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Screening for brain metastases in patients with stage III non-small cell lung cancer: Is there additive value of magnetic resonance imaging above a contrast-enhanced computed tomography of the brain?

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A B S T R A C T

Introduction: Stage III NSCLC patients are candidates for treatment with curative intent. Current guidelines advise post contrast magnetic resonance imaging (MRI) or contrast enhanced computed tomography (CE-CT) of the brain in these patients to exclude brain metastases (BM). In previous small studies MRI was reported to be superior to CE-CT. However, CT and MR technology have evolved and 18F-deoxyglucose-positron-emission-tomography (18FDG-PET) has been implemented in staging of NSCLC. If CE-CT is performed together with 18FDG-PET-CT shows the same yield of BM detection as an additionally performed MRI, substantial gain in time and resources is expected.

Methods: All NSCLC patients who underwent a staging 18FDG-PET-CT between January 2008 and September 2011 were reviewed. Neurological asymptomatic patients with stage III NSCLC who were eligible for treatment with curative intent were selected, without taking into account the results of brain MRI. CT was compared to MRI to investigate whether additional BM were detected on MRI. Development of BM within a year after negative MRI was recorded.

Results: 97/429 NSCLC patients who underwent a PET-CT had stage III disease. Three otherwise stage III patients already had occult BM on CE-CT. 77/97 (79%) patients underwent MRI, 45/77 (58%) CE-CT and 32/77 (42%) LD-CT. In none of the CE-CT, but in 5/32 (16%) LD-CT patients BM were detected on MRI. 9/72 patients (13%) without BM on MRI at diagnosis developed BM within a year.

Conclusions: This retrospective study suggests that there is no additive value of MRI to 18FDG-PET-CT with CE-CT in screening for BM in neurological asymptomatic patients with stage III NSCLC.

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1. Introduction

Around 30% of patients with non small cell lung cancer (NSCLC) present with stage III disease and are candidates for intense combined modality treatment with curative intent [1]. The outcome is however still poor, with 5 year survival rate of 15.1% [1].

As the brain is a common site for dissemination [2], national and international guidelines advise to exclude brain metastases before starting intense treatment in this patient population. The combined modality treatment with concurrent chemoradiotherapy is frequently associated with morbidity due to radiation esophagitis and pneumonitis [3–5]. It is estimated that, dependent on disease stage and choice of radiological evaluation, 10–24% of NSCLC patients at presentation have one or more asymptomatic brain metastases [2,6,7]. For example, up to 16% otherwise stage III NSCLC patients were diagnosed with brain metastases on post contrast magnetic resonance imaging (MRI). However, in this study published in 2003, the number of patients with stage III NSCLC was small (38 of 91 patients) and 18F-deoxyglucose-positron emission tomography (18FDG-PET) scanning was not performed to exclude extracranial metastases [2].

A whole body 18FDG-PET is in current guidelines advised in the diagnostic work up of all patients eligible for therapy with curative intent to exclude extracranial metastases [3–5]. 18FDG-PET-scanning alone is not effective in detecting (asymptomatic)
2.1. January 18FDG-PET-CT

The 18FDG-PET. with a diagnostic contrast enhanced CT (CE-CT) of the thorax and upper abdomen. Combination with CE-CT of the brain is also an option and feasible, but is not common practice [10]. 18FDG-PET-scanning with LD-CT for attenuation correction has already been proven not to be effective in detecting asymptomatic brain metastases when compared to MRI [11].

Post contrast MRI is reported to be superior to CE-CT in diagnosing occult brain metastases. However, these were mostly older studies, all including patients with mixed tumour types and tumour stages [7,12–14].

In addition, CT and MR technology both have evolved significantly. Moreover, in none of the studies mentioned above a 18FDG-PET(-CT) was part of the diagnostic work up, leading to a less well staged patient population [15].

Lung cancer guidelines advice routine screening for brain metastases with post contrast MRI or CE-CT in all patients with stage III NSCLC eligible for therapy with curative intent [3–5,15,16]. In 3 guidelines, NCCN, ESMO and the Dutch VIK, a post contrast MRI is advised [4,5,16]. However, in most hospitals MRI is difficult to arrange within a reasonable time scale. There are also contraindications for MRI as intracorporal metallic objects, pacemakers and claustrophobia.

The question whether post contrast MRI offers a benefit to CE-CT in the initial staging of patients with NSCLC has become more urgent in view of the increasing wide-spread use of 18FDG-PET-C T scanners. If dedicated CE-CT of the brain performed in the same setting as 18FDG-PET-CT could lead to the same yield of detection of brain metastases as 18FDG-PET-CT with a non-diagnostic LD-CT for attenuation correction and a separate post contrast MRI, a substantial gain in time and resources can be expected. In this retrospective study we evaluated whether there is additive value of post contrast MRI to CE-CT for the detection of asymptomatic brain metastases when both are performed in standard work-up including 18FDG-PET-CT.

2. Materials and methods

2.1. Patient selection

The 18FDG-PET-CT database of the university hospital Maastricht, The Netherlands, was reviewed. All patients who underwent 18FDG-PET-CT in the diagnostic work-up for lung cancer between January 2008 and September 2011 were further evaluated. Patients with stage III NSCLC disease after staging with the 18FDG-PET-CT and who were candidates for treatment with curative intent were selected. Patients with neurological symptoms requiring brain imaging were excluded. In our hospital standard work-up of patients admitted with suspicion of lung cancer includes a 18FDG-PET according to a specific lung cancer protocol which consists of a CE-CT of the brain, thorax and upper-abdomen combined with the 18FDG-PET. In case a CE-CT of the chest and upper abdomen is already performed separately the 18FDG-PET is combined with a non-diagnostic LD-CT for attenuation correction. As a consequence, in these cases only a non-diagnostic LD-CT of the brain was available. Both patients who underwent a LD-CT together with the PET-CT and patients who underwent a CE-CT were analyzed. The policy in our institute is to screen for brain metastases in otherwise stage III NSCLC patients by MRI, also when a CE-CT of the brain is already performed. The results of the MRI were studied to investigate whether additional asymptomatic brain metastases were detected on MRI. In addition development of symptomatic brain metastases within a year after a negative scan was scored.

This study has been approved by the medical ethical committee of the university hospital Maastricht.

2.2. Imaging protocols

2.2.1. MRI protocol

MRI was performed with a 1.5 T MRI system using a 8-channel Sens head coil (Philips Healthcare, Best, The Netherlands). The protocol included a T1 weighted spin-echo sequence with a magnetization pre-pulse (MTC) (TR 615, TE 14, NEX 2, matrix 256×154, with an on resonance pre-pulse), with and without 0.1 mmol/kg body weight of Gadobutrol. The addition of the MTC pre-pulse results in an increased enhancement equivalent to a double doses of gadolinium contrast. Additionally a T2 weighted turbo-spin echo sequence (TR 4632, TE 100, ETL 12, NEX 2, matrix 256 × 192) and a fluid attenuated inversion recovery sequence (TR 8000, TE 120, TI 2000, ETL 23, NEX 1, matrix 512 × 138). All sequence had a slice thickness of 5 mm with a gap of 0.5 mm. Additionally a T1 weighted gradient echo sequence was performed with isotropic voxels of 1 mm (TR 9, TE 4, NEX 1, matrix 256 × 256).

2.2.2. PET-CT protocol

Acquisition of 18FDG-PET-CT was performed using a PET camera equipped with time-of-flight (Gemini TF PET/64-slice CT scanner, Philips, Best, The Netherlands). PET scans were made from head to pelvis, using 10 bed positions of 2.5 min each, after injection of 18FDG. In selected cases imaging was continued. Reconstruction was performed using a standard protocol in 3D with a matrix size of 144 resulting in a voxel size of 4.0 mm × 4.0 mm × 4.0 mm. PET was preceded by a LD-CT (120 keV, 30 mAs, 4 mm slice thickness, 4.0 increment) for attenuation correction of the PET images. Supplementary high-dose, CE-CT was performed according to a protocol with a standardized sequence following injection of 150 ml and a flow rate of 3 ml/s of jopromide (Ultravist, Bayer, Berlin, Germany): The diagnostic brain CT (120 kV, 400 mAs) was performed with a slice thickness of 0.8 mm and reconstructed to 5 mm thick slices. The scan was performed 3 minutes after administration of the jopromide.

3. Results

4131 18FDG-PET-CT scans were reviewed. From the 510 18FDG-PET-CT’s performed in the diagnostic work-up for lung cancer, 429 patients were diagnosed with NSCLC. 3 patients with otherwise stage III disease had occult brain metastases on CE-CT. 112 of 429 patients were diagnosed with stage III disease after PET-CT. 97 of 112 (87%) stage III patients were eligible for therapy with curative treatment. 77 of 97 (78%) patients underwent MRI (Fig. 1). Patient characteristics of these 77 patients are shown in Table 1. Although the standard work-up consisted of a MRI, the MRI was not performed in 20 patients because of diagnostic work-up elsewhere (n = 3), contra-indication for MRI (n = 2), participation in a study in which MRI of the brain was not a requisite (n = 5), deterioration of clinical condition before MRI was made (n = 2) or patient decision not to undergo therapy with curative intent (n = 2). In 6 patients no reason was found for not performing MRI.

In 45 of 77 (58%) patients a CE-CT was performed and in 32 of 77 (42%) patients only a LD-CT was done together with the 18FDG-PET. In the LD-CT patient group a CE-CT of the thorax and upper abdomen was already available before the 18FDG-PET-CT was made. In these cases only a LD-CT was performed combined with the 18FDG-PET for attenuation. As a consequence, no diagnostic scan of the brain was available in these patients.
Table 1

<table>
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<th>Sex (male/female)</th>
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<tr>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
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<td>2</td>
</tr>
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<td>4</td>
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Stage (CE-CT/LD-CT)

<table>
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<th>IIIB</th>
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<td></td>
</tr>
<tr>
<td>cT2N2</td>
<td>13 (6/7)</td>
<td></td>
</tr>
<tr>
<td>cT3N1</td>
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<tr>
<td>cT3N2</td>
<td>8 (6/2)</td>
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<tr>
<td>cT4N0</td>
<td>12 (6/6)</td>
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<tr>
<td>cT4N3</td>
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<td></td>
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</tbody>
</table>

Pathology

| NSCLC-NOS | 20 |
| Adeno carcinoma | 30 |
| Squamous cell carcinoma | 24 |
| Large cell carcinoma | 3 |

Treatment

| Curative intent | 42 |
| Chemoradiotherapy | 67 |
| Surgery followed by chemo- and/or radiotherapy | 3 |
| Palliative/BSCa | 3 |
| Chemotherapy | 3 |
| Radiotherapy | 3 |
| No treatment | 1 |

Abbreviations: WHO: World Health Organization; NOS: not otherwise specified.
a The clinical condition of these patients deteriorated quickly during analysis, so only palliative treatment was offered.

In the negative CE-CT group, 19 of 45 patients (42%) had stage IIIA disease and 26 (58%) had stage IIIB. In the LD-CT group, 18 of 32 patients (56%) had stage IIIA disease and 14 (44%) had stage IIIB (T and N see Table 1).

In none of the 45 patients who had a negative CE-CT of the brain together with the 18FDG-PET scan, brain metastases were detected on MRI. In contrast, in 5 of 32 (16%) LD-CT patients brain metastases were detected on MRI (Fig. 2). The MRI showed 2 metastases in 1 patient (largest 16 (mm)), 3 metastases in 1 patient (all around 6 mm) and multiple metastases in the other 3 patients (largest 12 mm). Before MRI, these patients were staged as cT1N3, cT2N2, cT4N0, cT4N2 and cT4N3.

Within 1 year of the diagnosis of 9 of 72 (13%) patients without brain metastases on MRI at diagnosis developed symptomatic brain metastases, in 2 of 9 (22%) also progressive disease outside of the brain was shown (Figs. 3 and 4). Of these 9 patients, 2 were initially diagnosed with a squamous cell carcinoma (initially cT2N3M0 and cT4N0M0), 4 with an adeno carcinoma (initially cT4N2M0, cT2N2M0, cT4N2M0, cT4N0M0) and in the remaining 3 patients the NSCLC was not otherwise specified (initially cT2N2M0, cT2N2M0, cT3N2M0). Of these 9 patients, 3 had a CE-CT followed by MRI during their initial work-up for lung cancer, 6 had a LD-CT followed by MRI during the initial work-up. To evaluate whether these brain metastases were missed during the initial work-up the imaging data of these 9 MRI’s were reviewed by an experienced neuroradiologist (PH), but also in retrospect no brain metastases were found.

4. Discussion

Brain metastases are frequent in stage III NSCLC [2]. Historically MRI is supposed to be superior to CT in detecting brain metastases [2,7,12,14]. However, the question is whether MRI has a clinical relevant benefit above CE-CT in detecting asymptomatic brain metastases in stage III NSCLC when using up-to-date staging techniques. In this study, up-to-date MRI and CT techniques were used and extra-cranial metastases were excluded by
18FDG-PET-CT scanning. In this patient population MRI did not show additional brain metastases after a negative CE-CT of the brain combined with the 18FDG-PET-CT, but in three of 48 patients brain metastases were already found on the CE-CT.

Also, this study confirms that adequate imaging of the brain is mandated in these patients as in 16% of the patients who underwent solely a non diagnostic LD-CT of the brain, brain metastases were detected on MRI. This percentage is comparable to percentages of occult brain metastases found in other studies [2].

Substantial gain in time and resources can be expected when the whole diagnostic imaging work-up can be performed in one single procedure, this diagnostic work-up consisting of a 18FDG-PET directly followed by CE-CT of the brain, thorax and (upper) abdomen. Following this procedure there would also be no delay because of waiting time for MRI before starting therapy with curative intent. Furthermore, in most institutes access to CT is easier than to MRI.

Brain metastases are still a serious problem in patients with stage III NSCLC, in our series 13% of patients with an initially negative MRI developed brain metastases within a year. Probably it is worth to investigate whether these brain metastases can be detected at diagnosis when more sensitive MRI techniques are used. It is known that the sensitivity of a post contrast MRI can be increased by using higher dose of contrast or by 3.0 T MRI instead of 1.5 T. However, higher contrast doses also increases false positive findings [9,17,18]. Moreover, although 3.0 T MRI scanners seem more sensitive in detecting cerebral lesions, no studies exist that show the increased sensitivity of 3.0 T systems for the detection of cerebral metastases. In our series we used MTC prepulse, this prepulse results in an increased enhancement equivalent to a double dose of gadolinium contrast [19]. The addition of post-contrast fluid attenuated inversion recovery (FLAIR) sequence (which we
used) also improves diagnostic confidence in the evaluation of brain metastases [20]. Another option is to routinely follow stage III NSCLC patients treated for cure with MRI or CE-CT of the brain on a regular basis to detect brain metastases at a stage where radical treatment is possible. Trying to prevent the development of brain metastases is also an option. A recent phase III study showed that prophylactic cranial irradiation in NSCLC stage III without progressive disease after therapy decreased the rate of brain metastases but no effect on overall survival or disease free survival was found [21]. Another phase III randomized study addressing the same question is still open for patient enrolment (NVALT11/DLCRG 02).

There are some drawbacks of the current study. First, it is a retrospective study with a small sample size. However all consecutive patients were included in the analysis, decreasing the risk of bias. Second, not all stage III underwent a MRI. This was especially in 2008 when guidelines did not already advise post contrast MRI of the brain to exclude brain metastases. Third, not all patients were screened by CE-CT before MRI. In the LD-CT group a CE-CT of the thorax and upper abdomen was already available before the 18FDG-PET-CT was made (most times because the CT of the chest was made for other purpose than suspicion of cancer). In these cases the 18FDG-PET was only combined with a non-diagnostic LD-CT for attenuation. As a consequence no diagnostic scan of the brain was available. There were no differences in patient characteristics between the patients with LD-CT and CE-CT.

5. Conclusion

This retrospective study of a consecutive cohort of patients suggests that there is no additive value of post contrast MRI when 18FDG-PET-CT with CE-CT is performed in the diagnostic work-up of neurologically asymptomatic stage III NSCLC patients in screening for brain metastases. However, brain metastases is still an important problem as 13% of patients developed symptomatic brain metastases within 1 year after treatment with curative intent. Due to the possible impact of these findings on clinical practice a prospective trial (NTR3628) using up-to-date imaging techniques to validate these data has started.

Conflicts of interest statement

All authors declare no conflicts of interest.

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References