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 Diane Marshall

Thank you for the opportunity to revise this paper. We have looked carefully at the comments of the two reviewers and we believe they have identified some important shortcomings and inconsistencies in the original manuscript. Following the suggestions of reviewer 2 we have revised and shortened the paper to concentrate more on the incidence and survival and less on the weaker parts of the analysis that concerned different treatments for site specific groups of patients. Reviewer 1 also identified weaknesses in this part of the analysis and in the description of the method. We therefore respond first to reviewer 2 and then to reviewer 1.

We hope you find the paper improved and look forward to hearing from you.

Yours sincerely,

Sophia Wong, Medical Student
Reviewer 2

Major compulsory revisions

“I am not comfortable with figure 6 and 7 dealing with small groups of patients and historical data on treatment. The choice of treatment could easily be a consequence of site and stage and of not much interest for future discussions of optimal treatment.”

Response – Thank you. We have now decided to exclude figures 6 and 7 and not to include these analyses or draw attention to differences in survival by treatment that could simply be a consequence of disease site and stage.

Minor essential revisions

“The numbering of the figures is not consistent between text and the pages with the figures.”

Response – Thank you, we have now corrected the figure numbers.

Discretionary revisions

“I think that the strength of the findings are on the epidemiological part more than on the treatment aspects. Why do the incidence rates of EPSCC not change over time, any suggestions for the etiology etc. How many of the breast cancer tumors were discovered by the mammographic screening program, and was there any trend for breast cancer over the decades?”

Response – Thank you, we wondered whether the stable incidence was related to developmental factors uninfluenced by any environmental cause and we have now included this as a suggestion in the paper.

We only have data on screen-detected breast cancer for the period 1997 to 2006 so we cannot include information on screen-detected breast EPSCC for the entire study period 1970-2004. However, we do know that the incidence of breast cancer has increased in England during the study period, in part due to the screening programme. We have made brief mention of these points in the discussion.
Reviewer 1

General

1. There is no question, but the objectives are stated clearly at the end of the background.

Response – Thank you. We agree that we left our overall study question too implicit. It was to see if we could use the cancer registry dataset to obtain new information on this under-researched disease.

2. No data deposition is presented by this paper. The authors may wish to consider whether they should deposit a summary set of the data for record (they are public data, belonging to the UK NHS)

Response – Thank you. In the UK cancer registry data are held in publically funded data repositories and can easily be requested by interested parties. We have added this point to data section of the method.

Abstract

“Instead of ‘Further studies are needed to establish the most effective treatment for this disease at specific anatomical sites’, which is obvious, the conclusion could draw attention to the potential of prospective case-registers for uncommon diseases to collect data to guide therapeutic decisions.”

Response – Thank you, we now agree that this conclusion was obvious and we have included the new suggestion in both the conclusion and the abstract.

Background

1. “The authors use data from USA, while the paper is about a region in a European country. Could they provide data from the UK or Denmark, which have had complete cancer registration for many years?” (D)

Response – Thank you, we considered this but there are currently no available data or studies on EPSCC in Europe that we could quote. This was one factor that led us to consider starting this particular study and we have added this point to the introduction.

2. “Could the authors also indicate why using a register is an appropriate procedure, and indeed why/why not used before elsewhere?” (Min)

Response – Thank you. This is a very rare condition and the registry dataset is potentially an efficient initial way of using available information before undertaking a more extensive study. We can only speculate that so far there has been little funding available or clinical research interest in this disease area. We hoped that our work might stimulate more clinical work in other areas of Europe and we have added this point to the introduction.

Method
1. “Methods should reference the data collection organisation of the TCR, including the many aspects that provide caution in validity and reliability of cancer registry statistics. NB The TCR, where the authors work, was established in the mid 1980s, not the 1960s, although it holds data from three parent regional registers going back to the 1960. There are important issues in interpreting cancer registry data, and the authors should discuss them at the outset.” (Maj)

Response – Thank you. We have now included an additional description of the TCR history, its method of data collection, published work by Pollock and Vickers exploring data quality, the implications of high DCO rates and the much lower DCO rates recently published by the Registry.

2. “The very low level of DCO in Table 2 is quite unlike TCR in general over this period, indicating that this diagnosis is almost only made pre-mortem.”

Response – Thank you. We agree that the diagnosis of EPSCC is likely to be made by pathological analysis and therefore to be found written in the medical records of patients. This would indeed lead to a very low DCO rate and we have added this point to the results.

3. “Some clinicians would say that, for rare conditions, local case series may be more accurate (eg more complete initial data).” (D)

Response – We agree that local case series may be more accurate and include more complete initial data, but we are not aware of any such register in the UK. Such a database would need to be regional covering a large population to capture sufficient information on such a rare disease.

4. “The sentence ‘Data on clinical performance status is not routinely recorded in the UK either in clinical practice or by the Registry’ should consider the established prospective treatment case-registers (eg for bowel cancer), even if not for rarer tumours.” (Min)

Response – Thank you. We have added the point about prospective treatment registers recording this variable to the method.

5. “How certain are the authors of false positive and false negatives by the reporting pathologists when diagnosis is difficult since it ‘presents with a mixed morphology of small cell carcinoma and various other epithelial cell types’? (Min) or their recording across different ICD and the various Registers’ diagnosis lists?”

Response – Without histological review we have no way of assigning certainty to the diagnostic process undertaken by pathologists. All cancer registration processes have to rely on the pathological diagnoses that are provided. TCR quality assurance processes take care not to reinterpret what pathologists may have meant. We have now made this clear.

6. “The methods of collection (e.g. card v electronic, active versus passive follow-up, use of hospital-based or registry-based clerks) all varied during this 35-year period, affecting accuracy of data and ability to follow-up and level of DCOs, and between hospitals to unknown degree – this has been well documented by others and should be referenced.” (Maj)

Response – Thank you for pointing this out. We hope we have dealt with this issue in point 1 above.
Results

1. “Why were incidence rates calculated using the European standard population since period-adjusted population data for south-east England are readily available and more accurate.” (Min)

Response – Thank you. We used the European standard population so as to produce figures that would be comparable with future studies from other European countries. If we used local population data for England, the incidence figures could only be compared to future studies in the same area.

2. “Why does Figure 1 start at 1970? (ASR is not defined).” (Min)

Response – Thank you. We decided to start the study at 1970 because of concerns that the data may be unreliable for this rare disease before this point. We have made this point in the method and we have also defined ASR (Age-standardised incidence rate) in the figure 1

3. CIs for incidence please. (Min)

Response – It is not conventional to record confidence intervals for incidence rates, particularly when reporting trends over time.

4. “Presumably the changing sex-ratio for SCLC incidence is due to the falling smoking in males.” (Min)

Response – Thank you for pointing this out. We agree with your reasoning and have added this point to the discussion.

5. “Explain why authors include SCLC when the paper focus is on EPSCC.” (Min)

Response – Thank you for pointing out that the point of comparing data on SCLC in not clear. We initially included some data on SCLC because it is generally seen as a
related but more common disease. It also serves as example of a disease where more studies have concentrated.

6. “How many SCLC were there after the authors 'exclude secondaries and Merkel cell carcinomas'?” (Min)

Response – Thank you. We can make clear that all the SCLC (N=27510) were small cell carcinomas of the lung.

7. “We are told 'The median age at diagnosis for patients with EPSCC was 70 years (range, 0-85 years), but no comparative data for SCLC incidence is given." (Min)

Response – Thank you. We have now included the median age for SCLC too, 65 years (range 20-85) in the text.

8. “Why no five-year cohort analyses?” (Min)

Response – Thank you. We have concentrated on three-year survival because the prognosis is generally poor and a significant number of patients do not reach five years. The three-year survival analyses therefore seemed more informative.

Discussion

1. “One of the largest studies' needs appropriate references here.” (Min)

Response – Thank you. We have now referenced the largest study by Haider et al.

2. “While the incidence of EPSCC remained steady from 1970, the sex-difference, lacking CIs, quoted here did not (Fig 1). (Min) How are the (more than two-fold) differences in survival between authors’ results and reference six to be explained? Methodologies? Difference diagnosis levels? (Were incidence rates similar in the two studies, etc).”(Maj)

Response – Thank you. We note that the sex difference did not remain steady. However, the small numbers involved would tend to make us cautious about taking too great a note of this. The numbers involved in SCLC incidence are much larger and we have added the point about the change in the sex ratio here.

We note the difference in survival between the two studies. The study by Haider is much smaller (101 cases) and reports median survival only for EPSCC so it is not possible to directly compare the two studies. The study by Haider also does produce incidence rates for EPSCC.

3. “In TCR data, breast survival stands out alone from other diagnoses (not as implied in the final paragraphs, as top of a range).” (Min)

Response – Thank you. We agree that the breast survival does stand out alone from the other diagnoses and we have included this observation in the paper.

4. “The other sites were pretty similar survival. Discuss importance of different presentation, and possible overlap with other breast cancer pathologies?” (Min)

Response – Thank you. This is a limitation of our study.
5. “We were not able to review the pathology of each case included in 35 years of the study' is misleading. It should be changed to any of the cases, so the extent of misclassification is quite unknown (but the point on stable incidence is correct).” (Maj)

Response – Thank you. We have changed the sentence about the pathology review to make it clear that the extent of misclassification is quite unknown.

6. “In the discussion of treatment, page 15, it would be welcome for the authors to come out and say that no curative treatment appears to be better than any other - this could be an important finding from the study. Indeed ‘any surgery’ may be just the natural history (ie diagnosis).” (Maj)

Response – Thank you for pointing this out. Following the comments of reviewer 2 we have decided that we should not present these data.

7. “The case for ‘international trials’ using chemotherapy is not made, since given no evidence from these data of their superior benefit.” (Maj)

Response – Thank you. We now agree that this case is not made and that this sentence should be excluded.

8. “On the other hand, the authors should explore why breast EPSCCs had twice the likelihood of hormone therapy (Table 2), with its worse survival, yet breast survival was up to three times better than the rest (Fig 2). (Maj) This is quite anomalous. Are there could grounds here for recommending NEVER to give hormone therapy (primum non nocere). (Maj) But sadly, again, confidence intervals (or even numbers) are missing on this survival analysis; and we don’t know what ‘hormone’ therapy means (oopherectomy at one period, tamoxifen in another).” (Min)

Response – Thank you. We agree that there are no definite grounds for whether to give hormone therapy or not. As already noted we now realize that it is better that we do not present treatment data that could be confounded by stage of disease and where treatment itself may have changed with time. However, we hope that further studies, including those from other registries using more recent data, could answer this question.

9. “The statement in the Conclusion ‘As a treatment strategy for EPSCCC, combined treatment seemed most promising’ is not upheld by these data, and reflects wishful thinking rather than critical science. It would be unfortunate if it were quoted by others.” (Maj)

Response – Thank you. We now agree that this was rather wishful thinking and we have removed the sentence from the discussion.

10. “Finally, the authors say that SCLC is increasing in survival ‘in recent years’, quoting good sources. Yet, while this paper’s introductory objectives were to compare the incidence and survival of EPSCC and SCLC: TCR survival trend data could have been provided for SCLC, but are not. It is less pleasing to report others’ findings.” (Min)

Response – Thank you for pointing out this inconsistency. We have now removed the references to SCLC as we agree that it does not make sense to report this. Our aim was to compare the survival during this period and not trends in survival between
the two diseases.