Author's response to reviews

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

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RESPONSES TO REVIEWERS’ COMMENTS:

Healthcare Costs in Patients with Metastatic Lung Cancer Receiving Chemotherapy

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EDITOR

Comment #1: The main issue to address is to provide the rationale for the study, e.g. how will/could the results be useful in informing medical resource allocation in this patient population? Could the data be formatted to inform economic models, e.g. annual costs following alternative events? (e.g. see Karnon et al, British Journal of Cancer (2007) 97, 479 - 485).

Response: We agree that the rationale for the study could be strengthened -- as in the study on treatment costs for breast cancer recurrent events by Karnon and colleagues -- and we therefore added text in 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 (Karnon 2007). A few retrospective longitudinal studies [6-10] have estimated the cost of metastatic lung cancer in the US, but differences in patient populations, disease definitions, and methodologies preclude comparisons across studies. Moreover, the majority of studies did not analyze the 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 decision making about the optimal allocation of healthcare resources. 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.”

Comment #2: The authors should also address the concerns raised around the selection of the patient population, maybe doing some additional sensitivity analyses.

Response: Although a comprehensive assessment of the sensitivity and specificity of the case-finding method that we used to select study subjects is beyond the scope of this study, we did
assess the robustness of the study population to alternative sample-selection criteria and we have added text to the Discussion (page 8), as follows:

“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. While using only a single diagnosis code to identify lung cancer and metastatic disease, respectively, resulted in a significantly larger study population, we believe that a significant proportion of such patients did not have metastatic lung cancer and that their inclusion in the study population would substantially reduce the accuracy of study results. The extent of this phenomenon is unknown, and evaluating it is beyond the scope of this study.”

REVIEWER #1 -- JANNEKE GRUTTERS

General Comment: This is a well written, well executed and interesting study estimating lifetime healthcare resource utilization and costs and its components by setting and by type of service in patients with advanced lung cancer receiving chemotherapy. I have some comments that may help to further improve the paper.

Response: None required.

Comment #1 (major): The selection of patients on page 3 is probably a bit technical for the readership of BMC Health Services Research. I would prefer more explanation, as this is very important in order to understand the validity of the study.

Response: We agree, and we have reworded the section “Study Subjects”, as follows:

“Study Subjects. The study population consisted of all patients aged ≥18 years who initiated chemotherapy for metastatic lung cancer between January 1, 2000 and December 31, 2006, and who met all other inclusion criteria. Subjects were selected for inclusion in the study population as follows.

First, we identified all patients who had two or more healthcare encounters -- on different days -- with a diagnosis of lung cancer (ICD-9-CM 162.x, V10.1x) during the period of interest; all such patients were designated as having “lung cancer”. Second, from among these patients, we identified all those who also had two or more encounters with a diagnosis of distant secondary malignant neoplasm (ICD-9-CM 196.2, 196.5, 196.8, 197.1-199.0) during this period; this subgroup of patients was designated as having “metastatic lung cancer”. (We required two or more encounters for both lung cancer and metastatic disease to increase the specificity of our algorithm [i.e., reduce the number of false-positives].) Third, from among the subgroup of patients with metastatic lung cancer, we identified all those with any evidence of receipt of chemotherapy based on a procedure code for chemotherapy administration or receipt of a chemotherapy agent
(codes available upon request), beginning 45 days prior to the date of the earliest encounter with a diagnosis of secondary malignant neoplasm. (A 45-day window was employed to capture instances where chemotherapy might have been initiated prior to the first notation of metastatic disease on a health insurance claim.) The date of initial receipt of chemotherapy was designated the “index date”.

To minimize the possibility of including patients who may have received chemotherapy for primary tumors other than lung cancer, we excluded all patients with two or more encounters with a diagnosis of a primary malignant neoplasm other than lung cancer (ICD-9-CM 140-161, 163-172, 174-195, 200-208) 61 or more days prior to their first evidence of metastatic disease, unless the site of the other primary neoplasm and the site of metastases were the same (e.g., malignant neoplasm of bone [170.0] and metastasis to bone [198.5]). (The last exclusion was used to account for instances where a site of metastatic involvement might have been miscoded as a primary tumor.) The only exception was patients with malignant neoplasm of the skin, whom we retained in the sample because the skin is not a site of metastatic involvement in lung cancer. To ensure completeness in case ascertainment, we also excluded patients if they were not continuously eligible for comprehensive health benefits during the 12-month period preceding their index date.”

Comment #2 (major): I am not sure whether it is a good idea to include patients who were still alive, and thus making costs, at the end of the study. I guess this should underestimate the total average healthcare costs. How many of these patients are included? Approximately 3300 (4068-776?)? What are the mean cumulative healthcare costs if they are excluded?

Response: We agree that the inclusion of patients who were still alive at the end of the study period could -- without adjustment -- downwardly bias our estimates of lifetime costs. We therefore used the Kaplan-Meier Sample Average (KMSA) method and censored patients who were observed through the end of the study period (pages 4-5). By using this method, patients with incomplete follow-up contributed data to analyses through their last date of observation (i.e., the end of the study period), after which healthcare costs were estimated using data from patients remaining (i.e., still observed) in the study population. This form of censoring is widely used in retrospective and prospective studies (including randomized controlled trials) involving incomplete follow-up data.

We also undertook analyses focusing on patients who were not censored (i.e., they were observed through date of death). As noted (page 6), results for this group (n=776) and the full sample were comparable ($131,344 vs $125,849).

Comment #3 (major): I am not from the US, and our standard costs differ from those in the US. For me, and in general to make the paper more interesting for readers outside the US, it would therefore be helpful to provide more information on resource use. For example, for
Table II provide not only costs, but also the corresponding N. How many patients went to the hospital, how many had radiology diagnostic, etc?

**Response:** We agree, and have added a table (Table II) describing the use of healthcare resources by component of care.

**Comment #4 (major):** The authors spend a page (7) on other studies, but do not compare their results with results from these studies. Although I understand the differences, I would think some comparison could be made for part of the results?

**Response:** We agree with the reviewer that direct comparisons may not be meaningful given differences in study designs, data sources, study populations, and study measures, since any discrepancies in findings may be attributable to a multitude of factors. We did describe (Discussion, page 7) the reasons why comparisons among studies are not straightforward, and the exogenous factors that may explain any differences, including increases (over time) in spending for advanced lung cancer due to changes in detection and staging techniques as well as disease management, and increased use of chemotherapy and targeted therapies. We also note key differences between individual studies that might explain discrepancies in findings.

**Comment #5 (major):** The limitations section could be better structured. Numbering the limitations (first, second,..) could for example help to read this section.

**Response:** Revision implemented (i.e., limitations are now numbered), as suggested.

**Comment #6 (minor):** I would like to know whether the population (plan members) is generalisable to the general population. 10% are aged 65 or older: is this normal in the US? If not, how could this have impacted the results?

**Response:** Unlike most European countries, the US has a multi-payer health insurance system comprising private insurers (covering mostly employed persons aged <65 years and their dependents) and public insurers—notably, Medicare (covering mostly persons aged ≥65 years). While we believe that our study sample is representative of the population of privately employed persons with metastatic lung cancer, it may not be representative of the total US population of persons with this disease. We have added text to the Discussion (page 8) addressing the issue of generalizability of our findings to other populations, as follows:

"Third, caution should be exercised in generalizing from our results to the entire US population of patients with metastatic lung cancer (or other subpopulations of patients), since our study employed data from employer-sponsored health-insurance plans. Persons with such insurance 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 healthcare utilization and costs."

**Comment #7 (minor):** Lifetime healthcare resource utilization should also include diagnostics, and perhaps treatment before receiving chemotherapy. It was not completely clear to me whether these costs that occurred before chemotherapy were indeed included.
Response: Because the objective of our study was to characterize healthcare costs of patients receiving chemotherapy (i.e., from initiation of chemotherapy through end of life), and not to characterize the costs of metastatic lung cancer per se, costs incurred prior to initiation of chemotherapy (e.g., diagnostic work-up) were considered a “baseline” characteristic. We do, however, separately report healthcare costs in the 365 days prior to the index date in Table 1.

Comment #8 (minor): I very much like Figure 1. It is however a bit difficult to read the values from the Figure. I would therefore be interested to see actual values provided below Figure 1. It is then easier to see how much costs increase over the months.

Response: Revision implemented, as suggested.

Comment #9 (minor): The authors mention that they analyse characteristics of study subjects, but why were they not related to costs? As far as I am concerned it would be interesting to know how much age or presence of comorbidities impacts the total costs.

Response: While the suggested analysis is of interest, a thorough investigation of the relationship between patient characteristics and healthcare costs is beyond the scope of this study. We are, however, planning to undertake such an analysis as follow-up to the present study.

Comment #10 (minor): The authors mention that they did not adjust for inflation, I do not understand why they didn't?

Response: There is no consensus as to whether price inflators/deflators should be used in analyses of healthcare claims data such as ours. The only option would be to use a general price index, such as the Consumer Price Index (CPI), which may yield spurious findings when applied to specific patients in specific health plans who consumed specific healthcare services (i.e., and not the market basket of general goods and services that was used to construct the index). In these circumstances, however, presentation of findings in nominal (i.e., unadjusted) terms is often preferable to adjustment based on an index that may not be applicable. We also believe that the approach that we employed is acceptable when the period of observation spans only a few years. We now further address this issue in the Discussion (page 9).

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

REVIEWER #2 -- KLAZIEN MATTER-WALSTRA

Comment #1 (major): This paper does not really pose a question, rather a statement of what will be done, without acknowledging why this is necessary.

Response: While this study does not involve a specific hypothesis, it does address the question of what is the current economic burden of a subset of lung cancer patients with particularly high unmet need (i.e., those receiving chemotherapy for metastatic disease). We have added text to
the Introduction (page 1) describing the importance of producing information on the economic burden of metastatic lung cancer:

“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 (Karnon 2007). A few retrospective longitudinal studies [6-10] have estimated the cost of metastatic lung cancer in the US, but differences in patient populations, disease definitions, and methodologies preclude comparisons across studies. Moreover, the majority of studies did not analyze the 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 decision making about the optimal allocation of healthcare resources. 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.”

Comment #2 (major): There is some problem with the method. The identification of patients to be included in the study is by means of indicators also used for the analysis. As the authors state in the discussion, "this means that some patient may not be found in the database" because for example they have no chemotherapy. Would it not have been better to identify the patients by an independent source such as a cancer registry? To identify and analyze patients using the same variable bears a great risk of bias.

Response: We do not believe that our sample selection method would result in biased findings. Our objective was to estimate economic costs among the subgroup of patients with metastatic lung cancer who were receiving chemotherapy, and not to assess costs among all patients with metastatic lung cancer whether or not they received chemotherapeutic agents. Chemotherapy therefore was a selection criterion, and initiation of chemotherapy constituted the beginning of follow-up. Our approach is consistent with many of the studies noted in the Discussion (page 7), as well as burden of illness studies in other disease areas.

Comment #3 (major): As the authors state the results may not be generalizable the results of the study are difficult to put into context with other studies and only add up to the already existing other studies which "preclude comparison" (page 1).

Response: Unlike most European countries, the US has a multi-payer health insurance system comprising private insurers (covering mostly employed persons aged <65 years and their dependents) and public insurers—notably, Medicare (covering mostly persons aged ≥65 years). While we believe that our study sample is representative of the population of privately employed persons with metastatic lung cancer, it may not be representative of the total US population of
persons with this disease. We have added text to the Discussion (page 8) addressing the issue of generalizability of our findings to other populations, as follows:

“Third, caution should be exercised in generalizing from our results to the entire US population of patients with metastatic lung cancer (or other subpopulations of patients), since our study employed data from employer-sponsored health-insurance plans. Persons with such insurance 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 healthcare utilization and costs.”

Comment #4 (major): Conclusion: It is unclear how the results of the study “may be useful in informing medical resource allocation in this patient population”. Is there a need to change allocation or to decrease or increase costs spend on a certain type of care? The conclusion seems weak and without any impact.

Response: We agree, and have added text in the Discussion (page 10) that addresses the importance of study findings, as follows:

“The results of our study suggest that the economic burden of patients with metastatic lung cancer receiving chemotherapy is substantial -- exceeding $125,000. The results of our study also suggest that the majority of costs are associated with outpatient—rather than inpatient—care. Such findings may be important in informing the overall allocation of healthcare resources, in defining potential cost savings from disease prevention, and in evaluating the cost-effectiveness of new medical interventions.”

Comment #5 (minor): In the Introduction last sentence page 1 it is stated that lifetime healthcare utilization and costs are analyzed. What exactly is meant by lifetime, as only costs from a certain point in life until death or end of study were studied?

Response: In this study, lifetime is defined as the period from chemotherapy initiation to end of life. Although the term “lifetime” is often used in this fashion, we agree that its use may be confusing to readers, and we have changed the relevant sentences accordingly (e.g., in lieu of “lifetime”, we now state “from receipt of chemotherapy through end of life”).

Comment #6 (minor): ”indirect costs” (page 8 second last sentence) should be defined.

Response: Indirect costs are now defined as “the value of morbidity- and mortality-related productivity loss”.

Level of interest: An article of limited interest
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