Editorial

Economic burden of brain metastases in patients with non-small cell lung cancer: costs and implications

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Brain metastases are prevalent in patients with lung cancer. Up to 30% of the lung cancer patients will develop brain metastases during the course of their disease (1). Additional supportive treatments with or without brain-directed therapies are anticipated and the economic burden is undeniably substantial after the diagnosis (2).

Girard *et al.* recently published a retrospective study with a title of "Extra cost of brain metastases in patients with non-squamous non-small cell lung cancer (NSCLC): a French national hospital database analysis" (3). This study attempted to address an important medico-economic question which has not been fully answered by previous literatures. The cost of managing patients with non-squamous NSCLC who developed brain metastases at the time of diagnosis was found to be €2,979 (Euros 2017) per-patient-month, which represented a differential cost of €553 per-patient-month when compared with those with metastases at other sites. The authors concluded that the presence of brain metastases at the time of diagnosis of non-squamous NSCLC carried a significant burden.

This study retrospectively analyzed data extracted from a French national medical information database which covers all overnight and day hospitalizations. The in-hospital medical resource consumption was estimated based on the standard national tariffs that applied to medical procedures, nursing care, treatments, food and accommodation and investment costs for each hospitalization. Apparently, tremendous amount of data can be retrieved from this type of big data analysis based on administrative databases. Ultimately a total of 2,500 patients with 45,241 hospital stays were included in the final analysis. This considerable population size is appealing when compared with other previous similar studies (4-7) and may potentially add much value to the current study as presumably sufficient power and precision could be generated.

Retrospective databases in particular administrative claims databases provide extremely rich information which are readily available for big data research (8). These data are usually obtained from an unselected large population and theoretically represent the real-world situation. The current study captured up to one third of the incidence of metastatic non-squamous NSCLC in the whole country during the study year. It should provide a reasonably convincing overview on the national burden arising from brain metastases in this particular group of patients. However, many a time, these databases are constructed for purposes unrelated to the clinical research being conducted (8). Several methodological challenges are certainly inevitable due to the inherent properties of these databases. The extent to which relevant clinical questions could be addressed is also largely dependent on the constitution of the databases, and can sometimes be limited.

In this study, eligible patients and hospital stays were identified by International Classification of Diseases, 10th Revision (ICD-10) codes. With the absence of histological information in the ICD codings and the database, only

cohort with lung cancer in general could be identified rather than NSCLC specifically. Prescriptions of Pemetrexed or Bevacizumab were therefore used as proxy markers to indicate the non-squamous NSCLC cohort. Concerns could possibly arise on the generalizability of results to patients who did not receive the index treatments. At the time of study enrollment, the proxy markers could only be tracked in public hospitals, which confined the analysis to patients treated in the public sector. This specific methodological challenge of using proxy markers was also observed in previous studies using claims databases (4-7,9).

The use of Pemetrexed or Bevacizumab as proxy markers would probably pre-select patients with better performance status into the study cohort. In the real-world, a considerable proportion of patients presented with brain metastases are having poor performance status and not eligible for any systemic treatments to start with. The healthcare resource utilization between patients on best supportive care and those who can receive active anti-cancer treatments may essentially be very different (10).

A common issue on retrieving data from administrative claims databases is the lack of detailed clinical information. Having different baseline clinical characteristics, NSCLC patients with brain metastases can be fairly heterogeneous in terms of the disease trajectory and overall prognosis (1,11), and thus possibly the economic burden generated. In the current study, a general conclusion has been made for the brain metastases population as a whole. If more baseline clinical information indicating the composition of the study cohorts was available, it would be easier to appreciate whether the conclusion can be applicable to different subgroups of patients.

Oncogenic driver mutation status carries crucial health economics implications in the era of molecular targeted therapies (12). Patients with driver mutations usually have longer survival and better health utilities (1,11,12) which may potentially lead to a different spectrum of healthcare costs. The use of expensive molecular targeted therapies is nevertheless adding to the extra medical expenses. As mentioned by the authors, the subgroups of patients harboring epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements could not be identified in the study, it was uncertain about the proportion in the cohorts receiving tyrosine kinase inhibitors (TKIs). The reported median survival of the brain metastases cohort in the current study was around 8 months (250 days). It appeared to be much shorter than those with *EGFR* or *ALK* gene alterations where the survival can be up to 45 months (1,11). Possible explanations on the discrepancy include small proportion of patients carrying driver mutations or limited number of patients receiving TKIs in this study. Caution should be taken when generalizing the results to this population.

The prognosis of NSCLC with brain metastases also depends on the extent of disease and performance status of patients (1). Aggressive local treatments for brain metastases including surgical resection and stereotactic radio-surgery (SRS) are reserved for selected patients having oligometastases with favorable prognosis (13). While whole brain radiotherapy or best supportive care are usually indicated in patients with more extensive brain metastases or less favorable performance status. These individual treatment modalities attribute different healthcare costs and resource utilization (10,14,15). However, whether or not these medical expenses would ultimately convert into different overall economic burden is yet to be fully answered by previous literatures (16). As there was no stratification of the brain metastases cohort into different prognostic groups in the present study, the difference in the healthcare costs between patients with widespread brain metastases and those with oligometastatic disease remains an important question to be addressed in future studies.

Patients presented with synchronous brain metastases could have different symptom burden and associated costs from those with asynchronous metastases. The economic burden generated by patients with asynchronous brain metastases may not be derived from the results of the present study as this specific group has been excluded in the analysis. The information can be supplemented by a previous study conducted to assess the symptom and economic burden of NSCLC patients receiving EFGR-TKIs and in which there was stratification of cohorts according to the site and timing of metastases (4). There was an incremental healthcare cost of $20,301 (US dollars 2016) per-member-per-month (PMPM) after diagnosis of synchronous brain metastases. While the incremental cost from pre-cancer diagnosis to post-metastasis diagnosis was $14,494 PMPM in the cohort with asynchronous brain metastases. Although the analysis was not designed to compare the synchronous and asynchronous cohorts, a numerical difference was observed.

The reported median survival for patients without brain metastases was 204 days in comparison with the 250 days for those with brain metastases in the current study. Though there was no statistical testing to evaluate the significance of the difference observed, it would be rather unexpected for

the brain metastases cohort to have better survival. Perhaps one of the plausible postulations is the higher prevalence of extensive extra-cranial disease burden in the reference cohort. Even without the presence of brain metastases, patients with high-volume visceral involvement could also carry poor prognosis and incur substantial medical care needs and healthcare costs. If available, detailed information on the extent of extra-cranial metastases in the two study cohorts would be helpful to suggest whether the two groups are having balanced baseline characteristics and whether the differential cost was merely contributed by brain metastases. Understandably, these information would be difficult to collect from an administrative claims database.

Underestimation is one of the common concerns regarding claims database analysis, which has also been mentioned by the authors. Inevitably and unsurprisingly, not every single service in the healthcare system would be captured in these databases (8). In this study, only overnight or day hospitalizations can be retrieved from the database. Outpatient consultations, prescription of oral medications including TKIs, medical imaging performed in clinics and other community healthcare services including nursing care and home hospitalization were not captured in their database. In a prospective study on the resource utilization in patients with brain metastases, 20% of patients receiving active treatments were managed completely on an outpatient basis (10). The Agency for Healthcare Research and Quality in the United States estimated that 44% of the total healthcare expenditures was allocated to outpatient visits (17). This proportion is definitely not negligible. The economic evaluation by the present study reflects healthcare costs imposed by hospitalizations. To offer a comprehensive overview of the total healthcare expenses, the results from this study could be supplemented by information on the outpatient and community care costs. Nonetheless, previous literatures have demonstrated conflicting evidence on whether diagnosis of brain metastases in lung cancer patients would lead to an increase in outpatient care cost and clinic visits (5-7). This continues to be a research area that warrants further investigation.

The overall economic burden of cancer is constituted by both direct and indirect costs. The current study contributed information on the hospitalization cost which is part of the direct medical costs. Disability and absenteeism-related salary loss, disability benefits paid out to patients and total cost of productivity loss are considered as indirect costs (5). The indirect costs from loss of productivity due to illness or premature mortality contributed 60% of the total costs of cancer as estimated by the National Institutes of Health in the United States in 2010 (18). Data in the literature suggest significant cost from disability benefits and total salary and productivity loss after diagnosis of brain metastases, with a total cost of productivity loss of up to $17,655 per-person-per-6-months (US dollars 2013) (5). The impact of brain metastases on quality of life for both patients and caregivers is another intangible cost that is probably difficult to be addressed by studies focusing predominantly on data from claims databases.

The incremental cost due to brain metastases was €553 (Euros 2017) per-patient-month as reported by this study. The previously reported cost increase after diagnosis of brain metastases in NSCLC patients ranged from $6,029 to $20,301 per-patient-per-month (US dollars) (4-7). The inconsistent results could be due to differences in the composition of the study populations and the timing and methods of data capturing. Yet the estimated cost by the current study was still relatively low. This phenomenon may be partially explained by the reasons for underestimation as mentioned above. After all, the healthcare costs and policies of reimbursement could fundamentally be very different across various healthcare systems over the world. This is relevant even to countries with similar human development indices and adjacent geographical positions (19). Conclusions derived from claims database analysis would be valuable and representative for the population from which the data are collected and maybe for regions with similar healthcare systems and economic backgrounds. Further generalization probably cannot be assumed in other situations.

Given the potential economic burden from brain metastases, the authors concluded the article by emphasizing the need to identify effective strategies to prevent and eradicate brain metastases in patients with lung cancer. Up till now, there are no alluring treatment options that play pivotal roles in central nervous system (CNS) prophylaxis except for EGFR and ALK TKIs which may potentially serve the purpose (20). However, as long as patients with brain metastases and extracranial diseases cannot be completely cured, the costs from subsequent progression and palliative treatment would have to be paid at some point during the course of disease (10). Screening for brain metastases appears to be an attractive alternative as it may allow early detection of oligometastatic disease and aggressive local treatments can be offered accordingly. It is uncertain whether aggressive treatments such as SRS or surgical resection can truly eradicate brain metastases.

Unselected screening does not appear to be a cost-effective strategy, with a cost of up to $10,413.5 (Australian dollars) per brain metastasis detected (13). CNS prophylaxis using expensive TKIs and aggressive local treatments for oligometastatic disease may potentially delay the onset of complications and improve quality of life. The economic implication of these strategies remains to be defined.

The current study provides a general overview on the extra cost of brain metastases in non-squamous NSCLC patients. Given the inherent methodological challenges of claims database analysis, interpretation of the conclusion from this study would have to be supplemented by information from other available literatures. However, those data from previous publications were also largely obtained from claims database analysis, which were also subjected to the same limitations encountered by the present study. Ideally, a large population-based prospectively-collected database which ensures complete clinical and socioeconomic information would be helpful to provide a more comprehensive analysis.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Sperduto PW, Yang TJ, Beal K, et al. Estimating Survival in Patients With Lung Cancer and Brain Metastases: An Update of the Graded Prognostic Assessment for Lung Cancer Using Molecular Markers (Lung-molGPA). JAMA Oncol 2017;3:827-31.
2. Ray S, Dacosta-Byfield S, Ganguli A, et al. Comparative analysis of survival, treatment, cost and resource use among patients newly diagnosed with brain metastasis by initial primary cancer. J Neurooncol 2013;114:117-25.
3. Girard N, Cozzone D, de Leotoing L, et al. Extra cost of brain metastases (BM) in patients with non-squamous non-small cell lung cancer (NSCLC): a French national hospital database analysis. ESMO Open 2018;3:e000414.
4. Fernandes AW, Wu B, Turner RM. Brain metastases in non-small cell lung cancer patients on epidermal growth factor receptor tyrosine kinase inhibitors: symptom and economic burden. J Med Econ 2017;20:1136-47.
5. Guérin A, Sasane M, Dea K, et al. The economic burden of brain metastasis among lung cancer patients in the United States. J Med Econ 2016;19:526-36.
6. Guérin A, Sasane M, Zhang J, et al. Brain metastases in patients with ALK+ non-small cell lung cancer: clinical symptoms, treatment patterns and economic burden. J Med Econ 2015;18:312-22.
7. Burudpakdee C, Wong W, Seetasith A, et al. Economic impact of preventing brain metastases with alectinib in ALK-positive non-small cell lung cancer. Lung Cancer 2018;119:103-11.
8. Motheral B, Brooks J, Clark MA, et al. A checklist for retrospective database studies-report of the ISPOR Task Force on Retrospective Databases. Value Health 2003;6:90-7.
9. Benjamin L, Cotté FE, Mercier F, et al. Burden of breast cancer with brain metastasis: a French national hospital database analysis. J Med Econ 2012;15:493-9.
10. Nieder C, Norum J, Stemland JG, et al. Resource utilization in patients with brain metastases managed with best supportive care, radiotherapy and/or surgical resection: a Markov analysis. Oncology 2010;78:348-55.
11. Sperduto PW, Yang TJ, Beal K, et al. The Effect of Gene Alterations and Tyrosine Kinase Inhibition on Survival and Cause of Death in Patients With Adenocarcinoma of the Lung and Brain Metastases. Int J Radiat Oncol Biol Phys. 2016;96:406-13.
12. Labbé C, Leung Y, Silva Lemes JG, et al. Real-World EQ5D Health Utility Scores for Patients With Metastatic Lung Cancer by Molecular Alteration and Response to Therapy. Clin Lung Cancer 2017;18:388-95.e4.
13. Diaz ME, Debowski M, Hukins C, et al. Non-small cell lung cancer brain metastasis screening in the era of positron emission tomography-CT staging: Current practice and outcomes. J Med Imaging Radiat Oncol 2018;62:383-8.
14. Mehta M, Noyes W, Craig B, et al. A cost-effectiveness and cost-utility analysis of radiosurgery vs. resection for single-brain metastases. Int J Radiat Oncol Biol Phys 1997;39:445-54.
15. Halasz LM, Weeks JC, Neville BA, et al. Use of stereotactic radiosurgery for brain metastases from non-small cell lung cancer in the United States. Int J Radiat Oncol Biol Phys 2013;85:e109-16.
16. Peters S, Bexelius C, Munk V, et al. The impact of brain metastasis on quality of life, resource utilization and survival in patients with non-small-cell lung cancer. Cancer

Treat Rev 2016;45:139-62.
17. American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society, 2016.
18. American Cancer Society. Cancer Facts & Figures 2010. Atlanta: American Cancer Society, 2010.
19. McGuire A, Martin M, Lenz C, et al. Treatment cost of non-small cell lung cancer in three European countries: comparisons across France, Germany, and England using administrative databases. J Med Econ 2015;18:525-32.
20. Krawczyk P, Duchnowska R, Nicoś M, et al. Preventing central nervous system metastases in non-small cell lung cancer. Expert Rev Anticancer Ther 2018;18:1077-83.

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