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Optimising the treatment of patients with long bone metastases

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Chapter 3

Epidermal growth factor receptor mutations should be considered as a prognostic factor for survival of patients with pathological fractures of painful bone metastases from non-small cell lung cancer

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Abstract

Aims

This study aims to assess first, whether mutations in the epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma (kRAS) genes are associated with overall survival (OS) in patients who present with symptomatic bone metastases from non-small cell lung cancer (NSCLC) and second, whether mutation status should be incorporated into prognostic models that are used when deciding on the appropriate palliative treatment for symptomatic bone metastases.

Patients and Methods

We studied 139 patients with NSCLC treated between 2007 and 2014 for symptomatic bone metastases and whose mutation status was known. The association between mutation status and overall survival was analysed and the results applied to a recently published prognostic model to determine whether including the mutation status would improve its discriminatory power.

Results

The median OS was 3.9 months (95% confidence interval (CI) 2.1 to 5.7). Patients with EGFR (15%) or kRAS mutations (34%) had a median OS of 17.3 months (95% CI 12.7 to 22.0) and 1.8 months (95% CI 1.0 to 2.7), respectively. Compared with EGFR-positive patients, EGFR-negative patients had a 2.5 higher risk of death (95% CI 1.5 to 4.2). Incorporating EGFR mutation status in the prognostic model improved its discriminatory power.

Conclusion

Survival prediction models for patients with symptomatic bone metastases are used to determine the most appropriate (surgical) treatment for painful or fractured lesions. This study shows that NSCLC should not be regarded as single entity in such models.

Introduction

Lung cancer is the most common type of cancer worldwide and has the highest mortality.[1] Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers.[2-4] In addition to the histological classification (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) NSCLC is increasingly defined at the molecular level by mutations which underlie the disease process. The most common are mutations in the epidermal growth factor receptor (EGFR) gene, which is present in approximately 10 to 15% of patients, and the Kirsten rat sarcoma (kRAS) gene, which is present in approximately 30%.[5]

EGFR and kRAS function sequentially in the same signalling pathway and are therefore mutually exclusive.[6] The discovery of these oncogenes has led to the development of targeted systemic therapies in the form of tyrosine-kinase inhibitors (TKIs; e.g. erlotinib, gefitinib) for patients with an active mutation in the EGFR gene: these gave an increased survival of four to five months.[7-9] Similarly effective treatment is not currently available for kRAS mutations. The predictive role of kRAS mutations is still unclear: some trials report a worse overall survival,[10,11] while others do not identify a difference.[12,13]

Bone metastases occur in 30 to 40% of patients with lung cancer.[14] However, this figure can be expected to increase as the survival of patients with lung cancer improves with treatment that is more effective. The local treatment of BM consists of radiotherapy and/or surgery, depending on the presentation and symptoms. If pain is the most predominant symptom, radiotherapy is the mainstay of treatment: it is not invasive and reduces pain in more than 60% of patients.[15] Surgical treatments, whether for fracture or prophylaxis of impending fracture, range from minimal invasive procedures to extensive resection and reconstruction. It is usually indicated when mobility and/or neurological functioning are affected.

While the treatment of bone metastases can relieve pain and increase mobility and quality of life, it can also cause complications, additional toxicity, and co-morbidity. The need for local treatment should be weighed against a patients' predicted survival to ensure the best treatment.

Several methods of estimating survival have been developed to help patients and their doctors choose the most appropriate palliative local treatment for a painful or fractured metastatic lesion.[16-20] Although the models differ, they all include the primary tumour type as the most important variable. In all models, the primary tumour is subdivided into several categories, based on speed of tumour growth and, in some cases, the therapeutic possibilities. Currently, all NSCLC patients are categorized as having 'unfavourable/poor' tumours.

However, with the increased effect of mutations on outcome, consideration should be given to whether lung cancer should remain included as single tumour type. For example, patients with EGFR mutations might fit better in a 'moderate/intermediate' tumour profile. A different tumour profile in these models would give a more optimistic prognosis and result in other strategies of local treatment being considered. For example, a prosthesis might be used instead of an intramedullary nail to treat a pathologic fracture if a longer survival was expected.

The aim of this study was to determine first, if EGFR and kRAS mutations are associated with overall survival in patients with NSCLC who present with symptomatic bone metastases, and secondly whether mutation status can be used to differentiate between patients when estimating survival.

Patients and Methods

We carried out a retrospective analysis of all patients with NSCLC who had been treated for bony metastases of the spine, pelvis or long bones in the radiotherapy and/or orthopaedics departments of a tertiary referral centre between 2007 and 2014. Patients were identified from a search of our surgical and radiotherapy databases. Only patients with metastases in the spine, pelvis or long bones caused by histologically-proven NSCLC whose tumours had undergone analysis for EGFR and kRAS mutations were included. Patient characteristics at the time of treatment were collected from medical and pathology records and included age; gender; location of bone metastasis; presence of visceral or brain metastases; Karnofsky Performance Scale (KPS);[21] local treatment of the bone metastasis; (previous) systemic treatment for the primary tumour; mutation status and outcome (alive or dead).

The presence of visceral metastases was determined on radiology reports. Brain metastases were identified clinically; whole brain CTs or MRIs were not routinely undertaken. The KPS scores the functional ability of patients with a range from 0 to 100; with a higher score meaning the patient is better able to perform daily activities.[21] KPS scores were divided into two groups: 0 to 70 and 80 to 100. Systemic treatment was described as 'standard chemotherapy' for platinum-based chemotherapy regimens and 'targeted therapy' for tyrosine kinase inhibitors. The use of systemic treatment was registered at the time of treatment of local bone metastasis. Mutation status was defined as EGFR-positive, kRAS-positive, or 'wild type' if neither EGFR nor kRAS mutations were present. EGFR and kRAS mutations were determined by competitive allele-specific hydrolysis probes (Taqman) PCR technology (CAST).[22] If this proved inconclusive, additional classic DNA Sanger sequencing of exon 18 to exon 21 of

the EGFR-gene was undertaken. All analyses were performed in the same laboratory at the Leiden University Medical Center.

Statistical analysis

Survival time was calculated as the interval between the treatment for the bone metastasis and death or final follow-up. Survival curves were produced using the Kaplan-Meier method and compared with log-rank tests. Median follow-up was estimated with the reversed-Kaplan-Meier method.[23] The association between EGFR and kRAS mutations on overall survival (OS) was assessed using Cox proportional hazards models. A *p*-value of <0.05 was considered statistically significant.

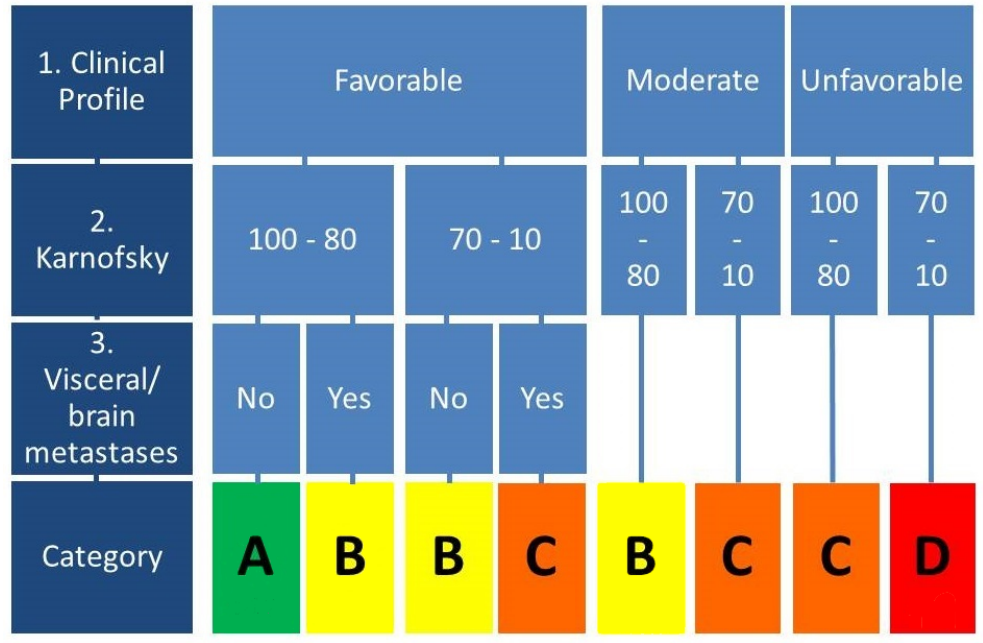

Figure 3.1 Prognostic model for overall survival as developed by Bollen et al.. Categories (A-D) correlate with expected survival in months.

To illustrate the association of EGFR with overall survival in survival prediction, the cohort was stratified according to a previously published model (figure 3.1)[16] both before and after adjusting the primary tumour type for the presence of the EGFR mutation. In the model, based on a Cox proportional hazards model, primary tumours are divided into three different tumour profiles: favourable (median survival 18.6 months; 95% confidence interval (CI) 15.1 to 22.1), moderate (median survival 5.9 months; 95% CI 4.8 to 7.0), and unfavourable

(median survival 2.2 months; 95% CI 1.9 to 2.6). In combination with two other factors (KPS and the presence of visceral and/or brain metastases) the tumour profile leads to a final category (A to D). These final categories correlate with survival. The median overall survival is 31.2 (95% CI 25.2 to 37.3), 15.4 (95% CI 11.9 to 18.2), 4.8 (95% CI 4.1 to 5.4) and 1.6 (95% CI 1.4 to 1.9) months for category A, B, C, and D respectively. Harrell's C-statistic was used to assess whether adding EGFR to the tumour profile improved the discriminatory ability of the prognostic model.

All analyses were performed using SPSS 23.0 (SPSS Inc., Armonk, New York).

Results

In the study period, 432 patients with lung cancer underwent local treatment for symptomatic bone metastases. The mutation status was available for 139 patients (32%) (53% male) with a mean age of 63.6 years (range 36.3 to 80.9). The baseline patient and tumour characteristics are presented in table 3.1. An EGFR mutation was present in 21 patients (15%) and a kRAS mutation was present in 47 patients (34%), 71 patients (51%) were wild type for both mutations.

All patients with EGFR mutations received TKIs at some point during their disease process, however only five (24%) were already on TKI treatment when they presented with symptomatic bone disease for a mean of 3.5 months (range 0.8 to 6.4). The other patients received TKIs after a mean of 2.3 months (range 0.1 to 10.1). The most commonly prescribed TKI was erlotinib (67%; 14 patients). Most patients without EGFR mutations (72%; 85 patients) underwent platinum-based chemotherapy: in 42% (36), chemotherapy was started after local treatment of the bone metastasis. The most common chemotherapy regimens were carboplatin/vinorelbine (20%) and carboplatin/pemetrexed (20%).

The median follow-up was 38.1 months (95% CI 26.9 to 49.3). Median OS was 3.9 months (95% CI 2.1 to 5.7), while mean OS was 8.4 months (95% CI 6.5 to 10.3). At final analysis, nine patients (6.5%) were still alive, four had EGFR mutations, two had kRAS mutations and two patients had 'wild type' NSCLC. No patients were lost to follow-up.

Overall survival differed significantly between patients with EGFR mutations, kRAS mutations and 'wild type' patients. For patients with EGFR mutations, the median OS was 17.3 months (95% CI 12.7 to 22.0), while the median OS was 1.8 months (95% CI 1.0 to 2.7) and 4.0 months (95% CI 1.2 to 6.8) for patients with kRAS mutations and 'wild type' patients, respectively (p = 0.001, log rank test; figure 3.2).

The difference in OS between patients with kRAS mutations and 'wild type' patients was not significant (p = 0.200, Cox regression), so kRAS was added to the wild type group, leading to a combined category 'EGFR-negative'. The median OS for the combined category was 2.8 months (95%CI 1.4 to 4.2). The corresponding hazard ratio (HR) for EGFR-negative compared with EGFR-positive for the endpoint overall survival was 2.5 (95% CI 1.5 to 4.2, p=0.001; figure 3.3).

Table 3.1 Patient and tumour characteristics in 139 patients with NSCLC treated with radiotherapy and/or surgery for symptomatic bone metastases

Characteristic	*All*	*EGFR mutation*	*kRAS mutation*	*Wild type*
Number of patients (% all patients)	139	21 (15)	47 (34)	71 (51)
Age; mean in years	63.6	62.5	64.8	63.2
Gender: male	73 (53)	7 (33)	17 (36)	49 (69)
Karnofsky Performance Score				
80 – 100	39 (28)	10 (48)	10 (21)	19 (27)
0 – 70	86 (62)	9 (43)	34 (72)	43 (61)
Unknown	14 (10)	2 (10)	3 (6)	9 (11)
Visceral or brain metastases				
Present	66 (48)	8 (38)	25 (53)	33 (47)
Not present	73 (52)	13 (62)	22 (47)	38 (54)
Location bone metastasis				
Spine	47 (34)	4 (19)	21 (45)	22 (31)
Long bone and/or pelvis	44 (32)	9 (43)	8 (17)	27 (38)
Spine & long bone and/or pelvis	48 (35)	8 (38)	18 (38)	22 (31)
Stage IV at diagnosis				
Yes	118 (85)	18 (86)	43 (91)	57 (80)
No	21 (15)	3 (14)	4 (9)	14 (20)
Treatment of primary tumor				
None	106 (76)	18 (86)	37 (79)	51 (72)
Radiotherapy	24 (17)	1 (5)	9 (19)	14 (20)
Surgery	6 (4)	1 (5)	0	5 (7)
Radiotherapy & surgery	3 (2)	1 (5)	1 (2)	1 (1)
Local therapy bone metastasis				
Radiotherapy	123 (89)	18 (86)	42 (89)	63 (89)
Surgery	1 (1)	0	0	1 (1)
Radiotherapy & surgery	15 (11)	3 (14)	5 (11)	7 (10)

EGFR: epidermal growth factor receptor; kRAS: Kirsten rat sarcoma.

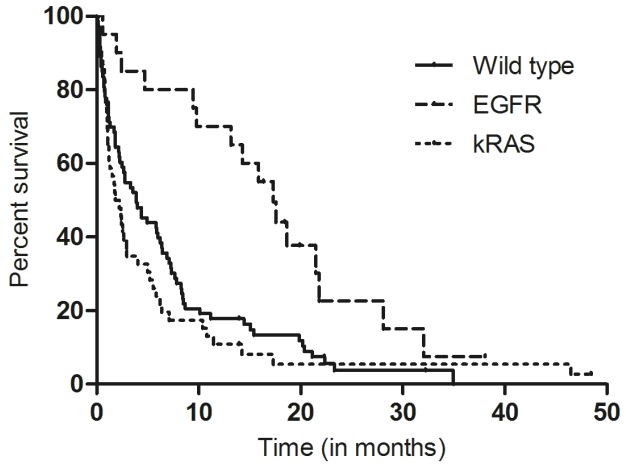

Figure 3.2 A Kaplan Meier curve shows the overall survival of 139 non-small cell lung cancer patients with bone metastases by mutation status ('wild type' for both mutations n = 71; epidermal growth factor receptor (EGFR) n = 21; Kirsten rat sarcoma (kRAS) n = 47) (p = 0.001). Time (0) = moment of local treatment of symptomatic bone metastasis.

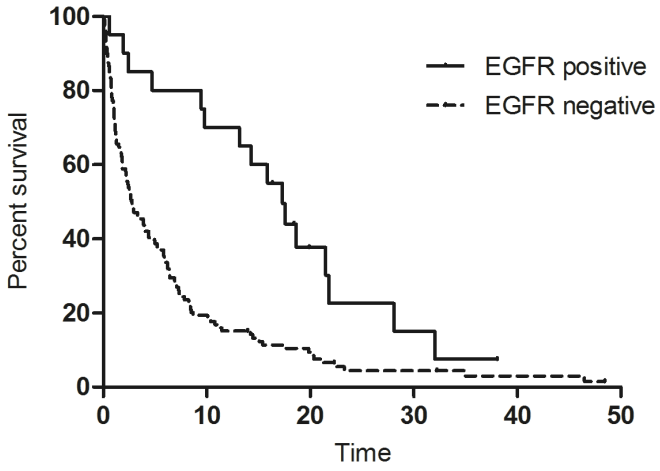

Figure 3.3 A Kaplan Meier curve shows the overall survival of 139 non-small cell lung cancer patients with bone metastases by epidermal growth factor receptor (EGFR) mutation status (EGFR-positive n = 21; EGFR-negative n = 118) (p = 0.000). Time (0) = moment of local treatment of symptomatic bone metastasis.

Table 3.2 Median survival times before and after model adjustment for EGFR mutation

*Predictive category**	*N (%)*	*Median OS (95% CI)*	*Hazard ratio*	*95% CI*	*p-value‡*
Before adjustment					
A	NA	NA	NA	NA	NA
B	NA	NA	NA	NA	NA
C	39	10.1 (3.0 – 17.2)	0.5	0.3 – 0.7	<0.001
D	86	2.0 (1.3 – 2.7)	-	-	-
After adjustment					
A	NA	NA	NA	NA	NA
B	10	17.3 (12.3 – 22.3)	0.3	0.1 – 0.6	0.001
C	38	6.0 (2.4 – 9.6)	0.5	0.3 - 0.7	0.001
D	77	1.8 (0.9 – 2.8)	-	-	-

*Categories A-D based on model in figure 3.1; ‡log rank test; OS: overall survival; CI: confidence interval; NA: not applicable (no patients in this category).

Based on the overall survival results, the classification of primary tumours in the model was re-evaluated. The median survival of patients with EGFR mutations differs from that of patients with an unfavourable profile. The classification was therefore adjusted and NSCLC with an EGFR mutation was categorized as 'moderate' profile. As a result, ten patients were reclassified as category B instead of category C and nine patients as category C instead of category D. The median survival of category C decreased from 10.1 months (95% CI 3.0 to 17.2) to 6.0 (95% CI 2.4 to 9.6) (table 3.2). The C-statistic was 0.60 before the adjustment and 0.63 after the adjustment, indicating an improvement in the discriminatory ability of the model.

Discussion

The aim of this study was to determine whether EGFR and kRAS mutations are associated with overall survival and can therefore be used as discriminating factors for survival in patients presenting with symptomatic bone metastases from NSCLC. The results show a significant difference in median survival between patients with EGFR mutations (17.3 months, 95% CI 12.7 to 22.0), kRAS mutations (1.8 months, 95% CI 1.0 to 2.7), and 'wild type' patients (4.0 months, 95% CI 1.2 to 6.8). The difference in overall survival between patients with kRAS mutations and wild type patients was not significant, but the lack of an EGFR mutation resulted in a significantly shorter overall survival compared with patients with EGFR mutation (HR 2.5; 95% CI 1.5 to 4.2). Applying this result to the tumour stratification category of a prognostic model improved the discriminative ability of the model.

An important limitation of this study is its retrospective design and associated risk of missing data. In particular, the mutation status was not available for many patients who could not therefore be included in the analysis. Due to the retrospective design, there is also a risk of indication bias about the systemic treatments that patients underwent. The aim of this study, however, was not to determine the effect of treatment but whether it is possible to distinguish patients who had a better survival. Therefore, although mutation status and treatment are inseparably linked, the impact of indication bias on our research question is limited. The period of illness will not have influenced the use of TKI because the cohort only contained patients from 2007 onwards to avoid bias from the availability of the treatment. When predicting survival, factors such as visceral metastases and performance score were taken into account as separate variables, so they need not be considered when categorising the primary tumour.

The development of TKIs has made EGFR a widely recognized positive predictive factor for survival in patients with both early and advanced disease.[24-26] With only standard platinum-based chemotherapy, patients with an EGFR mutation survived longer than patients without the mutation.[6] Although the percentage of detected EGFR mutations (15%) in the current study was lower than that in other studies (25% to 27%)[5,27] it was sufficient to detect a significant effect on overall survival. This difference in overall survival between patients with and without EGFR mutation must be attributed to the effect of TKIs.[7,24,28] However, considering all patients have stage IV disease, the difference in survival is astonishingly large. This makes one wonder whether the effect of TKIs is possibly even greater when patients present with symptomatic bone metastases than in earlier stage disease.

The current study does not explore the role of TKIs because all patients received TKIs at some point in the disease process. However, many patients did not receive TKIs until after treatment of the bone metastasis because the diagnosis of the bone metastasis was made at the same time as that of the primary tumour. Any effect of treatment after the baseline cannot be taken into account when determining the expected survival at baseline.

When using the results from the current study to predict survival in current clinical practice, it does not matter if the difference in survival is made by the treatment or the mutation, since most patients will receive or have received TKIs. The apparent difference in survival shown by this study applies to any NSCLC patient who presents with symptomatic bone metastases, whatever their previous course of disease and its treatment.

This single-centre study provides a comprehensive analysis of a recent cohort of patients with NSCLC and bone metastases. One of the relevant aspects of the current study is the timing of assessment (i.e. at presentation with symptomatic bone metastases). Although many studies have analysed the risk factors for developing symptomatic bone metastases in patients with NSCLC,[29-31] only a few have studied the prognostic factors once these symptoms become apparent.[32-35] It is exactly at this point that it is important to predict survival so that the appropriate local treatment can be chosen. Studies that have focused on this time-point are limited either because of the absence of EGFR and kRAS mutations in the analyses[33-35] or by the relatively small number of patients included.[32] Sugiura et al.[35] reported an increased survival with TKI treatment but did not state whether these patients had EGFR mutations. Bae et al.[32] have also described a protective effect of TKI treatment and, although they note lack of significance for an EGFR mutation, this is based on only ten patients with EGFR mutations.

The updated survival prediction model of Katagiri et al.[17] is currently the only method of distinguishing between different types of lung cancer, albeit in an indirect manner. In their model, patients treated with TKIs (gefitinib and/or erlotinib) were described as having a 'moderately growing' tumour, while all other lung cancer patients had 'rapidly growing' tumours. Classifications based on the medication received or the characteristics of the primary tumour (i.e. mutations) probably have the same outcome as it is assumed that most patients with an EGFR mutation receive these drugs. However, it is possible that a classification based on the medication received is more difficult to apply in daily practice because of changes over time in the use of medication. Meanwhile, the presence of a mutation is established at baseline and does not fluctuate over time, making it a constant variable.

In conclusion, this study shows that NSCLC patients with bone metastases and EGFR mutations who are treated with TKIs have an improved overall survival when compared with EGFR-negative patients. This is of importance for all those involved in the care of patients with metastatic bone disease from NSCLC because prediction of survival is crucial in determining the most appropriate treatment strategy, especially the type of surgical treatment, for painful or fractured lesions. The sub-types of NSCLC should be incorporated in prognostic models for survival of patients with bone metastases.

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