Author’s response to reviews

**Title:** Healthcare Costs in Patients with Metastatic Lung Cancer Receiving Chemotherapy

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**Version:** 3  **Date:** 12 October 2011

**Author’s response to reviews:** see over
RESPONSES TO REVIEWERS’ COMMENTS:

Healthcare Costs in Patients with Metastatic Lung Cancer Receiving Chemotherapy
(Manuscript: 1741745789517124)

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EDITOR
Comment: Can the authors provide more detail on how the presented cost estimates could be used as part of an economic evaluation, i.e. provide some specific examples.

Response: We agree that specific examples highlighting the potential uses of study findings in model-based economic evaluations would be helpful, and we have expanded the Introduction (page 1) as follows:

“Because the benefits of chemotherapy for metastatic lung cancer -- in terms of both extensions in life expectancy and enhanced quality of life -- are typically limited, the cost of such treatment (as well as associated follow-on care) is an especially important consideration in an era of increased emphasis on achieving an acceptable balance between the costs and benefits of medical interventions [6]. While a few retrospective longitudinal studies [7-11] have estimated the cost of metastatic lung cancer in the US, these studies employed varied designs and methods (i.e., in terms of patient populations, disease definitions, and measure of healthcare costs), did not track lifetime healthcare resource use and costs, or did not analyze cost components by setting or by type of service. Up-to-date data on resource use and costs among patients with metastatic lung cancer -- overall and by constituent component -- thus may help inform current decision-making about the optimal allocation of healthcare resources.

Contemporary data on resource use and costs in this patient population also may help inform cost-effectiveness evaluations of new strategies for the prevention, screening, and treatment of early stage and metastatic lung cancer; such information increasingly plays a role in regulatory and reimbursement decision making [6]. Evaluations of early stage interventions, for example, typically consider the economic consequences of disease progression (i.e., treatment failure), which may be characterized using data on levels of resource
use and costs among patients with metastatic lung cancer. We therefore used a large US private health insurance claims database to estimate cumulative healthcare resource utilization and costs through end of life in patients receiving chemotherapy for metastatic lung cancer.”

REFEREE #1 -- Klazien Matter-Walstra

Comment: All comments have been answered satisfactorily and changes included in the paper.

Response: None required.

Level of Interest: An article of importance in its field
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

REFEREE #2 -- Janneke Grutters

General Comment: The authors have solved most issues, and thereby improved the paper. The selected sample and its generalisability remains an important issue though, that cannot be solved. I think the authors could be more clear on this limitation and its potential consequences.

Response: We agree that this limitation is important and deserves additional attention, and we have revised and repositioned the relevant text in the Discussion (page 8) accordingly, as follows:

“Caution should be exercised in generalizing from the results of our study to other patient populations and settings. First, our study employed data from a large US private health insurance database comprising information from employer-sponsored health insurance plans on resource utilization and costs of active employees, early retirees, and their dependents along with Medicare-eligible retirees with employer-sponsored supplemental Medicare coverage. Because such persons may differ systematically from other patients with metastatic lung cancer (e.g., the elderly with traditional Medicare fee-for-service coverage, and the uninsured, who are not represented in our database)—in terms of health status and/or levels of resource utilization and costs—findings of similar analyses may differ in other patient populations. Second, our study used a novel algorithm for patient selection, the accuracy of which is unknown. Cooper and colleagues reported that the sensitivity and positive predictive value of using ICD-9-CM diagnosis codes with healthcare claims to identify patients with distant metastatic lung cancer was 58.3% and 88.2%, respectively, based on an analysis of Medicare claims data and information from the Surveillance, Epidemiology and End Results (SEER) program [14]. We note, however, that while Cooper and colleagues required only one Medicare claim with an ICD-9-CM
code for diagnosis of secondary malignant neoplasm (i.e., metastatic disease), we required two such claims to increase the specificity of our case-ascertainment methods. We also note that the size and composition of the study population was largely robust when employing alternative sample-selection criteria (e.g., excluding all patients with evidence of multiple primary tumors, irrespective of their relationship with the site of metastasis [3% of study population]), and when considering other evidence for lung cancer (e.g., chemotherapy regimen) among patients with multiple documented primary tumor types. However, because the study algorithms have not been formally validated, their accuracy (and by implication, any resultant bias) is unknown. Finally, because we focused attention on the subgroup of patients with metastatic lung cancer who received chemotherapy, the results of our study may not be generalizable to all patients with metastatic lung cancer, including those who did not receive chemotherapy.”

Comment #1 (minor): I am still a bit confused about the patients who are alive. There are so many of them that I do think this underestimates the total costs. I would appreciate it if the authors could elaborate on the bias that this may have caused.

Response: We respectfully disagree that bias may be introduced simply because a relatively large number of patients were censored in the analyses (i.e., because they were alive at the end of the follow-up period). Bias would be introduced—in this example—if and only if costs differ for censored and uncensored patients. Of course, such a difference in costs might bias results in important respects only if a relatively large number of patients are censored. A simple example may help.

Assume that a study population includes 400 subjects, 200 with one-year of follow-up (beginning January 1, 2006) and 200 with two-years of follow-up (beginning January 1, 2005); and that during the first-year of follow-up, each subject had observed healthcare costs of $5, and among those who had a second year of follow-up, observed costs were $10:

| Subjects 1-100 | $5 |
| Subjects 101-200 | $5 |
| Subjects 201-300 | $5 | $10 |
| Subjects 301-400 | $5 | $10 |

01/05 12/05 01/06 12/06
Start of Database End of Database

-3-
For our analyses, such data were arrayed relative to the first day of follow-up for each subject, as follows:

<table>
<thead>
<tr>
<th>Subjects 1-100</th>
<th>$5</th>
<th>$10/$20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects 101-200</td>
<td>$5</td>
<td>$10/$20</td>
</tr>
<tr>
<td>Subjects 201-300</td>
<td>$5</td>
<td>$10</td>
</tr>
<tr>
<td>Subjects 301-400</td>
<td>$5</td>
<td>$10</td>
</tr>
</tbody>
</table>

Mean Cost (based on observed data)

<table>
<thead>
<tr>
<th>Index Date (ie, Day 1 of Follow-Up)</th>
<th>Months Since Index Date (ie, Day 730 of Follow-up)</th>
<th>Mean Cost</th>
<th>Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Cost (based on observed cost and unobserved cost = $10, if the latter was observable)</td>
<td></td>
<td></td>
<td>$15</td>
</tr>
<tr>
<td>Mean Cost (based on observed cost and unobserved cost = $20, if the latter was observable)</td>
<td></td>
<td></td>
<td>$20</td>
</tr>
</tbody>
</table>

Thus, in the first year of follow-up, during which all subjects contributed data, mean cost would be $5. In the second year, during which only two subjects contributed data (because the other two were censored at the end of the first year), mean cost would be $10 (and thus total cost would be $15). Now, if the two subjects who were censored were actually observed during the second year of follow-up and their costs were similar to those of subjects who were observed and thus included in analyses, results of analyses based on observed data would not be biased. If, however, their costs were higher (e.g., $20), observed costs would be biased (i.e., not reflective of cost in the full population).

Thus, a necessary condition for bias is that there must exist systematic differences in costs between persons who are observed versus censored (i.e., censoring must be “informative”). (Note, however, that if only 1 subject [of the 400 subjects] has higher “unobserved” costs in year 2, then any resultant bias would be small and analytically ignorable because the vast majority of patients have similar cost profiles.) Because results of analyses focusing on patients who were not censored (n=776) were comparable to primary analyses using all available data ($131,344 vs $125,849, as noted on page 6), we believe the impact of informative censoring, if any, was negligible.

Comment #2 (minor): I appreciate the fact that it is not straightforward to compare the results with those of previous studies. The authors nicely explain this in the discussion section. Still, I would like to see them mention their own results in this section, to make it clear to the reader how different the figures are.
Response: We agree, and now state our results in this section, as follows:

“The majority of these studies did not track the full complement of lifetime costs among patients with metastatic lung cancer. We believe this is the primary reason why our estimate of mean healthcare costs ($125,849) is substantially higher than those previously published. Prior studies also did not report on the individual components of healthcare utilization and costs, which was an important objective of our study.”

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