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

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This paper is interestingly lead-authored by a medical student. Good work has been done in choosing a focus and drawing together the data set. However, while the general approach is a good scientific standard, there is incomplete description of the limitations of the registry, some inconsistencies in analysis and some clinical proposals that are not tenable.

1. Is the question posed by the authors well defined?
There is no question, but the objectives are stated clearly at the end of the Background.

2. Are the methods appropriate and well described?
The methods are appropriate but further description is required (see below)

3. Are the data sound?
There are some issues over data (see below)

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
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)

5. Are the discussion and conclusions well balanced and adequately supported by the data?
Advice on discussion and conclusions given below: some conclusions are not warranted by the facts presented.

6. Are limitations of the work clearly stated?
The limitations of the register should be stated at an earlier stage. Confidence intervals should be provided, and comparisons of the reliability of the data in different time periods

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
The authors do not provide enough references to descriptive studies of the validity and reliability of the register. The (limited) clinical field is referenced.

8. Do the title and abstract accurately convey what has been found?
The abstract objectives and results/discussion should state all forms of treatment analysed and discuss worse prognosis after ‘hormone therapy’.
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.

9. Is the writing acceptable?
It is well written in style.

The Abstract is generally clear, but should be adjusted as indicated above. (Min)

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

The 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. (Maj) 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 1960s... There are important issues in interpreting cancer registry data, and the authors should discuss them at the outset. (Maj) (NB – 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.)

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

The methods of collection (eg 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) The authors should state the years that were included for the ‘selection of patients’ (on p6), and the exclusion criteria at this stage (marginal, missing data). (Min) Difficulties/lack of treatment data,
common for TCR, should also be noted at this point (the proportion found, of 20% for EPSCC, is in line with other pathologies). (Min)

Results Why were incidence rates calculated using the European standard population? (Min) since period-adjusted population data for south-east England are readily available and more accurate. Why does Figure 1 start at 1970? (ASR is not defined). (Min) CIs for incidence please. (Min) Presumably the changing sex-ratio for SCLC incidence is due to the falling smoking in males (Min), but explain why authors include SCLC when the paper focus is on EPSCC. (Min) How many SCLC were there after the authors 'exclude secondaries and Merkel cell carcinomas'? (Min) 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) Why no five-year cohort analyses? (Min)

Discussion ‘one of the largest studies’ needs appropriate references here. (Min) 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)

In TCR data, breast survival stands out alone from other diagnoses (not as implied in the final paragraphs, as top of a range). (Min) The other sites were pretty similar survival. Discuss importance of different presentation, and possible overlap with other breast cancer pathologies? (Min)

‘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)

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

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)

The statement in the Conclusion ‘As a treatment strategy for EPSCC, 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)

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).

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