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ORIGINAL ARTICLE **CME**

Treatment Outcomes and Toxicities of Stereotactic Body Radiotherapy for Oligoprogressive Metastatic Non–Small-Cell Lung Cancer

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ABSTRACT

Introduction: *This study reviewed the toxicities and outcomes of stereotactic body radiotherapy (SBRT) for oligoprogressive metastatic non–small-cell lung cancer (NSCLC).*

Methods: *The cases of patients with oligoprogressive NSCLC receiving SBRT from 2015 to 2020 were reviewed retrospectively. Demographics were analysed by descriptive statistics. Important treatment outcomes including local control and survival were analysed by the Kaplan-Meier method. Simple and multivariable Cox regression analyses were carried out to investigate prognostic factors. Toxicities were reported using the Common Terminology Criteria for Adverse Event version 4.0.*

Results: *Forty-one cases with 51 oligoprogressive sites were included. The median age of the cohort was 65 years. The most commonly ablated sites were the lung (68.6%) and bone metastasis (17.6%). The most common driver mutation was the epithelial growth factor receptor mutation (82.9%). SBRT doses ranged from 30 to 60 Gy in 3 to 10 fractions. Median follow-up time was 64 weeks. SBRT achieved a 1-year local control rate of 85%. Median progression-free survival (PFS) after SBRT was 8.8 months and median time from SBRT to the next line of systemic treatment was 9 months. A robust response to pre-SBRT systemic treatment was significantly associated with longer PFS after SBRT. Median overall survival was 58 months. There was one case of grade 3 pneumonitis (2%) and one case of rib fracture (2%).*

Conclusion: *SBRT for oligoprogression in NSCLC is an effective strategy to prolong the time to the next systemic treatment with minimal toxicities.*

Key Words: *Carcinoma, non-small-cell lung; Radiation oncology; Radiosurgery; Stereotactic body radiotherapy; Treatment outcome*

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Ethics Approval: This research was approved by the Hong Kong East Cluster Research Committee of Hospital Authority, Hong Kong (Ref No.: HKECREC2022032). Informed consent was waived by the Committee due to the retrospective nature of the study.

中文摘要

寡進展轉移性非小細胞肺癌體部立體定向放射治療的療效及毒性

黃嘉誠、甘子揚、楊美雲、宋崧

簡介：本研究回顧寡進展轉移性非小細胞肺癌體部立體定向放射治療（SBRT）的毒性及結果。

方法：本研究回顧2015至2020年間接受SBRT的寡進展非小細胞肺癌患者個案。我們對患者的人口統計資料進行描述性統計，並使用Kaplan-Meier法分析重要的治療結果（包括局部控制及存活）以及簡單及多變量Cox迴歸分析研究預後因素。我們使用常見毒性標準（CTCAE）第4.0版本報告毒性。

結果：本研究包括了41例共51個寡進展部位。患者年齡中位數為65歲，最常見的消融部位是肺部（68.6%）及骨轉移（17.6%）。最常見的驅動基因突變是表皮生長因子受體突變（82.9%）。SBRT劑量介乎30至60 Gy，分3至10次。隨訪時間中位數為64星期。SBRT的一年局部控制率達85%。接受SBRT後的無惡化存活期中位數為8.8個月，而接受SBRT後至下次全身性治療的中位數時間則為9個月。接受SBRT前的全身性治療的顯著反應與較長的接受SBRT後的無惡化存活期顯著相關。整體存活期中位數為58個月。有一例3級肺炎（2%）及一例肋骨骨折（2%）。

結論：寡進展轉移性非小細胞肺癌SBRT在毒性減到最低的情況下能有效延長患者接受下次全身性治療前的存活期。

INTRODUCTION

Stereotactic body radiotherapy (SBRT) is a radiation technique that delivers a high dose of radiation to a small tumour target using highly conformal techniques.[1] It is widely used to treat early-stage non–small-cell lung cancer (NSCLC) with durable local control (LC) and a high cure rate.[2] Oligoprogressive disease (OPD) is defined as a clinical scenario in which there is initial polymetastatic disease that responds to systemic treatment until there is development of new subclones with drug resistance.[3] It refers to a limited number of new metastases with different authors quoting a range from a maximum of three to five sites of progression.[4,5] SBRT can be used to ablate these resistant clones before they proliferate and metastasise. Here we report the treatment outcomes and toxicities of SBRT for oligoprogressive metastatic NSCLC in our institution.

METHODS

We conducted a retrospective review of 41 patients who received SBRT for oligoprogressive NSCLC from 1 January 2015 to 31 December 2020. Only patients who had ≤ 3 foci of radiological progression during systemic therapy (excluding central nervous system progression) were included. Demographics were analysed by descriptive statistics using SPSS (Window version 23.0; IBM Corp, Armonk [NY], United States). Planning target volumes (PTVs) were generated by the Eclipse Treatment Planning System (Varian Inc, Palo Alto [CA], United States). Important treatment outcomes including LC and survival were analysed by the Kaplan-Meier method. Univariate and multivariate analysis were used to investigate prognostic factors. Toxicities were reported using the Common Terminology Criteria for Adverse Event version 4.0. Treatment response was monitored by interval computed tomography (CT) or positron emission tomography/computed tomography (PET/CT) scan at intervals determined by the patients' physicians and was reported by the RECIST (Response Evaluation Criteria in Solid Tumours) version 1.1 criteria. Progression-free survival (PFS) was defined as the time interval from date of initiation of SBRT to any progression or death. PFS from the previous systemic treatment (PFS1) was defined by the time from the start of the previous systemic treatment to the initiation of SBRT. Overall survival (OS) was defined as the time interval from the start of systemic treatment to the date of death from any cause. Complete follow-up data were available at the time of analysis. The study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines.

Our radiotherapy treatment protocol followed the Radiation Therapy Oncology Group trials protocol,[6,7]

the United Kingdom Stereotactic Ablative Radiotherapy Consortium guidelines,[8] and the American Association of Physicists in Medicine Task Group 101 report.[9] The details of treatment simulation scan, image co-registration, and PTV margins are described in Table 1. For lung lesions, three-dimensional CT with breath-hold was used for lower lobe tumours, while four-dimensional CT was used for upper lobe tumours. Contouring was performed on different respiratory phases and maximum intensity projection. Regarding spinal metastases, planning CT images were co-registered with diagnostic MRI. For liver and adrenal metastases, we used three-dimensional CT with breath-hold technique if possible. When PET/CT was available, it was registered to the planning CT to assist in gross tumour volume contouring, which was performed before treatment in 94.1% of our cases. For spinal metastases, we followed the International Spine Radiosurgery Consortium consensus guidelines[10] to contour different parts of the vertebra as our clinical target volume. For lung, liver, adrenal, and non-spinal bone metastasis cases, there was no margin expansion to form the clinical target volume. Treatment was prescribed at the 60% to 90% isodose line. The treatment aim was that 95% of the PTVs should receive at least the prescribed dose and 99% of the PTVs should receive at least 90% of prescribed dose. Positioning was verified with cone beam CT before each fraction. Treatment was delivered using intensity-modulated radiotherapy or volumetric modulated arc therapy, depending on the radiotherapists' preference.

RESULTS

A total of 51 SBRT sites were included. All patients had Eastern Cooperative Oncology Group performance status ≤ 2. There were 33 cases with a single site of OPD and 8 cases with > 1 site of OPD. Thirty-five cases had developed OPD during targeted therapy, and 6 cases had developed OPD during chemotherapy. The baseline demographics and SBRT treatment sites are depicted in Table 2.

The median age of the cohort was 65 years. Epithelial growth factor receptor (EGFR) mutation was the most common driver mutation (82.9%). The most commonly ablated site was the lung (68.6%), followed by bone metastasis (17.6%) as shown in Table 2. The SBRT dose and fractionation ranged from 30 to 60 Gy in 3 to 10 fractions depended on the location of the metastasis. Fractionation details are described in Table 2. Most treatments were given every 2 days and completed within

Table 1. Summary of planning images and planning target volume (PTV) margins.

	Lung	Spine	Liver	Adrenal
3DCT	Exhale breath-hold if tolerated for lower lobe tumour	Normal breathing	Exhale breath-hold, acquired in venous phase for GTV contour	Exhale breath-hold for GTV contour
4DCT	Using different respiratory phases and MIPs for contouring tumour, AVIP for contouring OARs and dose calculation	-	-	✓
		Co-registration		
MRI	-	T1-weighted gadolinium-enhanced and T2-weighted axial and sagittal sequences	Selected cases	-
PET/CT	✓	✓	✓	✓
		PTV margins		
	Lung	Spinal bone	Non-spinal bone	Liver and adrenal
3DCT with breath-hold	PTV = CTV + 8 mm	-	-	PTV = CTV + 5 mm in axial direction and + 8 mm in superior-inferior direction
4DCT	PTV = CTV + 5 mm	-	-	-
3DCT with normal breathing	-	PTV = CTV + 2 mm	PTV = CTV + 5 mm	-

Abbreviations: 3DCT = three-dimensional computed tomography; 4DCT = four-dimensional computed tomography; AVIP = average intensity projection; CTV = clinical target volume; GTV = gross tumour volume; MIP = maximum intensity projection; MRI = magnetic resonance imaging; OAR = organ at risk; PET/CT = positron emission tomography/computed tomography.

Table 2. Patient demographics (n = 41), treatment sites, dose and fractionations, and planning target volume (PTV) in different sites of metastases.*

Age at SBRT, y	
Median (range)	65 (31-87)
Sex, No. (%)	
Male	20 (48.8%)
Female	21 (51.2%)
Histology, No. (%)	
Adenocarcinoma	39 (95.1%)
Adenocarcinoma with neuroendocrine features	1 (2.4%)
Adeno-squamous carcinoma	1 (2.4%)
Driver mutations, No. (%)	
EGFR	34 (82.9%)
Anaplastic lymphoma kinase	2 (4.9%)
ROS-1 receptor tyrosine kinase	2 (4.9%)
RET fusion	1 (2.4%)
No mutations	2 (4.9%)
Types of EGFR mutations, No. (%) [n = 34]	
Exon 19 deletion	17 (50.0%)
L858R mutation	14 (41.2%)
L861Q mutation	2 (5.9%)
Exon 19 insertion	1 (2.9%)
Type of systemic treatment before SBRT, No. (%)	
Chemotherapy	6 (14.6%)
Targeted therapy	35 (85.4%)
SBRT target sites (n = 51)	
Adrenal	4 (7.8%)
Liver	3 (5.9%)
Lung	35 (68.6%)
Pelvis	4 (7.8%)
Rib	1 (2.0%)
Spine	4 (7.8%)
SBRT sites	Dose and fractionations†
Lung	Central lesion: 50 Gy/5 fr; 60 Gy/8 fr; 35 Gy/5 fr; 50 Gy/10 fr Peripheral lesion: 54 Gy/3 fr
Spine	35 Gy/5 fr; 30 Gy/5 fr
Rib	50 Gy/5 fr
Pelvis	35 Gy/5 fr
Liver	50 Gy/5 fr
Adrenal	40 Gy/5 fr
PTV, median (range), cm^3	
Lung	35.2 (11.3-102.2)
Adrenal	53.3 (31-95.5)
Spinal bone metastasis	34.4 (30.7-231.1)
Non-spinal bone metastasis	51.7 (40.9-101.4)
Liver	145.8 (114.6-230)

Abbreviations: EGFR = epithelial growth factor receptor; fr = fractions; RET = rearranged during transfection; SBRT = stereotactic body radiotherapy.

* Data are shown as No. (%), unless otherwise specified.

† Depend on the lesion location and surrounding organs at risk, where the choice is bounded by the guidelines quoted in the article (please refer to references 8 to 10).

2 weeks, except in peripheral lung lesions using 54 Gy over 3 fractions, in which treatments were separated by 4 days and completed within 2 weeks. Volume details of PTV in different SBRT sites are also reported in Table 2.

For the treatment outcome, 20 out of 41 patients (48.8%) were alive at last follow-up. With a median follow-up time of 64 weeks, a total of 7 out of 51 sites (13.7%) developed local failure. The 1-year LC rate was 85%. The median PFS after SBRT, which was defined by the time interval from date of initiation of SBRT to any progression or death, was 8.8 months. The median time from SBRT to the next line of systemic treatment was 9 months. The median OS was 58 months (Figure).

Possible prognosticators affecting PFS are assessed in Table 3. In simple Cox regression analysis, deeper response to previous systemic treatment and longer PFS1 (≥ 12 months) were significantly associated with longer PFS. In multivariable analysis, only PFS1 ≥ 12 months remained statistically significant. Meanwhile, sex, driver mutation type, lung or non-lung metastases, number of SBRT sites, degree of response to previous systemic treatment, and biological equivalent dose > 100 Gy did not significantly affect PFS.

We demonstrated a significant association between a better response to pre-SBRT systemic treatment (either partial response or complete response) and a longer PFS following SBRT. A longer PFS1 was also significantly associated with longer PFS after SBRT (Table 3).

For treatment-related toxicities, only one patient (2.4%) developed grade 3 pneumonitis, and one patient (2.4%) developed a rib fracture. There were no grade 4 to 5 toxicities. The patient who developed symptomatic pneumonitis had radiographic features of pneumonitis on CT scan. Pneumonitis was treated with a course of empirical antibiotics and a tapering course of steroids. EGFR tyrosine kinase inhibitor was temporarily suspended during management of pneumonitis. The patient was still alive at last follow-up and required 2 L/min of long-term oxygen therapy. For the rib fracture in our study, it was detected by follow-up PET/CT scan and the patient was asymptomatic without the need of analgesic.

DISCUSSION

Targeted therapy in NSCLC significantly changes the treatment landscape of metastatic NSCLC. However, disease progression is inevitable when a drug-resistant

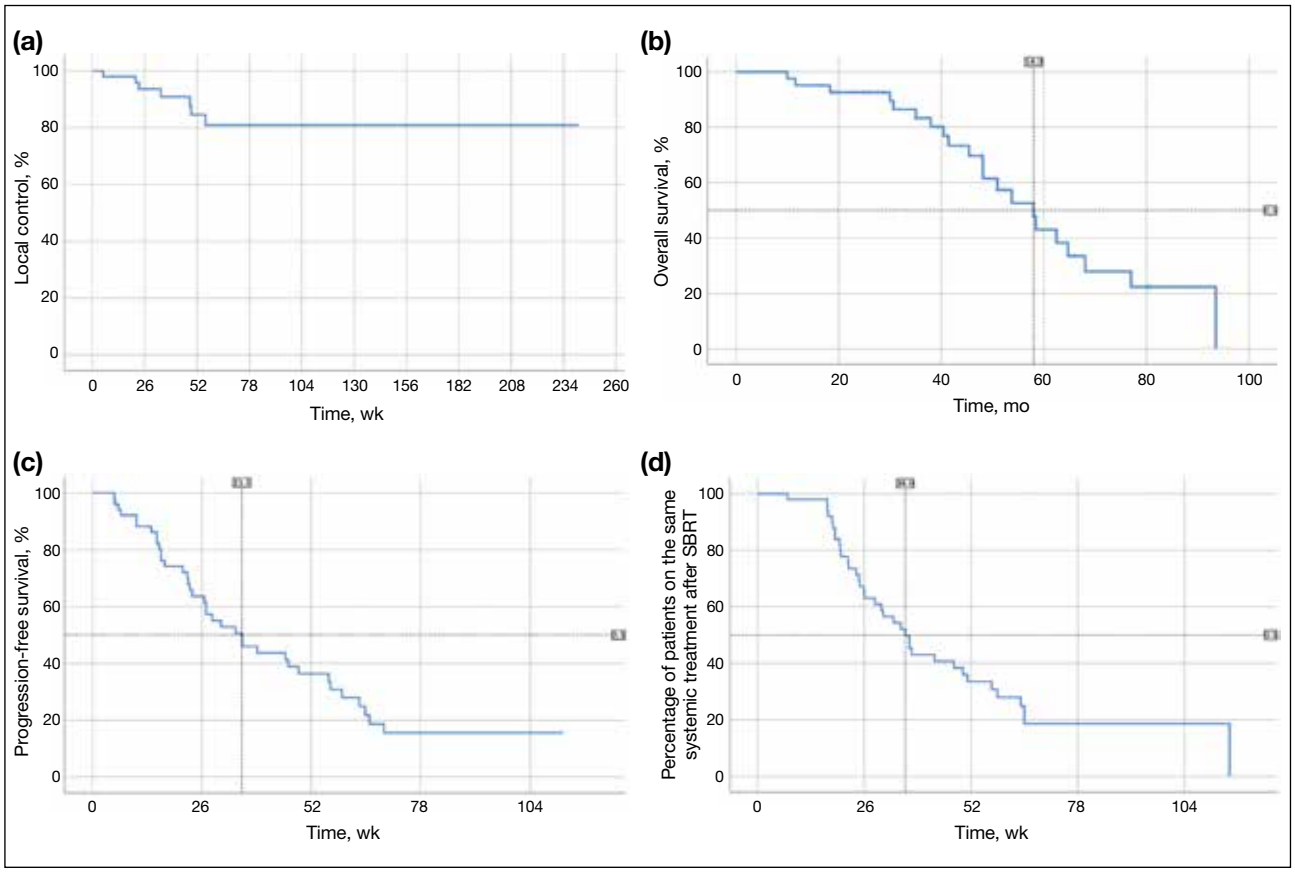

Figure. Kaplan-Meier estimates for the survival functions of (a) local control, (b) overall survival, (c) progression-free survival, and (d) time from stereotactic body radiotherapy (SBRT) to next line of systemic treatment.

Table 3. Cox regression analyses for progression-free survival.

Univariable analysis Variable	Hazard ratio (95% CI)	p Value (log-rank)
Sex (female vs. male)	0.941 (0.492-1.800)	0.855
L858R mutation vs. Exon 19 deletion	0.867 (0.453-1.661)	0.668
Lung vs. non-lung SBRT site	0.577 (0.291-1.143)	0.115
No. of SBRT sites = 1 vs. > 1	0.621 (0.320-1.204)	0.158
Response to previous systemic treatment (SD/PD vs. PR/CR)	3.343 (1.448-7.720)	0.005
BED < 100 Gy vs. ≥ 100 Gy	1.278 (0.581-2.812)	0.542
PFS1 < 12 mo vs. ≥ 12 mo	3.683 (1.784-7.603)	< 0.001
Multivariable analysis Variable	**Hazard ratio (95% CI)**	**p Value (log-rank)**
Sex (female vs. male)	0.681 (0.284-1.636)	0.391
L858R mutation vs. exon 19 deletion	1.158 (0.451-2.040)	0.913
Lung vs. non-lung SBRT site	0.431 (0.147-1.262)	0.125
No. of SBRT sites = 1 vs. > 1	0.414 (0.164-1.044)	0.062
Response to previous systemic treatment (SD/PD vs. PR/CR)	2.560 (0.531-12.351)	0.242
BED < 100 Gy vs. ≥ 100 Gy	0.570 (0.157-2.064)	0.392
PFS1 < 12 mo vs. ≥ 12 mo	3.906 (1.431-10.663)	0.008

Abbreviations: BED = biological equivalent dose; CI = confidence interval; CR = complete response; PD = progressive disease; PFS1 = progression-free survival from the previous systemic treatment; PR = partial response; SBRT = stereotactic body radiotherapy; SD = stable disease.

clone develops and proliferates. Oligoprogression is a distinct clinical entity which specifies a state where the number of progression sites is limited to ≤ 5.[4,5] A strategy for OPD is not yet well defined. Theoretically, eradicating the resistant subclone by SBRT will potentially prolong the use of tyrosine kinase inhibitors upon progression.

The benefits of SBRT in OPD have yet to be explored in prospective studies and current data mostly came from phase II studies. Most of the studies were retrospective in nature and they included a heterogeneous group of patients with different molecular profiles. Different local ablative therapies other than SBRT were included in some studies. Several retrospective studies of patients with EGFR or anaplastic lymphoma kinase–mutated NSCLC treated with local ablative therapy and continued treatment with EGFR- or anaplastic lymphoma kinase–targeted therapy resulted in improved PFS (Table 4),[11-14] with reported magnitudes of PFS ranging from 3.3 to 7 months.

Our data showed that SBRT delivers reasonably good LC at the metastatic sites, and our LC rate of 85% is on par with other different case series.[11-14] Also, our findings revealed that SBRT to OPD brings a benefit of PFS of 8.8 months, which is in line with the existing literature. This benefit is not only demonstrated on follow-up imaging, but it is also clinically meaningful in a sense that it can be translated into a delay in the use of the next systemic treatment by 9 months. With these data, the magnitude of benefit from SBRT in OPD can be quantified. Therefore, opening up the option of SBRT at the first appearance of OPD could potentially forestall the use of cytotoxic chemotherapy, and hence preserve the quality of life of patients for a longer period.

To maximise the benefit of SBRT, selecting the correct patients is crucial. Significant prognostic factors associated with longer PFS after SBRT include longer PFS1 and better radiological response to previous systemic treatment. These two factors constitute a favourable profile of tumours which are likely to derive sustained systemic response after SBRT for OPD. Hence, they can potentially serve as criteria when selecting suitable patients to receive SBRT and hence maximise the survival benefit.

Oligoprogression should also be well defined by sensitive imaging such as PET/CT before delivering SBRT. Treatment should be limited to a maximum of three to five sites of disease progression according to the literature.[4,5] However, we could not demonstrate a significantly shorter PFS for > 1 SBRT site in our study, probably due to the limitation of the small number of cases.

Merino Lara et al[14] reported 108 patients with metastatic NSCLC treated with extracranial SBRT, and revealed an incidence of grade ≥ 3 pneumonitis within 1 year of treatment of approximately 2%; SBRT-induced bone fracture was reported in 3% of the patients, and there were no grade 4 or 5 toxicities. Similar to their findings, the toxicities observed in our retrospective cohort aligned with these reported ranges.

Limitations

Our study has several limitations. First, the retrospective nature and small sample size (41 patients with 51 treatment sites) may lead to underreporting of toxicities and inadequate statistical power to detect significant differences. Also, retrospective studies are prone to selection and sampling bias. Second, our cohort predominantly consisted of patients who developed OPD during targeted therapy treatment. Therefore, we need to be cautious about the limitation when generalising the data on other patients who have OPD during non–targeted therapy treatment. As interval imaging post-SBRT is based on the clinician's discretion, the regular imaging to document local failure or progression is not as strict as in randomised trials. There is no randomisation and no control arm comparing the benefits of SBRT and changing systemic treatment at the first appearance of

Table 4. Summary of current data on stereotactic body radiotherapy (SBRT) in oligoprogressive non–small-cell lung cancer.

	Our study	Chan et al[11]	Weickhardt et al[12]	Qiu et al[13]	Merino Lara et al[14]
No. of patients	41	25	25	46 (only 8 on SBRT)	20
1-year local control rate	85%	76%	N/A	2-year OS: 65.2%	84.4%
Median PFS, mo	8.8	7	6.2	7	3.3
Grade ≥ 3 toxicity	Pneumonitis, 2.4%	Oesophagitis, 4%	Fatigue, 8%	Pneumonitis, 4.3%	Pneumonitis, 2%

Abbreviations: N/A = not available; OS = overall survival; PFS = progression-free survival.

OPD. Hence, the clinical question whether SBRT is better than changing systemic treatment at the discovery of OPD remains unanswered. Moreover, measuring the time from SBRT to the next systemic treatment as a surrogate of clinical benefit may be affected by the patient's decision and choice of treatment, instead of objective assessment using radiographic progression. Lastly, patients with limited metastases may have intrinsic biology that allows them to have a longer survival independent of the success of local or systemic therapies.

CONCLUSION

Our data concur with existing literature that SBRT to OPD in NSCLC is an effective and safe strategy to prolong the time to next systemic treatment with minimal toxicities. Further studies including the HALT study (Stereotactic Body Radiotherapy for the Treatment of OPD)[15] and the STOP trial [Randomized Study of Stereotactic Body Radiation Therapy (SBRT) in Patients With Oligoprogressive Metastatic Cancers of the Breast and Lung][16] will provide prospective data on PFS and OS for SBRT in the setting of OPD.

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