Author's response to reviews

Title: Disease-specific survival for limited-stage small-cell lung cancer affected by statistical method of assessment

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Author's response to reviews: see over
Responses to Reviewer 1.’s Requested 2nd Revisions:

General: A well-deserved acknowledgement has been added.

“The authors are grateful for the reviewers’ time and comments, which improved the exposition of this work.”

Major Compulsory Revisions:

1. The authors failed to respond to my query concerning the existence of a cure-rate component in the log-normal regression model (or “log-normal survival analysis” as the authors call it). If it is not contained in it, some justification of its absence would be desirable given its presence in the Boag model for the overall survival curve. – In addition, the estimation principle and method used in fitting the log-normal models is not yet specified in the “Statistical Analyses” section. Mentioning only the Excel programme or the BMDP procedure is not a sufficient documentation. These details are obviously not needed for the much better known proportional hazards (PH or “Cox model”), although mentioning the PHREG procedure of SAS would not take too much space.

⇒ The following was added as first paragraph on page 7 in response to the reviewer’s query concerning existence of a cure-rate component in the log-normal regression model.

“Log-normal survival analyses, like Cox regressions, utilize both censored and uncensored data, with estimates of survival at any point in time being with the survivor function. The proportion cured may be estimated, without a specific parameter, by the value of the survivor function at a time when few (or no) events are expected.”

There is also a sentence added in the Discussion, page 13, last sentence of second paragraph.

“The estimate of proportion cured, at a time when few or no events are expected, is derived directly with the survivor function for the Cox and log-normal survival analysis models.”
The program details are now expanded. For clarity, the test criteria, and description of process included in the last version have been moved to this same area on pages 8, 9.

“Boag log-normal analysis was performed with an Excel programme [5], a computerization of Boag's original spreadsheet, with some macros that improve efficiency of the iterative maximization; it is available from Dr P. Tai on request.

All other analyses were performed with SAS Version 8.2/9.1.3 (survival function estimates and confidence limits utilized separately the SAS procedures LIFETEST for Kaplan-Meier, PHREG for the Cox model and LIFEREG for the log-normal model; a plot was exported from SAS as a graphic file in .cgm format, which was incorporated into a Word file), and the Dynamic 7.0 version of the Biomedical Data Package [12, same as BMDP-XP: program 2L was used for Cox and for log-normal step-wise forward multivariate regressions, with the addition of another factor if there was a significant likelihood ratio test statistic \( p \leq 0.05 \) for a \( X^2_{(1)} \) test), and reported here if factors \( p \leq 0.10 \) in both Cox and log-normal survival analyses; Cox-Snell residual checks were used to assess the final models for both Cox and log-normal survival analyses, and standardized residual checks, for the log-normal model; plots of cumulative hazard graphically assessed the assumption of proportional hazards for the Cox model; and program 3D was used for Q-Q plot to check assumption of log-normality for time of SCLC deaths, an assumption employed for both Boag cure rate model and log-normal survival analysis.

When the same factors were indicated as significantly affecting DSS with both the Cox and log-normal models, categorizations of these factors were used to specify sets of
clinical characteristics of interest, for quantitation of DSS by the two model-types. DSS was determined quantitatively at 1-, 3-, and 5- years, and graphically demonstrated with survivor plots across the entire time period.”

2. Figure 1 is now more informative of the differences in the fitted survival curves between the POH and the log-normal model. However, it occurred to me not until now, that a simple graphical goodness-of-fit comparison of the fitted models could be executed by plotting in the same picture the simple Kaplan-Meier curves describing the observed survival proportions in the four clinical groups. It would be very interesting to see, whether the fitted log-normal curves would be closer to the KM curves than the fitted PH curves.

➔ This is an excellent idea, which we attempted to pursue. The four factors identified by multivariate analyses with both the Cox and log-normal survival analysis were subgrouped, and unfortunately, Kaplan-Meier analysis indicated the premise (page 7, first paragraph of Statistical Methods) that the sample size is too small for this fine subdivision. We added the following statement to the end of the Results section to forthrightly cover the situation.

“These subgroup effects for the four factors indicated by multivariate analyses, with both Cox and log-normal survival analyses, could not be considered here in a Kaplan-Meier framework. The subgroups contained a total of 8 patients and 4 events.”

and augmented page 13 of the Discussion to make the text

“The assessments in this cohort for both the Boag and Kaplan-Meier were limited to those with the full patient group due to the size of the SCLC patient cohort which precluded subgrouping with the four factors indicated by multivariate analyses, while more extensive modelling was possible for specific patient characteristics with both Cox and log-normal survival analysis….”
The limitation of subgrouping for the Kaplan-Meier method was a problem for the comparisons of Chapman, et al [8] too, that precluded the comparison that the reviewer requested. It is an interesting idea for future consideration.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct):

1. Abstract: The P-values associated with the selection of the prognostic factors are not adding any useful information and could be removed.

   ➔ The P-values have been removed.

2. Table 1: Some entries are clearly misprinted, e.g. numbers of patients in total and by sex.

   ➔ Thank you so much for pointing out this computer loss from a previous version of the manuscript. The Table has been corrected.

3. Tables 2: The table caption is incomplete. I would write. “Estimated disease-specific survival probabilities (in per cent, with 95% confidence intervals, CI) at 1, 3, and 5 years by different methods” After this the repeated percent symbols ‘%’ from the body of the table can be removed as unnecessary junk.

   ➔ The suggested caption has been used, and the %s removed.

4. Table 3: See the previous item.

   ➔ The same actions have been taken for Table 3.

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Responses to Reviewer 2.’s Requested 2nd Revisions:

General: A well-deserved acknowledgement has been added.

“The authors are grateful for the reviewers’ time and comments, which improved the exposition of this work.”

Major Compulsory Revisions:
None
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct):

Table 3. Add the number of patients in each group.

The four factors identified in multivariate analyses and the survival estimates for each group are based on the data and model values obtained for the 243 patients, rather than subgroups that would be used in say Kaplan-Meier estimation. We added the following statement to the end of the Results section to forthrightly cover the situation.

“These subgroup effects for the four factors indicated by multivariate analyses, with both Cox and log-normal survival analyses, could not be considered here in a Kaplan-Meier framework. The subgroups contained a total of 8 patients and 4 events.”

and augmented page 13 of the Discussion to make the text

“The assessments in this cohort for both the Boag and Kaplan-Meier were limited to those with the full patient group due to the size of the SCLC patient cohort which precluded subgrouping with the four factors indicated by multivariate analyses, while more extensive modelling was possible for specific patient characteristics with both Cox and log-normal survival analysis….”

Discretionary Revisions (which the author can choose to ignore)

Response to comment 1.
As the same patients were used and the Kaplan-Meier analysis is also presented in the present paper, I suggest that the sentences about validation are deleted.

This deletion was made.

Response to comment 9 (and minor comment 2).
My comment about the lack of information on important predictors was based on the text on page 8 (2nd para) where it is written that “due to incomplete data…we were unable to examine…type of chemotherapy, use of radiotherapy…TNM stage…” If the information is in fact available, could these factors not be considered at least in univariate analyses?”

This section needed clarification, and has been replaced on page 8 by the following:
“Best medical practice in Saskatchewan, under the Canadian National Health system was employed throughout accrual of the patient cohort. In clinical practice, the administration of more aggressive therapy to higher risk patients may mask therapeutic benefit. Changing chemotherapy and radiotherapy management schema and the small size of this cohort precluded investigations by current practice categorizations: type of chemotherapy (platinum vs. non-platinum), use of radiotherapy, radiotherapy dose/schedule, lactic dehydrogenase (LDH) or other lab results. Incomplete or no surgical resection in 230 (94%) of the 244 patients prevented the assignment of TNM stage. We did not systematically collect smoking history nor clinical history about prior malignancies or other co-morbid diseases in the database. However, the extensive clinical follow-up for this cohort was useful for the investigation’s focus on survival analyses.”

In a previous publication [5], univariate analysis had been done: In this series, the absence of mediastinal lymphadenopathy, complete or partial surgical resection, and higher chest radiotherapy dose were found to be favorable prognostic factors in the univariate analysis ($p<0.05$). The absence of mediastinal lymphadenopathy and a greater chest radiotherapy dose were significant in the multivariate analysis ($p<0.05$).

Response to comment 11.
In the reference cited, Chapman et al found that in breast cancer the proportional hazards assumptions of the Cox model did not hold. Here, there is no such issue. Perhaps the fact that although both models seem adequate the estimated survival curves appear to differ to a substantial extent (nicely illustrated in Figure 1), could be further emphasized in the text. Given also that when considered overall, the confidence intervals for the 3-year estimates do not overlap.

→ Page 13 has been augmented as requested:
“DSS at 3 years was 38% with log-normal survival analysis, 10-12% higher than with other methods. Multivariate 95% confidence limits for log-normal survival analysis did not overlap with those obtained for any of the other methods. In the breast cancer setting, Royston [4] also observed large differences in prognosis by model-type, that it differed by up to a year depending on whether a Cox or log-normal model was used, and Chapman, et al [8] found up to 8% absolute difference by model-type.”