Brain imaging in early stage non-small cell lung cancer

Editorial

Brain imaging in early stage non-small cell lung cancer: still a controversial topic?

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Brain metastases (BM) frequently occur in non-small cell lung cancer (NSCLC) patients. Approximately 10–20% of NSCLC patients already have BM at initial time of NSCLC diagnosis and around 40% will develop BM during the course of their disease (1). Known risk factors for the development of BM are adenocarcinoma histology, advanced nodal status, tumour stage and younger age (2-5).

The recommendation to screen for asymptomatic BM during NSCLC staging varies in current guidelines: all guidelines advise to screen stage III patients, but the recommendation for the earlier stages (I and II) differs (6-10) (*Table 1*). Preferred screening is with gadolinium enhanced magnetic resonance imaging (MRI) which is superior to a contrast-enhanced computed tomography (CE-CT) in detecting presence and especially number of BM (11-13).

Although MRI is more sensitive than a CE-CT, in daily practice CE-CT is often used because of contra-indications to MRI or poor MRI accessibility (14,15). Screening patients for BM is important, as a diagnosis of BM will change the treatment plan for a patient with otherwise early stage disease: either the treatment with radical intent is abandoned and systemic treatment (with/without local treatment for the BM) is initiated, or both the thoracic disease and the BM (when few in number) are treated with radical intent. Besides the implications for treatment, a diagnosis of BM can also have a negative impact on the quality of life (16).

As there is still limited data on incidence of BM in otherwise early stage NSCLC, we read with interest the article of Hudson *et al.*, published in *Ecancermedicalscience* (17). This retrospective single centre study, performed in the United Kingdom, evaluated the percentage of NSCLC patients that had BM before, or developed BM following curative intent NSCLC surgery. Because brain imaging was not routinely performed preoperatively, they also hypothesized how many BM that were detected postoperatively in patients without brain imaging before surgery, could have been detected by preoperative MRI by using a calculation method that used a volume doubling time of about 60 days. The maximum tumour diameter measured on the diagnostic scan was plotted against the number of days after surgery that the imaging was performed. The lesions that fell above the detection limit of MRI at the day of surgery were classified as likely visible had a pre-operative MRI been performed.

Four hundred and seventy-one NSCLC patients were included between January 2012 and December 2014. Five (1.1%) patients had neurological symptoms that led to brain imaging before surgery. These patients were treated with radical intent for their BM and local NSCLC. Another 18 (3.8%) were diagnosed with BM after surgical resection of their primary lung cancer, nine (50%) already within a year. Four of these nine patients had only a cranial relapse. Of these 18 patients, the postoperative stage was I in five (28%) patients, II in six (33%) patients and III in seven (39%) patients. Twelve (67%) out of these 18 patients had

Table 1 Overview of screening recommendations for brain metastases in NSCLC guidelines

Guideline, year	Advised imaging method	NSCLC stages advised to screen for BM [evidence level (EL)]	Brain follow up advised after completion of therapy with curative intent?
ESMO, early stage and locally advanced NSCLC 2017 (6)	MRI, optional CE-CT	Stage I–II: might be useful; stage III: mandatory (3B)	Not specified
NCCN version 4. 2018 (10)	MRI	Stage IA: not advised; stage IB: optional; stage II–III: mandatory (2A)	Not routinely indicated
NICE, 2011 (9)	MRI or CE-CT	All stages when eligible for therapy with curative intent: consider screening, especially stage III (EL not mentioned)	Not mentioned
BTS, 2010 (7)	MRI or CE-CT	All stages when eligible for therapy with curative intent: consider screening, especially stage III (C)	Not mentioned
ACCP, 2013 (8)	MRI or CE-CT if MRI is not available	Stage III and IV routine imaging, even when a negative clinical evaluation (2C)	Biannual brain MRI mentioned but not recommended

ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; BTS, British Thoracic Society; ACCP, American College of Chest Physicians; NSCLC, non-small cell lung carcinoma; MRI, magnetic resonance imaging; CE-CT, contrast enhanced-computer tomography; BM, brain metastases.

an adenocarcinoma. Fifteen of the BM patients were used for the calculation to evaluate whether their BM could have been visible on preoperative MRI. The other three patients were excluded from the analyses because two developed BM at over two years postsurgery, and one because information about timing of the BM was missing. The calculation method predicted that 3.3–3.8% (dependent on the detection threshold) of patients who underwent surgery already would have had BM detected by preoperative MRI (i.e., almost all or all patients that were diagnosed with BM postoperative would have been diagnosed when a MRI had been made preoperative).

Based on these results, the authors suggest that NSCLC patients should undergo preoperative brain MRI, regardless of stage, especially when they are diagnosed with an adenocarcinoma.

Should we indeed screen all neurologically asymptomatic early stage NSCLC for BM? And how to put these results into the context of existing literature?

The calculation method the authors use is interesting and hypothesis generating. However, as the authors already state, this cannot substitute for real brain imaging performed before surgery. Unfortunately, the percentage of patients with baseline or standard follow-up brain imaging was not known. Information on the percentage of patients with extracranial early stage NSCLC, but with BM that precluded surgery for their extracranial disease would have been helpful, as these patients were not included in the current study. Even in early stage NSCLC, the exact stage seems important in the decision making whether MRI of the brain has to be incorporated in the staging. This is reflected in the number of patients with stage IIIA NSCLC among the patients that developed BM after surgery. What would have been useful additional information is the percentage of stage I, II and III disease patients and information on the specific histology (adenocarcinoma *vs.* others) that was included in the study to calculate the percentage of patients for each stage and histology that developed BM after curative intent surgery. The importance of the exact stage is also reflected in other studies. When, during staging, otherwise early stage NSCLC patients are screened, the reported incidence of asymptomatic BM depends especially on the stage, with an increase from 0–1% in stage IA to 21% in stage IIIA (18-20). For example, when using the data available from the National Lung Screening trial, one in eight of the patients with clinical stage IA underwent brain imaging (MRI or CT), but none had intracranial metastases (18). Another retrospective analysis demonstrated that even with MRI screening, the incidence of BM in resectable NSCLC patients was low, with 0% in N0-disease, 5.2% in N1-disease and 4.7% in N2-disease (19). Finally, a prospective study (N=91) showed that with screening the incidence of BM in patients with large cell or adenocarcinoma type NSCLC was low in stage I/II (3%) but increased in stage IIIA (21%) (20). The percentages described in these studies mirror the

percentages found in the study of Hudson *et al.*, with a very low percentage in stage I disease.

As mentioned earlier, MRI is advised for screening, however access to MRI can be problematic (causing a delay to surgery) (14,15). Discovering asymptomatic BM in early stage NSCLC before surgery could change the treatment plan, but this should be weighed against a possible delay to surgery and the higher costs of screening all early stage patients to identify a few patients with BM. The additional costs for a staging MRI brain are high as it was shown that 32% of the staging costs were dedicated to brain MRI (21).

Moreover, in stage III NSCLC 13 % of patients with a negative staging MRI developed symptomatic BM within a year of a staging MRI without suspicious findings (22). In stage I and II the recurrence rate of BM after negative staging MRI is 6% within 5 years (majority within 2 years) (23). As even in early stages, risk for BM varies according to clinical characteristics, a score that predicts which patients are at an increased risk for BM would be useful. Besides clinical characteristics this score could for example include a miRNA signature in the near future, as certain miRNAs (involved in the regulation of several hundred genes) are associated with an increased risk for BM as was recently reviewed by Pedrosa *et al.* (24). MiRNA-328 for example was found to promote migration and subsequent BM formation in a NSCLC cell line, and was found to be overexpressed in both the primary and matched NSCLC BM. Similar results were found for miRNA-378 (24). The miRNAs are examined by microarray analysis of formalin-fixed paraffin-embedded specimens of surgical resection tissues (25).

The field of treatment of early stage NSCLC might change as multiple phase III trials are ongoing that compare adjuvant immunotherapy to placebo in NSCLC patients that had a complete resection of their NSCLC (PEARLS trial (NCT02504372), BR31 (NCT02273375) and ANVIL trial (NCT02595944). This is of interest regarding brain metastasis as the randomized phase III PACIFIC trial (NCT02125461), evaluating adjuvant durvalumab (programmed death ligand 1 antibody) versus placebo in stage III NSCLC treated with concurrent chemoradiation, showed that immunotherapy could have a role in reducing the incidence of BM after radical treatment (26). A secondary endpoint was the percentage of patients with distant metastases, this was reduced for the durvalumab group compared to the placebo group. Interestingly, after a median follow-up of 14.5 months the percentage of patients that developed BM was lower for durvalumab than for placebo (5.5% *vs.* 11%) (26).

In conclusion, we applaud Hudson *et al.* for their research on this important topic in lung cancer. We agree that attention should be paid to the option of brain imaging during staging in early stage NSCLC, but that possible delay to surgery and costs should also be taken into account. As the chance of having BM is low in stage I disease, in our opinion screening in this stage should not be recommended. In stage II disease screening is debatable and could be considered in patients with adenocarcinoma histology and younger age. Screening in stage IIIA should be mandatory, and is also recommended in the guidelines. Better risk prediction models are needed, and we eagerly await the results of the adjuvant immunotherapy trials in early stage disease, as the role of immunotherapy in the prevention of BM development should also be evaluated in this setting.

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Footnote

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