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Salvage lung SBRT may be a curative option after lobectomy

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ABSTRACT

Background: This study intends to analyze the feasibility and the outcomes of stereotactic body radiotherapy (SBRT) as a salvage treatment for lung cancer after primary surgery and compare them with the results of SBRT as the first treatment option.

Materials and methods: Retrospective analysis of early-stage non-small cell lung cancer (NSCLC) treated with SBRT, either as a primary treatment or as salvage treatment after primary surgery.

Results: From January 2017 to January 2022, 68 patients were analyzed. 80% were 65 years-old or above. Seven (10%) underwent SBRT as a salvage treatment after primary surgery. Most lesions treated with primary SBRT were peripheral (n = 33; 54.1%), opposed to the salvage group, where 71.4% were central lesions (n = 5). Patients who had previous surgery presented with lower forced expiratory volume in 1 second (FEV1) (p = 0.006). Median time between surgery and salvage SBRT was 35.4 months. Median follow-up was 29.3 months; median overall survival (OS) at 2 years and 3 years was, respectively, 73.5% and 67.6% (median 52.5 months), with no difference between groups. Median local, regional, and distant progression free survivals were not reached. Local control was 94.1% at 2 years and 92.6% at 3 years. Only 5 (8.2%) patients presented late grade 3–4 pneumonitis, and one, grade 5 (fatal), all in the primary SBRT group.

Conclusion: SBRT as salvage after primary surgery is feasible and seems to be safe. Outcomes are expected to be equivalent to those of the patients submitted to primary SBRT.

Keywords: non-small cell lung cancer; stereotactic body radiotherapy

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Introduction

Stereotactic body radiotherapy (SBRT) for early-stage non-small cell lung cancer (NSCLC) has been considered one of the possible standard-of-care curative options. This regimen of fractionation has already been proven superior to conventional fractionated radiotherapy [1].

Attempts to compare it to surgery have also been performed [2] with mixed results. In prospective comparisons, even though not conclusive, SBRT has been considered to yield a comparable result of local control to lobectomy, with 5-year overall survival over 87% and 5-year local control of 94%, comparable to surgical results [3]. It has also been proven that SBRT can achieve consistent complete responses, even in pathological assessment [4].

Lobectomy and nodal assessment are usually favored for patients with a good performance status

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[5] and preserved pulmonary function. Excellent results can be achieved, particularly with new technological approaches in surgery [6].

Even though local control is usually reported to be very high, patients sometimes relapse in the lung. SBRT has been suggested to be a possibility for salvage treatment in these patients [7]. Nevertheless, results for salvage SBRT have never been compared to first choice SBRT and it is still unknown whether patients can be salvaged from local failure after lobectomy. This study aimed to analyze the feasibility and the outcomes of salvage SBRT for recurrent NSCLC submitted to previous surgery and compare the results to SBRT used as primary treatment.

Materials and methods

We retrospectively reviewed the charts of all patients treated in a single university hospital from January 2017 to January 2022, with at least 6 months of follow-up. All patients had biopsy proven NSCLC and were staged following the institutional protocol, preferably with ^{18}F-fluoro-2-deoxy-2-D-glucose positron emission tomography (^{18}F-FDG PET) scan. For any suspicious nodal disease, biopsies were performed by endobronchial ultrasound (EBUS). Patients' evaluation included pulmonary function tests [mandatory spirometry, and diffusion capacity of the lungs for carbon monoxide (DLCO) test — if indicated].

Demographic, clinical and tumor characteristics were collected.

All patients underwent planning 4D CT scans [8], with or without abdominal compression. gross tumor volume (GTV) and internal tumor volume (ITV) were contoured in a series of acquisitions, including time-lapsed imaging. SBRT regimen varied according to tumor size and location, from 3 to 8 fractions. Patients were divided in two groups, depending on whether SBRT was used as primary treatment or salvage treatment after primary surgery (lobectomy).

Follow-up was performed with CT scans at least once every three or four months in the first two years, every six months until year five, according to the institutional protocol. ^{18}F-FDG-PET scans were performed once a year or if indicated according to the computed tomography (CT) findings.

Toxicities were assessed by the Common Terminology Criteria of Adverse Events (CTCAE) version 5.0 [9].

For statistical analysis, Fisher's Exact-test and *chi*-square tests were performed to address differences between the groups. Survival endpoints were considered from the end of SBRT. Overall survival (OS), local progression free (LPFS), regional progression free (RPFS), and distant progression free survivals (DPFS) were assessed by the Kaplan-Meier method. The Log-rank test was used for univariate analysis. Significance level was set at 5% ($p \leq 0.05$). Stata v18 software was used for calculations.

This retrospective study was approved by the local ethics committee in March 2022. This report follows the STROBE [10] statement, guidelines for publication.

Results

Sixty-eight patients were included in this analysis, with a mean age of 72.2 years (58.5–88.1). Most patients were female (52.9%), presented good Eastern Cooperative Oncology Group (ECOG) performance status (80.9%), adenocarcinoma histology (95.6%), and stage I tumors (72%). Tumor location and size were also evaluated, as well as comorbidities and pulmonary function. Table 1 presents the characteristics of the patients, according to the SBRT treatment. When comparing the groups: primary SBRT and salvage SBRT, no significant differences were observed, except for the worse pulmonary function [forced expiratory volume in 1 second (FEV1)] in the salvage group ($p = 0.006$) (Tab. 1). DLCO was assessed for three patients only (37%, 41% and 61%), considered severely ill, and thus was not analyzed in this study.

^{18}F-FDG PET scans were performed in 94.2% of patients with no difference between groups ($p = 0.485$). Lymph node biopsy through EBUS was performed in 11 patients (17.2%) also with no difference between groups ($p = 0.220$).

SBRT regimens included 60 Gy in 8 fractions [11] (13/19.1%), 50 Gy in 5 fractions [12] (11/16.2%), 48 Gy in 4 fractions [13] (28/41.2%) and 54 Gy in 3 fractions [14, 15] (16/23.5%). Dose schedule was then categorized in biologically equivalent dose (BED) of at least 100 Gy or below 100 Gy, based on previously reported findings and recommenda-

Table 1. Demographic characteristics of the 68 patients

	SBRT N = 61 (89.7%)	Salvage SBRT N = 7 (10.3%)	p
Age (at diagnosis)			
< 65 years	12 (19.7%)	1 (14.3%)	0.731
≥ 65 years	49 (80.3%)	6 (85.7%)	
Sex			
Male	31 (50.8%)	1 (14.3%)	0.067
Female	30 (49.2%)	6 (85.7%)	
ECOG			
0–1	49 (80.3%)	6 (85.7%)	0.731
2–3	12 (19.7%)	1 (14.3%)	
Location			
Central	23 (37.7%)	5 (71.4%)	0.136
Ultracentral	5 (8.2%)	1 (14.3%)	
Peripheric	33 (54.1%)	1 (14.3%)	
Size			
≤ 2.5 cm	35 (53.4%)	3 (42.9%)	0.405
> 2.5 cm	24 (42.6%)	4 (57.1%)	
Histology			
Adenocarcinoma	58 (95.1%)	7 (100%)	0.548
Squamous	3 (4.9%%)	0	
Stage			
IA	5 (8.2%)	0	0.054
IB	19 (31.2%)	2 (28.6%)	
IC	21 (34.4%)	2 (28.6%)	
IIA	11 (18.0%)	0	
IIB	2 (3.3%)	0	
III	2 (3.3%)	2 (28.6%)	
IV	1 (1.6%)	1 (14.3%)	
Dose (BED)			
≤ 100 Gy	10 (16.4%)	2 (28.6%)	0.581
> 100 Gy	51 (83.6%)	5 (71.4%)	
Comorbidities and pulmonary function			
Smoking			
Never	5 (8.2%)	0	0.573
No current smoking	46 (75.4%)	5 (71.4%)	
Smoker	10 (16.4%)	2 (28.6%)	
Chronic obstructive pulmonary disease			
No	34 (55.7%)	4 (57.1%)	0.812
Yes	27 (44.3%)	3 (42.9%)	
Charlson comorbidity index			
0–1	23 (37.7%)	3 (42.9%)	0.790
≥ 2	38 (62.2%)	4 (57.1%)	
FEV1			
≥ 80	40 (65.6%)	2 (28.6%)	0.006
< 80	11 (34.4%)	5 (71.4%)	
Supplemental oxygen			
No	57 (93.4%)	7 (100%)	0.485
Yes	4 (6.6%)	0	

SBRT — of stereotactic body radiotherapy; ECOG — Eastern Cooperative Oncology Group; BED — biologically equivalent dose; FEV1 — forced expiratory volume in 1 second

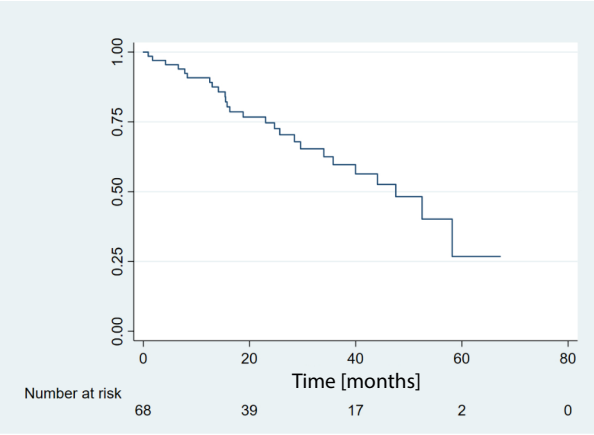

Figure 1. Overall survival (median 52.5 months)

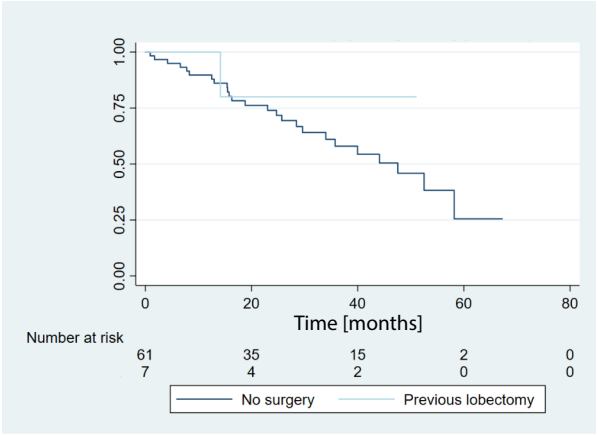

Figure 2. Overall survival comparing radical stereotactic body radiotherapy (SBRT) to salvage SBRT (median for radical SBRT 52.5 months and for salvage SBRT not reached, p = 0.533)

tions [16]. Indeed, the majority (82.4%) of the patients received doses above 100 Gy, with no difference between groups (p = 0.581).

Mean follow-up was 29.3 months (4.0–73.8 months). For the patients previously submitted to surgery, the median time between surgery and salvage SBRT was 35.4 months. There were 25 reported deaths in the period. Median OS was 52.5 months (Fig. 1) with no differences between groups (p = 0.533) (Fig. 2). Median local progression-free survival, regional progression-free survival and distant progression-free survival were not reached.

None of the studied variables had an impact on survival outcomes in the univariate analysis (Tab. 2).

Acute and late toxicity profiles were very favorable, with only five (8.2%) patients presenting late G3-4 pneumonitis, and one fatal outcome (G5) that occurred 39.9 months after treatment. All these toxicities were observed in the primary SBRT group. No rib fractures or hemoptysis due to treat-

Table 2. Univariate analysis

Patients' characteristics	N	OS			LPFS		RPFS		DPFS	
		Events	Median survival (months)	p	Events	p	Events	p	Events	p
Groups										
Primary SBRT	61	24	52.5	0.533	8	0.344	12	0.811	8	0.743
Salvage SBRT	7	1	NR		0		1		1	
Age (at diagnosis)										
< 65 years	13	1	NR	0.09	1	0.607	1	0.368	0	0.163
≥ 65 years	55	24	52.5		7		12		9	
Sex										
Male	32	11	61.8	0.07	4	0.669	5	0.151	3	0.128
Female	36	14	44.1		4		8		6	
ECOG										
0–1	55	20	52.5	0.436	6	0.704	11	0.573	9	0.09
2 or more	13	5	43.8		2		2		0	
Localization										
Central	28	13	52.5	0.413	1	0.07	4	0.398	4	0.712
Ultracentral	6	2	NR		0		1		0	
Peripheric	34	10	61.8		7		8		5	

Table 2. Univariate analysis

Patients' characteristics	N	OS			LPFS		RPFS		DPFS	
		Events	Median survival (months)	p	Events	p	Events	p	Events	p
Size										
≤ 2.5 cm	40	15	52.5	0.819	4	0.669	7	0.735	6	0.558
> 2.5 cm	28	10	44.1		4		6		3	
Histology										
Adenocarcinoma	65	24	52.5	0.534	7	0.293	12	0.653	8	0.437
Squamous	3	1	47.5		1		1		1	
Smoking										
Never	5	1	NR	0.499	0	0.264	0	0.239	0	0.514
Not current	51	21	52.5		7		12		8	
Smoker	12	3	47.5		1		1		1	
COPD										
No	38	8	73.8	0.07	6	0.251	6	0.894	3	0.103
Yes	30	17	47.5		2		7		6	
Charlson comorbidity index										
0–1	26	7	NR	0.524	1	0.131	3	0.273	1	0.095
≥ 2	42	18	52.5		7		10		8	
FEV1										
≥ 80	42	14	61.8	0.703	5	0.470	9	0.931	5	0.325
< 80	16	6	47.5		3		4		4	
Supplemental oxygen										
No	64	24	52.5	0.971	8	0.493	13	0.398	9	0.519
Yes	4	1	NR		0		0		0	
PET										
No	4	1	NR	0.852	0	0.522	0	0.421	0	0.555
Yes	64	24	52.5		8		13		9	
EBUS										
No	57	24	58.2	0.950	7	0.839	10	0.366	7	0.487
Yes	11	4	47.5		1		3		2	
RT dose (BED)										
≤ 100 Gy	14	4	47.5	0.680	1	0.804	7	0.735	1	0.878
> 100 Gy	54	21	58.2		7		6		8	

NR — not reached; OS — overall survival; LPFS — local progression free survival; RPFS — regional progression free survival; DPFS — distant progression free survival; ECOG — Eastern Cooperative Group performance status; COPD — chronic obstructive pulmonary disease; FEV1 — forced expiratory volume in the first second; PET — positron emission tomography; EBUS — Endoscopic bronchial ultrasound; SBRT — stereotactic body radiotherapy; RT — radiotherapy; BED — biologically effective dose.

ment were reported. Table 3 shows the main toxicities findings and comparison between groups.

Discussion

Our report compared the results for SBRT alone versus salvage SBRT in a retrospective cohort assessment. To our knowledge, these results are new and should stimulate the design of prospective studies on the matter. As a limitation, we must consider the retrospective nature and small sample of the study.

Patients were highly selected for treatment. The median time from surgery to salvage SBRT was 35.4 months, i.e. longer than 26.4 months reported by Sittenfeld et al. [7]. Local recurrence was observed in 11.8% of the patients, quite similar to that presented by Sittenfeld et al. (13%) and a previous Japanese report [17] (16%), with some remarks regarding the small sample of our salvage treatment cohort, and within boundaries of other retrospective studies [18].

Although there was no statistical difference between both groups, we must admit that salvaged

Table 3. Toxicities outcomes

N = 68	SBRT N = 61 (89.7%)	Salvage SBRT N = 7 (10.3%)	p
Acute toxicities			
Pain			
G0	61 (100%)	7 (100%)	-
G1–4	0	0	
Pneumonitis			
G0	53 (86.9%)	7 (100%)	0.594
G1–2	8 (13.1%)	0	
G3–4	0	0	
Esophagitis			
G0	61 (100%)	7 (100%)	-
G1–4	0	0	
Late toxicities			
Pain			
G0	58 (95.1%)	7 (100%)	0.835
G1–2	3 (4.9%)	0	
G3–4	0	0	
Pneumonitis			
G0	47 (77.0%)	6 (85.7%)	0.970
G1–2	8 (13.1%)	1 (14.3%)	
G3–4	5 (8.2%)	0	
G5	1 (1.6%)	0	
Esophagitis			
G0	60 (98.4%)	7 (100%)	0.548
G1–2	1 (1.6%)	0	
G3–4	0	0	

lesions were larger and more central, aspects that could highly influence outcomes. Another difference that could have impacted the outcomes was the pulmonary function, worse in the salvage group, very likely to be related to the previous surgical procedure. Nevertheless, no survival differences were observed between the primary and salvage SBRT groups. We admit, however, that this result should be interpreted with caution due to the small number of patients in the salvage group.

Furthermore, after comparing survivals for both groups, we consider that salvage SBRT is not only feasible, but also should be more often considered and investigated in prospective trials.

Conclusion

SBRT for local relapses of NSCLC after lobectomy is feasible and can achieve good overall and progression free survivals. Outcomes are expected to be equivalent to those of the patients submitted to primary SBRT alone. Proper patient selection is mandatory. Prospective data are needed.

Conflict of interest

Authors declare no conflict of interest.

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