A propensity-matched analysis of stereotactic body radiotherapy and sublobar resection for stage I non-small cell lung cancer in patients at high risk for lobectomy: the results in a Chinese population

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Abstract

Background: To investigate comparative effectiveness of stereotactic body radiotherapy (SBRT) and sublobar resection (SLR) in patients who had stage I non-small cell lung cancer (NSCLC) and a high risk for lobectomy.

Methods: From January 2012 to December 2015, patients who underwent SBRT or SLR for clinical stage I NSCLC were examined retrospectively. Propensity score matching (PSM) was performed to reduce selection biases in SBRT and SLR patients.

Results: 86 SBRT and 79 SLR patients were collected. Median follow-up periods of SBRT and SLR groups were 32 and 37 months, respectively. Patients treated with SBRT exhibited significant increased age, larger tumor diameter, lower FEV1, poorer PS and higher rates of male comparing with SLR. There were no significant differences in terms of 3-year overall survival (OS) (80.3% and 82.3%, P = 0.405), cause-specific survival (CSS) (81.3% and 83.4%, P = 0.383) and local control (LC) (89.7% and 86.0%, P = 0.501) were found in SBRT and SLR patients. 49 patients were identified from each group after performing PSM. The differences of matching factors were balanced based on age, gender, performance status, tumor characteristics and pulmonary function, as no significant differences in terms of 3-year OS (85.4% and 73.3%, P = 0.649), CSS (87.2% and 74.9%, P = 0.637) and LC (95.6% and 82.1%, P = 0.055) in matched SBRT and SLR patients were observed. The rate of grade 3 or the occurrence of worse adverse events was 0 and 10.2% in the matched SBRT and SLR groups (P = 0.056), respectively.

Conclusion: These results suggest that disease control and survival achieved by SBRT were equivalent to SLR in patients who had clinical stage I NSCLC and were at high risk for lobectomy. SBRT can be an alternative option to SLR in treating patients with a high operative risk.

Background

Lung cancer is a leading cause of cancer-related death worldwide [1-3]. The incidence of early-stage non-small cell lung cancer (NSCLC) is increasing due to the use of tobacco, aging and computed tomography(CT)-based screening [4-6]. Lobectomy with systematic lymph node evaluation is a recommended strategy for treating standard-surgical-risk patients with early-stage NSCLC, as it could achieve relatively optimal disease control and survival, compared with stereotactic body radiotherapy (SBRT) and sublobar resection (SLR) [7-10]. However, in stage I NSCLC patients, approximately 40% of elderly patients and those who have impaired cardiopulmonary function, medical comorbidities or refusing surgery do not undergo lobectomy at the early introduction of SBRT[11]. The treatment decision is essential to high-risk patients for surgery, and in order to achieve a better survival outcome, eclectic and effective treatment methods need to be studies.

Less amount of lung parenchyma has to be removed in sublobar resection, rendering significantly better functional preservation compared with lobectomy [12, 13]. In recent years, with the adoption of video-assisted thoracoscopic surgery (VATS) on sublobar resection, many perioperative morbidities caused by

thoracotomy could be mitigated. Sublobar resection is also a primary therapy for treating high-risk patients[13, 14]. Furthermore, though controversial, some retrospective studies have suggested that the outcomes of sublobar resection, especially in anatomical segmentectomy, may be similar to that of lobectomy for patients with peripheral small-sized tumor (lesion ≤ 2 cm) [15-20] [21, 22]. Stereotactic body radiotherapy, also known as stereotactic ablative radiation (SABR), is another important alternative to surgery. SBRT has emerged as an effective and well-tolerated strategy for treating stage I NSCLC patients who are medically inoperable [23-25]. Studies demonstrated that SBRT had a better local control and produced a longer overall survival outcome, comparing with conventional radiotherapy in treating patients with inoperable stage I NSCLC [26, 27]. The application of SBRT has ranged from medically inoperable to potentially operable patients [28-32], and the survival rate of SBRT is potentially comparable to surgery. Therefore, stereotactic body radiotherapy and sublobar resection are considered as main therapies for treating stage I NSCLC patients with a high risk of surgery.

The phase III randomized study (the American College of Surgeons Oncology Group[ACOSOG] Z4099/the Radiation Therapy Oncology Group [RTOG] 1021) compared SBRT with SLR in treating high-risk operable patients with stage I NSCLC [33] but was closed due to poor accrual. Currently, the outcomes of prospective randomized clinical trials are limited (although limited, can clarify the research work of these prospertive randomized clinical trials), and the optimal therapeutic regimen for high-risk operable patients with stage I NSCLC is still unclear.

The aim of present retrospective study was to compare outcomes of SBRT and SLR by using propensity score matching (PSM) analysis among high-risk operable patients with stage I NSCLC. We investigated the current evidence in the application of SBRT and SLR in stage I NSCLC to help guide clinical decision-making in the absence of randomized controlled trial.

Methods

Patient evaluation

The present study was a retrospective analysis. Data were collected from Zhejiang Cancer Hospital, Hangzhou, PR China. All consecutive patients who underwent SBRT or SLR had histologically-confirmed stage I NSCLC from January 2012 to December 2015 were examined and underwent SLR with compromised intention. The patients enrolled in the current study satisfied the following eligibility criteria: 1) patients with T1-2a (5 cm or less in greatest dimension) N0M0 NSCLC according to the 7th Edition of American Joint Committee Cancer Staging Criteria; 2) all SLR patients were ineligible for anatomic lobectomy; 3) the Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2. However, patients who met any of following criteria were excluded: 1) imaging findings of pure ground glass opacities (pGGOs); 2) patients with clinical stage T1-2a N0M0 NSCLC who were pathologically confirmed higher than stage T1-2a N0M0 after SLR; 3) neo-adjuvant chemotherapy or thoracic radiation therapy had been performed before SBRT or SLR; 4) patient without pre-treatment pulmonary function test.

Clinical staging of NSCLC and decision-making of treatment modalities were determined by a multidisciplinary oncology team, which consists of radiation oncologist, thoracic surgeon, medical oncologist, pathologist and diagnostic radiologist. The clinical stages of T and N were determined based on routine radiological findings of CT. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) was performed under the situations when patients were voluntary to receive pretreatment PET/CT staging or when lymph nodes or distant metastases were believed to be highly possible. In the data analysis, an age-independent Charlson Comorbidity Index (CCI) was used to record comorbidity scores[34]. Theraputic toxicity was graded according to Common Terminology Criteria of Adverse Events (version 3.0). Recurrence types were classified according to RTOG 1021/ACOSOG Z4099. Local recurrence was defined as tumor recurrence at primary site, staple line or involved lobe, while regional recurrence was defined as ipsilateral nodal recurrence in hilum or mediastinum, or as recurrence in the ipsilateral lung. Distant recurrence refers to recurrence other than local recurrence or regional recurrence. Recurrence was clinically determined either by tissue biopsy or by a radiation oncologist either using PET/CT or CT alone. Overall survival (OS) was defined as the period from the beginning of treatment to death or the last follow-up. Cause-specific survival (CSS) was the interval from the beginning of treatment to death resulted by recurrence, or treatment-related death or the last follow-up. Recurrence-free survival was defined as the interval from the beginning of treatment to death, or any recurrence or the last follow-up.

The Ethics Review Committee of Zhejiang Cancer Hospital approved this study.

Treatment

SLR was mainly performed through video-assisted thoracoscopic surgery. Thoracotomy was performed if VATS was not qualified in preoperative or intraoperative judgment. Segmentectomy or wedge resection, with or without hilar and mediastinal lymph node dissection, was decided by the surgeon in consideration of tumor location, size, generous margins, risk of surgery and intraoperative findings. Distance from the dissection margin to tumor edge was longer than the maximum tumor diameter or 20 mm. All removed lymph nodes were confirmed to be negative for metastatic disease by frozen section analysis. The negative resection margins were histologically confirmed before the operation is complete.

SBRT patients were immobilized with a vacuum pillow. Four-dimensional CT (4D-CT) accompanied by real-time position management were used in the patients for tracing their breath. Respiratory gating was used if tumor motion was greater than 15 mm on the 4D-CT scan. Gross tumor volume (GTV) was delineated in ten phases (from 0% to 90% breathing phases), and were combined to form internal target volume (ITV) on the maximum intensity projection (MIP). The ITV was uniformly expanded by 5mm to generate the planning target volume (PTV). Dose calculation was performed on the average intensity projection (AIP), which were optimized by using 9-15 coplanar or non-coplanar 6-MV photon beams and also can be used as the reference for image guidance.

Statistical analysis

A propensity score matching analysis was performed by giving priority to exact matches method in order to reduce biases of patient characteristics in SBRT and SLR patients. The following covariates were used to match the patients: age, gender, performance status, tumor diameter, cancer stage and forced expiratory volume in 1 second (FEV1). Differences in patient's characteristics between treatment groups or subgroups were assessed using Mann-Whitney U test and chi-square test for analyzing continuous data and categorical data. Survival probability was evaluated using Kaplan-Meier method, while survival difference between the treatment groups and subgroups were studied using log-rank test.

Statistical analyses were performed using IBM Statistic Package for Social Science software (version 22.0; SPSS, Inc, Chicago, IL). Statistical significance was defined as $P < 0.05$.

Results

Patient Characteristics

From January 2012 to December 2015, 86 patients who underwent SBRT and 79 SLR (include 35 wedge resection and 44 segmentectomy), with a median age at diagnosis of 75 and 65 years, respectively, were met the inclusion criteria and were recruited into the study. Characteristics of patient are shown in **Table 1**. Compared with those who received SLR, patients treated with SBRT were significantly older and had poorer PS, lower FEV1 and larger tumor diameter. A higher proportion of male patients was treated by SBRT than by SLR ($P = 0.019$). There was no significant difference in disease stage between SBRT and SLR patients ($P = 0.295$). There is significant statistical difference in the histologic subtypes for the difference groups (P=0.030). In the group of SBRT, adenocarcinomas, squamous cell carcinomas and other are 46.9%, 30.6% and 22.4%, respectively. In the group of SLR, adenocarcinomas, squamous cell carcinomas and other are 69.4%, 24.5 and 6.1%, respectively.

Table 1. Characteristics of all patients and propensity score matched patients.

	All patients			Propensity score matched patients		
	SBRT (n =86)	SLR (n =79)	P-value	SBRT (n = 49)	SLR (n = 49)	P-value
Age [year]	75(47-88)	65(31-83)	<0.001	67(47-84)	68(46-83)	0.727
Gender (Male: Female)	60:26	41:38	0.019	33:16	33:16	1.000
PS (0:1:2)	13:70:3	48:30:1	<0.001	13:36:0	22:26:1	0.085
FEV1 [L]	1.48(0.48-3.27)	1.80(0.78-3.90)	<0.001	1.61(0.48-3.27)	1.57(0.78-2.98)	0.534
Tumor diameter [mm]	22(7-47)	17(5-45)	0.007	22(7-45)	20(8-45)	0.730
Stage (IA: IB)	70:16	69:10	0.295	40:9	39:10	0.798
Histology			<0.001			0.030
Sq	25	18		15	12	
Ad	38	58		23	34	
Other	23	3		11	3	
Prior lobectomies	8	12	0.247	6	8	0.564
CCI	2(0-6)	2(0-5)	0.144	1(0-6)	2(0-4)	0.058
PET/CT	56	13	<0.001	30	9	<0.001

Abbreviations: SBRT, stereotactic body radiotherapy; SLR, sublobar resection; PS, performance status; FEV1, forced expiratory volume in 1 second; Sq, squamous cell carcinomas; Ad, adenocarcinomas; CCI, Charlson Comorbidity Index;PET/CT, positron emission tomography/computed tomography.

Values are shown in median (range) for continuous data.

A propensity score analysis was performed in SBRT and SLR groups. 49 patients were identified from each group, and no difference in terms of age, gender, PS, tumor size, FEV1 and cancer stage was found between matched SBRT and SLR patients (Table 1). The prior lobectomies did not show significant difference (6 and 8 patients, respectively, $P = 0.564$). FDG-PET/CT was performed in 30 (61.2%) SBRT patients, compared with 9 (18.4%) SLR patients ($P < 0.001$). 26 SLR patients underwent segmentectomy, and the rest 23 received wedge resection. Lymph-node systematic dissection or sampling was performed in 22 (84.6%) and 4 (17.4%) patients, respectively. The additional 4 and 19 patients did not undergo lymph node dissection, as no detectable lymph node was shown on preoperative CT/PET-CT examination or found during the surgery. VATS was performed in 41 (83.7%) SLR patients, among whom, 2 (4.1%) patients also had to take thoracotomy. 8 (16.3%) patients remained underwent SLR by taking thoracotomy. 2 (4.1%) patients had positive surgical margin after wedge resection, specifically, one patient with positive surgical margin did not have intraoperative frozen section analysis, while the operation in another patient was forced to complete due to a drop in oxygen saturation and blood pressure. SBRT patients mainly treated with 50Gy prescribed dose (prescribed to the PTV margin) in 5 fractions, and the biological effective dose (BED) was 100Gy ($\alpha/\beta=10$). The dose segmentation scheme was adjusted according to lung function, comorbidities and life expectancy.

Survival and Recurrence Differences

Prior to perform PSM, the median follow-up periods of SBRT and SLR groups were 32 and 37 months, respectively. The median overall survival in each group was not reached at the time of last follow-up. 21 SBRT and 16 SLR patients died during follow-up, among them, 34 patients died of lung cancer, while 3 died of other causes. One case of treatment-related death occurred after SLR due to cardiac tamponade. One SLR patient died of a fracture 6.87 months after receiving segmentectomy, whereas one SBRT patient died of pneumonia 2 months after taking radiotherapy. No significant differences in OS (80.3% and 82.3% for 3-year OS, $P = 0.405$) (**Figure 1a**) and CSS (81.3% and 83.4% for 3-years CCS, $P = 0.383$) (**Figure 1b**) were found.

At the time of the last follow-up, 28 SBRT and 25 SLR patients experienced disease recurrence, and difference in recurrence-free survival was not significant (62.4%, and 69.9% for 3-year recurrence-free survival, $P = 0.383$) between the 2 groups. In SBRT and SLR groups, 8 and 11 cases of local recurrence, 10 and 10 cases of regional recurrence and 22 and 21 cases of distant recurrence were observed, respectively. The rates of local (**Figure 2**), regional and distance control did not have significant difference (89.7% and 86.0% for 3-years local control, $P = 0.501$; 87.1% and 87.9% for 3-year regional control, $P = 0.884$ and 71.6% and 74.4% for 3-year distance control, $P = 0.662$, respectively).

After performing PSM, 10 patients treated by SBRT and 13 patients treated by SLR died before the last follow-up, among them, 9 SBRT and 11 SLR patients were died of lung cancer recurrence, while 3 died of other causes. No statistically significant difference was identified in OS (85.4% and 73.3% for 3-year OS, P = 0.649) (**Figure 3a**) and cause-specific survival (CSS) (87.2% and 74.9% for 3-years CCS, $P = 0.637$) (**Figure 3b**) between the matched SBRT and SLR groups.

14 SBRT and 19 SLR patients in the matched groups experienced disease recurrence, and the difference in recurrence-free survival was not significant (66.7%, and 63.2% for 3-year RFS, $P = 0.689$) between the 2 matched groups. In the matched SBRT and SLR groups, 2 and 9 cases of local recurrence, 4 and 8 cases of regional recurrence and 11 and 16 cases of distant recurrence were identified, respectively. The rates of local (**Figure 4**), regional and distance control did not show significant difference (95.6% and 82.1% for 3-year local control, $P = 0.055$; 91.4% and 85.2% for 3-year regional control, $P = 0.432$ and 73.7% and 68.3% for 3-year distance control, $P = 0.548$, respectively).

In a subgroup analysis of matched patients, the number of patients was limited in wedge resection and segmentectomy subgroup. No significant difference was identified in OS, CSS, recurrence-free survival, regional control and distance control between SBRT and segmentectomy or between SBRT and wedge resection ($P > 0.05$). Local control of SBRT patients was better than those received wedge resection (95.6% versus 67.4% for 3-year local control, $P = 0.005$). The patients treated with segmentectomy had a tendency of improved 3-year local control (95.7% versus 67.4%; $P = 0.075$) and recurrence-free survival (77.2% versus 49.3%, $P = 0.076$), compared with those underwent wedge resection. However, the patients who had wedge resection had a higher CCI, compared with those received segmentectomy ($P = 0.013$).

Treatment toxicity

Posttreatment adverse events in the matched SBRT and SLR patients are shown in **Table 2**. In the SBRT cohort, 7 (14.3%) patients experienced grade 2 respiratory adverse events, specifically, there were 6 cases (12.2%) of radiation pneumonitis and 1 case (2.0%) of cough, which were all respiratory complications, however, no other grade 3 or worse adverse events was observed. In the SLR cohort, 13 patients (26.5%) had grade 2 or worse adverse events, while 8 patients (16.3%), which included 5 cases (10.2%) of dyspnea and 3 cases (6.1%) of chest wall pain, experienced grade 2 adverse events. Grade 3, 4 and 5 adverse events occurred to 5 patients (10.2%), including 2 cases (4.1%) of atrial fibrillation, 1 case (2.0%) of pulmonary thromboembolism, 1 case of (2.0%) of hypoxia and 1 case (2.0%) of pericardial tamponade. Grade 3 or worse adverse events after SLR were frequently cardiovascular diseases. The rate of grade 3 or worse adverse events was 0 and 10.2% in matched SBRT and SLR groups, respectively ($P = 0.056$).

Table 2
Posttreatment adverse events in the matched SBRT and SLR patients

AEs	CTCAE grade	SBRT (n = 49)
fatigue	1	1(2.0%)
Chest wall pain	1	1(2.0%)
dyspnea	1	4(8.2%)
cough	1	11(22.4%)
	2	1(2.0%)
radiation pneumonitis	1	13(26.5%)
	2	6(12.2%)
AEs	**CTCAE grade**	**SLR (n = 49)**
fatigue	1	8(16.3%)
anorexia	1	1(2.0%)
chest wall pain	1	12(24.5%)
	2	3(6.1%)
dyspnea	1	11(22.4%)
	2	5(10.2%)
cough	1	11(22.4%)
Atrial fibrilation	3	2(4.1%)
hypoxia	4	1(2.0%)
Pulmonary thromboembolism	4	1(2.0%)
pericardial tamponade	5	1(2.0%)

Discussion

Stereotactic body radiotherapy is a preferred strategy for treating medically inoperable patients with stage I NSCLC. For patients with a high operative risk, sublobar resection, rather than lobectomy, is more commonly used resection, and as a potential alternative to surgery, SBRT is encouraged to be discussed within the multidisciplinary cancer care team [35]. To date, no phase III randomized controlled trials comparing SBRT to sublobar resection in high-risk operable patients have been completed. Patients

treated with SBRT were those who are medically inoperable as well as potentially operable. A retrospective direct comparison of outcomes between SBRT and sublobar resection is problematic due to the heterogeneous population [36]. Furthermore, defining operative risk is complicated and subjective, especially for patients with a combination of multiple comorbidities, impaired cardiopulmonary function and advanced age. The assessment of operative risk is recommended to be discussed within a multidisciplinary team and may not meet a strict high-risk and inoperable criteria that have been reported in prospective clinical trials (ACOSOG Z4032 and RTOG 0236) [24, 37]. Propensity score matching, by comparing the outcomes of SBRT and compromised SLR in high-risk operable patients with stage I NSCLC, can produce more comparable groups in the current retrospective study.

Some retrospective studies also have attempted to use PSM to balance selection bias of population in comparing the survival of SBRT and SLR. These studies were conducted based on institution case series or administrative data from large databases including the Surveillance, Epidemiology, and End Results (SEER) database and the National Cancer Database (NCDB). Port et al [38] reviewed 164 patients who underwent wedge resection or SBRT with clinical stage IA NSCLC and 99 patients were matched by age, sex, and histology, and no significant difference was identified in OS between the wedge resection and SBRT groups (3-year OS 87% vs. 75%, respectively; $P = 0.357$). Matsuo et al. [39] performed a survival comparison between SBRT and SLR in patients who had stage I NSCLC and were at high risk for lobectomy, and 115 SBRT and 65 SLR patients were enrolled, and the results showed that the 5-year OS of SBRT was shorter than SLR before perfomring PSM (40.3% and 60.5%, respectively; P = 0.008), and that the Cause-specific death at 5-years was not significantly different. After performing PSM, 53 patients were matched from each treatment group in terms of age, gender, performance status, tumour diameter, FEV1 and CCI. The differences in 5-years OS (40.4% and 55.6%, respectively, $P = 0.124$) and cause-specific death (35.3% and 30.3%, respectively; $P = 0.427$) were insignificant. Shirvani et al. [11] used the SEER database to compare survival outcomes between SLR and SBRT patients age above 66 with stage I NSCLC. In his study, lung cancer-specific survival (LCSS) were not significantly different between the matched SLR and SBRT groups (OS HR 0.82, 95%CI, 0.53–1.27, $P = 0.38$; LCSS HR 2.14, 95%CI, 0.87–5.26, $P = 0.10$). Ezer et al. [40] also performed retrospective analysis using the SEER database. Patients aged above 65 years old with stage I–II NSCLC and negative lymph nodes treated with SBRT or SLT were identified. The study showed no differences in OS (HR; 1.20, 95% CI: 0.98–1.49) and cancer-specific survival (HR: 1.48, 95% CI: 0.97–2.42) between two groups after PSM. Our results were consistent with the conclusions from the previous reports, as SBRT achieved comparable survival outcome, compared with SLR after PSM. Thus, our data supported the fact that SBRT could be used as an alternative treatment to SLR.

However, two additional population-based analyses were inconsistent with our findings. Paul, et al. [41] compared the survival outcome between thoracoscopic SLR and SBRT using SEER database, and patients aged above 66 with stage I (tumor size $\leq$ 2 cm) NSCLC were identified. The study found no significant difference in CSS (HR 1.32, 95% CI 0.77 to 2.26; $P = 0.32$) between two propensity matched groups, however, SLR had a significant advantage in OS, compared with SBRT (HR 1.80, 95% CI 1.33 to 2.43; $P < 0.001$). Furthermore, Yerokun et al. [42] used the National Cancer Database to compare

outcomes between wedge resection and SBRT patients with stage clinical-T1N0M0 (tumors ≤ 2 cm) NSCLC, and SBRT was found to be associated with significantly reduced 5-year survival, compared with wedge resection in both unmatched analysis (30.9% vs 55.2%, $P < 0.001$) and after PSM analysis (31.0% vs 49.9%, $P < 0.001$). Therefore, using SBRT as an alternative treatment option to SLR for treating high-risk operable patients for lobectomy is still controversial, thus, prospective study is required to be performed to determine survival rate in SBRT and sublobar resection.

Both SBRT and SLR have inherent disadvantages over lobectomy in terms of disease control. SBRT delivers a very precise and high dose of radiation to a lung tumor in a small number of fractions and achieves more than 90% of local control rate with prescribed dose of BED ≥ 100 Gy [23, 25, 30], however, tumor is still not removed. Low prescription dose of BED and insufficient dose coverage due to the uncertainty of internal tumor movement and/or patient set-up resulting in worse local control [43-45]. SLR increases inadequate or positive surgical margins and significantly increases the possibility of local recurrence, compared with lobectomy [7, 22]. Furthermore, both SBRT and SLR do not remove unsuspected intralobar tumor spread. It is still not clear whether SBRT or SLR has a better performance in disease control. Matsuo et al. [39] reported a higher local recurrence after SBRT, compared with SLR (28.3% and 14.1% at 5 years, $P = 0.059$). Port et al. [38] showed that overall recurrence (local and distant) was significantly higher after SBRT (30% VS. 9%, $P = 0.016$), however, SBRT group had a higher rate of prior lobar resection, which could predispose patients to clinical understaging if some patients had metastatic tumors rather than the second primary tumors. In our study, there were no significant difference in local, regional and distance control between two matched groups, supporting that SBRT could be used as an alternative treatment to SLR.

The type and severity of complications observed after treatments in potentially operable patients appeared different between SBRT and SLR groups. Adverse events were mostly respiratory injury in SBRT patients and more frequent and severe cardiovascular in SLR. SBRT-related toxicity was mild and similar to previous reports in potentially operable patients, as grades 2 and ≥3 radiation pneumonitis occurred in 13.6% and 1.1% to 2% of the patients [30, 31], rib fractures were seen in approximately 3% to 4.6% of the patients [31, 32] and grade 3 dermatitis were observed in 3.4% of the patients [32]. Adverse events might be more frequent and severe in medically inoperable patients with higher prescription dose in fewer fractions (54 Gy in 3 fractions) [24]. Perioperative mortality and morbidity in high-risk operable patients with NSCLC treated with SLR were moderate and similar to a randomized clinical trial(Z4032), in which 9 patients (12%) reported grade 3 respiratory adverse events. Perioperative mortality occurred in 1.4% of the patients [37]. In a study using the SEER-Medicare, unadjusted mortality of sublobar resection at 30-days and 90-days was 1.2% and 4.1%, respectively [11]. There was one treatment-related death after SLR in present work, and SBRT was found to decrease treatment-related toxicities, compared with SLR.

The superiority of present study was that the differences in matching variables were well balanced. Prior lobar resection and CCI, which were not matched, were also no significantly different. Furthermore, survival and disease control after SBRT in our study were consistent with the previous studies, as SBRT achieved high local control rates ranging from 85% to 96% and 3-years overall survival was 76% to 95%

for patients with potentially operable early-stage NSCLC [28-32, 46]. Our outcomes after sublobar resection were similar to a phase III randomized trial (ACOSOG Z4032) for high-risk operable NSCLC [41].

Several limitations of the present study have to be acknowledged, for example, treatment decision of NSCLC patients relied on proper staging. Sublobar resection is preferred over SBRT to determine nodal status [8]. We allowed for tumors up to 5cm in size to be included in the study (T1-2a N0M0 NSCLC according to the 7th Edition of AJCC Staging Criteria), which increased the risk of nodal disease and recurrence rates and would lead to uncertainty. Potential patients in a disease stage more advanced than stage I, who were associated with poorer prognosis [47], were excluded after SLR, therefore outcomes might be in favor of SLR. As patient selection was conducted by routine examination of PET/CT and appropriate use of invasive staging of mediastinal and hilar nodes with mediastinoscopy or endobronchial ultrasound (EBUS) in high-risk subpopulations with nodal metastases, it achieved higher accuracy and specificity in nodal staging [48-50]. On the other hand, as some radiation-induced modifications arise from inflammation and fibrosis, which limits the timely evaluation of tumor recurrences after SBRT. Thirdly, the surgical techniques employed during this study were significant heterogeneity, which would lead to uncertainty in the comparison of results and would make renders generalizability of the results challenging. Selection bias in treatment decision-making is unavoidable due to the different characteristics of each treatment modality and the nature of retrospective study. PSM was applied to reduce differences in patients between SBRT and SLR groups, however, the differences could not be eliminated completely in a single institutional retrospective study. Limited variables of propensity score matching and numbers of patients were less than those analyses, which were based on population-based database. Thus, prospective randomized trials are still required to be performed in the future.

Conclusions

These results suggest that SBRT achieved similar disease control and survival, compared with sublobar resection in patients who had clinical stage I NSCLC and were at a high risk for lobectomy. The two treatment strategies are both generally well tolerated in our patients. Though treatment-related toxicities may be milder in SBRT, SBRT can still be used as an alternative treatment option to SLR in high-risk operable patients. However, our findings should be confirmed in future prospective studies.

Declarations

Ethics approval and consent to participate

The Ethics Review Committee of Zhejiang Cancer Hospital approved this study.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

WC Chen, XS Yuan and YJ Liu contributed equally. All authors read and approved the final manuscript.

(I) Conception and design: WC Chen, XS Yuan, YP Xu; (II) Administrative support: YP Xu; (III) Provision of study materials or patients: QR Lin, XJ Sun; (IV) Collection and assembly of data: YJ Liu, JS Liu; (V) Data analysis and interpretation: WC Chen, XS Yuan, YJ Liu, QR Lin, XJ Sun; (VI) Manuscript writing: All authors.

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Figures

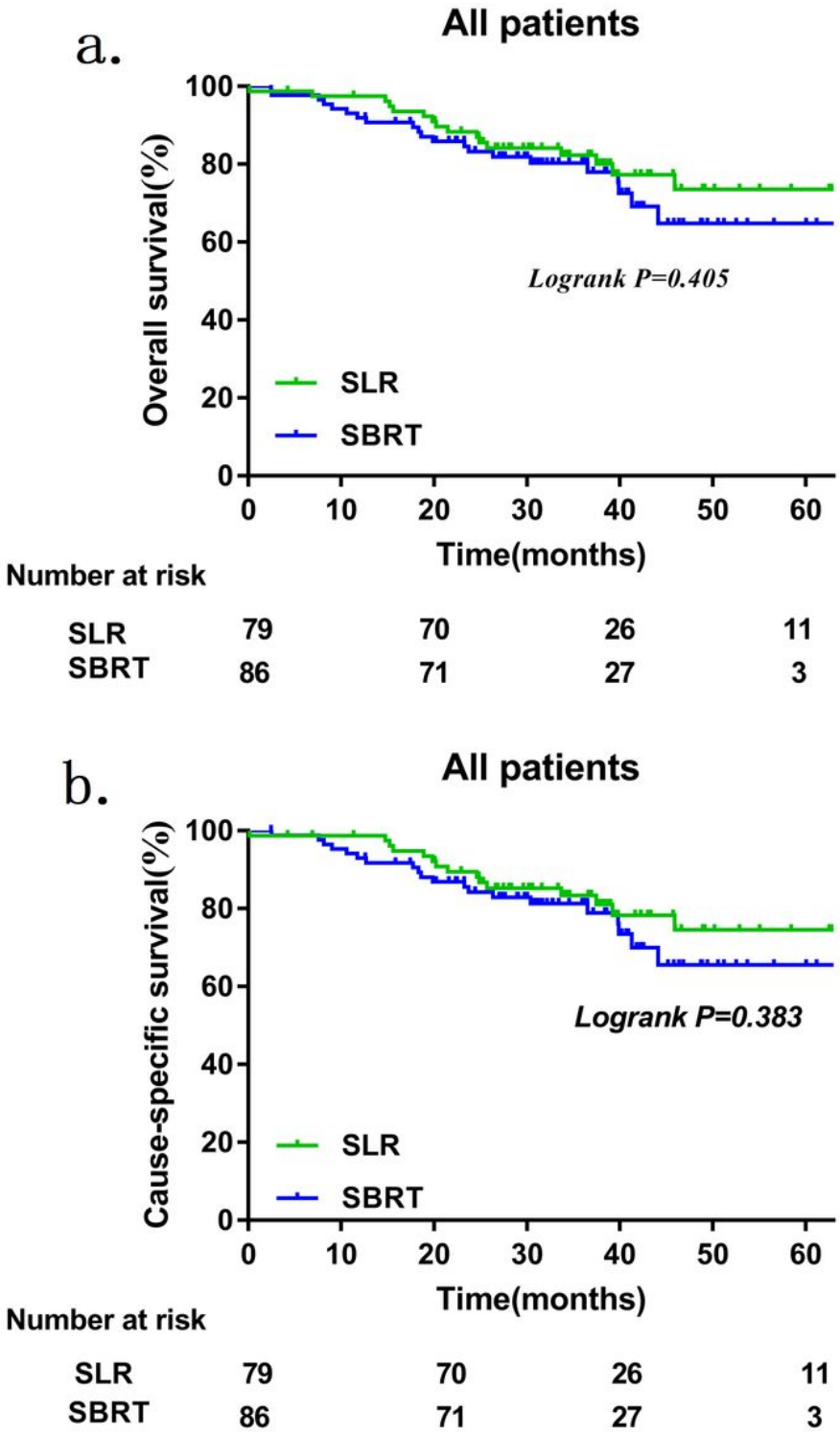
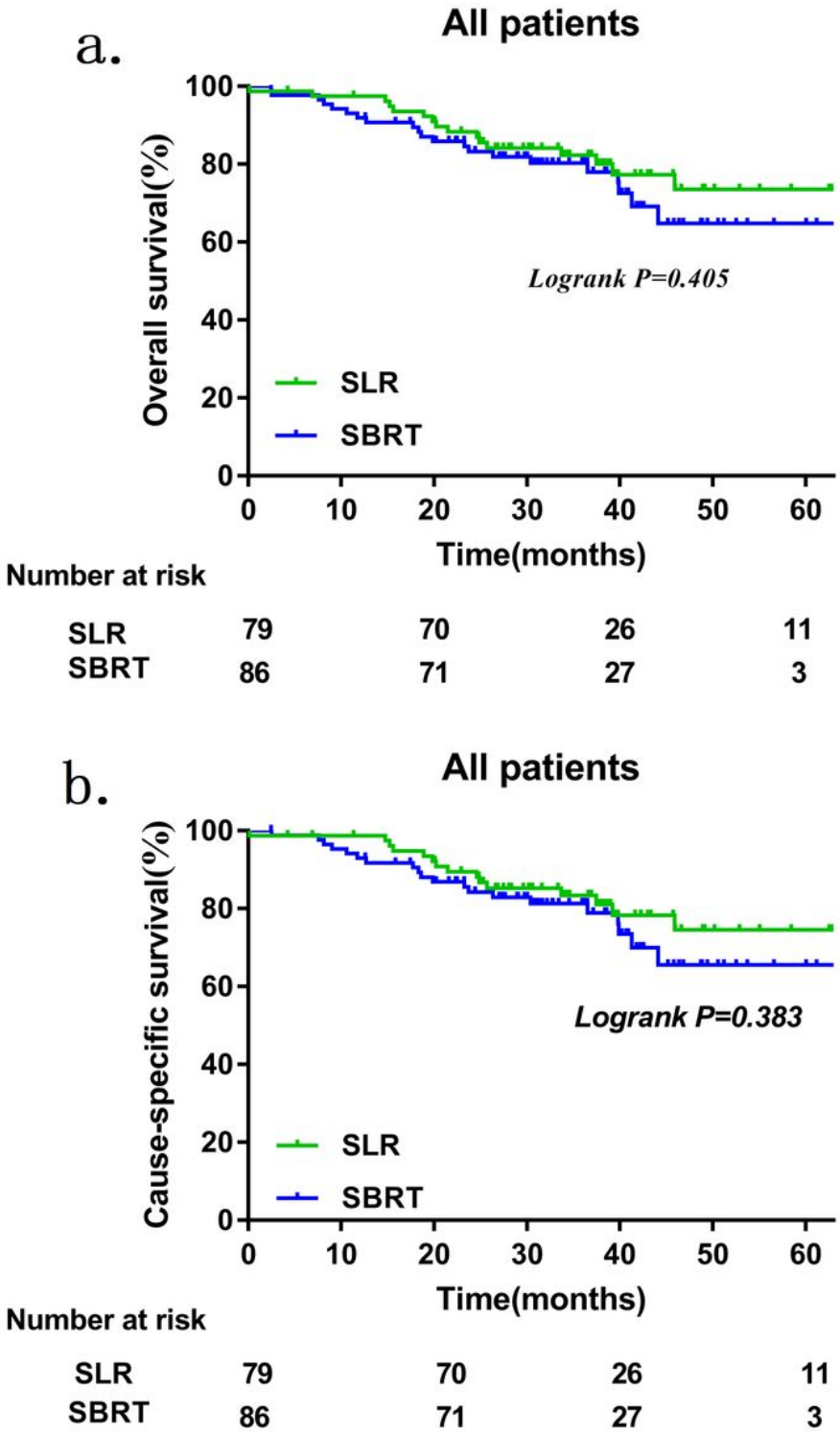


Figure 1

Overall(a) and cause-specific(b) survival in all patients



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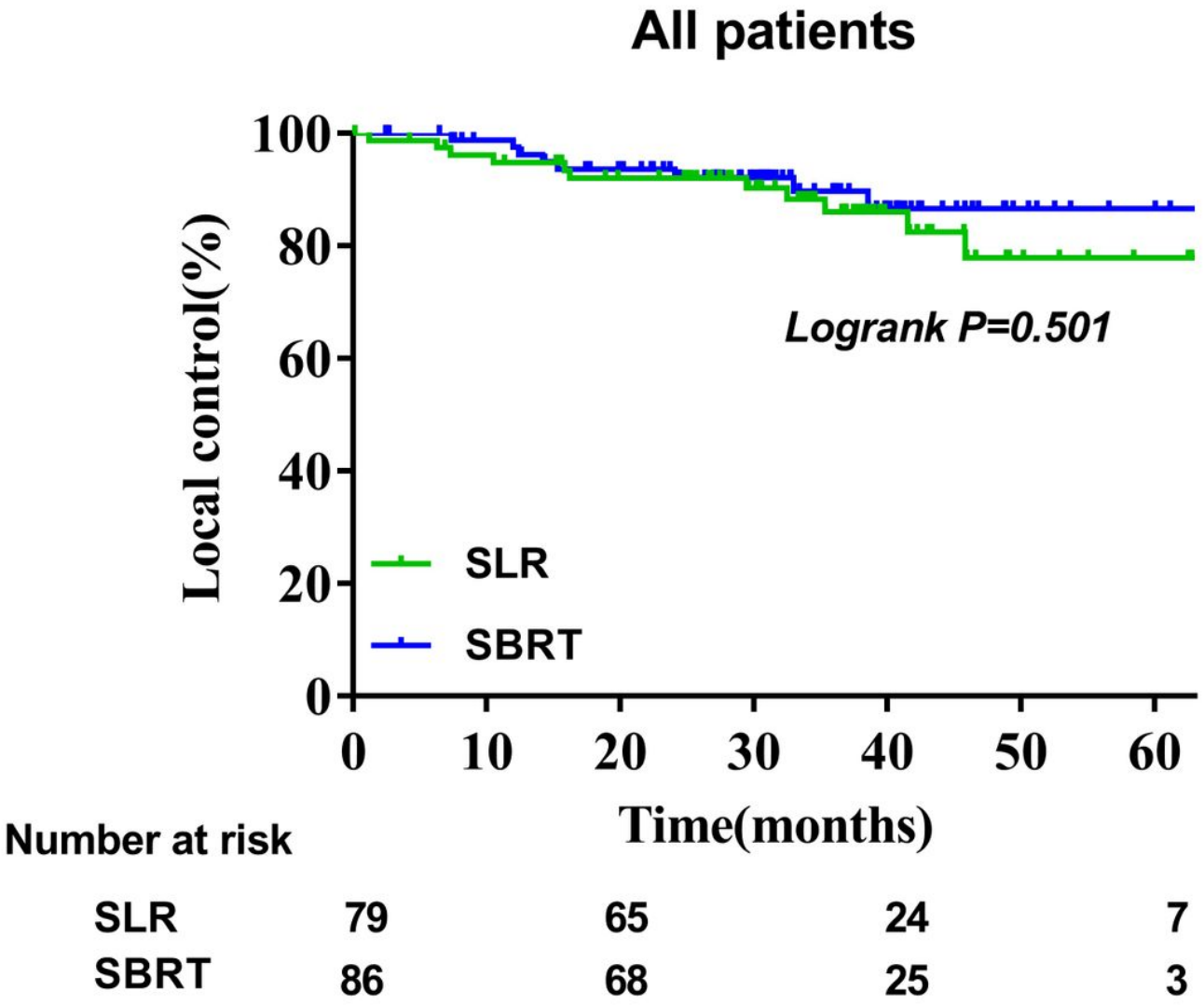
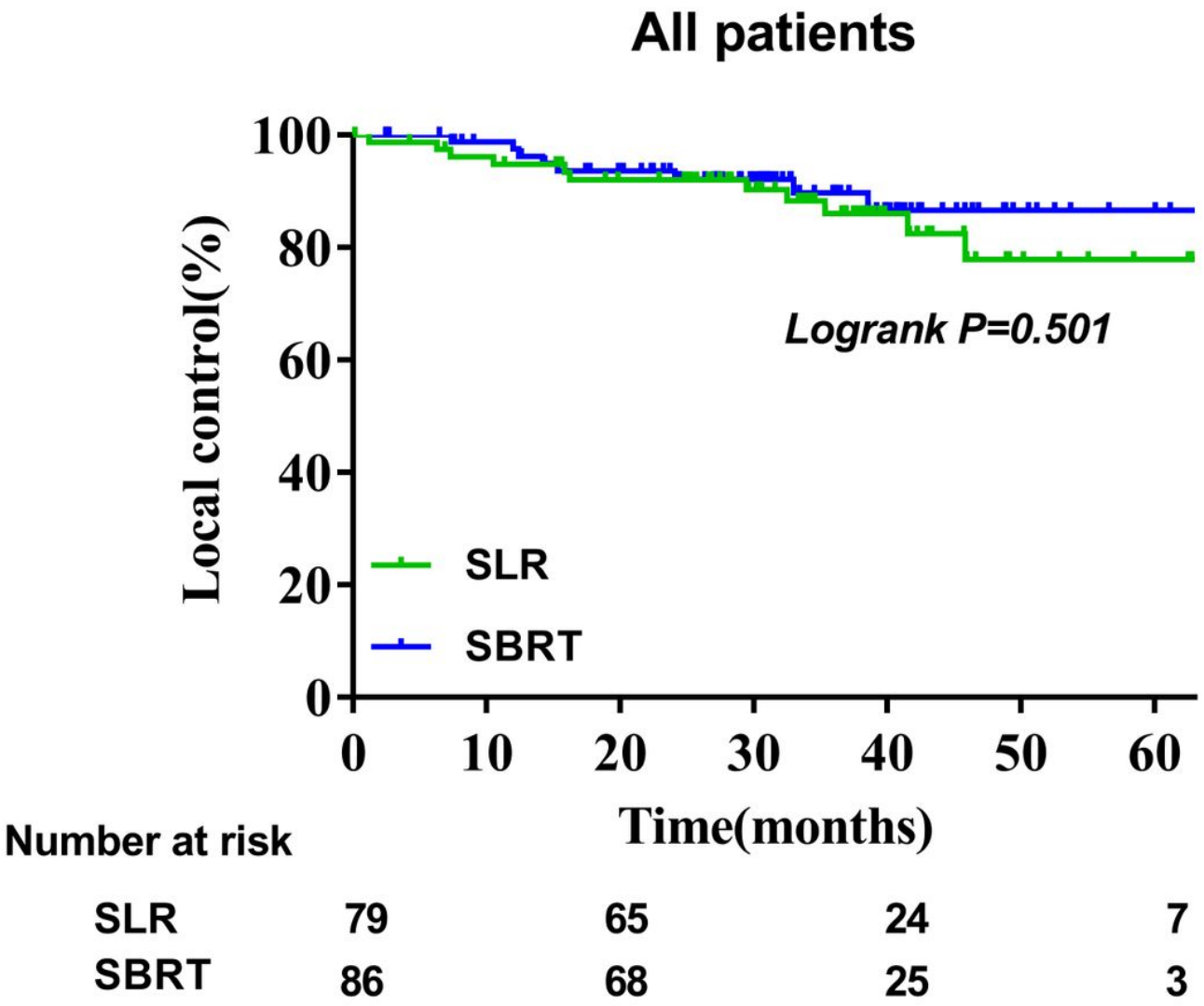


Figure 2

Local control in all patients



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Local control in all patients

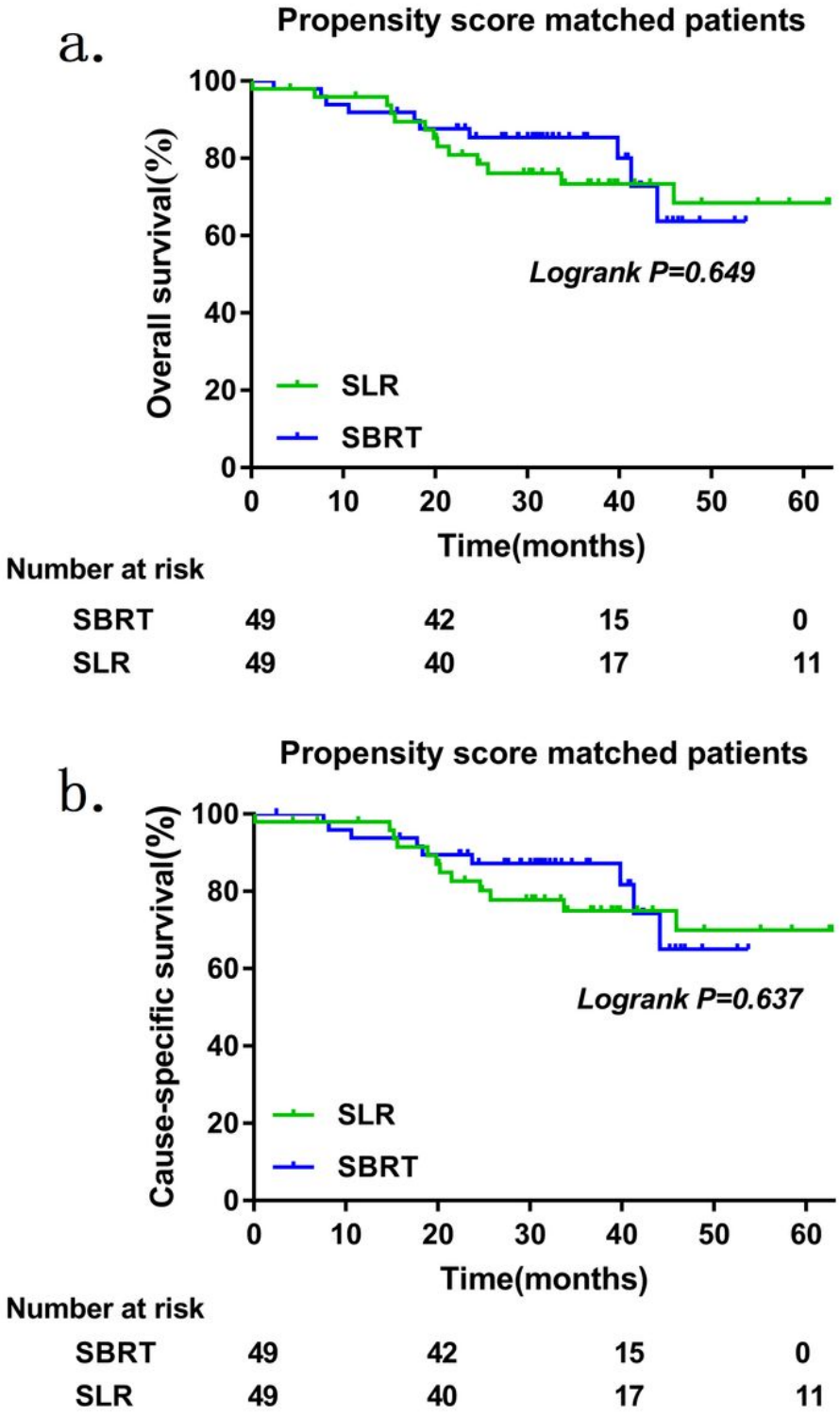
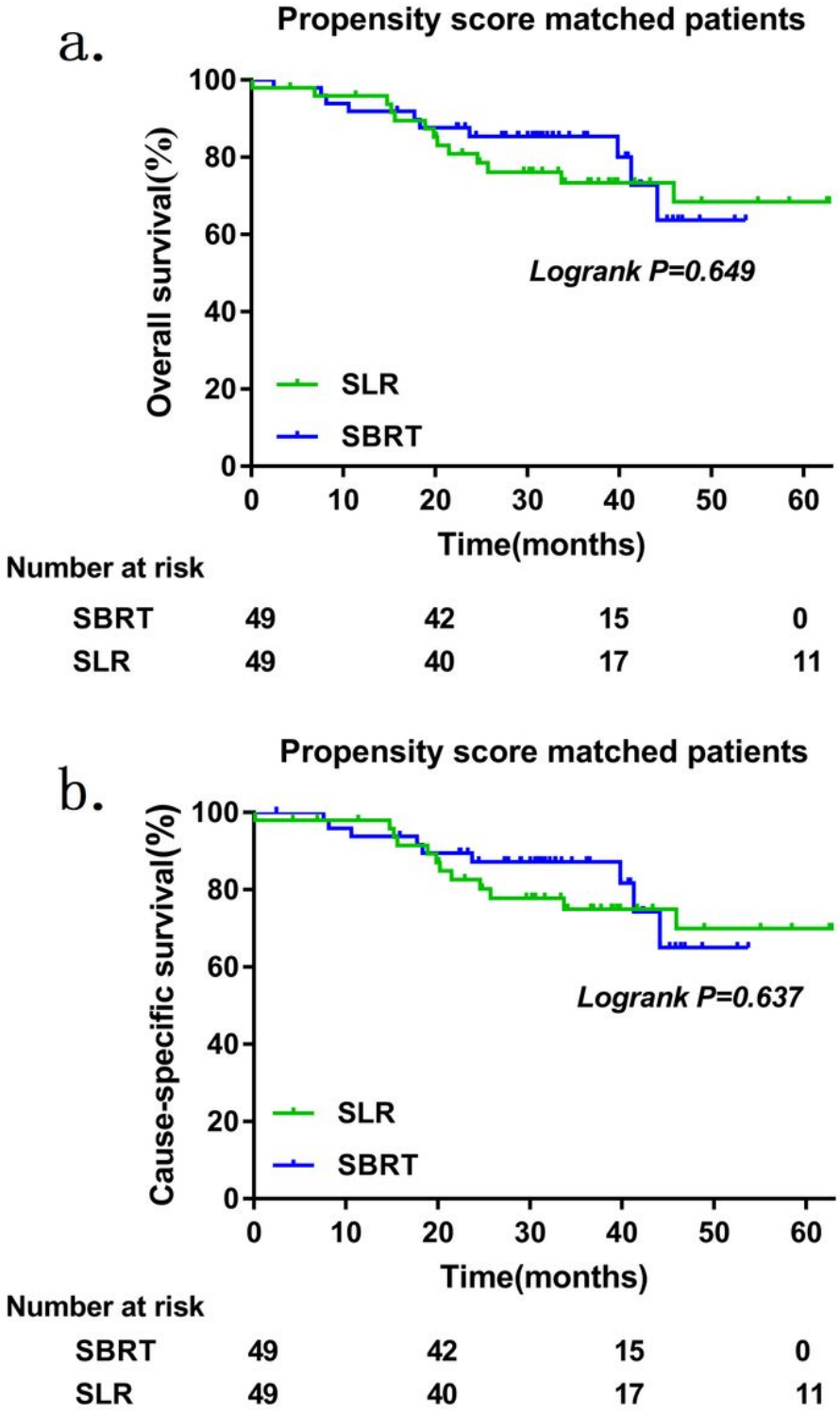


Figure 3

Overall(a) and cause-specific(b) survival in propensity score matched patients



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Overall(a) and cause-specific(b) survival in propensity score matched patients

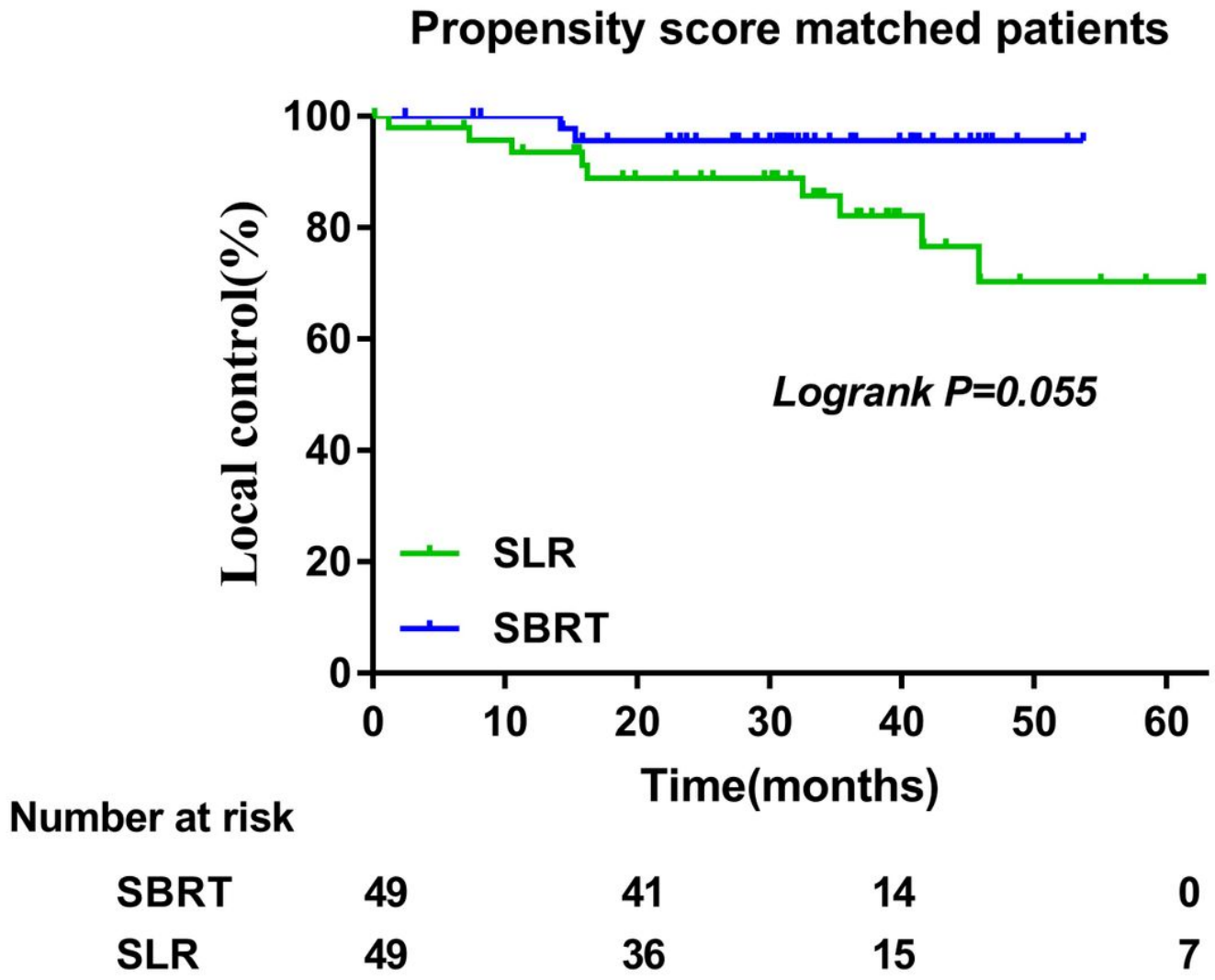

Figure 4

Local control in propensity score matched patients

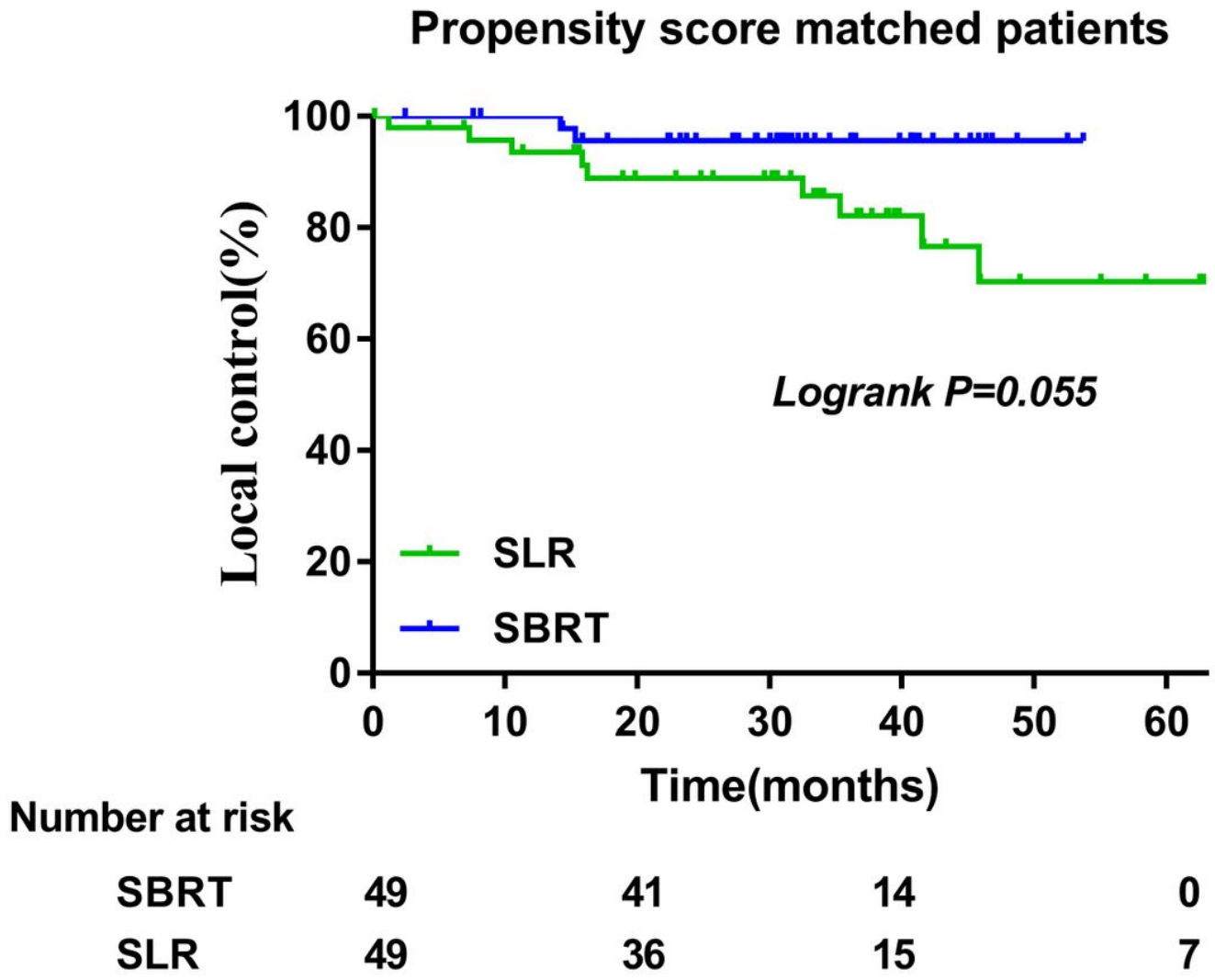

Figure 4

Local control in propensity score matched patients