Author's response to reviews

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

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Author's response to reviews: see over
Dear Dr Marshall,

Thank you for the opportunity to revise this paper. My colleagues and I have considered the detailed comments of the reviewer and set out our responses to each point below. We have incorporated the suggestions within the manuscript where we can and we have highlighted these in red for your ease of reference. We hope you find the revised paper acceptable and look forward to hearing from you.

Kind regards

Sophia Wong, Medical Student King’s College London

Response to reviewer 1

Major essential revisions

Comment 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?)

Response 1: Thank you. This is an interesting idea about aetiology – a topic which we mentioned only briefly in the discussion at the suggestion of the previous reviewer.

Contrasting EPSCC and SCLC as we have done shows the difference between the stable and very low incidence of EPSCC and the high but declining incidence of SCLC in men. If EPSCC were caused by smoking, then we might expect also to see a decline in its incidence in men with decreasing smoking rates as we see for SCLC. This is not clearly the case for EPSCC, although with such low incidence rates it is difficult to be entirely sure about this. For this reason we speculate that EPSCCs represent genetic and developmental influences rather than environmental carcinogens related to smoking. We have therefore expanded on these points at the beginning of the discussion. We are aware of few references to EPSCC in the smoking literature to guide the reviewer’s hypothesis. A small Turkish study by Cicin et al (2007) found that smoking was less common in EPSCC than SCLC patients, but this hypothesis might be tested by a new case control study of these patients which we have now recommended.

Comment 2: If LSCC is just one SCC, not separate, it could be included on Figure 4, and its survival compared with other SCCs – e.g. oesophageal SCC.

Response 2: Thank you. We have considered this but we still think that the difference in survival for SCLC is clear from the existing figure 2. Figure 4 is already rather busy and the lung survival curve risks getting lost within it if we add it. Considered together we hope Figure 3 and 4 provide all the necessary information.
Comment 3: By contrast the SCC that stands out (for survival) 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 a “deep” SCC? A nullifiable hypothesis would be to examine the survival of colo-rectal and prostate SCCs in this series and to see if their survival mimic more their tissue (ie found symptomatically and quite good survival) or their pathology (i.e. anaplastic and found at dissemination).

Response 3: Thank you. This too is a very interesting idea. Unfortunately even in this large series the number of patients with prostate and colorectal EPSCC is small, and we are not sure that the sample could confirm or disprove the argument. It seems to us that the question might best be answered by a new study using pooled data from published studies and we have recommended this in the discussion.

Comment 4: How was the literature searched? My cursory google search showed a recent paper: J Subramanian et al Clin Oncol 26: 2008 (May 20 suppl;abstr 22106) which reported 5510 with EPSCC. This was an abstract, and I did not follow it further, but presumably SEER has more on this)

Response 4: Thank you for pointing out this abstract which we missed when it was published during our submission period. We have contacted SEER and the lead author has informed us that the paper is in review and not yet published.

Comment 5: Can all the relevant 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 e.g. for specific issues.

Response 5: Thank you. We have now reviewed the references. We can find no large European population-based studies. Most studies from this region are either small single institution studies or case studies of which there are a large number and which it is very difficult to incorporate. We have included reference to one Italian and one Welsh study.

Comment 6: Has a search been done using the several names of this cell, by tissue, or only by EPSCC? When was “EPSCC” introduced (i.e. earlier reports would be missed)

Response 6: Our understanding is that the term “extrapulmonary” was increasingly used with the term “oat cell” from the 1980s and the term EPSCC is nearly always used from the 1990s onwards. We have searched using different terms, but concentrated on reporting the largest studies and reviews of the field. We have therefore recommended some pooling of data for specific sites where classification allows this.
Comment 7: 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 analysing treatment by site, what is the value of including treatment at all? 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.

Response 7: Thank you for pointing out this inconsistency. We had thought that a small amount of information on treatment was of some use. However, on reflection given the doubts expressed by both reviewers we have now decided to exclude this analysis from the paper.

Minor essential revisions

Comment 8: 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.

Response 8: Thank you. We have recommended more standardised diagnosis and European population-based studies in the conclusion.

Comment 9: 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 being also highly metastatic, frequently disseminated at diagnosis. They are resistant to treatment, and mainly have low survival. Indeed they may be diagnosed as metastases.

Response 9: Thank you. We have added these extra words to the background. We think that we have already made the point about poor prognosis and advanced disease.

Comment 10: 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 organisational history? – which defines the current registry’s population.

Response 10: Thank you. We can clarify that North Metropolitan data before 1985 was not included. This study included cases from South London, Surrey, Sussex and Kent for the period 1970-1984 and from 1985-2004 also included cases from North London, Hertfordshire and Essex. These well-defined areas have complete coverage for the time periods stated. We have added this more complete description to the methods.

The TCR reports define population coverage as well as providing organisational memory and are all retained.
Comment 11: 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.

Response 11: We have now referenced a study by Robinson et al 2007 which considers the DCO rate between 1994 and 2001 and the issue in the context of comparison of European survival.

Comment 12: Results. Title of Figure 2 should be cumulative survival

Response 12: Thank you. We have changed the title and made it clear in the methods that we are using crude survival.

Comment 13: 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...

Response 13: Thank you. We have included this point in our response to comment 1 above.

Comment 14: 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 survival is similar, then probably there’s nothing useful to say on treatment of EPSCCs...the trend to increasing chemo is just part of the continued search for anything that might change the natural history of most cancers.

Response 14: We have decided to exclude the treatment analysis in response to comment 7 above.