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Original Research

Screening for brain metastases in patients with stage III non–small-cell lung cancer, magnetic resonance imaging or computed tomography? A prospective study

Janna Schoenmaekers [a], Paul Hofman [b], Gerben Bootsma [c], Marcel Westenend [d], Machiel de Booij [e], Wendy Schreurs [f], Ruud Houben [g], Dirk De Ruysscher [g], Anne-Marie Dingemans [a], Lizza E.L. Hendriks [a,*]

[a] *Dept. of Pulmonary Diseases, GROW - School for Oncology and Developmental Biology, Maastricht University Medical Center+, Maastricht, the Netherlands*
[b] *Dept. of Radiology, Maastricht University Medical Center+, Maastricht, the Netherlands*
[c] *Dept. of Pulmonary Diseases, Zuyderland Hospital Heerlen, Heerlen, the Netherlands*
[d] *Dept. of Pulmonary Diseases, VieCuri Hospital, Venlo, the Netherlands*
[e] *Dept. of Radiology, Zuyderland Hospital Heerlen, Heerlen, the Netherlands*
[f] *Dept. of Nuclear Medicine, Zuyderland Hospital Heerlen, Heerlen, the Netherlands*
[g] *Dept. of Radiation Oncology (MAASTRO), GROW - School for Oncology and Developmental Biology, Maastricht University Medical Center+, Maastricht, the Netherlands*

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Abstract ***Introduction:*** Non–small-cell lung cancer (NSCLC) guidelines advise to screen stage III NSCLC patients for brain metastases (BMs), preferably by magnetic resonance imaging (MRI) or when contraindicated or not accessible a dedicated contrast enhanced –computed tomography (dCE-CT), which can be incorporated in the staging ^{18}Fluodeoxoglucose–positron emission tomography (^{18}FDG-PET-CE-CT). In daily practice, often a dCE-CT is performed instead of a MRI. The aim of the current study is to evaluate the additive value of MRI after dCE-CT, incorporated in the ^{18}FDG-PET-CE-CT.
Patients and methods: It is an observational prospective multicentre study (NTR3628). Inclusion criteria included stage III NSCLC patients with a dCE-CT of the brain incorporated in the ^{18}FDG-PET and an additional MRI of the brain. Primary end-point is percentage of patients with BM on MRI without suspect lesions on dCE-CT. Secondary end-points are

* *Corresponding author*: Dept. of Pulmonary Diseases, GROW-School for Oncology and Developmental Biology, Maastricht University Medical Center +, PO Box 5800, 6202 AZ, Maastricht, the Netherlands. Fax: +31(0)43-3871318.
E-mail address: lizza.hendriks@mumc.nl (L.E.L. Hendriks).

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percentage of patients with BM on dCE-CT and percentage of patients with BM ≤ 1 year of a negative staging MRI.
Results: Sixteen (7%) patients with extracranial stage III had BM on dCE-CT and were excluded. One hundred forty-nine patients were enrolled. 7/149 (4.7%) had BM on MRI without suspect lesions on dCE-CT. One hundred eighteen patients had a follow-up of at least 1 year (four with BM on baseline MRI); eight of the remaining 114 (7%) patients developed BM ≤ 1 year after a negative staging brain MRI.
Conclusion: Although in 7% of otherwise stage III NSCLC patients, BMs were detected on staging dCE-CT, MRI brain detected BMs in an additional 4.7%, which we consider clinically relevant. Within 1 year after a negative staging MRI, 7% developed BM.

1. Introduction

Brain metastases (BMs) frequently occur in non–small-cell lung cancer (NSCLC) patients, and risk increases with stage. About 20% of stage III NSCLC, patients have BM at baseline [1,2]. In all guidelines, it is advised to screen stage III NSCLC patients as usually only those without BM are eligible for intense combined modality treatment [3–6]. The preferred brain imaging modality is post contrast magnetic resonance imaging (MRI) or, when contra-indicated, a dedicated contrast enhanced–computed tomography (dCE-CT) [3–6]. However, access to MRI can be problematic, and there are also some contra-indications for MRI (*e.g.* some pacemakers, claustrophobia). In a United Kingdom (UK) survey (2014) on brain imaging in neurologically asymptomatic lung cancer patients, dCE-CT was preferred above MRI, presumably because of lack of access to MRI [7]. Another recently published European survey (462 responders) also showed that only 52.2% used MRI to screen for BMs. Moreover, only 63% screened stage III NSCLC patients [8].

Furthermore, in all patients eligible for therapy with curative intent, a whole body ^{18}F-deoxyglucose-positron emission tomography (^{18}FDG-PET) is advised to exclude distant metastases [3–5,9]. An ^{18}FDG-PET is performed with a non-diagnostic low-dose CT (LD-CT) for attenuation correction, but a dCE-CT of the thorax, upper abdomen and brain can be added [10]. ^{18}FDG-PET with a LD-CT is not suitable for BMs detection [11–15]. From older studies (patient inclusions from 1980 up to 2004), including patients with mixed tumour types and tumour stages, it is known that MRI of the brain is more sensitive than dCE-CT in detecting presence and especially number of metastases [16–20]. However, it has not been shown; this is still the case in the setting of screening for asymptomatic BMs in already ^{18}FDG-PET staged stage III NSCLC patients. In recent years, the techniques concerning CT as well as MRI have improved. In a retrospective study (N = 77) with these up-to date MRI and CT protocols (2008–2011), no additional BMs were found on MRI after ^{18}FDG-PET-CT with dedicated brain CE-CT in stage III NSCLC patients. In contrast, 16% of those with only a LD-CT were diagnosed with BM on MRI [15]. BM remain a serious issue as in this retrospective study, 13% with a negative staging brain MRI developed symptomatic BM within a year of NSCLC diagnosis [15]. A similar percentage of BM development was found in another large retrospective series (N = 838) of stage III NSCLC patients that underwent baseline brain imaging [21]. When dCE-CT of the brain performed in the same setting as ^{18}FDG-PET-CT could lead to the same yield of BM detection as ^{18}FDG-PET-LD-CT with a separate brain MRI, a substantial gain in time and resources could be expected. In this prospective observational multicentre study, we evaluated whether there is a clinically relevant additive value of MRI to dedicated brain CE-CT (performed as part of the ^{18}FDG-PET-CE-CT) in detecting asymptomatic BM in stage III NSCLC patients when both are performed in standard work-up.

2. Materials and methods

2.1. Study design and patient selection

This was a prospective, multicentre (N = 3) study in the Netherlands. In the participating hospitals, it is routine practice to perform a dCE-CT of the brain and chest together with the ^{18}FDG-PET-CT, when no recent diagnostic chest CE-CT is available. In addition, standard practice is to perform brain MRI in all stage III NSCLC patients eligible for therapy with curative intent. Patients were included by prospectively screening the agenda of the weekly multidisciplinary lung tumour boards of the participating hospitals. As according to Dutch guidelines, all lung cancer patients must be discussed in these tumour boards, no patients are missed. All stage III (7th tumour-node-metastasis [TNM]

edition) NSCLC patients scheduled for treatment with curative intent were included. For inclusion in this study, stage III was based on ^{18}FDG-PET-CE-CT with dCE-CT of the brain, i.e. without taking into account the results of MRI.

In addition, the number of patients with asymptomatic BM found on ^{18}FDG-PET-CE-CT in otherwise stage III NSCLC was scored. The exclusion criteria included a second primary cancer within 2 years of stage III NSCLC diagnosis (except recurring NSCLC eligible for treatment with curative intent, cervical cancer in situ or non-melanoma skin cancer), no dCE-CT of the brain during the ^{18}FDG-PET scan and no brain MRI and mixed histology (*i.e.* SCLC and NSCLC). Initially, the aim was also to exclude patients with a brain MRI performed more than 3 weeks after the ^{18}FDG-PET-CE-CT as it could not be excluded that BM not visible on dCE-CT of the brain became visible on MRI in a longer time period. However, during the study, it proved to be very difficult to obtain the MRI within this time, so all patients fulfilling the other criteria were included, irrespective of MRI timing.

The MUMC+ethics committee stated that patient informed consent was not mandatory according to the Dutch law 'Medical Research (human subjects) Act' as both ^{18}FDG-PET-CE-CT and MRI are standard workup according to the Dutch NSCLC guideline, and work-up and treatment were not influenced by the study (METC 12-4-126). The study was registered on the Dutch Trial Registry (NTR3628). Because of the observational study design, patients who already had had a CE-CT of the chest did not undergo a CE-CT combined with the ^{18}FDG-PET scan, as standard practice was to perform only a LD-CT combined with the ^{18}FDG-PET scan. If not already performed, brain MRIs were advised during the tumour boards, but the decision to perform a brain MRI was according to the treating physician.

2.2. Outcomes

Primary end-point was the percentage of patients with stage III NSCLC (based on ^{18}FDG-PET-CE-CT) diagnosed with BMs on MRI, but without suspect lesions on the dCE-CT of the brain. Secondary end-points were as follows: (1) the percentage of patients in which asymptomatic BM were found on ^{18}FDG-PET-CE-CT and (2) the percentage of patients developing symptomatic BM within 1 year after a negative brain MRI.

The following data were collected: age; gender; World Health Organisation performance score; smoking status; date of stage III NSCLC diagnosis; date of ^{18}FDG-PET-CE-CT and brain MRI; histology; whether molecular testing was performed; TNM; details on therapy modality (chemotherapy cycles, delivered radiation dose and whether treatment was completed) and development of BM during follow-up (date, number, treatment modality).

2.3. MRI and dCE-CT of the brain protocols (during ^{18}FDG-PET-CE-CT)

See supplemental data S1.

2.4. Statistical analyses

2.4.1. Sample size calculation

The primary end-point for this study was the percentage of patients diagnosed with BMs on MRI, but without suspect lesions on the dCE-CT of the brain. After intercollegial discussion, difference of more than 2% was considered clinically relevant. With an expected difference of 2% and a one-sided 95% confidence interval (95% CI) not exceeding 4%, a total of 118 ^{18}FDG-PET-CE-CT and brain MRI staged patients were needed to calculate a one-sided 95% CI around 2% that excluded the 4% threshold, given these assumptions. After 118 patients were included, we decided to continue including patients during the 1 year follow-up period of the first 118 patients to have more solid data for the primary end-point.

Statistical analysis was performed with SPSS (version 23; SPSS Inc., Chicago, IL). The secondary end-points and baseline characteristics were analysed using standard descriptive statistics.

3. Results

All NSCLC patients presented at the tumour boards from December 2012 until October 2017 were screened for eligibility. Three hundred thirty-eight consecutive patients had extracranial stage III NSCLC based on ^{18}FDG-PET. In 118/338 patients (35%), no dedicated brain CE-CT was performed together with the staging FDG-PET, 62 out of these 118 (52%) patients had only a LD-CT for attenuation correction, and after central revision of the CE-CTs of the brain, 56/118 (47%) had a CE-CT but without dedicated brain imaging protocol (i.e. wrong field of view and/or hands above the head). Seventy-one (32%) of the remaining 220 patients were excluded because of asymptomatic BMs on dCE-CT of the brain (N = 16, 7%), second primary (N = 11, 5%) or no brain MRI (N = 44, 20%). As a result, 149 patients were included, of whom 118 had a follow-up of at least 1 year (Fig. 1). Baseline characteristics are summarised in Table 1.

Median time (range) between ^{18}FDG-PET-CE-CT and MRI was 2.4 (0.0–8.1) weeks. In 24.7%, time from ^{18}FDG-PET to MRI was more than 3 weeks.

In 7/149 (4.7%) patients, BMs were detected on MRI despite no suspect brain lesions on dCE-CT. In retrospect, after central review of all the imaging, in one of these seven patients, a solitary BM could be identified

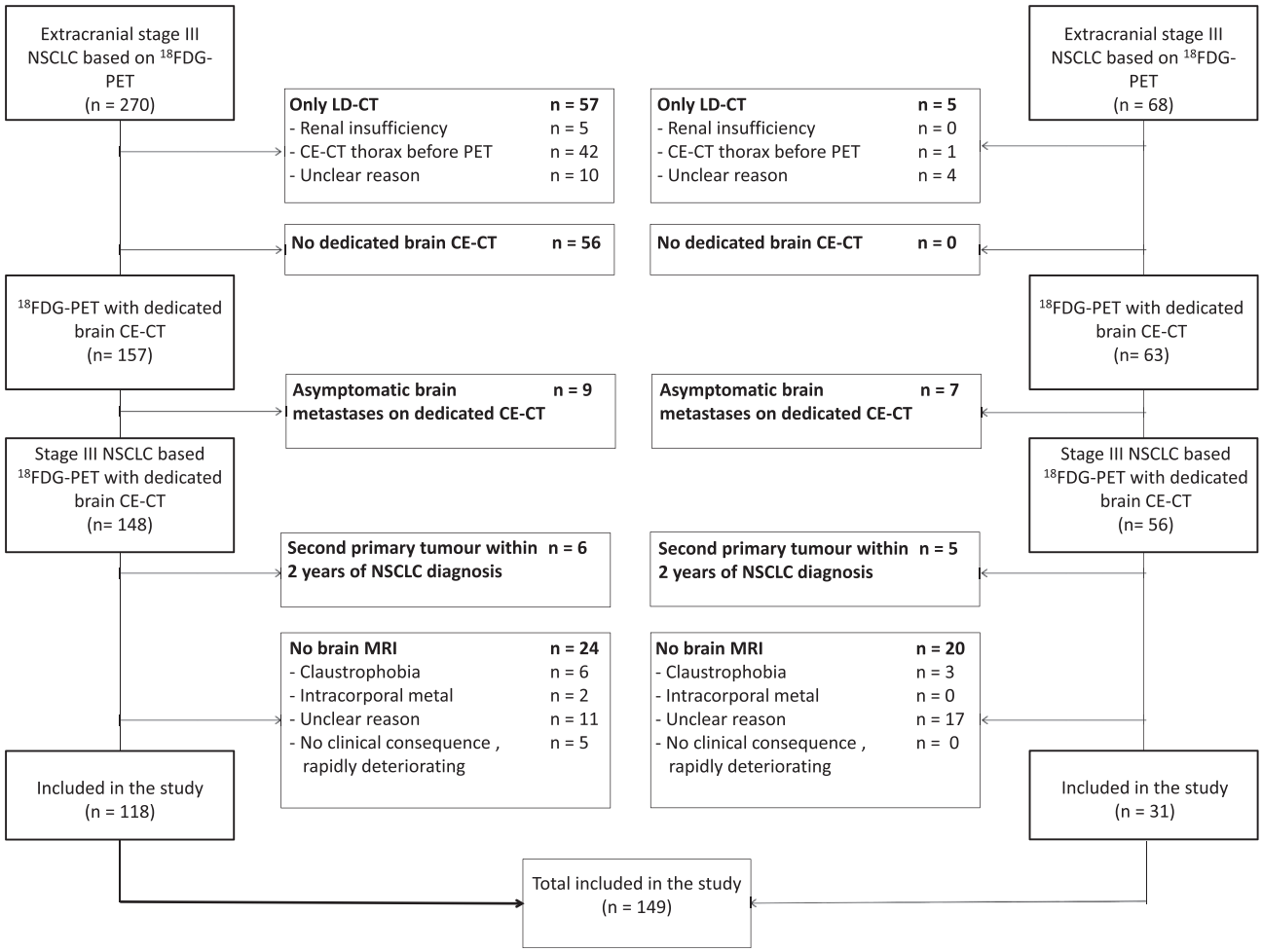

Fig. 1. Consort diagram. CE-CT, contrast enhanced–computer tomography; MRI, magnetic resonance imaging; NSCLC, non–small-cell lung cancer; ^{18}FDG-PET, ^{18}F-deoxyglucose–positron emission tomography; LD-CT, low-dose CT.

on the ^{18}FDG-PET-CE-CT. Characteristics of these seven patients are summarised in Table 2.

118/149 patients had a follow-up period of at least 1year. Treatment characteristics of these 118 patients are in Table 3. 4/118 had already baseline BMs on MRI (3.4%).

8/114 (7%) patients developed symptomatic BM within a year of a negative staging brain MRI. All but one of these patients completed the treatment for their stage III disease (six concurrent chemoradiation, one radical radiotherapy only). Characteristics of these eight patients are summarised in Table 4.

4. Discussion

In this prospective observational multicentre study, with up-to-date staging and imaging protocols, we evaluated whether brain MRI was superior to ^{18}FDG-PET-CE-CT with dCE-CT of the brain in detecting asymptomatic BM in otherwise stage III NSCLC patients. We defined a difference of more than 2% clinically relevant, as after multidisciplinary discussion, we felt that missing a higher percentage of BM would not be desirable as a BM diagnosis changes the treatment plan (*i.e.* either radically treat the BM or when not possible withhold patients from an intense multimodality treatment). In our study, brain MRI was superior to dCE-CT of the brain as an additional 4.7% of patients were diagnosed with BM on MRI. This study also shows that adequate brain imaging is necessary in this patient population, as despite the finding that 16 patients (7%) were diagnosed with asymptomatic BM on dCE-CT of the brain, brain MRI detects BM in an additional 4.7%. The total percentage of asymptomatic BM detected is comparable to previous studies [1,15].

In the participating hospitals, performing a MRI brain within a reasonable time period after ^{18}FDG-PET proved to be difficult, as in 24.7% the time from ^{18}FDG-PET to MRI was more than 3 weeks. This is not a problem unique for the participating hospitals, as in a United Kingdom survey (2014), CE-CT was preferred above MRI, presumably because of lack of access to MRI [7]. However, delay from ^{18}FDG-PET-CE-CT to MRI with subsequent growth of a microscopic BM does

Table 1
Baseline characteristics.

Patient characteristic	Group 1 (N = 118)	Group 2 (N = 31)	Total (N = 149)
Median age (years)	68	62	68
WHO PS, N (%)			
0	38 (32.2)	14 (45.2)	52 (34.9)
1	60 (50.8)	13 (42)	73 (49)
2	14 (11.9)	3 (9.7)	17 (11.4)
3	2 (2)	1 (3.2)	3 (2)
4	0 (0)	0 (0)	0 (0)
Unknown	4 (3.4)	0 (0)	4 (2.7)
Smoking status, N (%)			
Current	60 (50.8)	17 (54.8)	77 (51.7)
Former	54 (45.8)	12 (38.7)	66 (44.3)
Never	2 (1.7)	1 (3.2)	3 (2)
Unknown	2 (1.7)	1 (3.2)	3 (2)
cTstage, N (%)			
o/x	3 (2.5)	2 (6.5)	5 (3.4)
1a	4 (3.4)	1 (3.2)	5 (3.4)
1b	8 (6.8)	1 (3.2)	9 (6)
2a	24 (20.3)	1 (3.2)	25 (16.8)
2b	12 (10.2)	1 (3.2)	13 (8.7)
3	19 (16.1)	4 (12.9)	23 (15.4)
4	48 (40.7)	21 (67.7)	69 (46.3)
cNstage, N(%)			
o/x	12 (10.2)	9 (29)	21 (14.1)
1	5 (4.2)	3 (9.7)	8 (5.4)
2	72 (61)	15 (48.4)	87 (58.4)
3	29 (24.6)	4 (13)	33 (22.1)
cTNM (7th edition)			
IIIA	62 (52.5)	16 (51.6)	78 (52.3)
IIIB	52 (44.1)	12 (38.7)	64 (43)
IV (brain metastases diagnosed on baseline brain MRI)	4 (3.4)	3 (9.7)	7 (4.7)
Histology, N (%)			
Adenocarcinoma	56 (47.5)	11(35.5)	67 (45)
Squamous cell carcinoma	46 (39)	11 (35.5)	57 (38.3)
Large cell carcinoma	1 (0.8)	3 (9.7)	4 (2.7)
NOS	13 (11)	6 (19.4)	19 (12.8)
LCNEC	2 (1.7)	0 (0)	2 (1.3)
Molecular analysis, N (%)			
Not performed	62 (52.5)	23 (74.2)	85 (57)
Performed[a]			
EGFR/*KRAS* wt, *ALK*-	28 (50)	5 (62.5)	33 (51.6)
EGFR mutation	1 (1.8)	0 (0)	1 (1.6)
KRAS mutation	25 (44.6)	3 (37.5)	28 (43.8)
ALK translocation	1 (1.8)	0 (0)	1 (1.6)
Other	1 (1.8)	0	1 (1.6)

N, number; WHO PS, World Health Organisation Performance status; T, tumour; N, node; MRI, magnetic resonance imaging; NOS, not otherwise specified; LCNEC, large cell neuroendocrine carcinoma; EGFR, epidermal growth factor receptor; KRAS, Kirsten Rat Sarcoma viral antigen; ALK, anaplastic lymphoma kinase; wt: wildtype. Group 1: first cohort of included patients with year of follow up; Group 2: additional cohort of included patients during the year follow up of first group.

[a] Percentage computed only for those with known molecular analysis.

not seem to be the explanation for the lesions found on MRI for the seven patients in the present study, as median time (range) to MRI was 2.7 (0.4–6.4) weeks.

MRI can cause a delay in the workup of stage III NSCLC which is not desirable as, for example, according to the Dutch SONCOS document (SONCOS: 'Foundation for Oncological Collaboration') treatment has to start within 5 weeks of diagnosis [22]. Our results stress the importance of adequate screening for BM in this patient population and that a brain MRI is necessary, even after a dCE-CT of the brain (which can, as in our trial, be incorporated in the ^{18}FDG-PET or can be performed after a ^{18}FDG-PET). Screening with MRI should be more accessible and better integrated in the standard work-up as for example in the UK and European surveys, not all physicians screened their stage III patients and not all use MRI [7,8]. Even in our prospective study, in which MRIs, if not already performed, were advised during the tumour boards, not all patients without contraindications underwent MRI of the brain. In this observational study, no real-time check was performed to evaluate whether this advice was followed.

Detecting BM in this patient population is important as combined modality treatment is intense with a high incidence of adverse events [23,24]. Despite this intense treatment, the 5-year overall survival is only around 30% in recent series [25–27]. Most patients diagnosed with BM will not be eligible for this intensive treatment regimen, and some will be diagnosed with single or oligo-BM, potentially amenable to treatment with curative intent (surgery or radical radiotherapy) [28]. Our findings in stage III NSCLC also reinforce the recommendations recently published in the European Respiratory Journal to screen for BM in this patient population, and we show that MRI is more sensitive than dCE-CT [29,30]. The National Institute for health and care excellence in the UK recently updated their brain imaging advise, and MRI is now explicitly advised in the staging work-up of stage III NSCLC [6].

Another important issue is that 7.5–15% of stage III NSCLC patients with negative baseline brain imaging will develop (mostly symptomatic) BM within a year of NSCLC diagnosis [15,31]. With longer follow-up, this percentage increases further: in the NVALT-11/DLCRG-02 trial for example, which mandated baseline brain imaging with MRI or CT, 27.2% of patients developed symptomatic BM within 2 years after treatment with radical intent [32]. It is not known whether these metastases were already present at initial stage III diagnosis and were not detected by brain imaging or that these were newly developing metastases. Maybe some could have been detected with more sensitive MRI-techniques (higher contrast dose or higher Tesla), but this can also increase the possibility for false positive findings [33,34].

Regular follow-up brain imaging in high-risk patients is also an option to detect BMs when they are possibly still eligible for therapy with radical intent, but this is not recommended in NSCLC guidelines [3–5,9]. Known risk factors (adenocarcinoma, higher nodal stage and female gender) alone cannot predict reliably enough

Table 2
Patient characteristics of seven patients with BMs on MRI despite no suspect lesions on dCE-CT of the brain.

Patient characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Gender (M/F)	F	M	M	M	M	M	F
Age (years)	60	62	65	48	67	65	62
WHO PS score	0	1	1	1	1	0	0
cTstage	4	1b	3	3	2a	3	4
cNstage	3	2	1	2	2	2	2
Histology	Adeno	Adeno	Squamous	Squamous	Adeno	Squamous	Adeno
Molecular analysis	None	KRAS	Not performed	None	None	Not performed	None
Time between dCE-CT and MRI (weeks)	1.86	6.43	0.43	1.29	5.86	2.29	1.00
Thoracic treatment	Chemotherapy (cisplatin/ pemetrexed)	Chemotherapy (Carboplatin/ pemetrexed)	Neoadjuvant CRT (cisplatin/etoposide) + Lobectomy	Sequential CRT (gemcitabin/ cisplatin)	Sequential CRT, after 1 cycle progressive disease	Concurrent CRT (Cisplatin/ etoposide)	Concurrent CRT (cisplatin/ etoposide)

BMs, brain metastases; MRI, magnetic resonance imaging; CE-CT, contrast enhanced–computer tomography; WHO PS, World Health Organisation performance status; F, female; M, male; T, tumour; N, node; KRAS, Kirsten Rat Sarcoma viral antigen; dCE-CT, dedicated contrast enhanced–computed tomography; CRT, chemoradiation.

which patients will develop BM. In two studies (N = 317 and N = 527), single nucleotide polymorphisms in the PI3K-PTEN-AKT-mTOR pathway and microRNAs, respectively, were associated with the development of BMs in the follow-up [35,36]. However, serum tumour markers such as CEA, CYFRA21-1 and CA-125 were not associated with the development of BMs [37]. Future studies with larger samples are necessary to validate these findings.

Table 3
Treatment characteristics of patients with a minimum follow-up of 1 year.

Treatment characteristics	Group 1
	N = 118
Treatment modality, N (%)	
Concurrent CRT	75 (61.9)
Sequential CRT	26 (22)
Radical radiotherapy alone	2 (1.7)
Palliative chemotherapy[a]	2 (1.7)
Surgery[b]	9 (7.6)
BSC[a]	4 (3.4)
Radical treatment completed[c], N (%)	
Yes	92 (82.1)
No	20 (17.9)
Cycles chemotherapy when treated with CRT, N (%)	
1	9 (8.9)
2	6 (5.9)
3	82 (81.2)
4	4 (4)
Dose radiotherapy (Gy)	
Mean ± SD	66 ± 15

CRT, chemoradiotherapy; BSC, best supportive care.
[a] Radical treatment planned, but cancelled because of rapidly deteriorating physical condition.
[b] As part of multimodality treatment.
[c] For those who started radical intent therapy (N = 112).

Prophylactic cranial irradiation (PCI) to prevent the development of symptomatic BM is also an option. The randomised phase III NVALT11/DLCROG-02 study already mentioned above showed that PCI significantly decreases the proportion of patients developing symptomatic BM at 2 years after completion of chemoradiation (7.0% versus 27.2%), but at the cost of an increase in low-grade toxicity and without an improvement in overall survival [32].

Finally, immunotherapy could also have a role in reducing the incidence of BM after radical treatment, as shown in the randomised phase III PACIFIC trial (NCT02125461), evaluating adjuvant durvalumab (programmed death ligand 1 antibody) versus placebo in stage III NSCLC treated with concurrent chemoradiation. After a median follow-up of 25.6 months (from randomisation after completion of chemoradiation), the percentage of patients that developed BM was lower for durvalumab than for placebo (6.3% versus 11.8%) [38]. However, the percentage of BMs found is surprisingly low in this trial, as even the 11.8% in the placebo arm is approximately half of the percentage found in the comparator arm of contemporary stage III NSCLC PCI trials with baseline brain imaging (reviewed by Witlox *et al.*) [39]. Furthermore, in the PACIFIC trial baseline brain imaging was not mandatory, which should have resulted in a higher percentage of BM diagnosis during follow-up, as asymptomatic BM at baseline could have become symptomatic.

A possible limitation of our trial is the short follow-up, making comparison with other trials with longer follow-up difficult. However, our primary aim was to compare baseline dCE-CT and MRI brain, and one of our secondary aims was the percentage of patients with BM within a year of a negative brain MRI. Both these end-points are not influenced by the short follow-up.

Table 4
Patient characteristics of eight patients who developed BM within a year after negative baseline MRI.

Patient characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Gender (M/F)	M	F	F	M	M	F	M	F
Age (years)	67	57	51	69	70	60	74	70
WHO PS score	3	1	0	1	0	2	1	1
cTstage	T2a	T1b	T2a	T3	T2a	T4	T3	T2b
cNstage	N2	N2	N3	N2	N2	N2	N3	N2
TNM stage (7th edition)	IIIA	IIIA	IIIB	IIIA	IIIa	IIIB	IIIa	IIIA
Histology	Adeno carcinoma	Adeno carcinoma	Adeno carcinoma	Adeno carcinoma	Adeno carcinoma	Squamous cell carcinoma	NOS	Adeno carcinoma
Molecular analysis	None	None	KRAS	KRAS	KRAS	KRAS	None	None
Treatment for stage III NSCLC	Radical RTx (66Gy)	Concurrent chemoradiation (carbo/eto)	Concurrent chemoradiation (cis/eto)	Concurrent chemoradiation (cis/eto)	Concurrent chemoradiation (cis/eto)	Concurrent chemoradiation (cis/eto)	Concurrent chemoradiation (cis/eto)	Sequential chemoradiation (cis/eto)
Also extracranial progression	No	No	Yes	No	Yes	Yes	Yes	Yes

M, male; F, female; WHO PS, World Health Organisation performance status; c, clinical; T, tumour; N, node; M, metastases; KRAS, Kirsten Rat Sarcoma viral antigen; RTx, radiotherapy; Gy, Gray; carbo, carboplatin; eto, etoposide; cis, cisplatin; NOS, not otherwise specified.

The large proportion of patients excluded, because suboptimal brain CTs, make extrapolation to patients not screened with a dCE-CT difficult. However, we think it is also a strong point of our study that all included patients underwent the same, dedicated brain CT, and even with this dedicated CT-protocol, MRI detects asymptomatic BMs in more patients.

In conclusion, screening for BM is mandatory in the work-up of stage III NSCLC patients, and MRI is superior to a dedicated brain CE-CT. As the brain is a common site of relapse, prediction of BM development and prevention of BM should be the focus of clinical trials.

Conflict of interest statement

J.S. has none related to current manuscript; outside of current manuscript, J.S. received travel reimbursement from Roche.

D.D.R. has none related to current manuscript, and outside of current manuscript, D.D.R. is a member of advisory board of Bristol-Myers-Squibb, Astra Zeneca, Roche/Genentech, Merck/Pfizer and Celgene. Research grants have been received from Bristol-Myers Squibb and Boehringer Ingelheim. All income from the advisory board and from the research grants went integrally to the institution.

A.M.D. has none related to current manuscript, and outside of current manuscript, A.M.D. is member of advisory board of BMS, MSD and Roche.

L.H. has none related to current manuscript, and outside of current manuscript, L.H. received research funding from Roche and Boehringer Ingelheim (both institution) and is in advisory board of Boehringer and BMS (both institution, BMS also self) and received travel reimbursement from Roche, BMS (self), took part mentorship program with key opinion leaders funded by AstraZeneca and received fees for educational webinars: Quadia (self). All other authors have none to declare.

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Appendix A. Supplementary data

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