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ORIGINAL ARTICLE

Radical thoracic radiotherapy may provide favorable outcomes for stage IV non-small cell lung cancer

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Abstract

Background: This study investigates the outcome of synchronous stage IV non-small cell lung cancer (NSCLC) patients who received radical thoracic radiotherapy (TRT).

Methods: We retrospectively reviewed the charts of stage IV NSCLC patients treated with TRT between January 2007 and December 2011. Radiotherapy was considered radical if it was the primary therapy with non-symptom driven intent, or consolidation therapy after initial chemotherapy and the biologically equivalent dose ≥53 Gy halted disease progression. The patients' demographics, disease characteristics, and treatment parameters were uniformly collected.

Results: Eighty-one patients were irradiated with radical intent, including 52% with more than five metastatic lesions. The minimum follow-up was 31.5 months for survivors. The median overall survival (OS) was 20.8 months, with three and four-year OS rates of 23% and 18%, respectively. The median progression-free survival (PFS) was 8.2 months, with one and two-year PFS rates of 23% and 9%, respectively. Partial response (PR) after TRT and administration of targeted therapy were predictive of longer OS. The factors associated with favorable PFS included earlier local tunor node stage, absence of concurrent chemotherapy, and post-TRT PR. No correlation was found between the number of metastatic lesions and survival outcome. Incidences of grade ≥2 toxicities in the lung and esophagus were 9% and 26%, respectively.

Conclusions: Radical TRT may result in advantageous outcomes for selected stage IV NSCLC patients, regardless of the number of metastatic foci. Patients who achieved post-TRT PR attained the best outcomes.

Introduction

Lung cancer is the leading cause of cancer death worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers and almost half of all NSCLC patients have distant metastasis at diagnosis.[1,2] Platinum-based doublet chemotherapy is the conventional treatment strategy for stage IV NSCLC, resulting in overall survival (OS) ranging from 8 to 11 months and progression-free survival (PFS) of 4–6 months.[3,4] In recent years, targeted therapy has been proven to be effective in a subset of patients carrying specific genomic alterations, such as tyrosine kinase inhibitors (TKIs) in patients with epidermal growth factor receptor (EGFR) 19 or 21 exon mutations.[5,6] As a local therapy approach, thoracic radiotherapy (TRT) is typically utilized as palliative management for symptom relief or as a salvage approach for local disease progression in stage IV NSCLC.

However, randomized trials and large cohorts of retrospective studies have demonstrated that radical TRT can provide benefits with regard to both local-regional control and OS in extended-stage small cell lung cancer (SCLC) patients responding to systemic chemotherapy.[7–9] In addition, a growing body of recent data have also suggested promising outcomes of TRT for selected patients with advanced NSCLC, such as oligometastases, revealing a median OS ranging from 10–27 months.[10–24] The positive impact of aggressive local therapy has been recognized in the recent European Society for Medical Oncology guidelines, which listed the consideration of radical local RT as an option for patients with oligometastases.[4]

Encouraging survival results of TRT in patients with extended-stage SCLC, as well as in NSCLC patients with oligometastases, lead to the hypothesis that a subset of patients with advanced NSCLC suitable for radical local RT may include (but is not limited to) those with oligometastases; this local approach may be extrapolated to NSCLC patients with more disseminated diseases, such as those responding to systemic chemotherapy, with the expectation of improvement on local control and survival.

Herein, we retrospectively investigated the long-term survival, survival associated factors, treatment-related toxicities, and patterns of failure for stage IV NSCLC patients who received radical TRT, without limiting the number of metastatic foci.

Methods

Study population

We retrospectively reviewed the individual charts of patients who were diagnosed with synchronous stage IV NSCLC and treated with TRT in our center between January 2007 and December 2011. Patients' demographics, disease characteristics, and treatment parameters were uniformly collected. Tumor stages of all patients were double checked and reclassified using the seventh edition of the American Joint Committee on Cancer staging. TRT was considered radical if it was: (i) the primary treatment in patients who were not considered candidates for systemic therapy as a result of being medically unfit, had a low tumor burden, had metastatic lesions capable to be covered within the TRT target, or patient refusal; and (ii) consolidation management after chemotherapy halted disease progression. The biologically equivalent dose (BED10) of radiation was required to be ≥53 Gy for radical RT, which was, coincidentally, in accordance with that prescribed by recent publications of the definition of aggressive local therapy in stage IV NSCLC.[19,21] Accordingly, RT intent was considered palliative if patients required TRT as a result of post-chemotherapy disease progression or for symptom control. In the present study, our analysis focused on patients who received radical TRT. The study was approved by the local institutional review board.

Treatment regimen

All patients received TRT with or without concurrent chemotherapy. As a routine, all cases were discussed at the internal chart round by all of the thoracic radiation oncologists in the department before treatment commencement. Consensus was reached that administration of TRT to these patients was reasonable and all patients in the study signed informed consent before TRT implementation. Apart from the primary tumor, the radiation target included (but was not limited to) the involved lymph node region. The use of involved lymph node region irradiation (INI) or elective node irradiation (ENI) depended on the treating physicians' discretion. Inclusion of nearby metastatic lesions was permitted when the dose to normal tissue did not exceed the constraints. Management of metastatic lesions and the regimen of systemic therapy, such as chemotherapy or targeted therapy, were not taken into consideration in the selection of study patients.

Statistical analysis

Tumor response to RT was basically evaluated using Response Evaluation Criteria in Solid Tumors version 1.1.[25] Kaplan–Meier method was used to estimate survival, while a Cox hazard regression model was rendered for univariate and multivariate analyses of survival. OS was defined as the time elapsing from the commencement of any treatment to the last follow-up or death of any cause. PFS was defined as the duration between the commencement of any treatment and the first site of tumor progression, death of any cause, or last date of follow-up. National Cancer Institute-Common Terminology Criteria for Adverse Events 3.0 were adopted to evaluate treatment related toxicity. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 126 patients with stage IV NSCLC received TRT, including 81 patients with radical intent and 45 with palliative intent. If calculated from the first date of TRT administration, a significantly longer OS (16.6 vs. 9.9 months, $P = 0.001$) and PFS (4.6 vs. 3.1 months, $P = 0.016$) was observed in patients who received radical TRT. Herein, we only report detailed results of patients receiving radical TRT.

The general demographics and characteristics of study patients are shown in Table 1. The median age was 58 years and median BED10 to thoracic disease was 71.2 Gy. Local tumor node (TN) stage (ignoring M1 status) was I or II in 11 patients and stage III in 70 patients. Most patients experienced M1b disease. Seventy-seven percent of patients presented with synchronous single-organ metastasis and 52% carried >5 metastatic foci. Half of the patients received RT or surgical resection on all metastatic lesions. Pre-RT chemotherapy and concurrent chemotherapy were performed in 60% and 35% of study patients, respectively. The median duration between end of pre-RT chemotherapy and TRT start was 33 days. Twenty-five patients (adenocarcinoma : non-adenocarcinoma = 16:9) received targeted therapies, including 23 with TKIs and two with concurrent nimotuzumab during TRT. EGFR mutation status was not available for any of the patients who received targeted therapy.

Table 1 General characteristic of study patients

		Number of patients (%)
Age	Median	58 (36, 80)†
	≤60	47 (58)
	>60	34 (42)
Gender	Male	64 (79)
	Female	17 (21)
Weight loss	Yes	19 (24)
	No	62 (76)
Pre-TRT KPS	≥80	70 (86)
	<80	11 (14)
TN stage	I-II	11 (14)
	III	70 (86)
M stage	M1a	18 (22)
	M1b	63 (78)
Pathology	Adenocarcinoma	39 (48)
	Non-adenocarcinoma	42 (52)
Number of metastatic organ	Single	62 (77)
	Multiple	19 (23)
Number of metastatic lesions	Single	25 (31)
	Non-single	56 (69)
	1–5	39 (48)
	>5	42 (52)
Pre-TRT chemotherapy	Yes	49 (60)
	No	32 (40)
Interval between end of pre-TRT chemotherapy and TRT start	Median	33 (2, 161)†
Concurrent chemotherapy	Yes	28 (35)
	No	53 (65)
Management of metastatic lesions	RT all sites	39 (48)
	RT partial sites	12 (15)
	Surgical resection all sites	2 (2)
	None	28 (35)
BED10 (Gy)	Median	71.2 (53.1, 132)†
	<72 Gy	41(51)
	≥72 Gy	40 (49)
Nodal target	INI	53 (65)
	ENI	28 (35)
Targeted therapy	No	56 (69)
	Yes	25 (31)
	Pre-TRT	3 (12)‡
	During TRT	3 (12)‡
	Post-TRT	3 (12)‡
	Pre-, during and post-TRT	2 (8)‡
	Pre- and during TRT	1 (4)‡
	During and post-TRT	1 (4)‡
	Salvage after the post-TRT progression	12 (48)‡

†Range. ‡Proportion of patients who received targeted therapy. BED10, biological equivalent dose with α/β of 10; ENI, elective lymph node irradiation; INI, involved lymph node region irradiation; KPS, Karnofsky performance score; M stage, metastasis stage; TN stage, primary tumor and nodal stage; TRT, thoracic radiotherapy.

Survival analysis

After radiotherapy, 80 patients were assessable for response to TRT, including partial response (PR), stable disease (SD), and progressive disease (PD) in 33 (41%), 21 (26%), and 26 (33%) patients, respectively. The median follow up time was 49.1 months and the minimum follow-up for survivors was 31.5 months. Figure 1 details the survival curves and corresponding 95% confidence interval (95% CI) for OS and PFS. The median OS was 20.8 months (95% CI 13.3–38.3), with actuarial one, two, three, and four-year survival rates of 70% (95% CI 59%–79%), 42% (95% CI 31%–52%), 23% (95% CI 15%–33%), and 18% (95% CI 10%–29%), respectively. The median PFS was 8.2 months (95% CI 6.5–9.9), with actuarial one and two-year PFS rates of 23% (95% CI 15%–33%) and 9% (95% CI 4%–16%), respectively.

Multivariate analysis of survival

Univariate analysis for OS and PFS are listed in Table 2. Female gender, no weight loss, post-RT response of PR, and use of targeted therapy were factors associated with significantly longer OS, while local TN stage showed a borderline association with OS. Under multivariate analysis, post-RT response of PR (hazard ratio [HR] 0.529, 95% CI 0.315–0.889, $P = 0.016$; median: 28.6 vs. 13.9 months) and use of targeted therapy (HR 0.467, 95% CI 0.267–0.817, $P = 0.008$; median: 29.5 vs. 13.8 months) remained predictive of better OS. Female gender (HR 0.531, 95% CI 0.276–1.024, $P = 0.059$; median: 28.6 vs. 15.6 months) manifested a marginal significance in predicting OS (Fig 2a–c).

Univariate analyses of PFS are also shown in Table 2. Multivariate analysis revealed that earlier local TN stage (HR 0.347, 95%CI 0.165–0.729, $P = 0.005$; median: 11.7 vs. 7.2 months), absence of concurrent chemotherapy (HR 0.488, 95% CI 0.296–0.805, $P = 0.005$; median: 8.9 vs. 5.8 months) and post-RT response of PR (HR 0.338, 95% CI 0.201–0.571, $P < 0.001$; median: 10.8 vs. 6.8 months) were independent indicators for improved PFS (Fig 3a–c). The state of oligometastasis did not present a significant association with OS or PFS (Figs 2d and 3d).

Toxicity assessment

A total of 67 patients were assessable for radiation-related lung toxicity, including 28 patients with grade 0, 33 with grade 1, three with grade 2, and three with grade 3 toxicity, resulting in 9% grade ≥2 lung toxicity. Of the 76 patients eligible for evaluation of radiation associated esophagus toxicity, 34 had grade 0, 22 had grade 1, 19 had grade 2, and one had grade 3 toxicity, introducing a grade ≥2 toxicity of 26%. No grade 4 or 5 toxicity was observed.

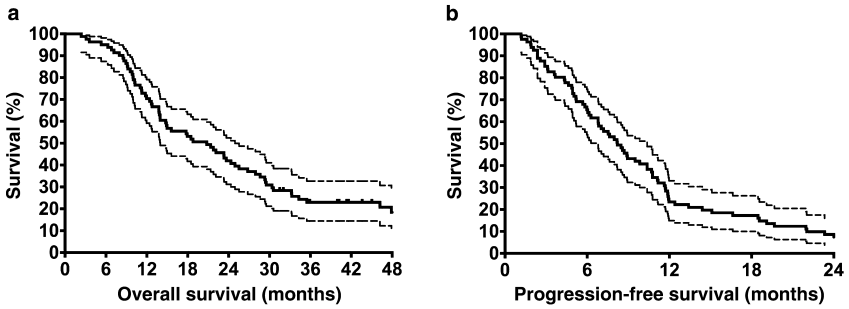

Figure 1 Survival for all patients receiving radical thoracic radiotherapy. (a) Overall survival; (b) progression free survival (solid lines represent estimated survival curves and dashed lines indicate 95% confidence intervals of survival).

Patterns of failure

Figure 4 depicts the patterns of failure for the study patients who experienced disease progression. Out of 81 patients, 73 developed disease progression at the last follow-up, including 25 (34%) with local-regional recurrence, 32 (44%) with failure at initial metastatic sites at diagnosis, and 46 (63%) with new metastases.

Table 2 Univariate analyses for survival endpoints

		Overall survival			Progression-free survival		
Factor		HR	95% CI	*P*	HR	95% CI	*P*
Age	≤60	Ref.			Ref.		
	>60	1.165	0.714, 1.903	0.540	1.176	0.745, 1.856	0.468
Gender	Male	Ref.			Ref.		
	Female	0.506	0.263, 0.974	0.041	0.731	0.419, 1.274	0.268
Weight loss	Yes	Ref.			Ref.		
	No	0.539	0.308, 0.942	**0.03***	0.729	0.429, 1.239	0.243
Pre-RT KPS	<80	Ref.			Ref.		
	≥80	0.798	0.405, 1.527	0.514	0.872	0.447, 1.669	0.687
TN stage	I-II	Ref.			Ref.		
	III	2.037	0.878, 4.729	**0.098***	1.857	0.923, 3.736	**0.083***
M stage	M1a	Ref.			Ref.		
	M1b	0.912	0.518, 1.606	0.750	1.279	0.744, 2.198	0.374
Number of metastases	1–5	Ref.			Ref.		
	>5	0.934	0.573, 1.524	0.785	0.843	0.536, 1.325	0.459
	Single	Ref.			Ref.		
	Multiple	1.048	0.588, 1.870	0.873	1.147	0.675, 1.950	0.612
Management of metastatic lesions	None	Ref.			Ref.		
	All (RT and resection)	1.194	0.697, 2.044	0.518	1.161	0.703, 1.915	0.560
	Partial	1.376	0.654, 2.894	0.401	1.532	0.767, 3.042	0.227
BED 10	<72 Gy	Ref.			Ref.		
	≥72 Gy	1.330	0.815, 2.170	0.254	1.122	0.713, 1.768	0.618
Nodal target	INI	Ref.			Ref.		
	ENI	0.922	0.550, 1.547	0.759	0.920	0.574, 1.474	0.728
Prior chemotherapy	Yes	Ref.			Ref.		
	No	1.312	0.802, 2.147	0.279	1.460	0.921, 2.314	0.108
Concurrent chemotherapy	Yes	Ref.			Ref.		
	No	0.929	0.557, 1.549	0.779	0.667	0.418, 1.065	**0.090***
Post-RT response	PR	Ref.			Ref.		
	SD + PD	1.702	1.021, 2.840	**0.041***	2.280	1.389, 3.741	**0.001***
Targeted therapy	No	Ref.			Ref.		
	Yes	0.471	0.272, 0.815	**0.007***	0.902	0.556, 1.464	0.677

**P* value < 0.1 as the criteria for factor selection into multivariate analyses. BED10, biological equivalent dose with α/β of 10; CI, confidence interval; ENI, elective lymph node irradiation; HR, hazard ratio; INI, involved lymph node region irradiation; KPS, Karnofsky performance score; M stage, metastasis stage; PD, progressive disease; PR, partial response; Ref., references; RT, radiotherapy; SD, stable disease; TN stage, primary tumor and nodal stage.

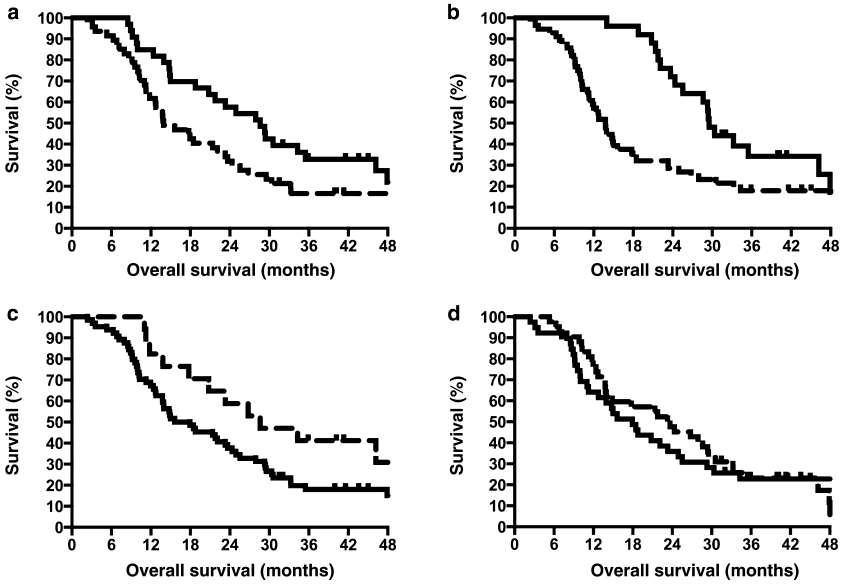

Figure 2 Overall survival stratified by variable factors. (a) Post-thoracic radiotherapy response. —⊥—, partial response (PR); — ⊥ —, stable disease (SD) + progressive disease (PD). (b) Use of targeted therapy. —⊥—, Yes; — ⊥ —, No. (c) Gender. —⊥—, Male; — ⊥ —, Female. (d) Number of metastatic lesions. —⊥—, 1–5 metastases; — ⊥ —, >5 metastases.

Discussion

In the stage IV NSCLC cohort who received radical TRT without limiting the number of metastases, we observed promising rates of OS and PFS, along with mild RT-related toxicities. The post-RT tumor response of PR and use of targeted therapy were found to be associated with prolonged OS. Accordingly, earlier initial TN stage, absence of concurrent chemotherapy, and post-RT tumor response of PR were independent predictors for better PFS. Distant failure was the dominant post-treatment pattern of failure.

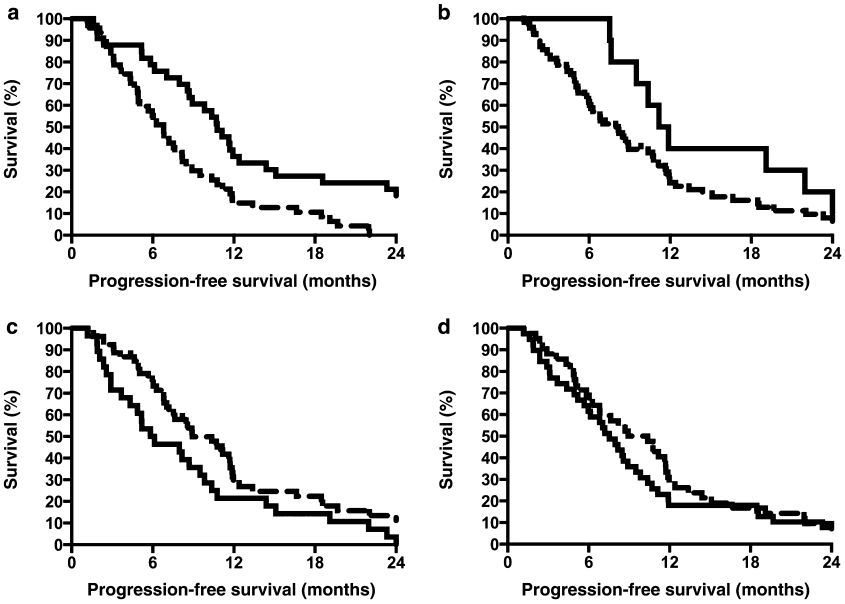

Figure 3 Progression-free survival stratified by variable factors. (a) Post-thoracic radiotherapy response. —⊥—, PR; — ⊥ —, SD + PD. (b) Local TN stage. —⊥—, I-II; — ⊥ —, III. (c) Concurrent chemotherapy. —⊥—, Yes; — ⊥ —, No. (d) Number of metastatic lesions. —⊥—, 1–5 metastases; — ⊥ —, >5 metastases.

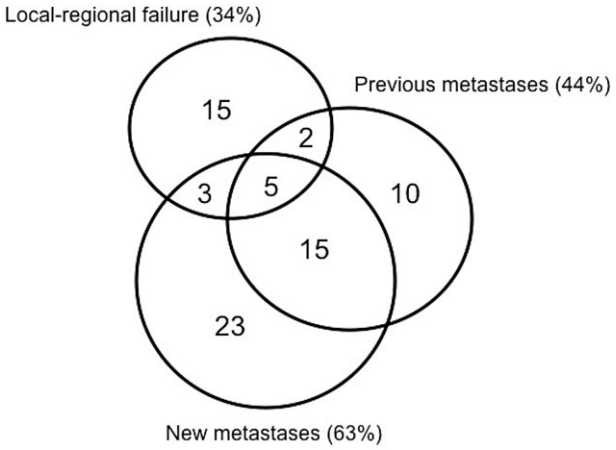

Figure 4 Patterns of failure of the study population who experienced disease progression ($n = 73$). Circle sizes are proportional to the number of patients with corresponding progression.

In recent years, increasing data have shown that the addition of local thoracic therapy to the systemic therapy could provide encouraging outcomes in selected patients with oligometastases, revealing a median OS ranging from 10–27 months and median PFS of 6.6–16 months (Table 3).[11–24] A small prospective study including 26 stage III/IV NSCLC patients with ≤3 metastatic organs (without limiting the number of metastatic lesions) also demonstrated excellent median OS of 21.8 months and median PFS of 10.2 months, as well as a tolerable toxicity profile after definitive TRT concomitant with TKIs.[26] Based on these promising data, there is room to extrapolate local TRT to patients with >5 metastases in the context of other potential favorable indicators, such as limited organ metastasis and response to previous chemotherapy or targeted therapy. Without limiting the number of metastatic foci, RT was considered radical if ≥53 Gy TRT was administered as first-line or consolidation therapy in patients who did not experience disease progression after first-line chemotherapy or targeted therapy. As expected, the subset of patients treated with radical TRT achieved significantly better OS and PFS than those who received palliative TRT, indicating that selected criteria for candidate identification for radical TRT were reasonable.

In the present study, in which half of the patients had more than five synchronous metastases, radical TRT led to median OS and PFS rates of 20.8 and 8.2 months, respectively. These survival data were obviously better than standard chemotherapy-based results and seemed comparable with results from previous studies that only included patients with oligometastases.[3,4,11–24] Furthermore, our survival data were more encouraging than the results of the overall population in IPASS study, which resulted in median OS and PFS of 18.6 and 5.6 months, respectively, among Asian patients with stage IIIB or stage IV adenocarcinoma receiving gefitinib, accompanied by a one-year PFS of 24%.[5] Notably, all of the enrolled patients in the IPASS study had adenocarcinomas and almost a quarter of the patients carried stage IIIB disease, which were well accepted favorable prognostic factors for advanced NSCLC. The long-term survivors were observed in our study population, with three and four-year OS rates of 23% and 18%, respectively. Despite survival data, radiation-related normal tissue toxicity should be carefully considered before making a decision to administer radical TRT. In our study, the

Table 3 Studies of NSCLC with oligometastases treated with TRT

Author, year	Trial design	Number of pts (met lesions)	Dose (Gy) (median)	MOS (months)	2-year OS	3-year OS	MPFS (months)
Iyengar, 2014[23]†	Pros	24 (52)	27–33/3F 35–40/5F 19–20/1F	20.4	NA	NA	14.7
Collen, 2014[22]‡	Pros	26 (48)	50/10F	23	67% (1 y)	NA	11.2
Gray, 2014[21]‡	Retro	66 (1–4)	Resection or >45 Gy RT	26.4	54%	29%	NA
Sheu, 2014[20]	Retro	69 (1–3)	Resection or RT of 15–74 (63)	27.1	NA	NA	11.3
Parikh, 2014[19]	Retro	53 (1–5)	45–70 (60)	19	NA	NA	NA
Su, 2013[18]	Pros	201 (312)	30–72 (63)	10	16.4%	9.6%	NA
Griffioen, 2013[17]	Retro	61 (74)	58.2 ± 9.5	13.5	38%	NA	6.6
Lopez Guerra, 2012[16]	Retro	78 (103)	45–74 (63)	NA	32%	25%	NA
Hasselle, 2012[15]	Retro	25 (62)	37.6–73.9 (64.6)§	22.7	NA	NA	7.6
De Ruysscher, 2012[14]	Pros	39 (45)	62.3 ± 10.1/35.9 ± 8.4 F	13.5	23.3%	17.5%	12.1
Chang, 2011[13]	Retro	23 (52)	40–50/16–20F	Not reached	82.5%	62.5%	16
Flannery, 2008[12]	Retro	42 (42)	45–68.4 (61.2)	18	34%	21% (5 y)	NA
Khan, 2006[11]	Retro	23 (26)	60 for chemoRT 40 for pre-OP	20	NA	NA	12

†SABR to all sites of diseases. ‡Synchronous brain only oligometastases (SBO). §Median equivalent dose in 2 Gy fractions for extracranial lesions (range). chemoRT, concurrent chemoradiotherapy; met, metastasis; MOS, median overall survival; MPFS, median progression free survival; NA, not available; NSCLC, non-small cell lung cancer; pre-OP, prior to surgical operation; Pros, prospective; Retro, retrospective; TRT, thoracic radiotherapy.

incidences of grade ≥2 lung and esophagus toxicities were 9% and 26% respectively, justifying the safety and feasibility of TRT in this subgroup of patients.

Under multivariate analysis, post-RT response was found to be predictive of both OS and PFS, and the earlier local TN stage was also associated with improved PFS. These factors suggest that a decrease in local tumor burden is important to eradicate residual disease after systemic treatment, prevent the spread of tumors, and further improve survival outcomes.

Another independent predictor for improved OS was the administration of targeted therapy. It could be argued that the intrinsic tumor biology advantages to TKIs in an East Asian population could have played a more important role than TRT in the promising median survival rate of 20.8 months. However, the following reasons may still support the positive role of radical TRT in this study set. First, the subgroup of patients without targeted therapy presented a median OS rate of 13.9 months (2-year OS of 29% and 4-year OS of 18%), which remained superior to the traditional chemotherapy-based results. Second, the use of targeted therapy was not found to be predictive of "better-than-expected" PFS of 8.2 months in the present study. Third, nine out of 25 patients who received targeted therapy in our study had non-adenocarcinoma and basically should not have responded to TKIs. Nevertheless, because of great heterogeneity in terms of the intervention timing, as well as elapsed duration of targeted therapy, a detailed analysis was inaccessible in the current study.

Interestingly, we did not find a clear survival benefit in patients with oligometastases compared with those carrying more metastatic foci. This result suggested that >5 metastases may not be considered a strict contraindication for aggressive local therapy in patients with other favorable indicators, such as overall low tumor burden, responding to previous chemotherapy, or tolerable to aggressive doses of TRT. Unexpectedly, our study showed a detrimental impact of concurrent chemotherapy along with TRT for PFS, which is hard to explain based on available data. Prognostic factors reported in other studies including age, metastases limited to the brain, single metastasis, RT dose, or baseline performance status did not present a significant association with OS in our study.[12,16–19] This diversity in prognostic indicators among studies may have resulted from the limitation of retrospective studies, as well as the small number of study patients.

We acknowledge the following limitations of our study. This is a chart review-based retrospective study. The heterogeneity in patient characteristics may influence the predictive power of factors related with survival. The non-standardized follow-up may result in toxicity assessment unreliability. Additionally, this is a single arm study in which all analyzed patients were treated with TRT; therefore, we can only compare survival and toxicity results with historical data from previous studies, rather than straightforwardly examine the impact of TRT on survival. Further well-designed prospective studies are warranted to assess the feasibility and efficacy of radical TRT in NSCLC with synchronous metastasis including (but not limited to) oligometastases.

Conclusions

Our results add to the growing body of evidence on the efficacy of local treatment of thoracic lesions in patients with synchronous oligometastatic NSCLC, and also provide encouraging data on the advantages of TRT in patients with a high number of metastatic lesions. Patients who achieved a post-RT response of PR had the best outcomes. We await the results of ongoing and future prospective clinical trials in order to continue to evaluate the role of radical TRT in stage IV NSCLC patients, and to identify the subset of patients who are more likely to benefit from radical TRT.

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Disclosure

No authors report any conflict of interest.

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