ORIGINAL ARTICLE

Association Between *EGFR* and *ALK* Mutation Status on Patient-Reported Symptoms After Palliative Radiation for Bone Pain in NSCLC

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ABSTRACT

Introduction: After palliative radiotherapy for bone metastases from NSCLC, up to 30% of patients may derive no symptomatic benefit, and there are a lack of biological predictors for this. The purpose was to investigate whether *EGFR* and *ALK* genetic rearrangements were associated with greater rates of pain response to palliative radiotherapy.

Methods: Patients were identified from a prospectively collected patient-reported outcomes database for all patients with lung cancer treated with conventional palliative radiotherapy for bone metastases from 2013 to 2016 in the province of British Columbia. Patients were divided on the basis of mutational status into the following: *EGFR* and *ALK* wild type (WT), *EGFR* mutation present (EGFR+), or *ALK* mutation present (ALK+). Patient-reported outcomes of global pain severity were collected before and after radiotherapy and on an ordinal scale of 0 to 4, with 0 representing no bone pain and 4 representing the maximal possible bone pain. The primary outcome was the rate of partial pain response (any improvement in score), and the secondary outcome was the rate of complete pain response (final pain score of 0). Stepwise, multivariable logistic analysis was used to compare response rates between treatment courses for different mutational statuses.

Results: The final cohort consisted of 388 treatment courses for 329 unique patients. For the WT, EGFR+, and ALK+ groups, there were 180, 63, and nine treatment courses, respectively. There were 92 patients with no *ALK* and *EGFR* testing. The most common treatment fractionations were 8 Gy in one fraction (188 of 388) and 20 Gy in five fractions (160 of 388), and use of multifraction radiotherapy did not differ between mutation status groups ($p = 0.3$). Partial pain response rates were as follows: WT 63%, EGFR+ 75%, and ALK+ 78%. On multivariable analysis, rates of partial response were higher for EGFR+ (OR = 5.4, $p < 0.001$) and for ALK+ (OR = 12.8, $p = 0.008$) in comparison to WT. Complete response rates were as follows: WT 20.5%, EGFR+ 35%, and ALK+ 67%. On multivariable analysis, complete response was not significantly increased in EGFR+ compared with WT (OR = 1.6, $p = 0.127$). ALK+ mutation status was associated with a higher rate of complete response compared with WT (OR = 5.2, $p = 0.031$).

Conclusions: There was an association between EGFR+ and ALK+ tumors and increased rates of partial pain response to palliative radiotherapy.

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Introduction

Conventional palliative radiotherapy (RT) is an effective treatment for most bone metastases; however, up to 20% to 40% of patients may not benefit at all. Identifying factors associated with a lack of improvement in outcomes can help identify metastases that may benefit from other treatment modalities, including stereotactic body RT.[1,2] Bone metastases from NSCLCs have been associated with a lower rate of response to RT, but there are no markers to identify precisely which NSCLC bone metastases are unlikely to respond.[3]

NSCLCs harbor driver mutation in the *EGFR* in 15% of cases and *ALK* genetic rearrangement in 3% to 5% of cases.[4,5] *EGFR* encodes for a transmembrane receptor tyrosine kinase, and mutations result in constitutive activation and unregulated growth signaling.[6] *ALK* transmits intracellular signals promoting cell proliferation and maturation and gene rearrangements, such as the EML4-ALK fusion gene product, which also results in constitutive activation.[7] Both *EGFR* and *ALK* mutations have been hypothesized to have differential responses to RT on the basis of prior preclinical studies and clinical work.[8–12]

The effect of *EGFR* and *ALK* mutations on clinical response to RT is not well known and has never been studied in the bone metastasis setting. The aim of this study was to determine whether the presence of an *EGFR* or *ALK* mutation in NSCLC is associated with a different rate of pain response after palliative RT.

Materials and Methods

Data Source and Inclusion Criteria

A population-based database of all patients undergoing palliative RT for bone metastases in the province of British Columbia from 2013 to 2016 was accessed for this study. Patient-reported outcomes were prospectively collected at baseline, before palliative RT, and at follow-up, 3 to 4 weeks after RT administration. The collected patient-reported outcomes used a standardized and validated scoring system evaluating health status, function, symptoms, and degree of symptom frustration that was based on the Functional Assessment of Cancer Therapy for Bone Pain questionnaire.[13] This study specifically analyzed patient responses to the degree of pain. Patients were asked by paper or electronic questionnaire, "Do you have bone pain? If yes, please rate the severity." Patients responded on an ordinal scale of zero to four, with zero representing no bone pain and four representing the maximal possible bone pain. Patients were asked the same question at baseline and in follow-up. The follow-up interval of 3 to 4 weeks was chosen because institutional data revealed that 5% of patients treated for bone metastases died within 3 weeks of RT. Thus, this time point was felt to be an appropriate interval for reassessment where a reasonable proportion of patients would be available for follow-up.[13]

Inclusion criteria consisted of the following: NSCLC bone metastasis treated with palliative RT, complete baseline and follow-up patient-reported outcome questionnaires, and baseline pain score of one of four or greater. Patients who had a second course of palliative bone radiation within the study window and again completed the Prospective Outcomes and Support Initiative questionnaire were eligible for repeat inclusion. Each course of treatment was considered independently. The radiation dose and fractionation were determined at the discretion of the treating physician. Retreatments could be included. This study included all treatment courses from 2013 to 2016. This study was approved by the institutional research ethics board.

The provincial electronic medical record of British Columbia was accessed to extract further demographic, histologic, treatment, and survival data. Histologic and mutational data were gathered retrospectively. *EGFR* testing was performed by polymerase chain reaction with amplification primers for exon 19 in frame deletions and exon 21 Leu858Arg substitutions. These account for 45% and 40% of NSCLC *EGFR* mutations, respectively. *ALK* mutations were screened by immunohistochemistry using *ALK* protein Ab 5A4. If the screen result was negative, no further testing was done and the sample was considered negative for an *ALK* mutation. If the screen result was positive or equivocal, this was confirmed with fluorescence in situ hybridization with an *ALK* 2p23 probe. To control for the effect of palliation from systemic treatment, data were also collected on chemotherapy, targeted agents, or immunotherapies started before RT administration or within the three-week time window. Analgesic information was not standardly collected in the medical records and thus was not available for this study. Previous work has revealed the collection of patient-reported outcomes in this patient population to be comparable with other studies measuring pain response, despite the lack of analgesic information.[13]

Analysis Groups

For analysis, lung cancers were grouped on the basis of mutation testing and status. Lung cancers that had *EGFR* and *ALK* testing, and had no mutations, were grouped as wild type (WT). We compared the pain

responses of patients with WT with those with a mutation in *EGFR* (EGFR+) or *ALK* (ALK+). Patients with no *EGFR* or *ALK* testing were not included in either the WT group nor the mutational group. They were analyzed in a separate group (unknown) and compared with the WT group.

Primary and Secondary Outcomes

Pain scores at baseline and follow-up after RT were taken. Pain was rated between zero and four, with zero representing no pain and four representing maximal amount of pain. The primary outcome was rate of pain response, defined as a follow-up pain score less than that of the baseline pain score. The secondary outcome was rate of complete pain response, defined as final pain score of zero.

Statistical Analysis

Characteristics of the patient population were compared by mutation status groups using Pearson's chi-square or analysis of variance where appropriate. The rate of pain response was compared using a multivariable logistic analysis. Variables were selected in the multivariable model using a backward stepwise selection process with a threshold for p equals to 0.15 for inclusion into the model. A p value of less than or equal to 0.05 was considered statistically significant for all statistical tests. Stata version 14.2 was used for the analysis (StataCorp).

Results

Patient and Treatment Characteristics

Between June 2013 and June 2016, there were 2272 treatment courses of palliative RT for bone metastases with complete baseline and follow-up patient-reported outcome questionnaires. Of these 2272 treatment courses, 444 treatment courses were for lung cancer bone metastases. A total of 52 treatment courses were excluded owing to a non-NSCLC primary. The final cohort consisted of 388 treatment courses of 329 unique patients. Of the 388 treatment courses, 180 were for *EGFR* or *ALK* WTs, 63 were for *EGFR* mutation positive (EGFR+), and nine were for *ALK* mutation positive (ALK+). There were 92 courses where *EGFR* and *ALK* mutation status was unknown (unknown). Table 1 presents the baseline patient and treatment characteristics across the groups. The mean age at treatment of the WT, EGFR+, ALK+, and Unknown groups was 66, 66, 60, 70, and 70 years, respectively. The most common treatment course was 800 cGy in one fraction (188 of 388) followed by 2000 cGy in five fractions (160 of 388). Treatment groups had similar rates of multifraction RT courses in WT (50.9%), EGFR+ (49.2%), ALK+ (44.4%), and Unknown (51.0, $p = 0.98$). Treated sites included the spine (35%), extremities (21%), pelvis (13%), ribs (7%), and other (6%). Rates of retreatment were not significantly different on the basis of mutation status ($p = 0.4$).

Pain Response

Across all groups, 66% of treatments resulted in pain response. In the remaining 34% of treatments, patients reported no change or worsening of pain at follow-up. The rates of partial pain response by mutation status were as follows: WT 63%, EGFR+ 75%, and ALK+ 78%. On stepwise multivariable logistic analysis, mutation status, age, and baseline pain score were significant in the final model (Table 2). Variables tested for inclusion in the model and not found to be significant included the following: start of recent systemic agent before RT, start of systemic agent between time of RT and follow-up survey, sex, multifraction RT, or retreatment (all $p > 0.05$). EGFR+ mutation status compared with the WT group was associated with a higher rate of pain response (OR = 5.4, $p < 0.001$). There was also an association between high rates of pain response and ALK+ mutation status compared with the WT group (OR = 12.8, $p = 0.008$). A higher baseline pain score was associated with a higher rate of pain response. The rate of partial response for Unknown mutation status group was 68%, and there was no statistically significant difference in rates of pain response between the WT versus the unknown mutation status group (Supplementary 1).

Complete Pain Response

Overall, the rate of complete response to pain (a pain score of 0 at follow-up) was 25%. The rates of complete response by mutation status were as follows: WT 20.5%, EGFR+ 35%, and ALK+ 67%. On multivariable stepwise analysis, mutation status, baseline pain score, and the start of a new chemotherapy before palliative RT were included in the final model (Table 3). Variables tested for inclusion in the model and not found to be significant included the following: start of recent targeted agent before RT, start of systemic agent between time of RT and follow-up survey, sex, multifraction RT, or retreatment (all $p > 0.05$). There was a trend between EGFR+ mutation status and increased rate of complete pain response (OR = 1.6, $p = 0.127$). ALK+ mutation status was associated with a higher rate of complete response compared with WT (OR = 5.2, $p = 0.031$). A higher baseline pain score was associated with a lower rate of a complete pain response (OR = 0.56, $p < 0.001$). Rate of complete response for the Unknown mutation status group was 23%, and these patients did not have a statistically significantly different rate of pain response on

Table 1. Characteristics of the Study Population

Characteristic	Entire Cohort N = 388	WT n = 220	EGFR+ n = 63	ALK+ n = 9	EGFR and ALK Status Unknown n = 96	*p* Value[a]
Age (y, mean)	67.2	66.8	65.7	60.3	69.7	0.3
Female sex	51% (196)	49% (107)	65% (41)	56% (5)	45% (43)	0.07
Baseline pain score (of 4)	2.6	2.7	2.2	1.8	2.5	0.7
Multifraction radiotherapy	51% (196)	51% (112)	49% (31)	44% (4)	51% (49)	1.0
Retreatment	22% (85)	25% (54)	14% (9)	22% (2)	21% (20)	0.4
Prior chemotherapy	37% (143)	44% (96)	22% (14)	22% (2)	32% (31)	0.008
Chemotherapy in assessment window	11% (42)	12% (26)	5% (3)	22% (2)	11% (11)	0.3

Note. Demographics are illustrated per treatment course.
[a]Bartlett's test for equal variances or chi-square where appropriate.
ALK+, ALK mutation positive; assessment window, time between palliative RT delivery and follow-up questionnaire; EGFR+, EGFR mutation positive; EGFR and ALK status unknown, no EGFR and ALK status testing; RT, radiotherapy; TKI, tyrosine kinase inhibitor; WT, wild type.

multivariable analysis in comparison to the WT group (Supplementary 2).

Squamous Cell Carcinoma and Pain Response

The WT group consisted of both adenocarcinoma (n = 180) and squamous cell carcinoma (SCC) lung cancers (n = 42). We conducted an analysis of the primary and secondary outcomes, comparing these two groups. On multivariable analysis, there was no statistically significant difference in pain response between these WT adenocarcinoma and SCC groups (Supplementary). There was also no difference in rates of complete response between the WT adenocarcinoma and SCC groups on multivariable analysis (Supplementary).

Effect of Chemotherapy or TKI on Mutation-Positive Patients

To evaluate the potential influence of systemic agents on the rates of pain response, we conducted a subgroup analysis of treatments of EGFR+ bone metastases (n = 63). Overall, 16% of the treatments were delivered to patients who had had prior chemotherapy, and 41% were delivered to patients who had had prior tyrosine kinase inhibitor (TKI). During the 3-week window between radiation treatment and follow-up assessment, 5% started a new chemotherapy drug and 18% started a new TKI. On exploratory analysis, we found having a TKI before RT, starting a new TKI during the follow-up window, or starting a new chemotherapy during the follow-up window did not significantly affect rates of pain response or complete pain response (all $p > 0.05$).

In seven of nine treatment courses of ALK+ tumors, patients had prior targeted therapy or started on a targeted therapy between the time of RT delivery and follow-up assessment. Of the two patients who had no TKI therapy, one of them had a partial pain response, whereas the other had no pain response to RT.

Discussion

Refining our ability to predict symptom response to palliative RT can help individualize palliative treatments.[1,2] To best of our knowledge, no study to date has evaluated NSCLC-specific molecular features and the rates of pain response to palliative RT for bone metastases. In this work, we found that patients undergoing palliative RT courses for EGFR+ and ALK+ NSCLC bone metastases reported higher rates of pain response compared with patients with palliative RT courses for EGFR and ALK WT NSCLC bone metastases. We also observed a higher baseline pain and older age to be associated with higher rates of response.

The rate of pain response for the overall cohort was 66%. This was lower than the 75% response rate

Table 2. Multivariable Logistic Model of Factors Affecting Partial Pain Response

Variable	Reference Group	OR	95% Confidence Interval	*p* Value
Mutation status				
EGFR+	WT	5.4	2.3-12.6	<0.001
ALK+	WT	12.8	2.0-83.8	0.008
Age (per increase in 1 y)	Continuous	1.1	1.02-1.08	0.001
Baseline pain score (per increase in 1 point)	Continuous	3.5	2.7-4.5	<0.001

Note. Courses with no EGFR and ALK status testing were omitted.
ALK+, ALK mutation positive; EGFR+, EGFR mutation positive; WT, wild type.

Table 3. Multivariable Logistic Model of Factors Affecting Complete Pain Response

Variable	Reference Group	OR	95% Confidence Interval	*p* Value
Mutation status				
EGFR+	WT	1.7	0.87-3.2	0.13
ALK+	WT	5.4	1.2-24.0	0.03
Started new chemotherapy in evaluation window period	No new chemotherapy started in evaluation window period	1.8	0.8-3.8	0.15
Baseline pain score (per increase in 1 point)	Continuous	0.56	0.45-0.68	<0.001

Note. Courses with no EGFR and ALK status testing were omitted.
ALK+, ALK mutation positive; EGFR+, EGFR mutation positive; WT, EGFR and ALK wild type.

observed in a previous study, which used the same QOL assessment tool and follow-up time as our study to evaluate bone metastases from all histologies.[13] The low response rate was even more marked for the WT cohort at 63%. The relatively lower rate of pain response is consistent with previous observations that bone metastases from lung cancers are associated with lower response rates after palliative RT.[3] For instance, Van der Velden et al.[3] reported that lung cancer bone metastases had an OR for RT pain response of 0.50 when compared with breast or prostate cancer bone metastases ($p < 0.001$). The overall rate of complete pain response rates in this study was similar to complete response rates observed for bone metastases of other histologies.[13,14]

In this study, palliative RT courses for EGFR+ bone metastases resulted in high rates of pain response (75%) and complete pain response (35%). Before this study, there were conflicting reports on the effect of *EGFR* mutation status on intrathoracic radiation response rates.[10,15–17] For instance, in the locally advanced NSCLC setting after chemoradiotherapy, Tanaka et al.[16] reported similar rates of response between EGFR+ and EGFR WT tumors (72.4% versus 72.0%), as did Yagishita et al.[17] (79% versus 76%). In contrast, Lim et al.[10] reported that EGFR+ tumors were associated with increased rates of response compared with EGFR WT after chemoradiotherapy for locally advanced NSCLC (89% versus 64%, $p = 0.023$). Although it is uncertain whether intrathoracic disease response truly does correlate with *EGFR* status, our work is nonetheless valuable as it is the first to evaluate the relevance of *EGFR* status in bone metastases, using a clinically relevant patient-reported pain outcome.

One potential explanation for why EGFR+ tumors may have high radiosensitivity is that targeted agents may sensitize tumors to RT.[18,19] In our subgroup analysis of EGFR+ patients, however, we did not observe an association between prior TKI administration or TKI administration after RT and rates of pain response. Another potential explanation may be that *EGFR* mutants lose the repair ability of *EGFR* as the receptor is no longer able to shuttle into the nucleus to participate in DNA repair.[20–22] According to this mechanism, we would expect to see increased radiosensitivity of EGFR+ NSCLC, regardless of targeted agent receipt.

The ALK+ cohort in this study was small consisting of only nine treatments in eight patients, and thus results should be taken with caution. There was a high rate of pain response in this cohort, with seven of nine courses resulting in a pain response and six of nine courses resulting in a complete resolution of pain. Previous work has revealed a potential mechanism for increased RT response in ALK+ tumors by a synergistic effect with crizotinib.[23] Interestingly, the two patients who did not respond to palliative RT had no prior history of crizotinib administration, either before or after RT in contrast to the other seven patients who received crizotinib as part of their treatment course. Nevertheless, given the small patient numbers, future work is required to confirm these observations.

As a higher proportion of *EGFR* and *ALK* mutations occur in adenocarcinomas compared with SCCs, a possible explanation for the difference in pain response may be due to histologic type, rather than tumor mutation. To address this, we compared the rates of pain response of patients with WT adenocarcinomas and SCCs and found no significant difference in the rates of response. Thus, it seems unlikely that SCC histologic type was responsible for the lower rates of pain response observed in the WT group.

There are some limitations in our study. There were 96 (25%) patients that did not have *EGFR* or *ALK* mutation testing. These patients did not have testing ordered owing to a variety of reasons including a potential low clinical suspicion of having a mutation (heavy smoking history), patient refusal, limited life expectancy, and patient refusal of any systemic agent. To minimize bias within the *EGFR* WT group, we did not combine those without mutational testing with the WT cohort. The rates of pain response in the Unknown group and WT cohort were similar, and thus inclusion or not within the WT analysis group would be unlikely to change our conclusions. Another limitation is the lack of data on rates of complicated bone metastasis. Because the rates

of MFRT were similar among the patient cohorts and the rates of baseline pain was not statistically significantly different, the rates of complicated bone metastasis are expected to be relatively equal among the groups. Moreover, pain at baseline was accounted for in the multivariable models. A final limitation was that analgesic information was not available for analysis. Previous work with the patient-reported outcomes collected in this study has revealed it to be similar to other studies incorporating analgesic information; however, future studies incorporating information from analgesia use before and after RT would be informative.[13,24] Our study evaluated *EGFR* and *ALK* mutations, which are the most common mutations in NSCLC; however, other mutations should be evaluated in the future because they may have different responses to RT.[4,5]

Patients with NSCLC with *EGFR* or *ALK* genetic mutations had higher rates of pain response after palliative RT for bone pain. To our knowledge, this is the first study to investigate the association between genetic alterations in patients with NSCLC and patient-reported outcome after RT. Given the lower rates of pain relief experienced by patients with NSCLC without *EGFR* or *ALK* mutations, development of successful palliative treatments for this patient population is especially critical.

CRediT Authorship Contribution Statement

Daegan Sit: Data curation, Conceptualization, Writing—original draft, Formal analysis, Investigation, Methodology.

Michelle Bale: Data curation, Writing—original draft, Formal analysis.

Vincent Lapointe: Data curation, Resources, Writing—review and editing.

Robert Olson: Conceptualization, Funding acquisition, Writing—review and editing.

Fred Hsu: Data curation, Conceptualization, Project administration, Writing—original draft, Supervision.

Data Availability

Research data will be stored in an institutional repository for 5 years and will be shared on request to the corresponding author.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100371.

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