



The challenge of brain metastases from non-small cell lung cancer is not only an economical issue

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The paper presented by Nicolas Girard is another attempt to estimate the direct cost of the management stage IV non-small cell lung cancer (NSCLC) especially considering the issue of brain metastases (1). The later increases the cost comparing of stage IV patient disease without brain metastases. The paper presents several limitations as already mentioned by the authors due to the study population and the retrospective nature of the study. The author identified the study population on the basis of all hospital stays in France and by the fact he completely neglected extra costs generated by outpatients. The paper is only focused on a specific NSCLC population of non-squamous. The absence of a specific ICD-10 code for the non-squamous NSCLC forced the author to select the study population based on treatment related disease by chemotherapy (bevacizumab and pemetrexed) registered on the FICHCAMP database. This later, at the time of enrolment, was only available for public hospital excluding de facto private hospitals. Moreover, this method of selection inherently cannot consider all other metastatic patients which never received bevacizumab or pemetrexed chemotherapy for the disease. Last but not least, patient cost related to medical management can be impacted by several other factors than brain metastasis as patient co-morbidities and therefore, study cohorts should also be adjusted based on this later. At the end of the paper, the author outlines to find strategy to eradicate successfully brain metastases and so lowering this burden. Nevertheless, it is clear that brain metastases are a major problem for lung cancer due to the high incidence either at diagnosis or during the patient follow-up. The symptoms or the risk of major

neurological complication will often require a local treatment either surgery, radiosurgery (RS) or whole brain radiotherapy (WBRT) increasing so the cost. Extra treatments and disabling symptoms will consequently increase the number of hospital-stays which finally burden the cost.

Brain relapse is a common pattern of failure for NSCLC with figure as high as 50% at 2 year and the occurrence varies depending on the histology and the tumor extent (2). Brain metastases may produce many symptoms having a direct impact on the patient quality of life, requiring a management going from steroids to surgery and radiotherapy including RS and WBRT. In the past the management of brain metastases was most often steroids with or without WBRT. The picture has markedly evolved over the last decades making the treatment decision a more complex issue as there are new treatments possibilities including targeted agents and the better survival leading also to repeat even the local treatment.

The first question is certainly: "Should all patients with brain metastases be treated aggressively?" The treatment decision should consider the patient general health, the symptoms, the possibility of systemic treatment and the local control of the primary lung as well as other metastatic sites. A recent phase III trial including patients with NSCLC and no candidate for RS has compared steroids without or with WBRT: at 8 weeks there was no difference in patient quality of life neither in the use of steroids (3). The study population included mainly patients in class recursive partitioning analysis (RPA) II and III (94%). In the real daily life, it is not easy to withhold WBRT due to the patient and family pressure but also from our colleagues. We should, also, point

out the need to use with caution radiotherapy regardless of the technique for palliation of patients with a very short life expectancy especially when alternative approaches are available. Indeed, in a large review of UK practice, 11% percent of the patients treated for brain metastases died within 30 days after treatment (4). Furthermore, the outcome of brain metastases has markedly evolved over the last years. As an example, using the graded prognostic assessment, including age (less or more than 70 years), the Karnofsky Performance Status (KPS), the presence or not of extra-cerebral metastases, the number of brain metastases and gene status, helps to select patients who will benefit from aggressive local brain therapeutics. Sperduto *et al.* observed that the median survival varies from 7 to 47 months for the bad to the best group, respectively (5). A major difference with the old RTOG study: the median survival was a couple of months for the worse group and 7.7 months for patients younger than 65 with a KPS above 70, the primary under controlled and no extra-cerebral metastases (6).

One of the problems that we encounter today is the local evolution within the brain while the disease is under control in the extra-cerebral sites. This supports the strategy of used of more aggressive local treatments either surgery, RS or even WBRT. Nowadays, for patients with mutation such as EGFR or ALK, systemic treatment with targeted agents provide a very good alternative to WBRT while patients with few lesions may remain candidate to surgery or RS depending on the extent of the disease and performance status (7). WBRT has several side effects including alopecia, hearing impairment, fatigue but mainly neurocognitive deterioration. A recent trial comparing WBRT to RS after surgical metastasis removal showed no difference in survival but the neurocognitive deterioration and severe hearing impairment were worse after WBRT. These later, even, occurred after a short follow-up of 1 year (8). In another study, WBRT alone let to statistically worse quality of life and all symptoms score compared to RS or surgery (9). Of note, patients selected for RS or surgery often presented less advanced disease, less brain metastases and a better performance status and functional well-being. Moreover, the neurocognitive function depends on the integrity of the hippocampus region and studies are on-going sparing this area through a specific RT technique keeping the dose below 8 Gy to see the safety looking both to the late effect but also to the absence of relapse in this spared area (10). Finally, the evolution of the radiotherapy technics, making more accessible RS, has for consequence a large reduction

of WBRT treatment in favour of RS.

Most economical studies have clearly outlined that the costs are driven by the treatments, especially today, that the treatments have let to prolong survival. Another study has tried to evaluate the cost for patients progressing after first-line treatment: overall oncology therapy was the cost drivers but there was a clear increase between first-line and third-line treatment with more RT and palliative care. In this study the cost was around 25,000 Euro, a figure not so different from the present paper with cost per month per patients between 2,500 and 3,000 Euros (11). Gu erin *et al.* observed a major increase in healthcare costs in the post-diagnosis period resulting in 25,000 per 6 months (12). Direct costs related to health care are only one side of the issue. Indeed, the indirect costs must be considered to obtain a complete view of the economic impact of stage IV lung cancer. These are related to patients and employers due to the disease and the work possibility after the diagnosis of brain metastasis, for example the salary loss due to missing working depending on the patients functioning possibilities. As previously mentioned, restricting the issue to brain metastases is a simplify view. Metastases in other organs may also require specific treatments which will impact the costs such as bone metastases with spinal cord compression which may also require surgery followed by radiotherapy. In a French study, the mean monthly costs for bone metastases were rising from 190 to 4,672 Euros for asymptomatic patients or patients with skeletal related event (13). Finally, direct and indirect costs in health care are only one figure of the problem. Nowadays, treatments and particularly costly treatments as immunotherapy or RS must also be analyzed in the perspective of quality of life and its economic impact [i.e., Quality-adjusted Life Year (QALY)]. In this view, the use of immunotherapy is more effective than standard chemotherapy for metastatic NSCLC expressing high level of PD-L1 or the use of stereotactic radiotherapy for stage I lung cancer in elderly patient with chronic obstructive pulmonary disease (COPD) is more cost effective than palliative care (14,15). The cost of RS in stage IV NSCLC with brain metastasis is usually higher than WBRT. Nevertheless, RS is more effective in term of quality-adjusted life years probably due to its higher local efficacy (16). Local therapy as radiotherapy or surgery demonstrated a benefit in term of QALYs for oligometastatic NSCLC (17). Of course, the costs and QALYs may vary from country to country depending on the national health insurance system and local practice.

Last but not least, it is clear that new treatments modalities such immunotherapy will directly have a major impact on the treatment cost but also indirectly by prolonging the patient life, this later will be more at risk of developing brain metastases requiring specific treatment. Furthermore, there is a major interest for combining immunotherapy, systemic treatment and local modalities especially in case of oligometastatic disease either to improve the local control or to hope for a possible immunologic response and an abscopal effect. There is a huge need for the National Health Insurance to evaluate prospectively the impact of all those new therapeutic approaches, not only in terms of cost but essentially in terms of QALYs.

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Footnote

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

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