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RADIOTHERAPY

Concomitant radiotherapy and TKI in metastatic EGFR- or ALK-mutated non-small cell lung cancer: a multicentric analysis on behalf of AIRO lung cancer study group

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Abstract

Purpose To investigate the role of radiotherapy (RT) in the management of EGFR- or ALK-mutated metastatic non-small cell lung cancer (NSCLC) treated with TKI.

Materials and methods Clinical data of 106 patients (pts) from five Institutions treated with RT concomitant to TKI were retrospectively revised. Overall survival (OS) and toxicities were analyzed as endpoints of the study.

Results Median age of pts was 65 years. TKIs were given for EGFR (81%)- or ALK (19%)-mutated metastatic NSCLC. Stereotactic RT (SRT) was delivered to 49 pts (46%). Patients with four or less metastasis were defined as oligometastatic/oligoprogressive (OM/OP); sites of RT were brain, bone, lung or others in 46%, 27%, 14% and 13%, respectively. Median OS was 23 months. At univariate analysis SRT, ECOG PS 0–1, OM/OP disease, lung sites and a TKI duration longer than median favorably affected OS (all $p < 0.001$). Multivariate analysis confirmed SRT (HR 0.355, CI 95% 0.212–0.595; $p < 0.001$) and median duration of TKI > 14 months (HR 0.17, 95% CI 0.10–0.30; $p < 0.001$) as independent factors related to better OS. Toxicities were rare.

Conclusions SRT seems to positively affect OS with limited toxicity in selected patients.

Keywords Stage IV NSCLC · EGFR mutated · ALK mutated · Radiotherapy · Stereotactic radiotherapy · Oligometastatic · Oligoprogressive

Introduction

Tyrosine kinase inhibitors (TKIs) have shown to significantly improve clinical outcomes in patients with stage IV non-small cell lung cancer (NSCLC) associated with EGFR mutations or anaplastic lymphoma kinase (ALK) rearrangements. Therefore, platinum-based chemotherapy has been replaced by anti-EGFR (Gefitinib, Erlotinib, Afatinib, Osimertinib) or anti-ALK (Crizotinib, Ceritinib, Alectinib) TKIs in the first-line treatment of this subset of patients [1–3].

Median progression-free survival (PFS) and overall survival (OS) of patients treated with TKIs range between 8–13 and 18–25 months, respectively. However, it is becoming clearer that patients with stage IV EGFR- or ALK-mutated NSCLC represent a heterogeneous group in terms of disease characteristics and, therefore, survival outcomes. Clinical presentation can occur with low or high burden of metastatic disease, and it can be affected by the number, dimension and/or location of the metastatic lesions [4–6].

Oligometastatic status represents a condition with a low disease burden at presentation (commonly 4–6 metastatic lesions). Oligoprogression is an oligometastatic status that occurs during/after a systemic therapy. Both these conditions are relatively frequent in stage IV EGFR or ALK mutant NSCLC and they may necessitate of a specific approach [7–11].

There is an increasing body of evidence suggesting that stereotactic radiotherapy (SRT) given timely in appropriately selected patients may favorably affect the natural history of the disease [12–15]. The effect of RT and TKIs is

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thought to be synergistic. RT can be given at progression or on residual disease after partial response on oligometastatic foci. This combined treatment has been reported to be safe and effective, both in prospective and retrospective series [9, 12, 15]. Despite these results, the daily clinical practice is heterogeneous, and the best timing of RT and TKIs sequence combination is still unknown. Also, there are still concerns about the toxicity profile of the concomitant administration of TKIs and RT.

We therefore conducted a multicentric retrospective study that aimed to investigate the pattern of use of RT combined with TKIs for patients treated for stage IV NSCLC, the current strategies of RT and TKIs administration and their efficacy and toxicity. On behalf of the Italian Society of Radiation Oncology (A.I.R.O.) Lung Study Group, five Italian radiation oncology departments collected retrospective data on this topic in order to make a picture of the current clinical practice.

Materials and methods

Using an institutional query system, all patients treated from January 2010 to December 2016 at five Italian Institutions with RT and TKIs for EGFR mutant or ALK-positive stage IV NSCLC were identified and all clinical records were reviewed. For this retrospective analysis were included all hystologically proven NSCLC stage IV patients receiving anti-EGFR or anti-ALK TKIs that underwent RT. RT could be performed during TKIs or within 30 days before or after TKIs administration. According to these inclusion criteria, patients were divided in three groups: those who underwent RT no more than 30 days *before* the beginning of the drug ("group A"), those who underwent RT no more than 30 days *after* the definitive suspension of the TKI ("group B") and those who underwent RT *during* the administration of the drug ("group C").

In terms of disease burden at RT presentation, the patients were classified in oligometastatic or oligoprogressive (OM/OP) state, defined as four or less metastatic lesions, and polymetastatic or polyprogressive (PM/PP) state, defined as more than four lesions, according to the institutional policy and supported by the literature [12].

All the dose fractionation schedules were considered; the term *hypofractionated RT* (HRT) includes treatments with a palliative aim, as 30 Gy in 10 fractions, 20 Gy in 5 fractions or 8 Gy in 1 fraction. The term *stereotactic RT* (SRT) means an ablative treatment able to deliver BED over 60 Gy in a few fractions (mean 80 Gy, range 60–178 Gy, considering an alpha/beta for the tumor equal to 10).

Mutation analysis was conducted by extracting DNA and identifying EGFR exon 19 deletion and exon 21 L858R mutations by standard sequencing and fragment analysis, while to detect ALK gene translocations fluorescence in situ testing (FISH) has been used. Also rare EGFR mutations were detected.

When RT was delivered concomitantly to TKIs, the prescribed doses were as follow: Gefitinib 250 mg/die, Erlotinib 150 mg/die, Afatinb 40 mg/die, Crizotinib 500 mg/die, Osimertinib 80 mg/die, continued after RT until progression or inacceptable toxicity ($\geq$G3 due to CTCAE 4.0 scale). Dose reductions were made only in accordance with clinical practice and not in relation of RT prescription.

The distribution of different clinical and therapeutic features (age, ECOG PS, driver mutation, TKI, TKI duration, previous systemic treatment, disease burden, site of RT, rt schedule) was compared with Chi-squared test in the OM/OP vs PM/PP state and HRT vs SRT schedule of RT. In order to analyze the efficacy of the combined treatment, overall survival (OS), defined as time from the beginning of drug treatment to death (any cause) or until the last follow-up, was estimated with Kaplan–Meier curves. The same variables reported above and potentially affecting OS were investigated at univariate analysis with the logrank test; multivariate analysis was performed with the Cox regression model, including all variables resulted statistically significant at univariate analysis. Level of significance was assumed for $p < 0.05$. Moreover, pattern of recurrence was evaluated in OM/OP. All toxicities reported in the medical records were scored using the common terminology criteria for adverse events rating scale (CTCAE 4.0). Acute toxicities, according to RT schedule, were defined as adverse events occurring at the site of irradiation within 90 days, whereas late toxicities are those becoming evident after 90 days. The statistical analysis was performed with SPSS (version 23.0, IBM).

Results

Between January 2010 and December 2016, 106 patients who met the inclusion criteria were identified. Median age was 65 years (range 24–84) and ECOG performance status was 0, 1 or 2 in 56 (53%), 44 (41%) and 6 cases (6%), respectively. Eighty-one percent of patients were EGFR-mutated and 19% ALK-rearranged. At the beginning of RT, the pattern of presentation was defined as OM/OP in 52 patients (49.1%) and polymetastatic/polyprogressive in 54 patients (50.9%). The majority of the patients (65, 61%) were naïve to previous chemotherapy; 33 (31%) were treated with a first chemotherapy line, while eight patients (8%) received two or more chemotherapy lines before TKI. Fifty-nine patients were treated with Gefitinib, 19 with Erlotinib, 18 with Crizotinib and 10 with other TKIs; four patients were on a second-line TKI (Osimertinib and Ceritinib). Stereotactic RT (SRT) with ablative aim was given in 49 cases (46%) and hypofractionated RT in the remaining 57 patients (54%). Sites of RT

were brain for 49 patients (46%), bone in 28 cases (27%), lung in 15 cases (14%) and other sites in 14 cases (13%). Patients characteristics are given in Table 1.

The clinical features of the group of patients with OM/OP disease were not significantly different from those of the polymetastatic/polyprogressive one, as far as ECOG PS, number of previous chemotherapy lines, age and sites of metastasis are concerned; however, but the patients with OM/OP disease were more frequently treated with SRS ($p < 0.001$) Table 1.

SRT has been performed more frequently for patients with ECOG PS 0–1 ($p < 0.001$), OM/OP disease ($p < 0.001$), lung metastasis sites ($p < 0.001$) and before or concomitant to TKI ($p = 0.03$). Moreover, stereotactic RT was significantly related to longer duration of TKI than palliative RT (19 vs 11 months, $p = 0.001$) Table 1.

Table 1 Patients characteristics

Variable	*n*	%	Disease burden					RT schedule				
			OM/OP		PM/PP		*p*	SRT		HRT		*p*
			n	%	*n*	%		*n*	%	*n*	%	
Age							ns					ns
≤ 70	60	56	26	50	34	63		28	57	32	56	
> 70	46	44	26	50	20	37		21	43	25	44	
ECOG PS							ns					ns
0–1	89	84	47	90	42	78		49	100	40	70	
2	17	16	5	10	12	22		0	0	17	30	
Driver mutation							ns					ns
EGFR	85	80	42	81	43	51		38	78	47	83	
ALK	21	20	10	19	11	20		11	22	10	17	
TKI							ns					ns
Gefitinib	59	57	26	51	33	61		23	48	36	63	
Erlotinib	19	18	11	22	8	15		11	22	8	14	
Crizotinib	18	17	8	16	10	19		10	20	8	14	
Others	10	13	7	11	3	5		5	10	5	9	
TKI duration							ns					
≤ 14 months	52	49	23	44	29	54		17	35	35	61	
> 14 months	54	51	29	56	25	46		32	65	22	39	
Previous cht							ns					0.005
No cht	65	61	36	69	29	54		29	59	36	63	
1 line	33	31	14	27	19	35		17	35	16	28	
2 or more lines	8	8	2	4	6	11		3	6	5	9	
Disease burden												< 0.001
OM/OP								35	71	17	30	
PM/PP								14	29	40	70	
RT site							0.024					< 0.001
Brain	49	46	23	44	26	48		24	49	25	44	
Bone	28	27	9	17	19	35		3	6	25	44	
Lung	15	14	12	23	3	6		15	31	0	0	
others	12	13	8	15	6	11		7	7	7	12	
RT schedule							< 0.001					
SRT	49	46	35	67	14	26						
HRT	57	54	17	33	40	74						
Timing							ns					0.035
Group A	26		14	27	13	24		11	22	16	28	
Group B	18		6	12	12	22		4	8	14	47	
Group C	62		32	61	29	54		34	70	27	25	

SRT stereotactic radiotherapy, *HRT* hypofractionated radiotherapy, *OM/OP* oligometastatic/oligoprogressive disease, *PM/PP* polymetastatic/polyprogressive disease, *ECOG PS* Eastern cooperative oncology group performance status

As for the timing of RT, 26 patients (25%) were classified as *group A* (RT within 30 days before TKI); 18 patients (17%) as *group B* (RT within 30 days of TKI cessation); finally, 62 (58%) patients resulted in *group C* (RT concomitant to TKI). The median time of TKI administration in the whole series was 14.0 months (range 1.7–68.4 months). Analyzing separately the three groups, median time of TKIs administration was 11 months (range 2.5–49.8) for Group A; 12.8 months (range 2.8–32.8) for Group B and 15.8 months (range 1.7–68.4) for Group C). RT–TKI timing is shown in Fig. 1.

After a median follow-up of 9.1 months (range 1–68 months), median OS was 23 months, and 1-, 2- and 3-year OS resulted 76.3%, 48.6% and 29.5%, respectively. At univariate analysis, SRT, ECOG PS 0–1, OM/OP disease, lung sites and a TKI duration longer than median (14.0 months) favorably affected OS (all $p < 0.001$, Fig. 2).

Multivariate analysis confirmed stereotactic RT and median duration of TKI > 14 months as independent factors related to better OS. (HR 2.8 for mild hypofractionated RT versus SRT, CI 95% 1.68–4.71; $p < 0.001$ and HR 0.17, 95% CI 0.10–0.30; $p < 0.001$ for TKI administration > of the median). Univariate and multivariate results are given in Table 2.

In the subgroup with OM/OP presentation, the pattern of recurrence was no progression in 17/52 pts (32.7%), oligoprogression in 20/52 pts (38.5%) and poliprogression in 15/52 patients (28.8%). Patterns of further progression characterized by oligoprogressive disease (or no progression) were significantly more frequent in OM/OP presentation in comparison with patients with polymetastatic disease (Chi-squared Test, $p = 0.002$).

Acute toxicities were strictly related to the treated disease site. Of the 49 patients treated for brain metastasis, 22 patients were treated with SRT and 27 patients with mild hypofractionated RT. Only two cases of G2 toxicity have been recorded in the SRT group, while 5, 7 and 2 cases with grade 1, 2 and 3 toxicities, respectively, were registered in the hypofractionated group. The events of toxicity were significantly more frequent in the hypofractionated schedule group ($p = 0.035$) than with SRT. Only one case of G3 toxicity was recorded in patients treated for bone metastasis; ten patients experienced mild pain exacerbation the first days of irradiation. The treatment was never suspended or definitively interrupted due to an adverse event. In our series, the majority of patients treated concomitantly to TKI did not interrupt temporarily the drug (38 cases out of 62, 63%). No unexpected toxicities have been found in this subgroup. Acute adverse events are given in Table 3. No late toxicity related to radiotherapy has been registered.

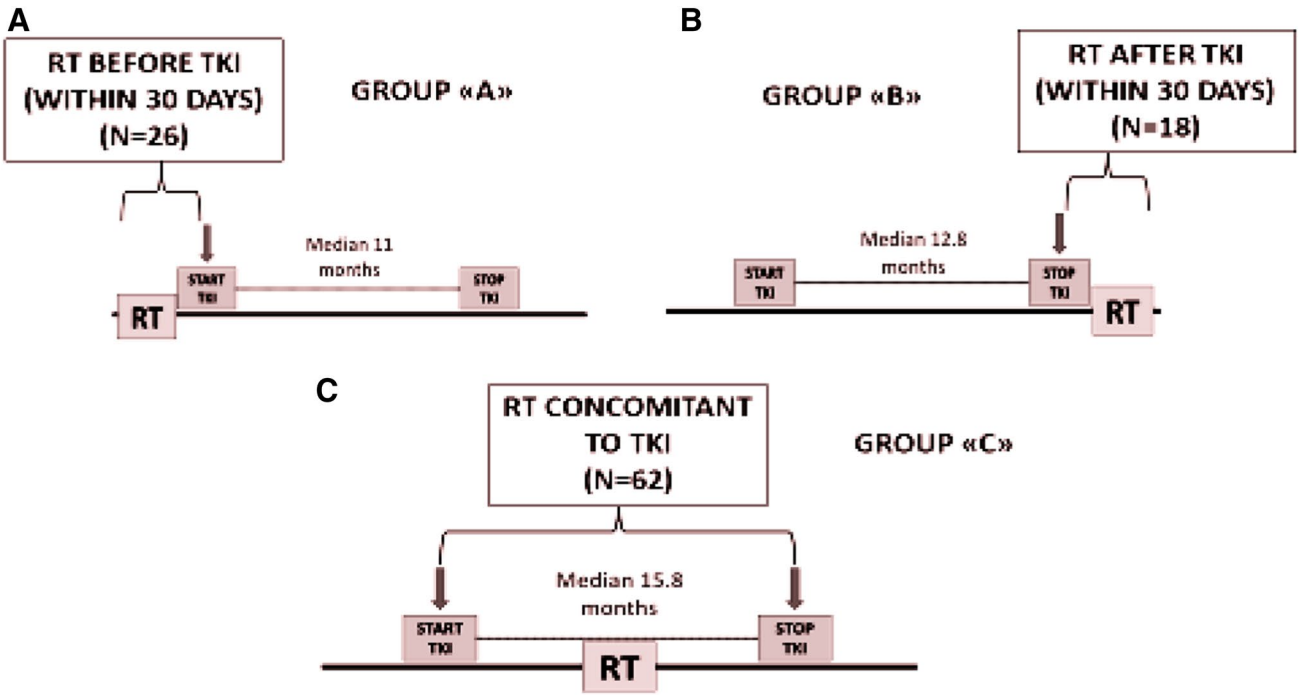
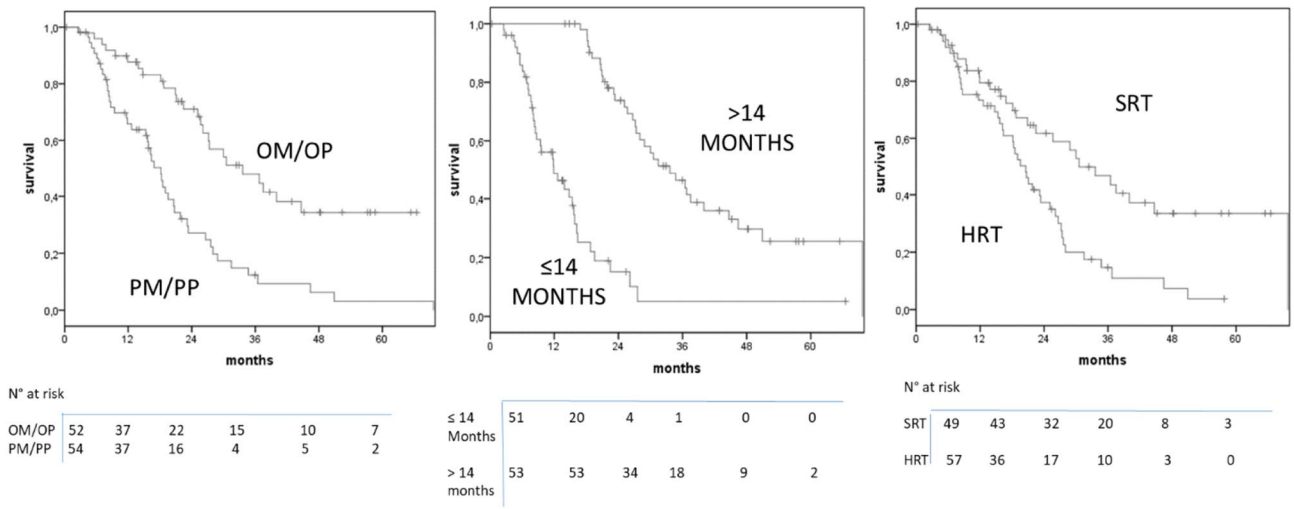


Fig. 1 TKI and RT timing in groups A, B, C



SRT= stereotactic radiotherapy, HRT= hypofractionated radiotherapy, OM/OP = oligometastatic/oligoprogressive disease, PM/PP = polimetastatic/poliprogressive disease.

Fig. 2 Overall survival of patients OM/OP versus PM/PP disease, TKI duration higher versus lower than median and treated with SRT versus HRT. *SRT* stereotactic radiotherapy, *HRT* hypofractionated radiotherapy, *OM/OP* oligometastatic/oligoprogressive disease, *PM/PP* polymetastatic/polyprogressive disease

Discussion

Preclinical studies demonstrate the possible synergistic effect of TKIs given concurrently with radiation at several levels, including effects on cell cycle kinetics, apoptosis induction and the targeting of accelerated cellular repopulation. A potential relationship between EGFR signaling and DNA damage repair has been recently supported by data regarding the inhibition of RAD51 expression, a protein involved in the cell double-strand break repair system. When combined with radiation, Erlotinib enhances the induction of apoptosis, inhibits EGFR autophosphorylation and RAD51 expression following radiation exposure, promoting an increase in radiosensitivity [16, 17].

Available data suggest that the OM/OP condition in NSCLC is characterized by better outcomes, also in the absence of ablative treatments [7]. Furthermore, some authors suggest that oligometastatic patients more frequently progress with a further oligoprogressive pattern in comparison with polymetastatic patients [18].

Recent retrospective and randomized prospective studies show that RT given at progression or on residual disease after partial response on oligometastatic foci fairly improves PFS and may allow longer disease-free intervals [9]. It is still unclear if ablative treatment of OM/OP disease may change the natural history of the disease and contribute to a real survival benefit [12–15].

Accordingly, recent retrospective and some prospective studies tried to identify which patients subgroup can achieve a clinical advantage from local treatments. In detail, presentation of metastasis (metachronous or synchronous to primary tumor), oligometastatic or oligoprogressive disease and ECOG performance status are parameters of outstanding importance. Nevertheless, some authors remark that the site of metastasis, a longer disease-free interval and the presence of driver mutations characterize patients who can benefit more from locally ablative treatment. Probably, these parameters indirectly reflect a more favorable tumor biology, in which SRT can sterilize metastatic foci, ablate lesion in "sanctuary" locations, overcome drug resistance and promote drug "holidays" [19, 20].

Our study corroborates these hypotheses, finding that SRT schedule is a factor independently associated with better OS at multivariate analysis. Moreover, stereotactic RT was significantly related to a longer duration of TKI therapy than palliative RT (19 vs 11 months, $p=0.001$). The analysis of the pattern of recurrence suggests that OM/OP patients treated with SRT experienced more frequently events of oligoprogression. Gan et al. reported the results of a retrospective study on 33 ALK-mutated NSCLC patients analyzing the durability and toxicity of body SRT. The authors find out that the ablation of all the metastatic foci in OP patients treated with Crizotinib allowed an extended duration of drug exposure and was associated with longer overall survival [21].

These retrospective findings have been recently confirmed by the preliminary results of a prospective randomized trial [22].

In our series, the majority of patients treated with concomitant TKIs did not interrupt the drug administration.

Table 2 Univariate and multivariate analysis

Variable	1 year OS (%)	2 years OS (%)	Univariate analysis *p*	Multivariate analysis *p* HR (C.I. 95%)
Age			ns	ns
≤ 70	72	48		1.33 (0.68–2.59)
> 70	81.8	41.9		1
ECOG PS			< 0.001	ns
0–1	79	53.2		1
2	61	20.8		1.6 (0.8–3.2)
Driver mutation			ns	ns
EGFR	77	48		0.4 (0.17–0.945)
ALK	75	48		1
TKI			ns	ns
Gefitinib	78	54		1
Erlotinib	78	42		1.2 (0.8–3.3)
Crizotinib	70	47		1.3 (0.9–4)
Others	70	40		2 (1.2–5)
TKI duration				**< 0.001**
≤ 14 months	46	15		**1**
> 14 months	98	73	< 0.001	**0.17 (0.1–0.27)**
Previous cht			ns	ns
No cht	77	52		1
1 line	69	44		1.2 (1.1–5)
2 or more lines	75	40		1.5 (1.3–7)
Disease burden at RT				
OM/OP	79	61.8	< 0.001	1
PM/PP	73	37.3		1.16 (0.64–2.1)
RT site				ns
Lung	94	92	< 0.001	0.44 (0.83–1.08)
Brain	71.9	39.7		1
Bone	70	32.6		0.85 (0.46–1.57)
Others	77	60.9		0.7 (0.26–1.8)
RT schedule				**< 0.001**
SRT	87.7	62.8	< 0.001	**0.355 (0.212–0.595)**
HRT	65.8	35		**1**
Timing			ns	ns
Group A	62.7	55.9		1.11 (0.59–2.07)
Group B	88.9	28.7		1.16 (0.54–2.5)
Group C	79	55		1

Bold values are shown in statistically *p* value

SRT stereotactic radiotherapy, *HRT* hypofractionated radiotherapy, *OM/OP* oligometastatic/oligoprogressive disease, *PM/PP* polymetastatic/polyprogressive disease, *ECOG PS* Eastern Cooperative Oncology Group Performance Status

No unexpected toxicities were found in this subgroup of patients. A recent review points out the relatively scarce literature on extracranial SRT combined with target therapy, remarking the potential risk of increased toxicity [23]. Thus, our data can help to increase awareness of the safety profile of this therapeutic combination.

There are some limitations in our analysis. First, due to the retrospective nature of the study, the patients population was heterogeneous in terms of treatments given before RT. Secondly, SRT was proposed more frequently to patients favorably selected for clinical and disease factors, such as ECOG PS 0–1 or lung as site of metastasis. Third, SRT was given more often to patients with OM/OP disease. Therefore, the advantage in terms of OS

Table 3 Acute toxicities and distribution in the SRT and HRT groups (CTCAE version 4.0)

Toxicity	Grade (CTCAE)	SRT n (%)	HRT n (%)	*P*
Neurological symptoms (49 brain RT)	0	20 (83)	13 (48)	0.035
	1	0 (0)	5 (19)	
	2	2 (17)	7 (26)	
	≥3	0 (0)	2 (7)	
Pain (28 bone RT)	0	3 (100)	7 (28)	ns
	1	0 (0)	7 (28)	
	2	0 (0)	10 (40)	
	≥3	0 (0)	1 (4)	
Respiratory disease (15 lung RT)	0	15 (100)	0 (0)	na

NS not significant, *NA* not applicable

observed in the SRT group may be at least partly due to these biases.

Conclusions

This retrospective study confirms that radiation therapy combined to TKI represents a safe and well-tolerated treatment. Our data are consistent with the available evidence identifying patients with a good performance status, OM/OP disease and the presence of a driver mutation as the best candidates for SRT. SRT can be safely administered also concurrently with TKIs.

Increasing evidences suggest that the ablative treatment of all sites of disease in patients with a limited number of metastases improves clinical outcomes. OM/OP conditions are relatively frequent in NSCLC with a driver mutation. A multi-disciplinary discussion each time this condition occurs is strongly encouraged.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The study was performed in accordance with the Declaration of Helsinki. The authors agree with the content of the article and give consensus for publication.

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