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EGFR mutated non-small cell lung cancer patients: More prone to development of bone and brain metastases?

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ABSTRACT

Objectives: Both bone and brain are frequent sites of metastasis in non-small cell lung cancer (NSCLC). Conflicting data exist whether EGFR mutant (+) patients are more prone to develop brain metastases or have a better outcome with brain metastases compared to EGFR/KRAS wildtype (WT) or KRAS+ patients. For bone metastases this has not been studied.
Methods: In this retrospective case-control study all EGFR+ (exons 19 and 21) patients diagnosed at two pathology departments were selected (2004/2008 to 2012). For every EGFR+ patient a consecutive KRAS+ and WT patient with metastatic NSCLC (mNSCLC) was identified. Patients with another malignancy within 2 years of mNSCLC diagnosis were excluded. Data regarding age, gender, performance score, histology, treatment, bone/brain metastases diagnosis, skeletal related events (SRE) and subsequent survival were collected.
Results: 189 patients were included: 62 EGFR+, 65 KRAS+, 62 WT. 32%, 35% and 40%, respectively, had brain metastases ($p = 0.645$). Mean time to brain metastases was 20.8 [±12.0], 10.8 [±9.8], 16.4 [±10.2] months (EGFR+–KRAS+, $p = 0.020$, EGFR+–WT, $p = 0.321$). Median post brain metastases survival was 12.1 [5.0–19.1], 7.6 [1.2–14.0], 10.7 [1.5–19.8] months ($p = 0.674$). 60%, 52% and 50% had metastatic bone disease ($p = 0.528$). Mean time to development of metastatic bone disease was 13.4 [±10.6], 23.3 [±19.4], 16.4 [±9.6] months ($p = 0.201$). Median post metastatic bone disease survival was 15.0 [10.6–20.3], 9.0 [5.2–12.9], 3.2 [0.0–6.9] months ($p = 0.010$). Time to 1st SRE was not significantly different.
Conclusions: Incidence of brain and bone metastases was not different between EGFR+, KRAS+ and WT patients. Post brain metastases survival, time from mNSCLC diagnosis to metastatic bone disease and 1st SRE did not differ either. Post metastatic bone disease survival was significantly longer in EGFR+ patients. Although prevention of SRE's is important for all patients, the latter finding calls for a separate study for SRE preventing agents in EGFR+ patients.

1. Introduction

Metastatic non-small cell lung cancer (mNSCLC) patients with activating epidermal growth factor receptor mutations (EGFR+) have, compared to KRAS mutated (KRAS+) or EGFR/KRAS wildtype (WT) patients, a longer progression free survival (PFS) and overall survival (OS) when treated with EGFR-tyrosine kinase inhibitors

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(TKI) [1–3]. Differences in tumor biology may also reflect metastatic pattern. Similar to patients with (EGFR/erB family member) HER2 positive breast cancer [4], the incidence of brain metastases may be higher in EGFR+ patients as compared to EGFR− patients[5–9]. One explanation is the inability of currently available EGFR-TKI to cross the intact blood-brain barrier at recommended doses [10]. In the above mentioned studies only patients with brain metastases were enrolled [5,7,9] and/or mutation status was not known for all included patients [6,8,9]. Thus, the question whether the time to development of brain metastases and outcome is different between EGFR+, KRAS+ or WT patients could not be answered. Next to brain, bone is a frequent site of metastasis in NSCLC exerting a negative impact on quality of life [11–13]. Brain metastases have also a negative impact on survival [14]. Different metastatic patterns may have implications for diagnostic strategies (e.g. screening) and treatment decisions (e.g. prophylactic treatment).

In this retrospective case-control study we compared EGFR+ to KRAS+ and WT mNSCLC patients to determine whether EGFR+ patients are more prone to develop brain metastases and/or metastatic bone disease, and whether they have a different survival following the detection of these metastases.

2. Materials and methods

This study was designed as a retrospective case-control study, using a prospectively collected database.

Patient selection: All EGFR+ patients who were diagnosed at the pathology departments of two university hospitals (MUMC+ and VUMC) were selected. For every EGFR+ patient the consecutive KRAS+ and WT NSCLC patient was selected. The MUMC+ database covers the period 01-10-2008 to 01-08-2012 and the VUMC database 01-11-2004 to 01-01-2012. The MUMC+ pathology department performs mutation analysis for the MUMC+ (both general and referral hospital) and four surrounding general hospitals. From the VUMC database only patients who underwent treatment at VUMC (mainly referral hospital) were selected in order to obtain sufficient follow-up data.

Inclusion criteria: mNSCLC and known mutation status (activating EGFR+: exon 19 deletion or exon 21 mutation, KRAS+ or WT (defined as: no EGFR or KRAS mutation)).

Exclusion criteria: exon 18 or 20 EGFR mutation, other active malignancy within 2 years of diagnosis of mNSCLC, mixed histology, EML4-ALK translocation positive (when testing was performed) or no follow-up data available (at least one visit after diagnosis of mNSCLC required).

The in- and outpatient medical records of all patients were retrieved and the following data were collected: age at diagnosis of mNSCLC; gender; smoking status; date of first diagnosis NSCLC and of mNSCLC; histology; treatment; development, number, symptoms and treatment of brain metastases; development, and treatment of metastatic bone disease, skeletal related event (SRE) and time of death. Last date of follow-up was August 2013.

Medical ethical committee approval was not obtained in accordance with local regulations, as it is a retrospective study with no interventions.

2.1. Mutation analysis

Mutation analysis for EGFR (exons 18–21) and KRAS (exons 2–3) was performed as part of standard of care with high resolution melting as pre-screening followed by Sanger sequencing to confirm genotype [15].

2.2. Statistical analysis

Statistics were performed using SPSS (IBM statistics, version 20). Descriptive statistics of demographic and clinical variables were obtained. Categorical variables were compared using chi-square tests, continuous variables were compared using ANOVA. For patients without metastatic bone disease or brain metastases at first diagnosis of mNSCLC, time to diagnosis of these metastases was calculated from diagnosis of mNSCLC and was expressed as mean with standard deviation (SD). Means were compared using ANOVA with, if statistically significant, post hoc Student's *t*-tests for pair wise comparisons. OS was defined as time from diagnosis of mNSCLC to death and post metastatic bone disease and post brain metastases survival was calculated from diagnosis of these metastases to death (patients without event were censored at last visit). Both were estimated using the Kaplan–Meier method. Survival curves were compared using the log-rank test. To estimate the hazard ratio (HR), Cox regression analysis was used.

3. Results

3.1. Patient characteristics

Respectively 59/603 (9.8%) and 26/346 (7.5%) NSCLC patients included in the MUMC+ and VUMC database carried an EGFR mutation. These 85 EGFR+ patients were paired with the consecutive KRAS+ and WT patients. The medical records of these 255 patients were analyzed. 3 EGFR+ patients had an exon 18 mutation and 8 had an exon 20 mutation; these patients were excluded together with the consecutive KRAS+ and WT patient. In addition, 33 patients were excluded because of: no metastatic disease ($N = 13$), another malignancy diagnosed within 2 years of mNSCLC diagnosis ($N = 10$), no follow up data ($N = 8$) or ALK translocation ($N = 2$). Finally, 189 patients were included in the analysis: 62 EGFR+, 65 KRAS+ and 62 EGFR/KRAS WT (WT). Patient characteristics are shown in Table 1. Most EGFR+ patients (58/62 (93.5%)) received an EGFR-TKI during the course of their disease, 41/58 (70.7%) as first line treatment.

Of the 62 EGFR+ patients, 41 had exon 19 deletions and 21 had exon 21 mutations (of which one combined with an exon 19 deletion).

3.2. Overall survival

Median OS [95% CI] was significantly longer for EGFR+ patients compared to KRAS+ and WT patients: 26.7 [20.4–32.9]; 11.0 [6.8–15.1] and 11.5 [7.6–15.3] months respectively (HR 1.379 [1.135–1.677], $p < 0.0001$, Fig. 1). Within the EGFR+ group, median OS was significantly longer for exon 19 than in exon 21 mutated

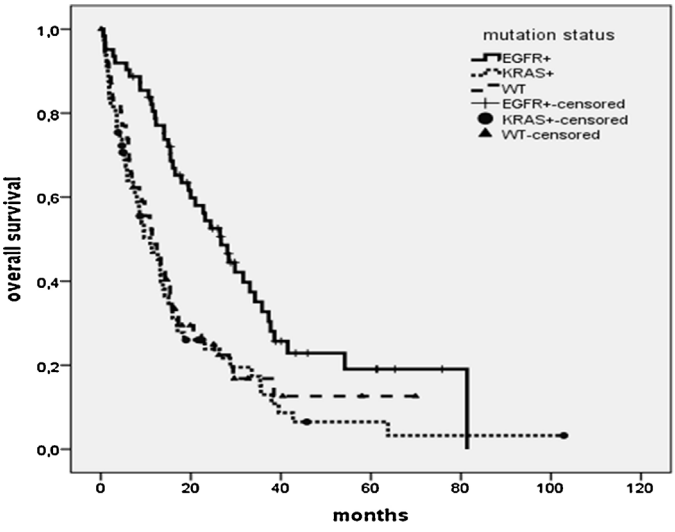

Fig. 1. Overall survival for EGFR+, KRAS+ arid WT patients.

Table 1
Patient characteristics.

Characteristics	EGFR+ N = 62	KRAS+ N = 65	Wildtype N = 62	
Female *N* (%)	46 (74.2)	38 (58.5)	26 (41.9)	0.001
Mean age, years (range)	60.7 (29.3–90.7)	61.0 (35.1–83.3)	63.0 (39.6–81.8)	0.532
Never smoker *N* (%)	25 (40.3)	2 (3.1)	9 (14.5)	<0.001
WHO PS 0–2 *N* (%)	59 (95.2)	62 (95.4)	60 (96.8)	0.164
Adenocarcinoma *N* (%)	57 (91.9)	53 (81.5)	52 (83.9)	0.217
Stage IV disease at first diagnosis *N* (%)	54 (87.1)	49 (75.4)	61 (83.9)	0.205
PET-CT at first diagnosis of metastatic disease *N* (%)[a]	38 (61.3)	46 (70.8)	48 (77.4)	0.232
Mutation analysis performed at first diagnosis of metastatic disease *N* (%)	42 (67.7)	45 (69.2)	47 (75.8)	0.480
1st line treatment *N* (%)				
None	3 (4.8)	8 (12.3)	11 (17.7)	0.080
Chemotherapy	18 (29.0)	55 (84.6)	46 (74.2)	<0.001
EGFR-TKI	41 (66.2)	2 (3.1)	5 (8.1)	<0.001
EGFR-TKI during course of disease *N* (%)	58 (93.5)	16 (24.6)	15 (24.2)	<0.001

EGFR, epidermal growth factor receptor; WHO PS, World Health Organisation Performance Score; TKI, tyrosine kinase inhibitor.
[a] Except for one wildtype patient and for four patients missing data: all other patients Ct-thorax/upper abdomen.

patients: 29.8 [22.1–37.5] and 15.5 [9.4–22.6] months, respectively (HR 1.550 [1.122–2.141], $p = 0.006$).

3.3. Brain metastases

Incidence of brain metastases was not different between the 3 groups: 20/62 (32.3%) EGFR+, 23/65 (35.4%) KRAS+ and 25/62 (40.3%) WT patients had brain metastases ($p = 0.645$). At diagnosis of mNSCLC brain metastases were present in 5/20 (25.0%), 9/23 (39.1%) and 13/25 (52.0%) patients ($p = 0.184$). Mean time [SD] to diagnosis of brain metastases for patients without brain metastases at initial diagnosis of mNSCLC was 20.8 [±12.0]; 10.8 [±9.8] and 16.4 [±10.2] months, respectively. EGFR+ patients had a significantly longer time to development of brain metastases than KRAS+ ($p = 0.020$) but not compared to WT patients ($p = 0.321$). No significant difference in median [95% CI] post brain metastases survival was observed: 12.1 [5.0–19.1]; 7.6 [1.2–14.0] and 10.7 [1.5–19.8] months (HR 1.119 [0.801–1.565], $p = 0.674$, Table 2, Fig. 2).

All 15 EGFR+ patients who developed brain metastases after initial diagnosis of mNSCLC were treated with an EGFR-TKI during the course of their disease (9/15 (60%) first line, 12/15 (80%) before development of brain metastases). Mean time [SD] to development of brain metastases was not significantly different between EGFR+ patients who were in first line treated with an EGFR-TKI versus patients who received it in a later line (21.3 [±12.9] months versus 18.8 [±9.2] months $p = 0.760$) nor was there a significant difference in time to brain metastases for patients who received an EGFR-TKI or only chemotherapy before development of brain metastases (21.4 [±12.4] months versus 17.3 [±12.5] months, $p = 0.675$). In the latter group ($N = 3$) EGFR-TKI treatment was started after diagnosis of brain metastases. Median survival [95% CI] post brain metastases was not significantly different between patients receiving an EGFR-TKI before or after development of brain metastases (6.8 [0.0–18.9] months compared to 11.0 [9.1–12.8] months) ($p = 0.808$). In addition no difference in OS was observed (37.3 [16.5–58.1] months and 31.6 [12.2–51.1] months, respectively, $p = 0.861$).

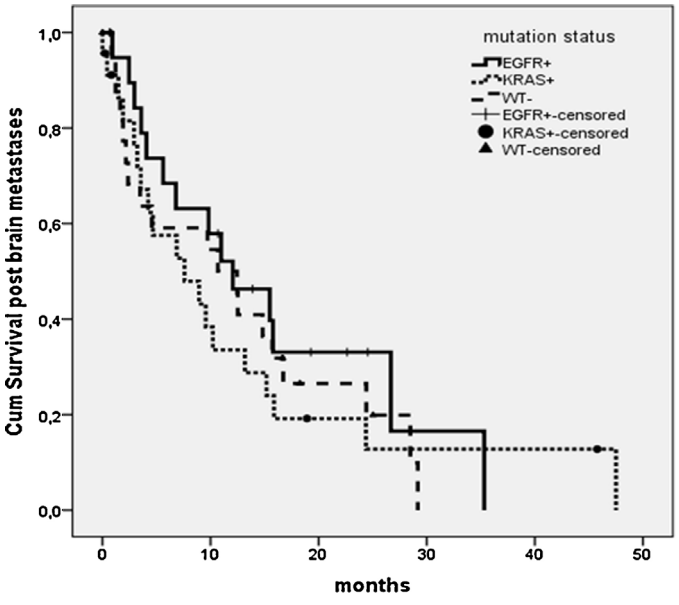

Fig. 2. survival post brain metastases for EGFR+, KRAS+ and WT patients.

3.4. Metastatic bone disease

Incidence of bone metastases was also not different between EGFR, KRAS+ and WT patients: 37/62 (59.7%) EGFR+, 34/65 (52.3%) KRAS+ and 31/62 (50.0%) WT patients were diagnosed with or developed metastatic bone disease during the course of their disease ($p = 0.528$). Of these 20/37 (54.1%), 26/34 (76.5%) and 18/31 (58.1%), respectively, had metastatic bone disease at diagnosis of mNSCLC ($p = 0.121$). Mean time [SD] to first diagnosis of metastatic bone disease for patients without metastatic bone disease at initial diagnosis of mNSCLC was respectively 13.4 [±10.6]; 23.3 [±19.4] and 16.4 [±9.6] months for EGFR+, KRAS+ and WT patients, ($p = 0.201$). No difference in SRE's was observed: 19/37 (51.4%), 22/34 (64.7%) and 15/31 (48.4%), respectively ($p = 0.361$). Also, time to first SRE was equal ($p = 0.213$). However, post metastatic bone disease survival was significantly longer in the EGFR+ group: median [95% CI] of 15.5 [10.6–20.3] months compared to 9.0 [5.2–12.9] months for KRAS+ and 3.2 [0–6.9] months for WT patients. (EGFR+–KRAS+, $p = 0.049$, EGFR+–WT, $p = 0.004$), Table 2, Fig. 3). Mean time [SD] to development of metastatic bone disease was longer, however not significant, for EGFR+ patients first line treated with EGFR-TKI (15.9 [±11.1] months) compared to those treated initially with chemotherapy (7.3 [±6.7] months) ($p = 0.380$).

4. Discussion

It is well known that patients presenting with an activating EGFR mutation have a better prognosis than KRAS+ or WT patients [1–3]. Although it is frequently suggested that EGFR+ patients, like HER2 positive breast cancer patients, are more prone to develop brain metastases during the course of their disease [5–9], this could not

Table 2
Mutation status and bone/brain metastases.

	EGFR+ *N* = 62	KRAS+ *N* = 65	Wildtype *N* = 62	*p*-Value
Brain metastases				
Imaging at 1st diagnosis of mNSCLC N (%)				
MRI	15 (24.2)	19 (29.2)	18 (29.0)	0.417
CT	20 (32.3)	25 (38.5)	28 (45.2)	
None[c]	25 (40.3)	19 (29.2)	16 (25.8)	
Missing	2 (3.2)	2 (3.1)	0 (0.0)	
Brain mets N (%)				
Yes	20 (32.3)	23 (35.4)	25 (40.3)	0.645
At diagnosis	5 (25.0)	9 (39.1)	13 (52.0)	0.184
During follow up	15 (75.0)	14 (60.9)	12 (48.0)	
No	42 (67.7)	42 (64.6)	37 (59.7)	
Time to brain mets months [SD]	20.8 [±12.0]	10.8[±9.8]	16.4 [±10.2]	EGFR/KRAS 0.020, EGFR/WT 0.321
EGFR-TKI before brain mets N (%)- (first line)	15 (100.0)–12 (80)	1 (7.1)	4 (33.3)	< 0.001
Symptomatic *N* (%)	16 (80.0)	17 (73.9)	24 (96.0)	0.097
WBRT *N* (%)	12 (60.0)	11 (47.8)	20 (80.0)	0.028
SRS *N* (%)	2 (10.0)	8 (34.8)	6 (24.0)	0.161
Surgery *N* (%)	0 (0.0)	3 (13.0)	1 (4.0)	0.260
Post brain mets survival months [95% CI]	12.1 [5.0–19.1]	7.6 [1.2–14.0]	10.7 [1.5–19.8]	0.674
Bone metastases				
Imaging at 1st diagnosis of mNSCLC N (%)				
PET-CT	38 (61.3)	46 (70.8)	48 (77.4)	0.232
CT[a]	17 (27.4)	13 (20.0)	11 (17.7)	
Bone scintigraphy[b]	5 (8.1)	4 (6.2)	2 (3.3)	
Missing	2 (3.2)	2 (3.0)	1 (1.6)	
Bone mets N (%)				
Yes	37 (59.7)	34 (52.3)	31 (50.0)	0.528
At diagnosis	20 (54.1)	26 (76.5)	18 (58.1)	0.121
During follow up	17 (45.9)	8 (23.5)	13 (41.9)	
No	25 (40.3)	31 (47.7)	31 (50.0)	
Time to bone mets months [SD]	13.4 [±10.6]	23.3 [±19.4]	16.4 [±9.6]	0.201
SRE+ *N* (%)	19 (51.4)	22 (64.7)	15 (48.4)	0.361
Time to 1st SRE months [95% CI]	12.9 [5.0–20.7]	7.3 [0.0–14.9]	3.5 [0–7.7]	0.213
Post bone mets survival months [95% CI]	15.5 [10.6–20.3]	9.0 [5.2–12.9]	3.2 [0–6.9]	EGFR/KRAS 0.049 EGFR/WT 0.004

EGFR: epidermal growth factor receptor; 95% CI = 95% confidence interval; SD = standard deviation; SRE = skeletal related event; EGFR-TKI = epidermal growth factor receptor; WBRT = whole brain radiotherapy; SRS = stereotactic radiosurgery.

[a] Ct-thorax/upper abdomen.

[b] When both PET-CT and bone scintigraphy were performed, patients were scored for "PET-CT".

[c] Only low dose CT brain during PET-CT was scored as "none".

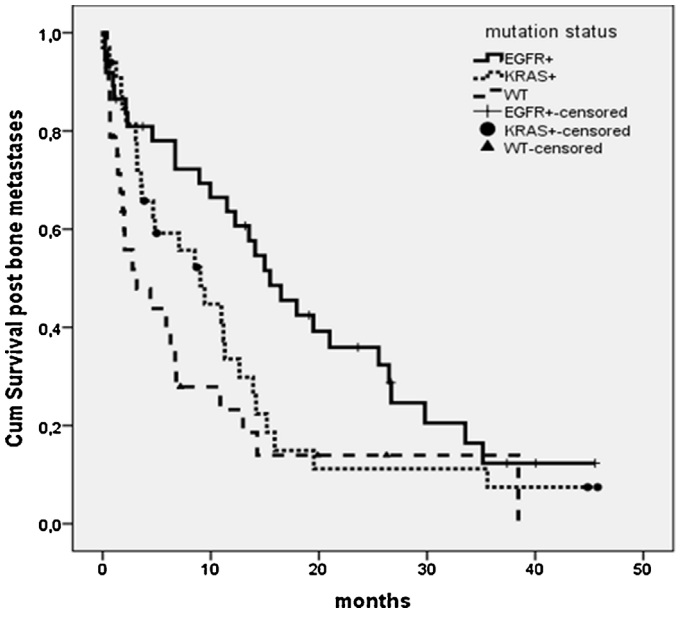

Fig. 3. Survival post bone metastases for EGFR+, KRAS+ and WT patients.

be confirmed in our retrospective case-control study. To our knowledge, this is the first case control study of EGFR+, KRAS+ and WT patients with follow-up from first diagnosis of mNSCLC to evaluate incidence of brain and bone metastases and survival thereafter. Although this was a retrospective study, bias regarding staging and treatment has been minimized by not selecting exclusively patients with brain metastases at diagnosis, but including all consecutive patients with an activating EGFR mutation and comparing the pattern of metastasis with consecutive KRAS+ and EGFR/KRAS WT patients. In the literature, one study is available that investigated the prevalence of metastases at first diagnosis of mNSCLC however without follow-up data [16]. In this study (209 consecutive nonsquamous mNSCLC patients, 39 EGFR+, 49 KRAS+, 41 ALK+ and 80 triple negative) comparable results were obtained. The percentage of bone and brain metastases was not significantly different between EGFR+, KRAS+, ALK+ and triple negative patients at initial diagnosis of mNSCLC [4].

In our study time to development of brain metastases was significantly longer in EGFR+ patients compared to KRAS+ patients, but survival post brain metastases was not significantly different. Although different treatments (EGFR-TKI versus chemotherapy) might influence development of and survival after brain metastases in EGFR+ patients in our study time to development of brain metastases was not significantly different for EGFR+ patients treated with EGFR-TKI compared to chemotherapy. However, with only 15 EGFR+ patients developing brain metastases after initial

diagnosis of mNSCLC, numbers are too small to draw firm conclusions. In contrast, in a retrospective study of Heon et al., including 155 EGFR+ patients, time to central nervous system progression was significantly longer in the EGFR-TKI than in the chemotherapy group (median of 56 versus 31.6 months) [17]. In this study CNS progression was defined not only as newly diagnosed brain metastases, but also as growth of pre-existing metastases. Brain metastases in EGFR+ patients respond to treatment with EGFR-TKIs [5,10,18–22] and radiation therapy [22,23], with median survival post brain metastases of 12–19 months [5,9,20,22]. Little is known of post brain metastases survival in EGFR+ patients treated with EGFR-TKI who develop brain metastases. In two retrospective studies (N_Y = 100 and N = 155), median survival after diagnosis of brain metastases was 5.5 [24] and 5.9 months [17]. Although not significant, in our study survival after diagnosis of brain metastases was shorter when a patient was on EGFR-TKI treatment compared to starting EGFR-TKI treatment after diagnosis of brain metastases (6.8 vs 11.0 months).

More aggressive treatment of EGFR+ patients developing brain metastases while on EGFR-TKI treatment might prolong post brain metastases survival. For example, treatment with irreversible EGFR-TKIs or pulse therapy EGFR-TKI has been studied [25–27]. In a phase I trial with afatinib, a NSCLC patient developed brain metastases during treatment with afatinib 10 mg once daily, but had a 10 month lasting intracranial response on afatinib 40 mg once daily [27]. In another study, 6/9 patients with EGFR mutant lung cancer who developed brain metastases during treatment with regular doses of EGFR-TKI had a partial response to pulse therapy erlotinib (median of 1500 mg weekly), another 2 had stable disease. Median time to central nervous system (CNS) progression was 2.8 months (range 0.8–14.5)[26]. Another option is radiotherapy and continuation of EGFR-TKI, especially when the brain is the only site of progressive disease [28,29]. In one study, CNS response rate and disease control rate were 41% and 76%, respectively. Median OS was 408 days [28]. In another study, PFS was 1.7–11.1 months, OS was not mentioned [29].

Our study did also not show a different incidence and time to development of metastatic bone disease between EGFR+, KRAS+ and WT patients. Survival post metastatic bone disease was significantly longer in the EGFR+ group, but incidence of first SRE and time to first SRE was not different. Based on these results, it seems that EGFR+ patients have a longer survival with SREs. Prevention of metastatic bone disease and subsequent development of SREs (for example with bisphosphonates or denosumab) is important for all patients, but may be especially important in this subgroup of patients due to a longer survival with metastatic bone disease and the higher change of developing a SRE. This calls for a separate study of the effects of SRE preventing agents in EGFR+ patients. Strengths of the presented study include its multicenter character, the prospectively collected database and the case-control design. Limitations include its retrospective nature and the small number of patients with brain or bone metastases. As not all EGFR mutations confer the same sensitivity to TKIs, only patients with exons 19 and 21 mutations were included. Some patients only received best supportive care, but results did not change when we performed a subgroup analysis excluding these patients (data not shown). Finally, as current practice is not to screen for metastatic bone disease or brain metastases in mNSCLC, in our series patients did not undergo standard imaging at first diagnosis of metastasized disease or during follow-up, leading to a possible underdiagnosis of metastatic bone disease and brain metastases. Since the lack of brain and/or bone imaging at first diagnosis of mNSCLC was similar for the three groups, bias is less likely. To determine whether this influenced our data at first diagnosis of mNSCLC, we reanalyzed the data excluding patients who had no brain or bone imaging at first diagnosis of mNSCLC. Results were similar (data not shown).

5. Conclusion

Incidence of metastatic bone disease and brain metastases was not different between EGFR+, KRAS+ and WT patients. Furthermore, survival post metastatic bone disease was significantly longer in the EGFR+ group, which stresses the impact of bone management especially in these patients and probably warrant more intense screening for metastatic bone disease.

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Conflict of interest statement

The authors have declared no conflict of interest.

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