Received: 19 October 2020 | Revised: 22 December 2020 | Accepted: 5 January 2021

DOI: 10.1002/cnr2.1339

ORIGINAL ARTICLE

Cancer Reports | WILEY

Outcomes of sublobar resection vs lobectomy for invasive clinical stage T1N0 non-small-cell lung cancer: A propensity-match analysis

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Funding information
Hadassah France, Grant/Award Number: Research Donation to Dr Ori Wald; Katz family scientist award program, Grant/Award Number: Research award granted to Dr. Ori Wald; Beare Foundation, Grant/Award Number: Research Donation to the Department of Cardiothoracic surgery

Abstract

Background: The role of sub lobar resection (SLR; either segmentectomy or wedge resection) vs lobectomy (LBCT) for invasive clinical stage T1N0 non-small-cell-lung-cancer (NSCLC) has not been fully established yet.

Aim: We aimed to characterize the preoperative parameters leading to selecting SLR and compare the overall survival (OS) and disease-free survival (DFS) of these two surgical approaches.

Methods: Clinical data on 162 patients (LBCT-107; SLR-55) were prospectively entered in our departmental database. Preoperative parameters associated with the performance of SLR were identified using univariate and multivariate cox regression analysis. The Kaplan-Meier method was used to compute OS and DFS. Comparison between LBCT and SLR groups and 32 propensity-matched groups was performed using Log-rank test.

Results: Median follow-up time for the LBCT and SLR groups was 4.76 (Inter-quartile range [IQR] 2.96 to 8.23) and 3.38 (IQR 2.9 to 6.19) years respectively. OS and DFS rates were similar between the two groups in the entire cohort (OS-LBCT vs SLR $P = .853$, DSF-LBCT vs SLR $P = .653$) and after propensity matching (OS-LBCT vs SLR $P = .563$ DSF-LBCT vs SLR $P = .632$). Specifically, Two- and five-year OS rates for LBCT and SLR were 90.6.% vs 92.7%, 71.8% vs 75.9% respectively. Independent predictors of selecting for SLR included older age ($P < .001$), reduced FEV1% ($P = .026$), smaller tumor size ($P = .025$), smaller invasive component ($P = .021$) and higher American Society of Anesthesiology scores ($P = .014$).

Abbreviations: SLR, SLR resection; LBCT, lobectomy; NSCLC, non-small-cell-lung-cancer; ASA, American Society of Anesthesiology; OS, overall survival; DFS, disease free survival; IQR, inter-quartile range; C/T, consolidation to tumor size; CT, computed tomography; PET-CT, positron emission tomography-computed tomography; HTN, hypertension; CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; TIA, transient ischemic attack; DM, diabetes mellitus; FEV1%, forced expiratory volume in 1 second % from predicted; PFTs, pulmonary function tests; SD, standard deviation; SUVmax, maximum standardized uptake value of ^{18}F-fluorodeoxyglucose; IS, in-situ; MI, minimally invasive; CI, confidence interval; HR, hazard ratio.

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Conclusions: In 162 consecutive and 32 matched cases, SLR and lobar resection had similar overall and disease-free survival rates. SLR may be considered as a reasonable oncological procedure in carefully selected T1N0 NSCLC patients that present with multiple comorbidities and relatively small tumors.

KEYWORDS
lobectomy, NSCLC, sub-lobar resection

1 | INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide, and NSCLC is the most common type.[1] Despite advances in multimodality treatments including target therapy and immunotherapy, the long-term survival of patients with advanced-staged lung cancer remains poor. The incidence of early-stage lung cancer, defined as clinical T1-2N0M0 disease, has increased in recent years, mainly because of low-dose computed tomography (CT) screening programs, enabling detection, treatment, and cure of many of early stage lung cancers.[2]

LBCT, accompanied by hilar and mediastinal lymph node dissection, has been adopted as the surgical standard of care for early stage lung cancer, based on the results of the randomized trial, conducted by the Lung Cancer Study Group.[3] In recent years, there is an increasing evidence suggesting that an SLR (a wide wedge resection or anatomical segmentectomy) may provide an equivalent oncologic outcome as LBCT, in selected groups of patients.[4] Appropriate criteria for selecting the patients for this procedure is crucial. SLR is primarily preserved for peripheral small tumors (<2 cm), predominantly in patients with advanced age or with reduced cardiopulmonary reserve.

SLR has become an evidence-based procedure for pure ground-glass nodules and part solid nodules with a consolidation to tumor size (C/T) ratio less than 0.25.[5,6] These nodules are associated with adenocarcinoma in-situ and minimally invasive adenocarcinoma, consisting of purely lepidic growth without invasion or less than 0.5 cm invasion.[7] Accumulating evidence suggests that the C/T ratio is a reliable parameter for predicting invasive histology, spread through air spaces, and lymph node involvement.

Consolidation/tumor size ratio <0.5 remains the standard criteria for selecting the appropriate surgical approach before the results of two ongoing randomized controlled trials (CALGB140503 and JCOG0802) are reported.

The objective of this study is to compare the immediate and long-term outcome of SLR vs LBCT in patients with invasive (C/T ratio > 0.5 cm) clinical stage T1N0 NSCLC.

2 | MATERIAL AND METHODS

2.1 | Patients

We retrospectively reviewed our prospectively maintained departmental Society of Thoracic Surgeons (STS) general thoracic surgery database to identify all patients having surgery for clinically invasive stage T1N0 (cT1N0) NSCLC between June 2008 to January 2018 (in total, the database included 320 patients with a presumed diagnosis of lung cancer, all stages). Overall, 162 consecutive cases of cT1N0 tumors with a confirmed pathological diagnosis of NSCLC were identified. Patients with carcinoid tumors, or metastatic lesions were excluded from the study. Driver mutation status for patients participating in the study was not available. The Hadassah Hebrew University Hospital institutional review board approved this study (protocol number HMO-0299-19).

2.2 | Preoperative staging and surgical technique

Preoperative clinical staging was based on contrast-enhanced CT of the chest, and positron emission tomography-CT (PET-CT) in all patients. Invasive cT1N0 tumors were defined according to the eighth edition of the international association for the study of lung cancer staging system (tumor solid component diameter between 0.6 cm to 3 cm on CT and N0M0 state by PET CT; Mediastinoscopy/EBUS were not performed on the study population given that the PET CT scan indicated a N0 status).

Surgical procedures included formal anatomical LBCT and two types of SLR-formal segmentectomy or a wide wedge resection (defined as resection margin greater than at least 1.5 cm or the diameter of the tumor). Overall 162 surgeries were performed of these 107 were anatomical lobectomies, and 55 were sub-lobar resections (34 anatomical segmentectomies and 21 wide wedge resections). Systematic lymph node dissection was performed in the vast majority of cases (154/162 of cases = 95%, in 8 cases no lymph nodes were sampled).

2.3 | Follow up

Patients were seen in our clinic every 4 months during the first postoperative year, every 6 months during the second postoperative year and yearly thereafter. A low dose non-contrast CT scan of the chest was obtained prior to clinic visit. Locoregional recurrence was defined as recurrent tumor within the same lobe and/or in the ipsilateral hilar/mediastinal lymph nodes. Distant recurrence was defined as recurrence in a different lobe, pleural space, or elsewhere outside the hemi-thorax. OS was calculated from the date of surgery until the date of death or last follow-up. DFS was measured from the date of

surgery until an abnormal imaging test was detected during follow-up. All patients had a follow-up period of at least 2.44 years (893 days) unless death or a recurrence event occurred earlier. Further, the median follow-up time for the LBCT and SLR groups was 4.76 (IQR 2.96 to 8.23) and 3.38 (IQR 2.9 to 6.19) years respectively.

2.4 | Statistical analysis

Continuous variables were expressed as M ± SD or median and interquartile range. Categorical variables were expressed as absolute numbers with percentages. Categorical variables were analyzed using the Chi square test or Fisher exact test as appropriate. Continuous variables were analyzed using two-tailed Student's *t* test or the Mann-Whitney *U* test, as appropriate. Multivariate Cox regression analysis (on all variables obtaining a *P* value < .05) was performed to identify the variables that independently differentiate between the LBCT and SLR groups. Thereafter, these specific variables (in particular age, %FEV1, American Society of Anesthesiology [ASA] score, total tumor size, and tumor solid component) were incorporated into a propensity match scoring model to generate a score between 0 to 1 for each patient (LBCT and SLR score range 0.003 to 0.896 and 0.03 to 0.97 respectively). After rigorous matching, maximal score difference among pairs <0.02, we came up with 32 propensity matched pairs. The Kaplan-Meier method was used to compute actuarial overall survival and disease-free survival. Differences in survival between groups were analyzed using the Log-rank test. To identify predictors of overall survival in the entire cohort, we performed univariable analysis on preoperative clinical characteristics and on postoperative pathological characteristics to identify the variables that predict survival with a *P* values <.05 (age, CAD, HTN, blood creatinine level, FEV1%, ASA score, and pathological stage). Next, these variables were entered into a multivariate Cox regression model to identify those that independently predict survival. The type of surgery (LBCT vs SLR) was forced into the model. Statistical significance was set at $P < .05$. Statistical analyses were performed using the SPSS statistical software, version 22.0 (SPSS Statistics for Windows, IBM Corporation, Armonk, NY).

3 | RESULTS

3.1 | Baseline clinical and surgical characteristics

We identified 162 consecutive patients presenting with cT1N0 NSCLC who had surgery in our department between June 2008 to January 2018. Overall, 107 LBCT and 55 SLR (34 anatomical segmentectomies and 21 wide wedge resections) were performed. The preoperative clinical characteristics as well as the radiological tumor characteristics of patients having either LBCT or SLR are presented in Tables 1 and 2 respectively. Systematic lymph node dissection was performed in 100% of patients who underwent LBCT and 85% of patient who had SLR ($P < .01$). Further, the number of sampled lymph-node stations and the total number of lymph-nodes sampled were significantly higher in the LBCT group Table 3. Patients who had SLR were older, they had lower FEV1% values, and in addition, they had higher ASA scores and creatinine levels. Furthermore, patients who underwent SLR had smaller-size tumors with a lower standardized uptake value of ^{18}F-fluorodeoxyglucose on PET-CT (SUVmax). The C/T ration was similar between the two groups. These data suggest that we selected older patients with multiple co-morbidities and with relatively smaller tumors for SLR.

3.2 | Tumor pathology

The pathological evaluation of the LBCT and SLR specimens is summarized in Table 3. The most common histological tumor type in both groups was adenocarcinoma (LBCT-79.4%, SLR-83.6%) followed by squamous cell carcinoma (LBTC-10.3%, SLR 12.7%).

Complete (R0) resection was achieved in 100% of patients. However, the average distance of the tumor from the surgical margin was larger in the LBCT group compared to the SLR group.

Pathological upstaging, from clinical stage I disease to pathological stage II disease, occurred in 29/107 (27.1%) and 4/55 (7.2%) of LBCT and SLR cases, respectively. Pathological down-staging from clinically invasive carcinoma to carcinoma in situ, occurred in one LBCT case and in two SLR cases. Further, upstaging from clinical N0 to pathological N1 or N2 occurred in 20/107 (18.6%) and 3/55 (5.4%) of LBCT and SLR cases, respectively. Overall, Patients who underwent LBCT had a more advanced pathological T stage and a higher proportion of pathologically confirmed positive lymph nodes. Taken together, these findings suggest that patients in the LBCT group had more advanced disease compared with patients who had SLR .

The differences in pathological staging were eliminated after propensity matching Table 3.

3.2.1 | Early outcomes

The 30-day mortality was 0.9% (1/107) for LBCT and 3.6% (2/55) for SLR ($P = .266$) with no additional deaths at 90 days. Causes of early deaths were: pulmonary embolism—two cases, septic shock—one case.

3.3 | Long-term outcomes

Follow-up was achieved in 100% of patients. Median follow-up for the entire cohort was 4.48 (IQR-2.91 to 7.13) years. Length of follow-up did not significantly differ between the groups (median follow-up time for LBCT and SLR groups 4.76 (IQR 2.96 to 8.23) and 3.38 (IQR 2.9 to 6.19) years, respectively, $P = .12$).

The two- and five-year OS and DFS rates for LBCT and SLR were as follows, in the entire cohort: OS-LBCT vs SLR-two-year 90.6.% vs 92.7%, five-year 71.8% vs 75.9%, and DFS-LBCT vs SLR—two-year 84.1% vs 89.1%, five-year 67.6% vs 69% respectively; in the propensity matched pairs: OS-LBCT vs SLR-two-year 90.6.% vs 93.7%, five-year 66.7% vs 76.5% and DFS - LBCT vs SLR - two-year 84.4.% vs 81.2%, five-year 66.7% vs 60%, respectively. Kaplan-Meier OS and DFS curves

TABLE 1 Clinical characteristics

	Lobectomy (n = 107)	Sub-lobar (n = 55)	*P* value	Lobectomy (n = 32)	Sub-lobar (n = 32)	*P* value
Clinical characteristics						
Age (y)			**<.001**			.704
Mean ± SD	64.44 ± 9.57	69.44 ± 7.06		68.06 ± 7.6	67.34 ± 7.46	
Sex			**.041**			.127
Male/female	48 (44.9%)/59 (55.1%)	34 (61.8%)/21 (38.2%)		16 (50%)/16 (50%)	22 (68.7%)/10 (31.3%)	
Comorbidities						
HTN	52 (48.6%)	31 (48%)	0.349	20 (62.5%)	15 (46.9%)	0.209
CAD	21 (19.6%)	11 (20%)	0.955	8 (25%)	6 (18.8%)	0.545
CHF	2 (1.9%)	1 (1.8%)	1	1 (3.1%)	1 (3.1%)	1
CVA or TIA	9 (8.4%)	9 (16.4%)	0.127	6 (18.8%)	4 (12.5%)	0.491
DM	21 (19.6%)	13 (23.6%)	0.553	9 (28.1%)	8 (25%)	0.777
History of cancer	7 (6.5%)	7 (12.7%)	0.238	2 (6.3%)	5 (15.6%)	0.426
ASA score			**.001**			.711
1	66 (61.7%)	22 (40%)		18 (56.2%)	16 (50%)	
2	32 (29.9%)	16 (29.1%)		8 (25%)	11 (34.3%)	
3	9 (8.4%)	17 (30.9%)		6 (18.8%)	5 (15.7%)	
Hemoglobin level (gr%)			.849			.648
Mean ± SD	13.12 ± 1.42	13.16 ± 1.59		13.28 ± 1.59	13.1 ± 1.46	
Blood creatinine level (micromol/L)			**.012**			.306
Mean ± SD	74.32 ± 19.94	84.04 ± 30.56		78.66 ± 23.81	86.06 ± 32.9	
Smoking status			.1			.376
Ever/never	77 (72%)/30 (28%)	46 (83.6%)/9 (16.4%)		23 (71.9%)/9 (28.1%)	26 (81.3%)/6 (18.8%)	
FEV1%			**.029**			.243
Mean ± SD	91.7 ± 16.64	83.91 ± 23.2		91.66 ± 18.06	86 ± 20.25	

Note: The preoperative clinical characteristics of patients in the lobectomy and sub-lobar groups are shown on the left side of the table. On the right, the same data is presented for the 32 matched pairs.

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; DM, diabetes mellitus; FEV1%, forced expiratory volume in 1 second % from predicted; HTN, hypertension; PFTs, pulmonary function tests; TIA, transient ischemic attack.

showing similar survival rates between the groups in the entire cohort and after propensity matching are depicted in Figure 1, (OS-LBCT vs SLR *P* = .853, DSF-LBCT vs SLR *P* = .653) and after propensity matching (OS-LBCT vs SLR *P* = .563 DSF-LBCT vs SLR *P* = .632).

Disease recurrence patterns were as follows: in the LBCT group 29 (27.1%) recurrence events were recorded, of these 3 (10.3%) were local, 11 (37.9%) were distant and 15 (51.7%) manifested both locally and as distant metastasis.; in the SLR group 11 (20%) recurrence events were recorded, of these 3 (27.2%) were local, 1 (9%) was distant and 7 (63.6%) manifested both locally and as distant metastasis.

3.4 | Determinants of OS in the entire cohort

Independent predictors of overall survival in the entire cohort were age, CAD, blood creatinine level, FEV1% and pathological disease stage Table 4. Compared with LBCT, SLR type of procedure did not have a measurable impact on survival.

4 | DISCUSSION

Our current study reports the outcome of SLR vs LBCT for invasive clinical stage T1N0 NSCLC. The key findings, including a propensity-match analysis, show a non-inferior OS and DFS for selected group of patients who underwent an SLR, mainly older with a small tumor size, and reduce FEV1. Further, our analysis of risk factors associated with OS includes age, CAD, blood creatinine level, FEV1, pathological stage, and not the extent of surgery.

The randomized trial conducted by the Lung Cancer Study Group between 1982 and 1988 established lobar resection rather

TABLE 2 Tumor characteristics

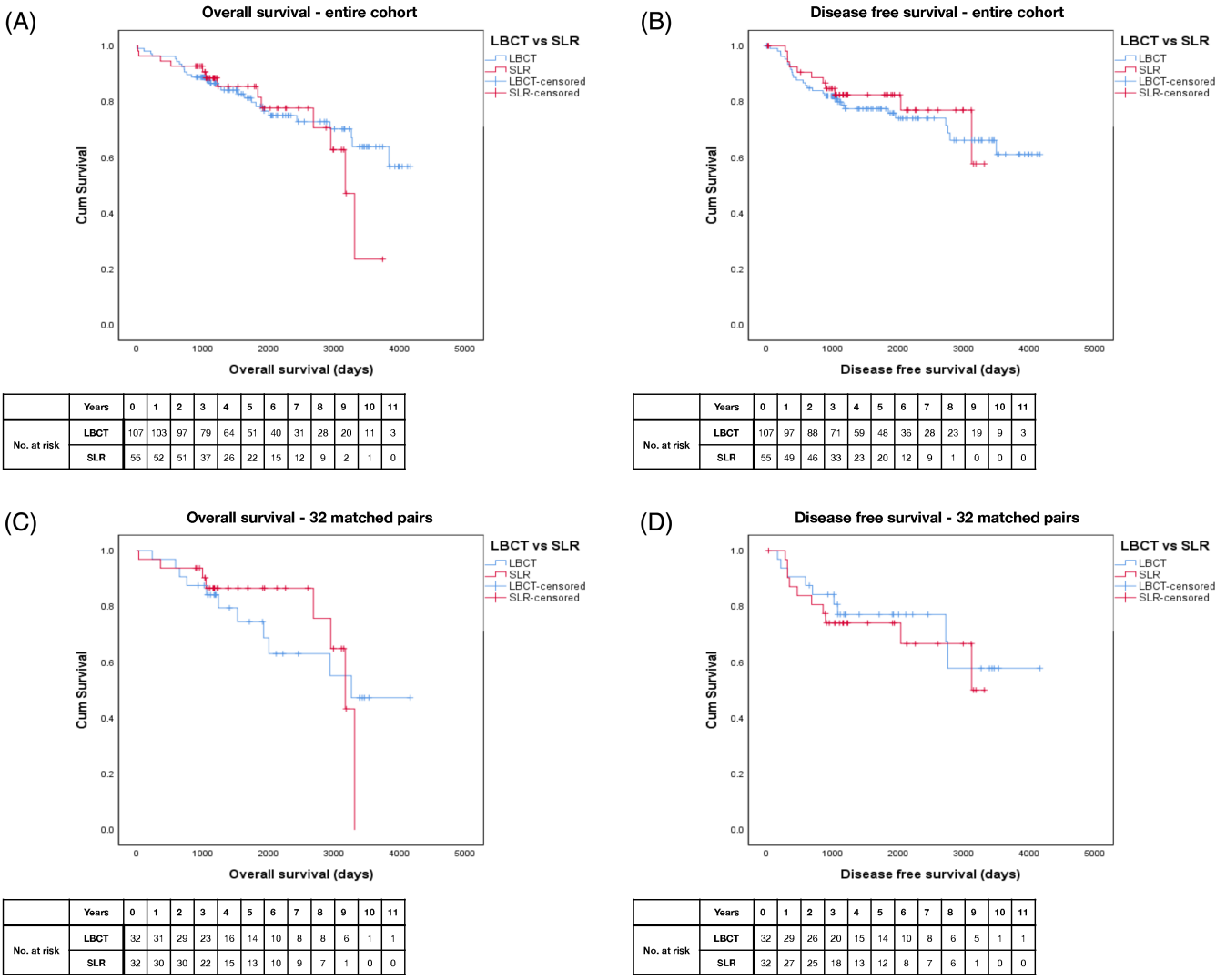
	Lobectomy (n = 107)	Sub-lobar (n = 55)	*P* value	Lobectomy (n = 32)	Sub-lobar (n = 32)	*P* value
Tumor characteristics						
Intralobar location			.092			.351
Central/peripheral	28 (26.2%)/79 (73.8%)	8 (14.5%)/47 (85.5%)		8 (25%)/24 (75%)	5 (15.6%)/27 (84.6%)	
Total tumor size (cm)			**<.001**			.882
Mean ± SD	2.39 ± 0.75	1.9 ± 0.63		2.05 ± 0.73	2.08 ± 0.69	
Solid component (cm)			**<.001**			.838
Mean ± SD	1.89 ± 0.7	1.41 ± 0.63		1.54 ± 0.65	1.58 ± 0.68	
Consolidatoin/tumor ratio			.107			.672
Mean ± SD	0.81 ± 0.22	0.75 ± 0.24		0.79 ± 0.26	0.77 ± 0.23	
SUVmax			**.007**			.3
Mean ± SD	7.23 ± 5.46	5.06 ± 3.13		4.54 ± 2.82	5.41 ± 2.98	

The preoperative radiological characteristics of the tumors of patients in the lobectomy and sub-lobar groups are shown on the left side of the table. On the right, the same data is presented for the 32 matched pairs.
Abbreviations: SUVmax, maximum standardized uptake value of fluorodeoxyglucose F 18.

TABLE 3 Pathological characteristics

	Lobectomy (n = 107)	Sub-lobar (n = 55)	*P* value	Lobectomy (n = 32)	Sub-lobar (n = 32)	*P* value
Pathological characteristics						
Pathological T			**.007**			.594
IS/MI	2 (1.9%)	6 (10.9%)		1 (3.1%)	4 (12.5%)	
1(1A/1B/1C)	52 (48.6%)	34 (61.8%)		20 (62.5%)	17 (53.1%)	
2(2A/2B)	45 (42.1%)	14 (25.5%)		10 (31.1%)	10 (31.1%)	
3	8 (7.5%)	1 (1.8%)		1 (3.1%)	1 (3.1%)	
Pathological N			.135			.478
0	87 (81.3%)	44 (93.6%)		25 (78.1%)	26 (89.7%)	
1	15 (14%)	3 (6.4%)		6 (18.8%)	3 (10.3%)	
2	5 (4.7%)	0 (0%)		1 (3.1%)	0 (0%)	
Pathological stage			**.008**			.298
0	1 (0.9%)	2 (3.6%)		0 (0%)	2 (6.3%)	
All stage I (IA1/IA2/IA3/IB)	77 (72%)	49 (89.1%)		24 (75%)	26 (81.2%)	
All stage II (IIA/IIB)	22 (20.6%)	4 (7.3%)		7 (21.9%)	4 (12.5%)	
All stage III (IIIA/IIIB)	7 (6.5%)	0 (0%)		1 (3.1%)	0 (0%)	
Pathological tumor size (cm)			**<.001**			.501
Mean ± SD	2.47 ± 0.91	1.95 ± 0.8		2.15 ± 0.77	2.01 ± 0.92	
Distance of tumor from surgical margin (cm)			**.023**			.258
Mean ± SD	2.63 ± 1.46	2.07 ± 1.31		2.47 ± 1.6	2.03 ± 1.42	
Number of sampled lymph node stations			**<.001**			**<.001**
Mean ± SD	4.2 ± 1.44	2.27 ± 1.73		4.25 ± 1.48	2.47 ± 1.87	
Number of sampled lymph nodes			**<.001**			**<.001**
Mean ± SD	8.69 ± 3.95	3.53 ± 3.22		8.84 ± 3.88	4.03 ± 3.64	

Note: The pathological characteristics of the tumors of patients in the lobectomy and sub-lobar groups are shown on the left side of the table. On the right, the same data is presented for the 32 matched pairs.
Abbreviations: IS, in-situ; MI, minimally invasive.



	Years	0	1	2	3	4	5	6	7	8	9	10	11
No. at risk	LBCT	107	103	97	79	64	51	40	31	28	20	11	3
	SLR	55	52	51	37	26	22	15	12	9	2	1	0

	Years	0	1	2	3	4	5	6	7	8	9	10	11
No. at risk	LBCT	107	97	88	71	59	48	36	28	23	19	9	3
	SLR	55	49	46	33	23	20	12	9	1	0	0	0

	Years	0	1	2	3	4	5	6	7	8	9	10	11
No. at risk	LBCT	32	31	29	23	16	14	10	8	8	6	1	1
	SLR	32	30	30	22	15	13	10	9	7	1	0	0

	Years	0	1	2	3	4	5	6	7	8	9	10	11
No. at risk	LBCT	32	29	26	20	15	14	10	8	6	5	1	1
	SLR	32	27	25	18	13	12	8	7	6	1	0	0

FIGURE 1 Kaplan-Meier curves, showing the OS (A and C) and DFS (B and D) of patients having either lobectomy (blue line) or sub-lobar resection (red line) in the entire cohort (A and B) and among the 32 matched pairs, (C and D) are shown, (OS-LBCT vs SLR P = .853, DSF-LBCT vs SLR P = .653) and after propensity matching (OS-LBCT vs SLR P = .563 DSF-LBCT vs SLR P = .632). The number of patients at risk in each group are presented below the curves. DFS, disease free survival; OS, overall survival

than SLR as the standard of care for peripheral T1N0 NSCLC.[3] Higher death rates and 3 fold-higher local recurrence rates were reported in patients who underwent SLR. Since that report in 1995, the trial's results have been challenged by the introduction of advanced imaging and staging modalities, along with screening programs, leading to the detection of more small and curable tumors. In recent years, studies with strict and well-defined patient selection criteria have demonstrated comparable oncological outcomes in selected patients for SLR vs LBCT for early stage NSCLC, yet others have not.[6,8-14] This debate has resulted in 2 separate large randomized clinical trials, a North American trial (Alliance/ CALGB 140503) and a Japanese trial (JCOG/WJOG 0802) both pursuing to test the hypothesis that SLR is noninferior to LBCT for peripheral clinically node negative tumors 2 cm or less. Both trials have completed accrual, and long-term oncologic results are forthcoming.[15,16]

When deciding on the extent of resection for clinical T1N0 NSCLC the following are mainly considered: tumor-related variables like size and location, consolidation/tumor (C/T) ratio, adequate free margins, accurate lymph nodes dissection, anatomical segmentectomy vs wedge resection, as well as the patient's comorbidities, including lung function, malnutrition, and frailty.

Based on the results of a prospective multi-institutional study on the relationship between radiologic and pathologic findings in peripheral lung cancer,[7] the Japan Clinical Oncology Group defined a radiologically determined noninvasive lung cancer as a < 2 cm lung cancer tumor with a C/T ratio of 0.25 or less in diameter on thin-section CAT. The JCOG0804/WJOG4507L was a nonrandomized confirmatory phase III trial that evaluated the efficacy and safety of sub-lobar resection for peripheral less than 2 cm tumor with C/T ration <0.25. The results of this study confirmed that SLR resection offers sufficient local control (100%) and relapse-free survival (5 years 99.7%) for

TABLE 4 Determinants of overall survival in the entire cohort

Determinants of overall survival in the entire cohort	Adjusted HR	95.0% CI for HR		*P* value
		Lower limit	Upper limit	
Age (per year)	**1.073**	1.030	1.119	**.001**
CAD (yes/no)	**2.908**	1.421	5.951	**.003**
Blood creatinine level (per gr%)	**1.024**	1.013	1.036	**<.001**
FEV1%	**0.969**	0.952	0.987	**.001**
Pathological stage	**2.374**	1.067	5.282	**.034**
LBCT vs SLR	1.844	0.776	4.385	.166

Note: The adjusted HR for parameters determining the OS in the entire cohort are presented. Values < .05 were considered significant and provided in bold.

Abbreviations: CAD, coronary artery disease; CI, confidence interval; FEV1%, forced expiratory volume in 1 second % from predicted; HR, hazard ratio.

peripheral GGO dominant lung cancer.[5] Based on these results we elected to extend the scope of this group of patients with early lung cancer, and to analyze the outcome of peripheral invasive (C/T ratio > 0.25) T1N0, including 2-3 cm tumors. In the propensity-match groups, the mean tumor size was 2.05 and 2.08 cm (LBCT/SLR, respectively), and the mean C/T ratio was 0.79 and 0.77 (LBCT/SLR, respectively). OS and DFS were similar in both groups, and in both analyses (Figure 1). Most contemporary observational studies and trials comparing lobar and SLR have enrolled patients with tumor size <2 cm.[16] A more recent study examined the association between tumor size and the comparative prognosis of 140,043 patients undergoing segmentectomy (5%) and LBCT (95%), using the National Cancer Database (2004-2015). A graph of the interaction between tumor size and type of surgery showed that the survival curves of patients receiving LBCT or segmentectomy began to diverge beyond a tumor size of about 10 mm, suggesting that patients experienced a substantial survival benefit with LBCT with increasing tumor size beyond 10 mm.[14]

The 2020 National Comprehensive Cancer Network (NCCN) guidelines recommend LBCT combined with systematic hilar and mediastinal lymph node dissection as the standard surgical procedure for NSCLC, which identifies patients who may benefit from subsequent chemotherapy and target therapy (https://www.nccn.org). However, the optimal number of lymph nodes to be dissected for patients with NSCLC 2 cm or less during sub-lobar resection has not been standardized. In our cohort of patients, there is a significant difference in the number of sampled lymph node stations (4.2 vs 2.27, $P < .001$) and number of sampled lymph nodes (8.69 vs 3.53, $P < .001$) among the two groups, LBCT and SLR, respectively. Further, microscopic pathological N1/N2 was in the range of 18.7% (LBCT) and 6.4% (SLR). These figures may address the importance of accurate lymph node sampling or dissection during limited resection. A very recent study[17] has reported the prognostic impact of lymphadenectomy on outcomes of sub-lobar resection for NSCLC ⊆ 1 or >1 to 2 cm, among 7627 patients with tumor 2 cm or less (identified from the Surveillance, Epidemiology, and End Results database between 2010-2015). The results showed that patients with NSCLC ≤2 cm who underwent ≥4 lymph nodes dissection had better overall survival and lung cancer specific survival compared with those who underwent dissection of 1 to 3 lymph nodes, or who had no lymph nodes dissection after sub-lobar resection. These results support the growing established data that the extent of lymph nodes dissection is associated with the survival outcomes in patients with NSCLC ≤2 cm after sub-lobar resection.

The extent of the SLR, segmentectomy, or wedge resection, is not well standardized within the various comparative studies, and its significance on long term survival is uncertain. It is not clear whether a small peripheral tumor that requires a segmentectomy would be more easily removed by a large wedge resection without compromising the oncologic outcome. A recent meta-analysis of 19 studies, involving 14,197 patients, examined survival outcome after SLR for stage I NSCLC. Overall survival (HR = 0.82), cancer-specific survival (HR = 0.77) and disease-free survival (HR = 0.73) were significantly better with segmentectomy than with wedge resection.[12] The Japanese trial (JCOG0802) only compared segmentectomy with LBCT, whereas the SLR arm in the North American trail (Alliance/CALGB 140503) allowed for both segmental and wedge resection to be done. The results of these landmark studies are forthcoming, and they may provide answers to these and other questions that will affect the surgical care for NSCLC for years to come. At our practice, we use both techniques, mainly dependent on the location and size of the tumor. The SLR group was too small to analyze a superiority of one type of resection over the other. However we did compared the distance of the tumor from the surgical margins in the LBCT and SLR groups and we found a significant difference (2.63 cm vs 2.07 cm, $P = .023$ LBCT/SLR, respectively). Even though, we achieved R0 in all patients.

Currently, it is apparent that the majority of patients who underwent SLR were high-risk patients limited by decreased cardiopulmonary function or the presence of significant comorbid disease. These patients have no choice but to undergo less than an LBCT or receive other local treatment modalities such as stereotactic body radiation or radiofrequency ablation.[18] In our report patients in the SLR group were older (69.4 vs 64.4, $P < .001$), had higher ASA 3 score (30.9% vs 8.4%, $P = .001$) and lower predicted FEV1% (83.9% vs 91.7%, $P = .029$). These observations are similar to the conclusions of a very recent systematic review comparing the

outcome of LBCT vs SLR resection in patients with NSCLC.[19] The results of this analysis showed that SLRs seem to be indicated in elderly patients with a high comorbidity index and reduced respiratory functional reserve, and LBCT still remains safe and oncologically suitable method in patients with good performance status, reducing the risk of recurrence.

Our study has several limitations. As a retrospective analysis, the patient population undergoing intentional SLR may have been highly selective. Our current guidelines for selecting this type of procedure are primarily based on tumor- related variables and patients' comorbidities. To clarify this confounding bias we performed a laborious propensity matching process. This allowed a precise comparison among 32 pairs of patients. Although we are unable to control for inherent selection biases that go into the surgical decision-making for these patients, we believe that by controlling for demographic and tumor-related factors in propensity-matched groups, we were able to minimize those biases to the best extent possible. In addition, we grouped patients undergoing wedge resection and segmentectomy together, but it is not clear that they are equal methods of SLR. We do think that the role of wedge resection in particular needs to be better clarified. Nevertheless, our prospective data collection of patients is meticulous and accurate (The STS Database platform). A defined pre-operative multidisciplinary evaluation of the patients is crucial to personalize the correct surgical procedure. This was 100% completed in all patients including accurate the eighth edition of clinical staging (chest CT, CT-PET, and brain MRI or EBUS as indicated), pulmonary function test, and any additional cardiac or functional evaluation. Finally, given that a single surgical team performed all surgeries, the unity in surgical skills and judgment is assured throughout the study.

5 | CONCLUSION

In Conclusion: Our study suggests that SLR has a comparable outcome to LBCT in carefully selected patients with invasive T1N0 NSCLC. Large randomized trials are underway to define the clinical role of limited resections results are keenly awaited. It is clear and well established that LBCT and systematic lymph nodes dissection should still be the first line therapy for patients with early stage lung cancer, especially for patients with known high-risk of recurrent predictors such as radiographic solid-appearance and tumors with high SUVmax uptake.

ACKNOWLEDGEMENT

This work was supported by research grants provided to Dr Ori Wald by Hadassah France, by the Beare Foundation and via the Katz family scientist award program.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, W. O.; I. U.; *Data curation*, S. B. M., B. A. T.; *Formal analysis*, W. O., S. B. M., B. A. T.; *Funding acquisition*, E. E., S. O. M.; *Resources*, E. E., S. O. M.; *Supervision*, W. O., I. U.; *Visualization*, S. B. M.; *Writing*, W. O., S. B. M., (as part if his MD thesis), S. O. M., I. U.

ETHICAL STATEMENT

The Hadassah Hebrew University Hospital institutional review board approved this study. The ethical comity exempted the researchers from obtaining patient consent based on the retrospective and non-interventional characteristics of the study (protocol number HMO-0299-19).

DATA AVAILABILITY STATEMENT

The clinical data collected for this study is maintained by the senior author of the manuscript, and would be shared upon request.

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How to cite this article: Wald O, Sadeh BM, Bdolah-Abram T, Erez E, Shapira OM, Izhar U. Outcomes of sublobar resection vs lobectomy for invasive clinical stage T1N0 non-small-cell lung cancer: A propensity-match analysis. *Cancer Reports*. 2021;4:e1339. https://doi.org/10.1002/cnr2.1339