



Original Research Article

EGFR mutant locally advanced non-small cell lung cancer is at increased risk of brain metastasis

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ABSTRACT

Background and purpose: Small studies of primarily metastatic non-small cell lung cancer (NSCLC) have suggested an association between EGFR mutation (EGFR+) and likelihood of brain metastasis. However, these studies are confounded by follow-up time bias. We performed a competing risk analysis of brain metastasis in a more uniform locally advanced NSCLC (LA-NSCLC) cohort with known tumor genotype. **Materials and methods:** Between 2002 and 2014, 255 patients with LA-NSCLC underwent tumor genotyping for EGFR, ALK and/or KRAS (180 patients had follow-up brain imaging). Cumulative incidence and Fine-Gray regression were performed on clinical variables including genotype and risk of brain metastasis, with death as a competing event.

Results: The proportion of tumors with aberrations in EGFR, ALK and KRAS were 17%, 4% and 28%, respectively. The median follow-up was 68 months. On multivariate analysis, EGFR+ was significantly associated with risk of brain metastasis in the full patient cohort (HR 2.04, 95% CI 1.22–3.39, $p = 0.006$) as well as in the subset of patients with brain follow-up imaging (HR 1.91, 95% CI 1.17–3.13, $p = 0.01$). This translated to a higher cumulative incidence of brain metastasis in EGFR+ patients at 3 and 5 years (33.3% vs. 23.2 and 43.8% vs. 24.2%, $p = 0.006$).

Conclusion: Patients with EGFR+ LA-NSCLC have a significantly higher likelihood of developing brain metastasis after standard combined modality therapy, independent of their longer overall survival. This high-risk genotypic subgroup may benefit from routine surveillance with brain MRI to allow early salvage with targeted systemic- and/or radiation-therapies.

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1. Introduction

Brain metastases (BM) are common in patients with non-small cell lung cancer (NSCLC) but how tumor genotype influences the risk of BM is not well characterized. [1–3]. While multiple groups have reported high rates of BM in patients with EGFR+ tumors, these analyses have typically not taken into account the competing risk of death, have been unable to compare EGFR status to multiple other lung tumor genotypes, have been limited to patients with

stage IV disease, and/or have been potentially confounded by delivery of active treatment with mutation-directed therapy [4–9]. Multiple investigators have also examined the effect of other major genetic drivers such as KRAS and ALK on the likelihood of BM with variable results [5,10–15].

Predicting which LA-NSCLC patients are most likely to develop BM may improve the ability of early therapy to often prevent or delay rapid deterioration in quality of life. The goal of the current study was to perform a competing risk analysis to investigate if genotype (EGFR, ALK, KRAS or none of the above) is associated with the likelihood of developing BM in a cohort of patients with LA-NSCLC treated without upfront mutation-directed therapies and to use the cumulative incidence of BM to inform a potential screening approach for patients at highest risk.

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2. Materials & methods

2.1. Patient selection

An IRB-approved retrospective review of the medical record was performed for 255 consecutive patients with newly diagnosed LA-NSCLC, who received conventional radiation with curative intent (prescribed >45 Gy) as part of standard of care combined modality therapy between 2002 and 2014 and met the following criteria [1]: brain imaging at diagnosis [2], tumor genotyping of EGFR, ALK and/or KRAS performed during their clinical course [3], no upfront genotype-directed therapy and [4] minimum follow up of 3 months.

All analyses were performed on both the full cohort as well as the subset of patients for whom follow-up brain imaging, after initial staging work-up, was available (n = 180). To investigate whether this subset of patients differed from those who did not have follow-up brain imaging, patient, disease and treatment characteristics between these two cohorts were compared by Fisher's exact test for categorical variables and by the Wilcoxon rank sum test for continuous variables.

2.2. Tumor genotyping

Tumor genotyping for EGFR, KRAS and/or ALK was performed for all patients between 2005 and 2014 as part of routine clinical care. Briefly, DNA was isolated from paraffin-embedded tumor specimens carrying at least 50% tumor nuclei. For patients who underwent genotyping of EGFR or KRAS before 2014, mutational analysis was performed by direct Sanger sequencing and/or polymerase chain reaction with capillary gel electrophoresis using primers specific for codon 18–21 of EGFR and codon 12, 13 and 61 of the KRAS gene [16]. The eight patients who had tumor genotyping performed in 2014 underwent genotyping by OncoPanel, a genomic assay to detect somatic mutations, copy number variations and structural variants in tumor DNA by surveying 200 cancer genes and 113 introns across 35 genes for detection of rearrangements using massively parallel sequencing with the solution-phase Agilent SureSelect hybrid capture kit and an Illumina HiSeq 2500 sequencer [17]. Tumor genotyping for ALK was performed by Fluorescence In Situ Hybridization (FISH) using Vysis LSI ALK Dual color, Break Apart Rearrangement Probe (Abbott Molecular) except for in 6 patients who underwent immunohistochemistry alone and were deemed negative for the ALK oncogene by lack of over-expression.

Since the indications for and scope of genotyping changed during the follow-up period (e.g. development of ALK assays during a later period), not all patients were genotyped for all three oncogenes. Given that concurrent genetic aberrations in EGFR, KRAS and ALK are rare, case-reportable events, patients found to harbor ALK amplification or an activating mutation in EGFR or KRAS were analyzed as being negative for the other oncogenes when that information was missing [18–21].

2.3. Covariates

Patient, disease and treatment characteristics were collected for each patient as possible clinical covariates. For EGFR+, KRAS+ or ALK+ patients, additional information collected included the date of genotyping and the timing of any molecularly targeted systemic therapies.

2.4. Follow-up

Patient follow-up after treatment completion was at the discretion of the treating providers, and per institutional standards typically involved clinical evaluation and chest CT with contrast every

3–6 months for 3 years, every 6 months for 2 years, and annually thereafter. More frequent imaging was performed to follow radiographic abnormalities. Brain imaging was not considered standard surveillance and was only performed for symptoms, known disease recurrence at another site or clinical trial enrollment. All brain MRIs were performed as standard high resolution post-contrast MRI brain scans on a 1.5 T or 3 T MRI scanner.

2.5. Outcomes

The primary outcome was diagnosis of first BM, defined as a new, enhancing lesion on brain MRI radiographically consistent with a brain metastasis. To examine how the development of BM fit within the overall disease trajectory, information about site and time of first distant metastasis (DM) as well as overall survival (OS) was also collected. Time to BM or DM was defined as the interval from date of first LA-NSCLC-directed therapy (including surgery, radiation or systemic therapy) to development of BM or the radiographic evidence of metastatic disease, respectively. OS was similarly defined from date of first LA-NSCLC-directed therapy to date of death.

For the time-to-BM analysis, patients who did not develop BM were censored using two different strategies: censoring at time of last negative brain imaging (including head CT) and censoring at time of last follow-up without symptoms of BM (regardless of intra-cranial imaging). For time-to-DM analysis, patients who did not develop DM were censored at the time of last negative CT imaging. For OS, patients who were alive at last known follow-up were censored at the last time known to be alive.

2.6. Competing risk analysis

To evaluate the associations between BM and patient demographics as well as disease characteristics, competing-risks regression was performed with death as a competing event [22]. Variables with $p < 0.05$ in the univariable analysis were included in the multivariable model. If overall disease stage and N stage were both significant, the variable with smaller p value was included in the multivariable model.

3. Results

3.1. Patient, disease and treatment characteristics

The patient, tumor and treatment characteristics of the full cohort of patients included in this study as well as the 180 (71%) for whom follow-up brain imaging was available are shown in Table 1. The 180 patients with follow-up imaging did not significantly differ from the 74 patients who did not have follow-up imaging across any of these characteristics except for those with follow-up imaging being significantly younger than those without follow-up imaging (median 61 years vs. 66 years, $p = 0.0006$).

Approximately 60% of patients underwent surgery as part of definitive management with lobectomy being the most common operation. Eighty-three percent of patients (n = 211) received chemotherapy concurrently with radiation. The majority (n = 96) of patients receiving additional chemotherapy after chemoradiation and/or surgery received a platinum doublet.

The distribution of tumor genotype is shown in Table 2. Forty-three percent (n = 110) had alterations in one of the 3 genes evaluated for this study. There was no statistically significant difference in the distribution of tumor genotype between patients who had or were missing follow-up brain imaging.

Table 1
Patient, tumor and treatment characteristics for patients with LA-NSCLC treated with curative intent radiation as part of combined modality therapy (n = 255).

		All patients (n = 255)		Subset with follow up brain imaging (n = 180)	
<i>Patient characteristics</i>					
Median age at start of treatment (yr ^a)		64 (33–93)		61 (33–86)	
Gender					
	Male	96	37.6%	72	40.0%
	Female	159	62.4%	108	60.0%
Performance Status					
	0	126	49.4%	88	48.9%
	1	118	46.3%	82	45.6%
	2	10	3.9%	9	5.0%
	3	1	0.4%	1	0.6%
Smoking status at diagnosis					
	Never	50	19.6%	37	20.6%
	Former	129	50.6%	84	46.7%
	Current	76	29.8%	59	32.8%
<i>Disease characteristics</i>					
Histology					
	Adenocarcinoma	217	85.1%	157	87.2%
	Adenosquamous	4	1.6%	3	1.7%
	NSCLC NOS ^b	34	13.3%	20	11.1%
Pathology grade					
	1	6	3.0%	4	2.9%
	2	71	35.5%	49	35.0%
	3	123	61.5%	87	62.1%
	Unknown	55	–	40	–
Disease Stage					
	IIA	1	0.4%	1	0.6%
	IIB	1	0.4%	1	0.6%
	IIIA	168	65.9%	120	66.7%
	IIIB	85	33.3%	58	32.2%
Nodal stage					
	N0	4	1.6%	4	2.2%
	N1	9	3.5%	8	4.4%
	N2	177	69.4%	125	69.4%
	N3	65	25.5%	43	23.9%
<i>Curative-intent treatment</i>					
		All patients (n = 255)		With brain imaging (n = 180)	
Pre-RT Chemotherapy		36	14.1%	24	13.3%
Median RT ^c dose (Gy ^d)		60 (44–70)		60 (44–70)	
Surgery					
	None	106	41.6%	69	38.3%
	Wedge	29	11.4%	22	12.2%
	Lobectomy	114	44.7%	83	46.1%
	Pneumonectomy	6	2.4%	6	3.3%
Post-RT Chemotherapy		117	45.9%	84	46.7%

Key: a) yr-year, b) NSCLC NOS-non small cell lung cancer not otherwise specified, c) RT-radiation, d) Gy-gray.

Table 2
Distribution of tumor genotype.

		All patients (n = 255)		With brain imaging (n = 180)	
EGFR					
	Positive	42	16.7%	31	17.5%
	Negative	209	83.3%	146	82.5%
	Unknown	4	–	3	–
KRAS					
	Positive	59	27.8%	42	27.5%
	Negative	153	72.2%	111	72.5%
	Unknown	43	–	27	–
ALK					
	Positive	9	4.4%	8	5.4%
	Negative	194	95.6%	139	94.6%
	Unknown	52	–	33	–

3.2. BM characteristics, treatment and outcomes

While most patients had a brain MRI at diagnosis, 21% (n = 54) had an initial head CT. All patients who had follow-up brain

imaging had a follow-up brain MRI. Twenty-seven percent of patients (n = 70) had at least one BM during the 68-month median follow-up from initiating LA-NSCLC-directed therapy (range 3–146 months). A BM was the first documented site of metastatic

disease in 61% of patients who developed BM (n = 43). Twenty-nine percent of patients who developed BM (n = 20) had a prior local-regional disease recurrence.

The impetus for follow-up brain imaging in patients found to have BM varied. Sixty-four percent (n = 45) had imaging due to symptoms concerning for intracranial disease, 21% (n = 15) had imaging in the context of other sites of disease progression, 6% (n = 4) had imaging to determine clinical trial eligibility and 9% (n = 6) had imaging as part of overall disease restaging. Of the patients who had symptoms leading to brain imaging, the most common presenting symptom was headache (38%, n = 17), followed by altered mental status (31%, n = 14) and dizziness or ataxia (27%, n = 12). Other presenting symptoms included changes in vision, new nausea, weakness, numbness, speech deficits or seizure.

The median number of intracranial lesions among patients with BM was 2 (range 1–30). All except 8 patients underwent brain-directed treatment with further details described in Supplemental Table 1. Eighty-three percent (n = 58) of patients with BM died during the follow-up period, at a median of 8 months after BM diagnosis (range 0–126 months).

3.3. Predictors of BM in the overall patient cohort

A competing risk analysis of time to BM, with death as a competing event, was performed to determine the risk of BM across various patient subgroups. Table 3 shows the association of patient and disease factors with the likelihood of BM across the complete patient cohort (n = 255). On univariate analysis, age <65, N3 nodal status and EGFR+ were associated with increased risk of BM. ALK and KRAS status were not associated with risk of BM. Twenty four percent of patients with EGFR wild-type tumors versus 45% of patients with EGFR+ tumors developed BM (HR 1.9, 95%CI 1.16–3.10, p = 0.01). A multivariate model showed that the effect of EGFR mutation and advanced nodal stage continued to be strongly associated with BM (EGFR: HR 2.04, 95%CI 1.22–3.39, p = 0.006; N stage: HR 1.92, 95%CI 1.15–3.20, p = 0.01) while age became only borderline significant (p = 0.05).

Fig. 1 shows the cumulative incidence of BM in patients with and without EGFR mutations. The 3-year BM rate was 23% in EGFR

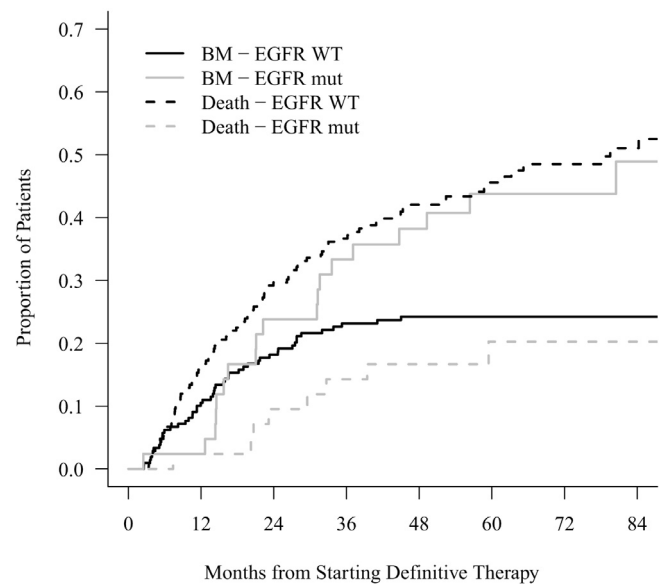


Fig. 1. Cumulative incidence of brain metastasis or death by EGFR genotype. Solid lines illustrate the proportion of patients in the overall cohort who developed brain metastasis during follow-up from the start of definitive therapy for their locally advanced NSCLC. Dashed lines illustrate the proportion of patients who died during this time.

wild-type tumors vs. 33% in EGFR+ tumors. The 5-year BM rate was 24% EGFR wild-type tumors vs. 44% in EGFR+ tumors. In contrast, the cumulative incidence of death was significantly higher in patients with EGFR wild-type tumors, both at 3-years (37% vs. 14%) and at 5-years (46% vs. 20%). Of note, patients with EGFR+ tumors had significantly longer median survival after diagnosis of brain metastasis (29 vs. 7.5 months, p = 0.0019).

3.4. Predictors of BM in the subset with follow-up imaging

Seventy-one percent of patients in the overall cohort (n = 180) had at least one brain MRI after initial staging scans. To address

Table 3
Association of clinical factors with risk of brain metastasis in the complete patient cohort.

		n ^a	w/ ^b Brain Met	Univariable Model			Multivariable Model		
				HR ^c	95% CI ^d	p	HR	95% CI	p
Age	≤65	152	33% (50)	Ref ^e	–	0.03	Ref	–	0.05
	>65	103	19% (20)	0.56	0.33–0.93		0.6	0.35–1.00	
Gender	Female	159	26% (42)	Ref	–	0.56	–	–	–
	Male	96	29% (28)	1.16	0.71–1.87		–	–	–
Smoking status	Never	50	36% (18)	Ref	–	0.49	–	–	–
	Former	129	26% (34)	0.76	0.45–1.30		–	–	–
	Current	76	24% (18)	0.71	0.37–1.34		–	–	–
Histology	Adenocarcinoma	217	28% (60)	Ref	–	0.94	–	–	–
	Other	38	26% (10)	0.98	0.50–1.92		–	–	–
Disease stage	IIA/IIIB/IIIA	170	26% (44)	Ref	–	0.37	–	–	–
	IIIB	85	31% (26)	1.25	0.77–2.03		–	–	–
N stage	N0–N2	190	24% (46)	Ref	–	0.03	Ref	–	0.01
	N3	65	37% (24)	1.73	1.05–2.84		1.92	1.15–3.20	
EGFR mutant	No	209	24% (50)	Ref	–	0.01	Ref	–	0.006
	Yes	42	45% (19)	1.9	1.16–3.10		2.04	1.22–3.39	
	Unknown	4	25% (1)	–	–		–	–	
KRAS mutant	No	153	29% (45)	Ref	–	0.67	–	–	–
	Yes	59	25% (15)	0.88	0.49–1.59		–	–	–
	Unknown	43	23% (10)	–	–		–	–	–
ALK mutant	No	194	29% (57)	Ref	–	0.25	–	–	–
	Yes	9	11% (1)	0.32	0.05–2.20		–	–	–
	Unknown	52	23% (12)	–	–		–	–	–

Key: a) n-number, b) w/-with, c) HR-hazard ratio, d) CI-confidence interval, e) Ref-reference, i.e. 1.0.

the possibility that the patients who did not have follow-up brain imaging were skewing the overall analysis, a competing risk analysis of time to BM with death as a competing event was also performed in the subset of patients who had at least one brain MRI after initial staging scans. Table 4 shows the association of various patient and disease factors with the likelihood of subsequent detected BM in patients with follow-up brain MRI. On univariate analysis, N3 nodal status and EGFR mutation continued to be associated with increased risk of BM, while younger age was no longer associated. A multivariate model confirmed the association of both variables with the risk of BM (N stage: HR 2.19 95%CI 1.32–3.64, $p = 0.003$; EGFR: HR 1.91, 95%CI 1.17–3.13, $p = 0.01$). ALK and KRAS status continued to show no association with risk of BM.

3.5. Distant metastasis-free survival

To examine if the association of EGFR mutations and BM was simply the result of EGFR mutations being negatively prognostic in this patient cohort, the relationship between various patient and disease factors with distant metastasis-free survival was also examined (Supplemental Table 2). In this analysis the presence of EGFR mutation was protective against death or distant metastasis (69% vs. 79%, $p = 0.02$).

3.6. BM as the first site of metastatic disease

The relationship between various patient and disease factors and BM as the first site of metastatic disease was examined by a competing risk analysis for first BM with other metastasis or death as a competing risk (Supplemental Table 3). While age <65 and advanced nodal status were both associated with early BM, EGFR status (as well as KRAS status) did not show a significant association.

A similar analysis was also performed for BM as the first site of metastatic disease in the subset of patients for whom follow-up brain imaging was available (Supplemental Table 4). Advanced nodal stage was the only factor which showed a significant association.

3.7. The use of targeted therapy in patients with EGFR mutation

Of the 42 patients found to have an EGFR mutation, 74% ($n = 31$) received EGFR-directed therapy at any point between genotyping and last follow-up. Given the era of this study, erlotinib was used in all cases except for 2 patients receiving gefitinib, 2 receiving afatinib and 1 receiving vandetanib. Fifty-five percent ($n = 17$) of patients taking EGFR-directed therapy developed BM (vs. 22% of patients who did not receive targeted therapy). Among the 14 patients carrying EGFR+ NSCLC who received targeted therapy but did not develop BM, 6 received EGFR-targeted therapy after the last brain MRI showed no evidence of BM.

Of the 17 patients who received targeted therapy and developed BM, 29% ($n = 5$) were started on this therapy after diagnosis with BM while 71% ($n = 12$) were started on this therapy before BM diagnosis. The median time lapse from starting EGFR-directed therapy to diagnosis of BM in patients who were treated with targeted therapy before BM was 20 months (range 4–51 months).

4. Discussion

The primary finding of the current study is that patients with locally advanced EGFR+ adenocarcinoma of the lung are at higher risk of developing BM, independent of their relatively lower competing risk for death. While others have previously reported a correlation between EGFR+ and increased likelihood of BM, this is the first study to account for the competing risk of death and specifically look at patients with LA-NSCLC treated with combined modality therapy (largely Stage III) [4–6,8]. Given that one-third of patients with EGFR+ LA-NSCLC developed BM within 3 years of initiating definitive therapy and almost half of these patients developed BM within 5 years, our findings provoke the question of whether a diagnostic or therapeutic intervention may improve outcomes in this selected cohort.

One possible intervention that could be considered would be prophylactic cranial irradiation (PCI) in patients with locally advanced EGFR+ NSCLC. Three randomized studies have looked at the role of PCI in unselected Stage III NSCLC patients in the mod-

Table 4
Association of clinical factors with risk of brain metastasis in the patient cohort with follow-up brain imaging.

	n ^a	w/ ^b Brain Met by Imaging	Univariable Model			Multivariable Model			
			HR ^c	95% CI ^d	p	HR	95% CI	p	
Age	≤65	116	43% (50)	Ref ^e	–	0.12	–	–	–
	>65	64	31% (20)	0.66	0.39–1.12	–	–	–	–
Gender	Female	108	39% (42)	Ref	–	0.9	–	–	–
	Male	72	39% (28)	0.97	0.60–1.57	–	–	–	–
Smoking status	Never	37	49% (18)	Ref	–	0.7	–	–	–
	Former	84	40% (34)	0.94	0.56–1.58	–	–	–	–
	Current	59	31% (18)	0.77	0.41–1.44	–	–	–	–
Histology	Adenocarcinoma	157	38% (60)	Ref	–	0.55	–	–	–
	Other	23	43% (10)	1.24	0.62–2.46	–	–	–	–
Disease stage	IIA/IIIB/IIIA	122	36% (44)	Ref	–	0.35	–	–	–
	IIIB	58	45% (26)	1.26	0.77–2.04	–	–	–	–
N stage	N0–N2	137	34% (46)	Ref	–	0.009	Ref	–	0.003
	N3	43	56% (24)	1.95	1.18–3.21	–	2.19	1.32–3.64	–
EGFR mutant	No	146	34% (50)	Ref	–	–	Ref	–	0.01
	Yes	31	61% (19)	1.74	1.09–2.78	0.02	1.91	1.17–3.13	–
	Unknown	3	33% (1)	–	–	–	–	–	–
KRAS mutant	No	111	41% (45)	Ref	–	–	–	–	–
	Yes	42	36% (15)	0.86	0.47–1.57	0.63	–	–	–
	Unknown	27	37% (10)	–	–	–	–	–	–
ALK mutant	No	139	41% (57)	Ref	–	–	–	–	–
	Yes	8	13% (1)	0.23	0.03–1.55	0.13	–	–	–
	Unknown	33	36% (12)	–	–	–	–	–	–

Key: a) n-number, b) w/-with, c) HR-hazard ratio, d) CI-confidence interval, e) Ref-reference, i.e. 1.

ern era treated in a multi-institutional setting with all three having slower than expected accrual and showing variable benefits [23–25]. A systematic review and meta-analysis including the two older studies as well as four additional trials from an earlier era also suggested that PCI decreases the risk of developing BM without an improvement in OS [26]. None of these studies included follow-up brain imaging unless symptoms suggestive of BM were present.

It is well documented that the decrease in BM risk with PCI is accompanied by the potential for significant neurocognitive toxicity [27,28]. Given the lack of overall survival benefit, PCI would still likely result in over-treatment. This is particularly true in the era of modern EGFR-directed tyrosine kinase inhibitors (TKIs) and stereotactic radiation therapy which can often effectively act as first line BM treatment while sparing patients the neurocognitive effects of whole brain radiation [29–32].

An alternative approach may be suggested by the extensive-stage small cell lung cancer (ES-SCLC) literature where a phase 3 study from Japan showed that systematic MRI surveillance negated any benefit of PCI in improving survival [33]. Several single institution retrospective studies have also suggested a benefit to brain MRI surveillance in NSCLC, but randomized data are lacking [34,35].

In determining how to design a trial to investigate the question of whether brain MRI surveillance may be helpful in EGFR+ NSCLC, two important variables would be the interval of brain MRIs after upfront therapy and the appropriate intervention at the time of identifying new BM. Based on the current study, it appears the risk of BM rises most rapidly from 1 year after initiating definitive therapy through 5 years. As a result, we would suggest surveillance brain MRI every 6 months, beginning at a year after treatment initiation and ending at 5 years.

Multiple studies have shown that with a limited burden of intracranial disease, stereotactic radiosurgery (SRS) is an excellent option to promote local disease control with a favorable side effect profile. The efficacy of this approach has been particularly well characterized in the context of EGFR+ or ALK+ NSCLC BM [29–31,36–38]. How SRS would best be combined with TKIs is also under active investigation. One recent study has suggested that upfront EGFR-directed therapy and deferral of SRS is associated with inferior OS in TKI-naïve patients, suggesting SRS followed by EGFR-directed therapy may be the optimal treatment paradigm [32]. However, there are several important caveats to this study. Specifically, patients were treated in the pre-osimertinib era when the efficacy of EGFR-directed therapy may have been somewhat less than what is now standard-of-care. In addition, the number of TKI-naïve EGFR+ NSCLC patients who develop BM may be a shrinking cohort going forward. At our institution, for TKI-naïve patients with limited, asymptomatic, new intracranial disease, our practice is to initiate EGFR-directed therapy with short interval follow-up brain MRI to assess for disease response with a low threshold for salvage SRS in the setting of progression.

While our work helps provide a foundation for the next generation of studies investigating how best to manage patients with EGFR+ NSCLC, we acknowledge several limitations of our study. One limitation is that 21% of patients had a CT head at baseline which could lead to downstaging at diagnosis. Another limitation is our inability to draw definitive conclusions regarding the role of ALK+ status in risk of BM given the low number of patients with this mutation in our patient cohort. Similarly, while BM are commonly seen in ALK-rearranged (ALK+) NSCLC, it is not clear if BM are more common in this subgroup than in other genetic subtypes of disease [5,13–15]. In addition, given that patients included in this study were treated between 2002 and 2014, the effect of the latest generation of EGFR-directed therapies, such as osimertinib, were not able to be evaluated. However, we have been able to

demonstrate that patients with EGFR+ LA-NSCLC have a significantly higher likelihood of developing BM compared to patients with EGFR wild type tumors, independent of their longer overall survival. In this context, patients with EGFR+ tumors may benefit from prospective evaluation of whether routine surveillance with brain MRI improves quality of life by allowing early initiation of salvage targeted systemic- and/or radiation-based therapies.

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Declaration of Competing Interest

RM – Astra Zeneca – Scientific Advisory Board; Varian – Consulting. All other authors declare they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2019.06.008>.

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