Treatment of lung recurrence after radical resection of non-small cell lung cancer: a single-center retrospective analysis using body stereotactic radiotherapy vs. reoperation

Qing Wu
The Second Clinical Medical College of Zhejiang Chinese Medical University
Baiqiang Dong
Zhejiang Cancer Hospital Department of Chest Radiotherapy
Jianan Jin
Zhejiang Cancer Hospital Phase I clinical trail ward
Qingqing Hang
The Second Clinical Medical College of Zhejiang Chinese Medical University
Xiaohui Liu
The Second Clinical Medical College of Zhejiang Chinese Medical University
Yujin Xu
Zhejiang Cancer Hospital Department of Chest Radiotherapy
Chen ming (chenming@zjcc.org.cn)
Zhejiang Cancer Hospital https://orcid.org/0000-0003-2570-0858

Research

Keywords: non-small cell lung cancer, stereotactic body radiotherapy, surgical treatment, intrapulmonary recurrence

Posted Date: October 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-970791/v1

Abstract

Purpose

After radical surgery for non-small cell lung cancer (NSCLC) patients, 3-10% of patients have recurrent lung lesions. For these patients, stereotactic body radiation therapy (SBRT) and recurrence surgery are optional treatments. This study aimed to compare the efficacy of SBRT and surgery in treating lung recurrence after radical NSCLC.

Methods

A retrospective analysis of NSCLC patients who had undergone radical surgery at the Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital) from November 2012 to December 2018 and had received SBRT or reoperation because of postoperative lung recurrence was performed. The Kaplan–Meier method was used to calculate the survival rates, and the log-rank test was used to compare groups. Cox regression was used for univariate and multivariate analysis.

Results

Among 62 eligible patients, 33 received SBRT and 29 received reoperation. The median follow-up times of the two patient groups were 45.8 months and 37.4 months. The 3-year locoregional control rate (LRCR) of SBRT and surgical patients was 79.8% vs. 90.2% (P=0.936); progression-free survival (PFS) was 58.5% vs. 42.3% (P=0.072); and overall survival (OS) was 78.0% vs. 85.5% (P=0.714). Multivariate analysis suggested that the treatment method and Charlson comorbidity index (CCI) were independent prognostic factors for PFS (P=0.033 and P=0.001, respectively).

Conclusion

For patients with lung recurrence after radical NSCLC, no significant difference exists in the efficacy of SBRT and surgery.

Introduction

The current standard treatment for patients with early non-small cell lung cancer (NSCLC) is stereotactic body radiation therapy (SBRT) or surgery. Studies have shown that SBRT and surgery show no significant difference in efficacy. Furthermore, compared with surgery, SBRT is better tolerated [1–3]. However, in clinical practice, most patients choose surgery, and 3-10% of patients have recurrent lung lesions after radical surgery [4–6]. For these patients, the critical factor in determining treatment is whether the lesion is a metastatic or second primary lesion. Although the current National Comprehensive Cancer Network guidelines recommend surgery as a priority, the patient's ability to tolerate the adverse reactions of reoperation is significantly reduced, making the indications for the second operation difficult to clarify [7, 8]. Presently, few studies have compared the efficacy of SBRT and reoperation. This study aimed to investigate the difference in efficacy between SBRT and reoperation in NSCLC patients with lung recurrence after radical surgery.

Patients And Methods

Patient population

Patients who had received SBRT or surgical treatment of lung lesions at the Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital) from November 2012 to December 2018 were included, and the clinical stage before treatment was T1-3N0M0. Before receiving SBRT or surgical treatment, they had received radical surgery for carcinoma of the lungs. The postoperative pathological report confirmed that the margin was negative, and the pathological type was non-small cell lung cancer. The following patients were excluded: patients who had multiple primary lesions at the time of the first radical resection and those who had received SBRT or a second surgery for the unresected lesions after the operation; patients whose first surgical pathology report and postoperative adjuvant treatment were unknown; patients who were lost to follow-up; patients with a

history of other malignant tumors or other malignant tumors; patients whose recurrence was super-central and could not undergo SBRT. The pathological staging of patients after radical resection of the primary tumor was based on the 8th edition of the American Joint Committee on Cancer TNM staging. The diagnosis and staging of recurrent lung lesions after surgery were based on imaging evidence or pathological evidence. Bronchoscopy or mediastinoscopy was performed by the doctor as appropriate for patients with uncertain imaging results. Each patient was recommended to undergo positron emission computed tomography (PET-CT), the results of which could also be used to stage patients who could not obtain a pathology examination or had refused to undergo puncture examination.

Treatment procedures

The appropriate treatment method was selected after multidisciplinary treatment by thoracic surgeons and thoracic radiotherapists based on the size, depth and location of the tumor and the characteristics of the primary lesion. Surgical methods included thoracotomy or laparoscopy to remove the mass and corresponding regional lymph node dissection. Patients who could not undergo or had refused to undergo surgery because of comorbidities chose SBRT. The gross tumor volume (GTV) included the root of the short burr around the primary tumor and pleural invasion area. The internal target volume (ITV) included the active area of the tumor, which was evaluated by 4D-CT technology. The planning target volume (PTV) was expanded by 3-55 mm from all directions based on the ITV. The formula to calculate the biologically effective dose (BED) is BEDα/β = nd (1+d/α/β), where n is the number of divisions, d is the dose of a single division, and the value of α/β for tumor tissue is 10 Gy[9].

Follow up evaluations

The follow-up content included medical history, physical examination, tumor markers, and chest/abdominal CT, usually performed every 2-3 months in the first year after treatment, every 3-6 months in the second year after treatment, and then every 6 months after two years [9, 10]. If necessary, head magnetic resonance imaging (MRI), SPECT, and PET-CT were also performed. When pathological confirmation or imaging showed that the local ground-glass mass persistently had increased persistently for more than 6 months and the solid component in the mass continued to increase, local tumor recurrence was diagnosed [11]. For patients with a high suspicion of recurrence, PET-CT is recommended. PET-CT shows strong uptake, and a maximum standard uptake value of fluorodeoxyglucose ≥ 2.5 is considered tumor recurrence [12].

Survival ending

The starting point of the survival outcome is the time of receiving SBRT or time of reoperation. The endpoints as follows: (1) overall survival (OS): the date when the patient died from any cause; (2) progression-free survival (PFS): the date when a patient had recurrence and metastasis at any site or death due to tumor progression; (3) locoregional control rate (locoregional control rate, LRCR): the date when the patient experienced local or regional recurrence;

Survival outcomes were calculated based on the patients, and cases in which the end point did not occur at the last follow-up were recorded as censored.

Locoregional recurrence was defined as follows: recurrence in the same lobe that was subjected to surgery (wedge or segment resection) or recurrence at the surgical incision (lobectomy); progression of lesions receiving SBRT; recurrence of mediastinal and/or hilar lymph nodes.

Statistical analysis

Statistics and graphing were performed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA) software. The survival outcome index was calculated using the Kaplan–Meier method, and comparisons between groups were performed using the log-rank test. The median follow-up time was calculated using the inverse Kaplan–Meier method. The Cox risk model was used for univariate and multivariate prognostic analyses. In addition to the treatment methods, variables with $P<0.05$ in univariate regression were included in multivariate regression. $P<0.05$ was considered significantly different.

Results

Patient characteristics

From November 2012 to December 2018, 62 patients with simple recurrence in the lung were treated at the Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital) after radical resection. Among them, 33 patients had undergone SBRT treatment, and 29 patients had undergone surgery. Six patients had multiple foci (3 in the SBRT group and 3 in the surgery group), and 14 recurrent foci were found (8 in the SBRT group and 6 in the surgery group). No significant differences were found between the two treatment groups regarding gender, age, lung function, physical status, postoperative pathology, or recurrence interval. In the SBRT group, 12 patients (36.4%) had received PET-CT, and 24 patients (72.7%) had no pathology data. Twenty-four patients (26 lesions) had a BED of 100.0 Gy (Table 1). The dosage and division plan are shown in Table 2. In the surgical group, 13 patients (44.8%) had undergone lobectomy, 6 patients (20.7%) had undergone segmental resection, and 10 patients (34.5%) had undergone wedge resection. The postoperative pathological stage was T1 in 25 cases (86.2%), T2 in 4 cases (13.8%), N0 in 26 cases (89.7%), and N1 in 3 cases (10.3%).

Table 1
General characteristics of patients in the SBRT and surgery groups

Factor	Overall cohort, n(%)	SBRT,n(%)	Surgery,n(%)	P
Age(years)				
＜65	23(37.1)	11(33.3)	12(41.4)	
≥65,＜75	23(37.1)	10(30.3)	13(44.8)	
≥75	16(25.8)	12(36.4)	4(13.8)	0.123
Gender	36(58.1)	20(60.6)	16(55.2)	0.665
Male	26(41.9)	13(39.4)	13(44.8)	0.328
Female	5(8.1)	3(9.1)	2(6.9)	0.24
FEV1(%) predicted	25(40.3)	11(33.3)	14(48.3)	0.533
＜50	20(32.2)	10(30.3)	10(34.5)	0.086
≥50,＜80	12(19.4)	9(27.3)	3(10.3)	0.253
≥80	13(21.0)	6(18.2)	7(24.1)	0.649
Untested	37(59.7)	18(54.5)	19(65.5)	0.449
FEV1/FVC(%)	12(19.4)	9(27.3)	3(10.3)	0.092
＜70	32(52.5)	18(56.3)	14(48.3)	0.827
≥70	29(47.5)	14(43.8)	15(51.7)	0.000
Untested	57(91.9)	28(84.8)	29(100)	0.856
Smoking index	5(8.1)	5(15.2)	0(0)	0.122
＜400	48(77.4)	25(75.8)	23(79.3)	
≥400	11(17.7)	6(18.2)	5(17.2)	
KPS	2(3.2)	2(6.1)	0(0)	
≥90	1(1.6)	0(0)	1(3.4)	
＜90	52(83.9)	27(81.8)	25(86.2)	
CCI	6(9.7)	3(9.1)	3(10.3)	
0	4(6.5)	3(9.1)	1(3.4)	
1	15(24.2)	9(27.3)	6(20.7)	
2	43(69.4)	23(69.7)	20(69.0)	
3	4(6.5)	1(3.0)	3(10.3)	
First Tumor characteristics	17(27.4)	12(36.4)	5(17.2)	
Stage	45(72.6)	21(63.6)	24(82.8)	
I	32(51.6)	18(54.5)	14(48.3)	
II	17(27.4)	9(27.3)	8(27.6)	
III	13(21.0)	6(18.2)	7(24.1)	
Postoperative pathology	11(17.7)	3(9.1)	8(27.6)	
Squamous	24(38.7)	4(12.1)	20(69)	
Adenocarcinoma	3(4.8)	2(6.1)	1(3.4)	

Factor	Overall cohort, n(%)	SBRT,n(%)	Surgery,n(%)	P
NSCLC-NOS	24(38.7)	24(72.7)	0(0)	
Recurrent lesions	7(11.3)	3(9.1)	4(13.8)	
PET-CT	55(88.7)	30(90.9)	25(86.2)	
Yes	49(81.7)	23(74.2)	26(89.7)	
No	11(18.3)	8(25.8)	3(10.3)	
Recurrence interval (years)				
2				
≥2,4				
≥4				
Postoperative pathology				
Squamous				
Adenocarcinoma				
NSCLC-NOS				
Probable				
Combined drug therapy				
Yes				
No				
cT stage before treatment				
1				
2				

Table 2
Fractionation scheme for patients in the SBRT group

Dose(Gy)	BED(Gy)	n
(50)5.0×10	75	3
(40)8.0×5	72	1
(60)6.0×10	96	7
(50)10.0×5	100	23
(40)7.5×8	108	2
(50)12.5×4	112.5	11
(70)7.0×10	119	1
SBRT, stereotactic body radiotherapy; BED, biological effective dose.		

Survival analysis

As of the last follow-up, 6 patients had died in the SBRT group, 5 were related to tumor progression, and 1 was due to an unknown cause. Two patients had died in the surgery group, 1 was related to tumor progression, and 1 had died of acute myocardial

infarction. The median follow-up time in the SBRT group was 45.8 months (range: 38.8-52.8), and the median follow-up time in the surgery group was 37.4 months (range: 32.2-42.7). In the SBRT group, 14 patients developed progression, among whom 8 had locoregional recurrence (2 had distant metastases), and 6 had distant metastases. In the surgery group, 14 patients had progression, among whom 5 patients had local regional recurrence (3 patients had distant metastases), and 12 patients had distant metastases.

The 1-year, 3-year, and 5-year OS rates in the SBRT group were 94.1%, 78.0%, and 78.0%, respectively. In the surgery group, the OS rates were 91.0%, 85.5%, and 85.5%, respectively. The 1-year, 3-year, and 5-year LRCRs of patients were 84.6%, 79.8%, and 71.8%, respectively, in the SBRT group and 96.0%, 90.2%, and 54.1%, respectively, in the surgery group. The PFS rates of patients at 1, 3, and 5 years were 74.8%, 58.5%, and 39.0%, respectively, in the SBRT group and 56.2%, 42.3%, and not reached, respectively, in the surgery group. The log-rank test indicated no significant differences in the LRCR, OS, and PFS between the SBRT group and surgery group (P=0.936, P=0.714, and P=0.072, respectively) (Figure 1).

Age, gender, KPS, CCI, smoking index and other variables were included in the univariate Cox regression analysis. The factors beneficial to OS were female gender (P=0.009), the smoking index <400 (P=0.024), and a first postoperative pathology of adenocarcinoma (P=0.021). Favorable factors for the LRCR were a smoking index <400 (P=0.012), a CCI of 0 (P=0.006), and a first postoperative pathology of adenocarcinoma (P=0.006). The favorable factor for PFS was a CCI of 0 (P=0.004) (Table 3).

Table 3. Univariate Cox regression of various factors regarding the OS, LRCR, PFS

Factor	Definition	n	OS		n	LRCR		n	PFS	
			HR(95% CI)	P		HR（95% CI）	P		HR（95% CI）	P
Gender	Male	29	1		30	1		31	1	
	Female	26	0.17(0.02-1.32)	0.09	25	0.38(0.10-1.40)	0.15	26	0.67(0.31-1.46)	0.31
Age(years)	≥70	27	1		26	1		27	1	
	＜70	28	0.91(0.24-3.40)	0.89	29	0.68(0.22-2.11)	0.50	30	1.45(0.67-3.14)	0.35
FEV1/FVC（%）	≥70	34	1		34	1		36	1	
	＜70	10	1.50(0.27-8.20)	0.64	10	2.51(0.70-9.00)	0.157	10	1.45(0.56-3.74)	0.448
	Untested	11	2.05(0.46-9.20)	0.35	11	1.41(0.35-5.68)	0.627	11	1.18(0.46-3.05)	0.735
Smoking index	≥400	22	1		23	1		24	1	
	＜400	33	0.09(0.01-0.73)	0.024	32	0.19(0.05-0.70)	0.012	33	0.54(0.26-1.15)	0.11
KPS	≥90	50	1		50	1		52	1	
	＜90	5	3.01(0.62-14.52)	0.15	5	1.83(0.40-8.40)	0.43	5	0.96(0.31-3.46)	0.96
CCI	0	43	1		44	1		45	1	
	1	10	1.16(0.23-5.76)	0.857	9	4.92(1.57-15.43)	0.006	10	1.58(0.66-3.79)	0.305
	2	2	3.07(0.37-25.61)	0.301	2	5.01(0.60-42.20)	0.138	2	9.74(2.08-45.54)	0.004
First Tumor characteristics										
Postoperative pathology	Squamous	11	1		12	1		12	1	
	Adenocarcinoma	40	0.21(0.06-0.80)	0.021	39	0.21(0.07-0.64)	0.006	41	0.47(0.21-1.02)	0.057
	NSCLC-NOS	4	0.00(0.00)	0.989	4	0.000	0.987	4	0.000	0.976
Recurrent lesions										
PET-CT	Yes	16	1		17	1		17	1	
	No	39	3.96(0.49-31.71)	0.162	38	1.04(0.318-3.37)	0.95	40	1.01(0.45-2.23)	0.99
Recurrence interval (years)	＜2	25	1		26	1		27	1	
	≥2，＜4	17	0.61(0.12-3.16)	0.558	17	0.18(0.02-1.42)	0.103	17	0.71(0.29-1.78)	0.470
	≥4	13	0.74(0.14-3.80)	0.715	12	0.88(0.26-2.95)	0.84	13	0.88(0.35-2.19)	0.783
＜2 years	Yes	30	1		29	1		30	1	
	No	25	1.50(0.40-5.57)	0.549	26	2.04(0.67-6.23)	0.213	27	1.27(0.60-2.68)	0.53
＜4 years	Yes	13	1		12	1		13	1	

	No	42	1.15(0.24-5.54)	0.86	43	0.76(0.23-2.50)	0.647	44	1.01(0.43-2.38)	0.99
Postoperative pathology	Squamous	7	1		8	1		8	1	
	Adenocarcinoma	29	0.33(0.05-2.31)	0.262	20	0.41(0.09-1.84)	0.25	22	0.80(0.28-2.32)	0.687
	NSCLC-NOS	26	1.11(0.10-12.20)	0.935	3	0.98(0.16-6.11)	0.99	3	0.70(0.13-3.66)	0.668
	Probable	27	0.51(0.09-2.78)	0.435	24	0.29(0.06-1.34)	0.11	24	0.44(0.15-1.34)	0.151
Combined drug therapy	Yes	28	1		7	1		7	1	
	No	34	0.95(0.12-7.56)	0.96	48	0.37(0.10-1.37)	0.12	50	0.42(0.16-1.12)	0.084
cT stage before treatment	1	10	1		44	1		46	1	
	2	11	0.45(0.06-3.60)	0.45	11	1.60(0.48-5.34)	0.44	11	1.11(0.47-2.64)	0.82
Treatment	SBRT	22	1		32	1		32	1	
	Surgery	33	0.77(0.19-3.09)	0.714	23	1.05(0.33-3.31)	0.936	25	2.04(0.93-4.49)	0.077

For the Charlson Comorbidity Index score, the patient's primary tumor and hypertension were not included.

Based on univariate analysis, multivariate analysis showed that patients in the surgery group had a worse PFS (HR: 2.47; 95% CI: 1.08-5.65; P=0.033) than those in the SBRT group; patients with a CCI of 2 had a worse PFS than those with a CCI of 0 (HR: 18.89; 95% CI: 2.83-126.35; P=0.001). The other factors did not affect the OS and LRCR (Table 4).

Table 4
Multivariate Cox regression of various factors regarding the OS, LRCR, and PFS

Factor	Definition	n	OS		n	LRCR		n	PFS	
			HR(95% CI)	P		HR(95% CI)	P		HR(95% CI)	P
Smoking index	≥400	22	1		23	1		-	-	
	400	33	0.12(0.01-1.07)	0.057	32	0.42(0.10-1.75)	0.231	-	-	-
CCI	0	-	-	-	44	1		45	1	
	1	-	-	-	9	3.24(0.94-11.13)	0.062	10	1.58(0.66-3.81)	0.307
	2	-	-	-	2	7.00(0.51-95.94)	0.145	2	15.77(3.09-80.45)	0.001
First Tumor characteristics									-	-
Postoperative pathology	Squamous	11	1		12	1		12		
	Adenocarcinoma	40	0.50(0.12-2.16)	0.353	39	0.28(0.07-1.15)	0.077	41	-	-
	NSCLC-NOS	4	0.000(0.000)	0.989	4	0.000(0.000)	0.988	4	-	-
Recurrent lesions										
Combined drug therapy	Yes	-	-	-	-	-	-	7	-	
	No	-	-	-	-	-	-	50	-	-
Treatment	SBRT	32	1		32	1		32	1	
	Surgery	23	1.19(0.28-5.08)	0.812	23	2.53(0.61-10.42)	0.199	25	2.47(1.08-5.65)	0.033

Adverse reactions

Six patients died in the SBRT group, and 5 cases (83.3%) were related to tumor progression. Acute radiation pneumonitis occurred in 14 patients (42.4%), among whom 10 (30.3%) were grade I, 3 (9.1%) were grade II, and 1 (3.0%) was grade III. Other common acute adverse reactions were cough and sputum, fatigue, and radiation dermatitis, which improved after symptomatic treatment. No adverse reactions of grades 4-5 occurred.

Discussion

For NSCLC patients with local recurrence in the lung after radical surgical treatment, surgery and SBRT are both optional treatments according to the treatment of primary NSCLC [1–3]. However, when a local disease progresses to a systemic disease, local treatment is usually considered to have limited benefits. Additionally, many studies have shown that local treatment of lesions that only metastasize to the lungs prolongs survival [13–15]. Furthermore, Lewis et al. [16] surveyed 1,007 radiation oncologists from 43 countries and found that the lung and liver are the main organs for SBRT treatment of extracranial oligonucleotide metastases. Among the patients, approximately 90% had received SBRT because of lung lesions. A retrospective study evaluated 110 patients with oligonucleotide metastases of the lung, among whom 42 had received SBRT and 68 had received surgery. The 5-year OS rates were 49% and 41% (P=0.43), although each patient decides on treatment after multidisciplinary discussion, surgical resection was the first choice (62%), and SBRT was the second choice (38%). Patients who had chosen SBRT were usually older, and the primary tumor was more malignant and shorter. Regarding the metastasis survival time, the survival curve after SABR was higher than that

after surgery [17]. Another propensity score matching analysis compared the efficacy of SBRT and surgery in metachronous lung cancer. Although patients in the surgery group had a better physical status and better lung function, the 5-year OS of the two patient groups before and after propensity score matching was not significantly different [18].

Previous studies have shown that the physical status before treatment, maximum diameter of the lesion, histopathology of the primary tumor, number of metastatic lesions, and time interval between the diagnosis and treatment of tumor lesions all significantly affect OS [19]. In the present study, the baseline between the SBRT and surgery groups was not significantly different, and the OS, LRCR, and PFS were not significantly different (P=0.714, P=0.936, and P=0.072, respectively). The 1-year, 3-year, and 5-year OS rates were 94.1% vs. 91.0%, 78.0% vs. 85.5%, 78.0% vs. 85.5%, respectively. Although our study did not clearly distinguish the lesion as a second primary tumor or metastasis, both the SBRT group and surgery group had a very good 5-year OS (85.5% and 78.0%). These values were similar to the OS of SBRT and surgery for early primary NSCLC [20–23]. The present study confirmed that the histopathology of the recurrent lesions was the same as that of the previous lesions, and the possibility of a second primary lesion was ruled out. The 5-year locoregional recurrence rate was only 10.3%. Although the radical treatment used by 18 patients (30.5%) in the present study was nonsurgical, it still has certain reference value for this study [25].

In the study of SBRT regarding the treatment of primary NSCLC, when the biologically effective dose (BED) of SBRT reached at least 100 Gy, the local control rate was equivalent to that of surgery. In this study, 5 patients (11 lesions) had BEDs less than 100 Gy, but no significant difference was found in the LRCR between the SBRT and surgery groups (P=0.936). The 1-year, 3-year, and 5-year LRCRs were 84.6% vs. 96.0%, 77.0% vs. 81.0%, and 70.2% vs. 48.6%, respectively, but their values were significantly higher than those in previous retrospective studies for the treatment of patients with primary early NSCLC [3, 26] ,and the LRCR of the SBRT group in the present study also had a certain gap compared with the results in the prospective study. The reason may be that this study did not clearly distinguish recurrent lung lesions as metastases or second primary lesions. Regarding distinguishing between metastasis and a second primary lesion, a unified view has not yet been reached clinically. Presently, the view of N Martini et al. [27] is generally accepted: when the pathology is the same, the recurrence interval is > 2 years or the lesion is located in a different lung lobe, without lymph node or distant metastasis, second primary lung cancer can be considered. However, no prospective study has verified this view. In the present study,24 patients in the SBRT group had no pathology data, 11 of whom had a recurrence interval ≤ 2 years; of 9 patients with pathology data, 8 had the same pathology, 1 of whom had a recurrence interval ≤ 2 years located in the same lung lobe. Twenty-five cases had the same pathology in the operation group, 14 of which had a recurrence interval of less than 2 years; 1 case had lymph node metastasis, and 1 case was located in the same lung lobe. According to N Martini, 12 patients in the SBRT group were considered to have metastasis, and 21 patients were considered to have a second primary tumor; 2 patients in the surgical group were considered to have metastasis, and 27 patients were considered to have a second primary tumor. According to the multivariate Cox regression, the recurrence interval had no significant effect on the LRCR, OS, or PFS. The recurrence interval alone may not be accurate to distinguish the source of the lesion, but the findings of the present study are only based on the analysis of existing situation of patients, the above conclusions must be interpreted carefully.

In addition to the interval between recurrences, imaging can also distinguish primary tumors from metastases. Studies have shown that using FDG-PET scanning for more accurate staging before SBRT significantly improved the 1-year and 2-year OS (82.7% vs. 72.8% and 64.8% vs. 52.6%, respectively; P=0.012). The reason is that FDG-PET shows that patients with multiple metastases are more likely to receive systemic treatment than local SBRT [28], further illustrating the importance of distinguishing metastases from second primary lesions. Patients considered to have metastasis should receive systemic treatment rather than local treatment alone. In the present study, 3 patients in the SBRT group had received adjuvant drug therapy and 4 patients in the surgery group had received adjuvant drug therapy. Because of the small sample size, no further studies have been conducted to confirm this conclusion. We anticipate larger studies to verify this view. Additionally, distinguish between recurrence after SBRT treatment and local changes in radiation pneumonitis or fibrosis on lung CT is challenging [29, 30], causing delays in the diagnosis of disease progression in SBRT patients; it is more beneficial to the SBRT group, as shown statistically. This finding may explain why patients in the SBRT group had better PFS than those in the surgery group. Additionally, compared with the second operation, some patients with SBRT cannot obtain a pathology examination, possibly affecting the diagnosis and causing biased results.

The shortcomings of this study are the retrospective nature and small sample size of the single-center study, which cannot avoid confounding bias. For some recurrent lesions in the SBRT group, a pathology examination was not obtained because of the small diameter or inconvenient puncture at the location close to large blood vessels; thus, it was impossible to determine whether the

recurrent lesion was metastatic or a second primary lesion, and the interpretation of the Cox regression results was also affected. Based on the existing evidence, clarifying which topical treatments can benefit patients more is challenging; thus, relevant prospective studies are needed. We anticipate a larger-scale multicenter collaboration to further explore the efficacy of surgery and SBRT on recurring lung lesions after radical NSCLC surgery.

Conclusion

For patients with simple lung recurrence after radical NSCLC, based on existing evidence, no significant difference was found in the efficacy of SBRT and surgery. Additionally, clarifying the source of the lesion is an important factor in deciding the use of local treatment and/or systemic treatment, and it is also an important research topic.

Abbreviations

NSCLC: Non-small cell lung cancer

SBRT: Stereotactic body radiation therapy

PET-CT: Positron emission computed tomography

BED: biologically effective dose

OS: overall survival

PFS: progression-free survival

LRCR: locoregional control rate

Declarations

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgements

We would like to sincerely thank the staff in the Department of Radiation Oncology, Zhejiang Cancer Hospital.

Funding

Null

Author information

Qing Wu, Baiqiang Dong, Jianan Jin have contributed equally to this work.

Affiliations

The Second Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou

Qing Wu, Qingqing Hang, Xiaohui Liu

Institute of Cancer and Basic Medicine IBMC Chinese Academy of Sciences Department of Chest Radiotherapy, Cancer Hospital Affiliated to University of Chinese Academy of Science (Zhejiang Cancer Hospital), Zhejiang Provincial Key Laboratory of Radiation Oncology, Hangzhou, China

Baiqiang Dong, Yujin Xu

Institute of Cancer and Basic Medicine IBMC Chinese Academy of Sciences Phase I clinical trail ward, Cancer Hospital Affiliated to University of Chinese Academy of Science (Zhejiang Cancer Hospital), Hangzhou, China

Jianan Jin

Sun Yat-sen University Cancer Center, Guangzhou 510060, China

Ming Chen

Contributions

QW JNJ carried out the literature searching and manuscript drafting, BQD JNJ QQH XHL YJX carried out the sequence alignment and revision of the manuscript, MC proposed the whole idea of the paper and context editing. All authors read and approved the final manuscript.

Corresponding author

Correspondence to Ming Chen

Ethics declarations

Ethics approval and consent to participate

The ethics committee of Zhejiang Cancer Hospital and Institute approved the study. The informed consent was exempted due to the retrospective nature of the study. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

All authors have approved the manuscript and agree with submission to Radiation Oncology.

Competing interests

The authors declare no conflicts of interest.

References

[1]. Dong, B., et al., Comparison of the outcomes of sublobar resection and stereotactic body radiotherapy for stage T1-2N0M0 non-small cell lung cancer with tumor size ≤ 5 cm: a propensity score matching analysis. J Thorac Dis, 2020. 12(10): p. 5934-5954.

[2]. Dong, B., et al., Comparison of the outcomes of stereotactic body radiotherapy versus surgical treatment for elderly (≥70) patients with early-stage non-small cell lung cancer after propensity score matching. Radiat Oncol, 2019. 14(1): p. 195.

[3]. Chang, J.Y., et al., Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol, 2015. 16(6): p. 630-7.

[4]. Endo, C., et al., Results of long-term follow-up of patients with completely resected non-small cell lung cancer. Ann Thorac Surg, 2012. 93(4): p. 1061-8.

[5]. Lou, F., et al., Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. J Thorac Cardiovasc Surg, 2013. 145(1): p. 75-81; discussion 81-2.

[6]. al-Kattan, K., et al., Disease recurrence after resection for stage I lung cancer. Eur J Cardiothorac Surg, 1997. 12(3): p. 380-4.

[7]. Erhunmwunsee, L. and B.C. Tong, Preoperative Evaluation and Indications for Pulmonary Metastasectomy. Thorac Surg Clin, 2016. 26(1): p. 7-12.

[8]. Petrella, F., et al., Which factors affect pulmonary function after lung metastasectomy? Eur J Cardiothorac Surg, 2009. 35(5): p. 792-6.

[9]. Chinese Medical Association Radiation Oncology Therapy Branch, Chinese Anti-Cancer Association Oncology Radiation Therapy Professional Committee, and Chinese Medical Doctor Association Radiation Therapist Branch, Chinese Expert Consensus on Stereotactic Radiotherapy for Early Non-small Cell Lung Cancer (2019 Edition)

Chinese expert consensus on stereotactic body radiation therapy for early stage non-small cell lung cancer (2019 Edition) %J □□□□□□ %J Chinese Journal of Oncology. 2020. 42(7): p. 522-530.

[10]. Liu Lunxu, et al., Consensus of Chinese Thoracic Surgery Experts on Follow-up of Non-Small Cell Lung Cancer

Chinese thoracic surgery experts consensus on postoperative follow-up plans for non-small cell lung cancer patients %J □□□□□□□□□□□□ %J Chinese Journal of Clinical Thoracic and Cardiovascular Surgery. 2021. 28(1): p. 4-10.

[11]. Caulo, A., et al., Integrated imaging of non-small cell lung cancer recurrence: CT and PET-CT findings, possible pitfalls and risk of recurrence criteria. Eur Radiol, 2012. 22(3): p. 588-606.

[12]. Keidar, Z., et al., PET/CT using 18F-FDG in suspected lung cancer recurrence: diagnostic value and impact on patient management. J Nucl Med, 2004. 45(10): p. 1640-6.

[13]. Pfannschmidt, J., et al., Surgical intervention for pulmonary metastases. Dtsch Arztebl Int, 2012. 109(40): p. 645-51.

[14]. Corona-Cruz, J.F., et al., Lung metastasectomy: long-term outcomes in an 18-year cohort from a single center. Surg Oncol, 2012. 21(3): p. 237-44.

[15]. Jang, J.W., et al., Simultaneous multitarget irradiation using helical tomotherapy for advanced hepatocellular carcinoma with multiple extrahepatic metastases. Int J Radiat Oncol Biol Phys, 2009. 74(2): p. 412-8.

[16]. Lewis, S.L., et al., Definitive Stereotactic Body Radiotherapy (SBRT) for Extracranial Oligometastases: An International Survey of >1000 Radiation Oncologists. Am J Clin Oncol, 2017. 40(4): p. 418-422.

[17]. Widder, J., et al., Pulmonary oligometastases: metastasectomy or stereotactic ablative radiotherapy? Radiother Oncol, 2013. 107(3): p. 409-13.

[18]. Miyazaki, T., et al., Surgery or stereotactic body radiotherapy for metachronous primary lung cancer? A propensity score matching analysis. Gen Thorac Cardiovasc Surg, 2020. 68(11): p. 1305-1311.

[19]. Rieber, J., et al., Stereotactic body radiotherapy (SBRT) for medically inoperable lung metastases-A pooled analysis of the German working group "stereotactic radiotherapy". Lung Cancer, 2016. 97: p. 51-8.

[20]. Onishi, H., et al., Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer, 2004. 101(7): p. 1623-31.

[21]. Timmerman, R., et al., Stereotactic body radiation therapy for inoperable early stage lung cancer. Jama, 2010. 303(11): p. 1070-6.

[22]. Nagata, Y., et al., Prospective Trial of Stereotactic Body Radiation Therapy for Both Operable and Inoperable T1N0M0 Non-Small Cell Lung Cancer: Japan Clinical Oncology Group Study JCOG0403. Int J Radiat Oncol Biol Phys, 2015. 93(5): p. 989-96.

[23]. Crabtree, T.D., et al., Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg, 2010. 140(2): p. 377-86.

[24]. Senthi, S., et al., Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol, 2012. 13(8): p. 802-9.

[25]. Sun, B., et al., Long-Term Outcomes of Salvage Stereotactic Ablative Radiotherapy for Isolated Lung Recurrence of Non-Small Cell Lung Cancer: A Phase II Clinical Trial. J Thorac Oncol, 2017. 12(6): p. 983-992.

[26]. Lagerwaard, F.J., et al., Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys, 2012. 83(1): p. 348-53.

[27]. Martini, N. and M.R. Melamed, Multiple primary lung cancers. J Thorac Cardiovasc Surg, 1975. 70(4): p. 606-12.

[28]. Rieber, J., et al., Influence of Institutional Experience and Technological Advances on Outcome of Stereotactic Body Radiation Therapy for Oligometastatic Lung Disease. Int J Radiat Oncol Biol Phys, 2017. 98(3): p. 511-520.

[29]. Huang, K., et al., Radiographic changes after lung stereotactic ablative radiotherapy (SABR)--can we distinguish recurrence from fibrosis? A systematic review of the literature. Radiother Oncol, 2012. 102(3): p. 335-42.

[30]. Mohammed, N., et al., Radiographic and metabolic response rates following image-guided stereotactic radiotherapy for lung tumors. Radiother Oncol, 2011. 99(1): p. 18-22.

Figures

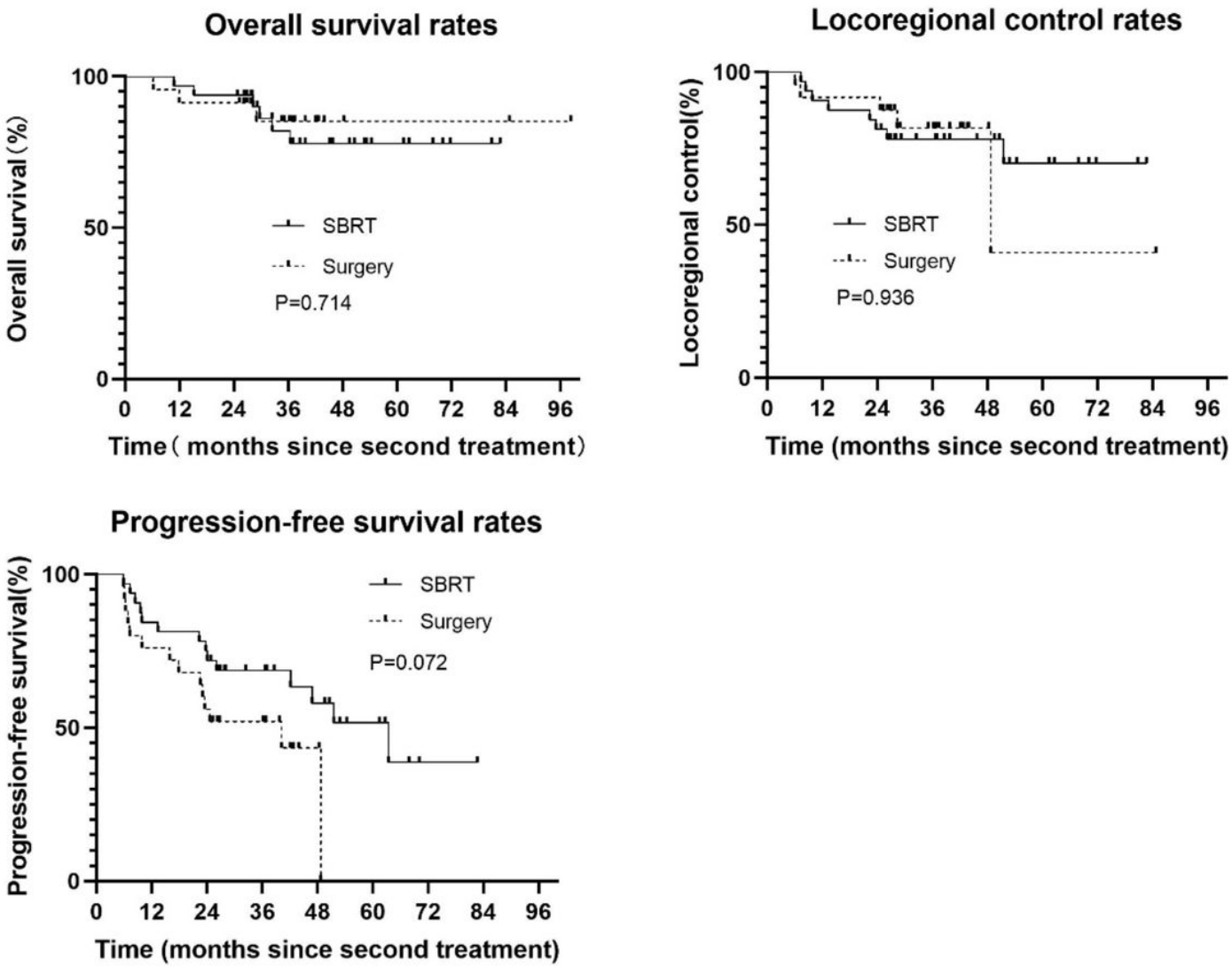

Figure 1

Survival curves of OS, LRCR and PFS in the SBRT and surgery groups