCCs and SCLCs could be equal parts of small cell cancers, and not necessarily to contrast them. While SCLC has much higher incidence than other EPSCCs, is this due to smoking? (SCC rates are very low in non-smokers. Indeed – could EPSCC be the non-lung effects of smoking as well: what does the smoking literature say?) If LSCC is just one SCC, not separate, it could be included on Figure 4, and its survival compared with other SCCs – eg oesophageal SCC.

By contrast, the SCC that stands out is breast. Has this less to do with ‘screening’ (which identified very few of these breast cancers) and perhaps more to do with being a superficial rather than ‘deep’ SCC? A nullifiable hypothesis would be to examine the survival of colo-rectal and prostate SCCs in this series, and see if their survival mimics more their tissue (ie found symptomatically and quite good survival) or their pathology (ie anaplastic and found at dissemination).

2. To give further attention to the literature.

How was the literature searched? My cursory google showed a recent paper: J. Subramanian, et al, Clin Oncol 26: 2008 (May 20 suppl; abstr 22106) which reported 5510 cases with EPSCC. (This was an abstract, and I did not follow it further, but presumably SEER has more on this.)

Can all the relevant comparable literature be put in the opening, rather than introduced in the discussion?

The ‘European’ perspective needs attention. There are references to papers from Canada and Korea, but there are at least clinical reports from European countries, eg for specific tissues.

Has a search been done using the several names of this cell, by tissue, or only EPSCC? When was ‘EPSCC’ introduced (ie earlier reports would be missed

3. Treatment. The objectives (in the Background) now do not mention treatment.
Since the data are very limited in detail, and seriously missing (27% for the EPSCC cases), and numbers prevent the authors analyzing treatment by site, what is the value of including treatment at all clear? However, if treatment is to be included, why not compare TCR treatment modalities for other common tissue types by the EPSCC sites: the null hypothesis would be that 'EPSCC treatment' is non-specific, reflecting site treatment rather than treatment of the SCC pathology.

* Minor Essential Revisions

The Abstract gives EPSCC rates, but not SCLC rates for ‘comparison’. In the conclusion, could the authors call for more standardised diagnosis and more European population studies, rather than ‘therapeutic decisions’ which were not the focus of the study.

The Background could explain that there are many words for this pathology (anaplastic, oat-cell etc). SCCs, being non-surface (except breast), usually have ‘late’ diagnosis, and also being highly metastatic, frequently disseminated at diagnosis. They are resistant to treatment, and mainly have low survival. Indeed, they may be diagnosed as metastases.

Methods. Welcome to include now details of the data sources from TCR. Did the cases analysed include North (NE, NW) Metropolitan before 1985 (NE were not electronic)? Is this dependent on memory, or is there a publication describing this organizational history? – which defines the current registry’s population.

A reference should be made to a study by the Registry (since Pollock’s work) interpreting how the high DCO rate affects interpretation of TCR cancer survival in general, even if as the authors say, even including DCOs, EPSCC diagnosis is mainly by pathology.

Results Title of Fig 2 should be Cumulative survival.

Discussion. The opening paragraph makes a genetic/environmental contrast, but could also consider that while SCLC (‘LSCC’) is directly due to smoking, EPSCC (‘non-LSCC’) could also be indirectly due to smoking … in smaller carcinogen exposures. A mention of the embryology of the site tissues would not go amiss … these are mostly midline structures …

I think the data on treatment should consider a clinical perspective. Does the literature say how SCC diagnosis affects the treatment plan? If SCCs are treated by the standard tissue treatment approach, and the survival is similar, then probably there’s nothing useful to say on treatment of EPSCCs… the trend of increasing chemo is just part of the continued search for anything that might change the natural history of most cancers.

**Level of interest:** An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests