

# The crucial role of predicting brain metastases development in non-small cell lung cancer patients

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Over the past ten years we have witnessed many advances in the management of non-small cell lung cancer (NSCLC), with the 5-year over survival (OS) in the advanced disease that has shifted to approximately 15% both in NSCLC patients with epidermal growth factor receptor (EGFR) + NSCLC treated with tyrosine kinase inhibitors (TKIs) (1) and in those treated with immune-checkpoint inhibitors (ICPIs) (2) and up to approximately 50% in NSCLC patients with anaplastic lymphoma kinase (ALK)+ tumours following first-line crizotinib (3).

Despite this, prognosis remains rather poor even in early stages (4). The development of brain metastasis (BM) represents the most negative clinical prognostic factor and occurs in 30–50% of NSCLC patients (5). Nearly 10% of them presents already with BM at the time of diagnosis (6). Nevertheless, routine brain imaging at the disease presentation remains controversial. Several Investigators reported that the frequency of BMs in early-stage NSCLCs without neurological symptoms was quite low, thus not warranting extrathoracic disease staging, particularly brain imaging (6,7). Based on this retrospective evidence, the National Comprehensive Cancer Network (NCCN) and American College of Chest Physicians (ACCP) guidelines currently do not recommend brain screening if the patients are asymptomatic and with a clinical stage I disease (8). However, BMs have been reported to occur silently in 7.5% of early-stage NSCLC patients and in 19% of them with N0 disease (9). Indeed, unlike the American guidelines,

the Japanese Lung Cancer Society guidelines recommend screening for BMs in all NSCLC patients irrespectively of the stage of the disease, while the European Society for Medical Oncology (ESMO) suggests that screening for BMs by MRI might be considered for patients treated with a curative intent (10).

Thus, the editorial by Schoenmaekers *et al.* is extremely interesting. The Authors reviewed the article by Hudson *et al.* (10) and, although agreeing in principle with the importance of performing brain imaging in all NSCLC patients who are potential candidates for surgery (including those with early-stage disease), they concluded that screening for BMs should be strongly recommended in stage III, whereas it could be omitted in stage I (since the low likelihood of BMs), and to be considered in stage II for younger patients or for the ones with adenocarcinoma histology.

We believe that the answer to this question cannot be based only upon general clinical factors (i.e., stage, histology or age). Instead we'd need to seek for other predictive factors that play a role in the development of BMs in NSCLCs.

Most clinical guidelines recommend brain imaging in NSCLC patients based on histology (i.e., adenocarcinoma) or clinical stage (i.e., stage III) (10). Notably, the recommendation on histology is based on retrospective analyses, where patients with BMs and adenocarcinoma were overrepresented (11), probably reflecting only

the higher incidence of adenocarcinoma compared to squamous cell tumor rather than a real brain tropism of adenocarcinoma. As far as stage concerns, the assumption that asymptomatic BMs might prevail in earlier stage NSCLCs, may not be completely true, as it was recently pointed out by Ando *et al.* (12) who reported that at least 63% of the BMs occurred in completely asymptomatic stage IV NSCLC patients.

Regarding other biological predictive factors for BMs, the same Authors (12) highlighted the role of EGFR mutations, that was associated with the risk of developing BMs. Furthermore, even if prospective comparative data are lacking, data from clinical trials with tyrosine-kinase inhibitors strongly support that NSCLC patients having ALK rearrangement might represent a population at higher risk of developing BMs (3).

The identification of these biological predictive factors of BM development in NSCLC is crucial not only for the selection of patients to screen with brain imaging in the preoperative setting but also, in the foreseen future, for preventive strategies, such as prophylactic cranial irradiation (PCI).

Recently, the NVALT-11/DLCRG-02 study (13) showed the benefit of PCI in stage III NSCLC in term of reduction of BM incidence, although a benefit in OS was not demonstrated. This has once more raised the importance of identifying patients who could really benefit from preventive treatments, for at least three reasons: the first one is that the benefit of a prophylactic treatment is expected to be more pronounced in a population where the prevalence of the expected event is elevated; the second one is the need to spare unnecessary and ineffective treatment in low-risk patients; the third one is the possibility to identify potentially targetable factors.

We have already tried to identify new biological biomarkers for BMs moving from the mechanisms that could confer the ability to cancer cells to migrate and grow in the brain, such as the chemokine trafficking and particularly the CXCR4/CXCL12 axis in operable patients (14). We observed an increased ratio of CXCR4/CXCL12 in the specimens of NSCLC patients with BM compared to those without BM, thus suggesting this as a possible biomarker to prospectively validate. Moreover, an anti-CXCR4 agent is already available and could be tested in selected NSCLC patients.

So, what should we do now? A possible answer might probably come soon from ongoing adjuvant trials that are prospectively screening all NSCLC patients with brain

imaging and they could help us to estimate the impact of this procedure in terms of costs and cost-effectiveness. For now, we believe that screening for BMs should be considered for all NSCLC patients, as long as evidence supporting guidelines will be really based on prospective data.

In conclusion, selecting the right patients to screen for BM and to whom propose prophylactic treatments has become a strong need, hence future trials to prospectively identify and validate biological markers predictive of BM development are strongly warranted.

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### Footnote

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

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