Understanding the Impact of Histology on the Post-Surgery Prognosis for Patients 70 Years and Older With I A Stage Non-Small Lung Cancer

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Research

Keywords: Lung adenocarcinoma, lung squamous cell carcinoma, sublobar resection, lobectomy

Posted Date: December 16th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-127800/v1>

Abstract

Objectives: Few studies investigated whether the types of histology had an influence on the postsurgical prognosis for patients 70 years and older with stage A non-small lung cancer (NSCLC).

Methods: The study population in our study were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program.

Results: A total of 10,376 eligible patients were included in our study. In both lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LSQCC) patients with TS ≤ 10 mm, sublobar resection (SR) achieved similar overall survival (OS) (LUAD: HR=0.843, 95% CI (0.673, 1.062), P=0.149; LSQCC: HR=0.799, 95 %CI (0.615, 0.036), P=0.091) and LCSS (LUAD: HR=1.074, 95% CI (0.626, 1.843), P=0.795; LSQCC: HR=0.987, 95 % CI (0.532, 1.833), P=0.967) to lobectomy (LT). For LUAD patients with TS >10 mm & ≤ 20 mm, LT was associated with better OS (HR=0.785, 95% CI (0.703, 878), P<0.001) but not LCSS (HR=0.962, 95% CI (0.766, 1.209), P=0.741); while for LSQCC, LT yielded similar OS (HR=0.864, 95% CI (0.746, 1.005), P=0.051) and LCSS (HR=0.872, 95% CI (0.675, 1.128), P=0.297). LUAD patients with TS >20 mm & ≤ 30 mm received SR were at a significant risk of reduction of OS (HR=0.816, 95% CI (0.709, 0.938), P=0.004) but not LCSS (HR=0.954, 95% CI (0.732, 1.244), P=0.729); while for LSQCC, patients received LT had a better OS (HR=0.742, 95% CI (0.624, 0.883), P<0.001) but not LCSS (HR=0.776, 95% CI (0.563, 1.071), P=0.123).

Conclusion: The postsurgical prognosis differed in patients with different histology, and SR maybe acceptable for elderly LUAD patients with TS ≤ 10 mm and LSQCC patients with TS ≤ 20 mm.

Introduction

Non-small lung cancer (NSCLC) including lung squamous cell carcinoma (LSQCC) and adenocarcinoma (LUAD) constitute approximately 85% of lung cancer cases[1]. Although great advances have been achieved, the survival of lung cancer patients still remains poor. In earlier years, LSQCC was more prevalent than LUAD; while in recent years, LUAD became the most common histologic type[2]. Several years ago, there were some researches demonstrating that the prognosis of LUAD was similar to that of LSQCC[3–5]. However, recent studies pointed out that some crucial prognostic factors and prognosis are quite different between those two types of lung cancers, and that they should be differently analyzed[5, 6]. Wang et al. [5] found that LUAD was significant different from LSQCC in gender, location, age, smoking status and survival; LUAD was more common in younger populations compared to LSQCC; moreover, LUAD patients were likely to have favorable long-term outcome than that of LSQCC patients in all tumor stage. Therefore, the postsurgical outcomes of LUAD and LSQCC need to be well researched.

Currently, it is widely acknowledged that surgical resection might be the curative treatment for early-stage NSCLC. However, controversy still remains about whether sublobar resection (SR) could achieve a similar outcome to lobectomy (LT) for early-stage NSCLC. Moreover, patients with an older age received pulmonary resection were likely to be associated with higher risks of perioperative morbidities and

mortality rates, worse cardiopulmonary function and shorter life expectancy[7, 8]. As mentioned, LUAD and LSQCC were different in gender, age, smoking status and survival. Thus, whether histology had a significant influence on postsurgical outcome of elderly patients with early-stage NSCLC? Despite the fact that numerous studies have investigated the impact of histology on survival, these studies were mainly focused on other prognostic factors than surgery and didn't deeply and comprehensively investigate into the relationship between histology and prognosis. Therefore, in the present study, the clinical data from the Surveillance, Epidemiology, and End Results (SEER) database were collected to investigate the prognostic significance of histology on survival of patients who underwent surgery.

Material And Methods

The study population

Eligible patients were selected from the SEER database which was funded by the National Cancer Institute of the United States. The database provides the cancer incidence and survival data which were collected from several registries that covers more than 30% of the U.S. population. And the clinical data have been collected for numerous high-quality clinical studies[9–14].

The inclusion criteria in our study include: a) pathologically confirmed primary T1N0M0 NSCLC, only LUAD and LSQCC with a tumor size(TS) ≤ 30 mm; b) no history of chemotherapy before or after surgery; c) history of surgery, excluding extended lobectomy, pneumonectomy and extended pneumonectomy; d) no record of radiation treatment before or after surgery; e) tumor was not located in main bronchus; f) age > 18 ; g) Only active follow-up was included; h) survival of less than 3 months after the operation was excluded.

Using SEER data from 1 Jan 2004 to 31 Dec 2011, we collected available data including the demographic information (age at diagnosis, sex, race, marriage status), tumor details (tumor size, histology, differentiation grade, TNM stage, location, and literally, the number of resected regional lymph nodes), treatment records (surgical procedures, radiation, chemotherapy) and predictors of survival (OS and lung cancer specific survival (LCSS)).

The histologic types of all enrolled cases were identified according to the 3th edition of International Classification of Diseases for Oncology (ICD-O-3). The histologic types were included as follows: adenocarcinoma (8140–8141, 8200, 8250–8255, 8470, 8480–8481, 8550–8551, 8570–8573) and squamous cell carcinoma (8052, 8070–8076, 8078, 8083–8084)[15–17]. The whole cohort was divided into two cohorts according to the types of histology (LUAD and LSQCC). The marriage status was divided into married, unmarried (including divorced, separated, single and widowed) and others group(unknown). Surgical procedures (SP) were divided into SR (surgery code: 21, 22) and standard LT (surgery code :30, 33). SR was comprised of wedge resection and segmentectomy. Grade well/moderate group included grade I and II, and poor/undifferentiated one included III and IV.

Statistical analysis

In our study, the primary endpoints were OS and LCSS. The length of time from diagnosis to the last follow up or individuals' death of any cause was defined as the OS. The length of time from diagnosis to the last follow up or individuals' death due to lung cancer was defined as LCSS. The last update on the follow-up time was Dec 31, 2016. OS and LCSS were assessed by Kaplan-Meier analysis. Log-rank tests were used to estimate survival differences between two types of histology. Multivariate analyses were conducted to remove biases as many as possible (Only when univariate analysis indicted a significant statistical difference, multivariate analysis was conducted).

Pearson's χ^2 tests were used for categorical variables and the Wilcoxon tests were used for continuous variables. R 3.6.1 (R Development Core Team, Vienna, Austria) was used to establish Kaplan–Meier survival curves in our study. Univariate and multivariate Cox-regression analyses was performed to calculate hazard ratios (HRs) and its 95% confidence intervals (CIs) using SPSS 22.0 (IBM, Armonk, NY). All statistical analyses were two-sided, and P value less than 0.05 revealed a statistically significance.

Results

Baseline characteristics

As shown in Table 1, a total of 10,376 NSCLC patients (only adenocarcinoma and squamous cell carcinoma) were included. Among them, 7,197 patients were diagnosed with LUAD and 3,179 with LSQCC. The full cohort was categorized into adenocarcinoma and squamous cell carcinoma cohort. In LSQCC patients, 1048 received SR and 2131 received LT; while for LUAD, 2248 received SR and 4949 received LT. In both LUAD and LSQCC, sublobar resection was likely to be performed in patients with a smaller TS and was also associated with a smaller number of resected lymph nodes. More details were available in Table 1.

Table 1
Baseline characteristics the study population

	Squamous cell carcinoma(n = 3179)		Adenocarcinoma(n = 7197)	
	Sublobar resection (n = 1048)	Lobectomy (n = 2131)	Sublobar resection (n = 2248)	Lobectomy (n = 4949)
Sex	0.553		0.659	
Male	544(51.9%)	1130(53.0%)	950(42.3%)	2064(41.7%)
Female	504(48.1%)	1001(47.0%)	1298(57.7%)	2885(58.3%)
Race	0.872		0.043*	
White	959(91.5%)	1946(91.3%)	2037(90.6%)	4398(88.7%)
Black	59(5.6%)	117(5.5%)	90(4.0%)	800(4.6%)
Others	30(2.9%)	68(3.2%)	121(5.4%)	846(6.7%)
Grade	0.045*		< 0.001*	
Well/moderate	567(54.1%)	1178(55.3%)	1628(72.4%)	3755(75.9%)
Poor/UD	430(41.0%)	887(41.6%)	400(17.8%)	870(17.6%)
Unknown	51(4.9%)	66(3.1%)	220(9.8%)	324(6.5%)
Resected LNs	< 0.001*		< 0.001*	
0	527(50.3%)	84(3.9%)	1082(48.1%)	192(3.9%)
1–3	252(24.0%)	395(18.5%)	556(24.7%)	876(17.7%)
≥ 4	221(21.1%)	1545(72.5%)	513(22.8%)	3611(73.0%)
Unknown	48(4.6%)	107(5.0%)	97(4.3%)	270(5.5%)
Tumor size (mm)	< 0.001*		< 0.001*	
≤ 10	153(14.6%)	174(8.2%)	470(20.9%)	408(8.2%)
11–20	602(57.4%)	1012(47.5%)	1260(56.0%)	2507(50.7%)
21–30	293(28.0%)	945(44.3%)	518(23.0%)	2034(41.1%)

* indicates that the difference was statistically significant.

Abbreviations: UD, undifferentiated; LN, lymph node.

Squamous cell carcinoma(n = 3179)			Adenocarcinoma(n = 7197)	
Marriage status	0.012*		0.006*	
Married	883(52.2%)	2308(56.5%)	1209(53.8%)	2858(57.7%)
Unmarried	747(44.2%)	1645(40.3%)	956(42.5%)	1934(39.1%)
others	61(3.6%)	133(3.3%)	83(3.7%)	157(3.2%)
Location	0.298		< 0.001*	
Upper	645(61.5%)	1318(61.8%)	1304(58.0%)	3048(61.6%)
Lower	357(34.1%)	694(32.6%)	833(37.1%)	1524(30.8%)
others	46(4.4%)	119(5.6%)	111(4.9%)	377(7.6%)
Laterality	0.037*		< 0.001*	
Left	493(47.0%)	919(43.1%)	1039(46.2%)	1912(38.6%)
Right	555(53.0%)	1212(56.9%)	1209(53.8%)	3037(61.4%)
* indicates that the difference was statistically significant.				
Abbreviations: UD, undifferentiated; LN, lymph node.				

Survival analyses for overall survival and lung cancer specific survival

As shown in Figs. 1 and 2, survival curves analyses showed that LT yielded better OS (HR = 0.647, 95% CI (0.606, 0.689), $P < 0.001$) and LCSS (HR = 0.834, 95% CI (0.731, 0.951), $P = 0.007$) than SR in A stage LUAD patients; while in LSQCC, LT yielded better OS (HR = 0.706, 95% CI (0.649, 0.769), $P < 0.001$) but not better LCSS (HR = 0.884, 95% CI (0.740, 1.055), $P = 0.171$). To further confirm the results, multivariate cox-regression analyses were performed. As shown in Tables 2 and 3, LT was associated with better OS (HR = 0.806, 95% CI (0.743, 0.873), $P < 0.001$) but not LCSS (HR = 0.992, 95% CI (0.841, 1.170), $P = 0.920$) in patients with LUAD compared with SR. In patients with LSQCC, LT was associated with better OS (HR = 0.804, 95% CI (0.722, 0.895), $P < 0.001$) in patients compared with SR. In addition, we also found that male and a larger tumor size were closely associated with lower OS and LCSS in A stage patients with LUAD or LSQCC. Interestingly, advanced tumor grade predicted worse OS (Multivariate: HR = 1.492, 95% CI(1.383, 1.610), $P < 0.001$) and LCSS (Multivariate: HR = 1.823, 95% CI(1.582, 2.101), $P < 0.001$) in A stage patients with LUAD; while in LSQCC, the difference was not observed (Univariate: OS, HR = 1.148, 95%CI (0.944–1.077), $P = 0.806$; multivariate: LCSS, HR = 1.067, 95%CI(0.942–1.209), $P = 0.307$). The number of resected lymph nodes (LNs) was strongly related to the outcome of the patients. Both univariate and multivariate analyses showed that a larger number of resected LNs predicted shorter OS and LCSS in LUAD and LSQCC patients (Table 2, Table 3, Supplementary table 1 and Table 2). We also notice that female was

associated with favorable OS and LCSS in LUAD; while in LSQCC, male was associated with worse OS but not LCSS.

Table 2
Multivariate regression analyses for overall survival

	Adenocarcinoma			Squamous cell carcinoma		
	HR	95% CI	P	HR	95% CI	P
Sex						
Male	1			1	-	-
Female	0.671	0.628–0.717	< 0.001*	0.776	0.715–0.842	< 0.001*
Marriage status						
Married	1			-		
Unmarried	1.294	1.209–1.384	< 0.001*	-	-	-
Others	1.082	0.902–1.299	0.396	-	-	-
Grade						
Well/moderate	1			-	-	-
Poor/UD	1.492	1.383–1.610	< 0.001*	-	-	-
Unknown	0.997	0.886–1.121	0.959	-	-	-
Resected LNs						
0	1			1		
1–3	0.749	0.678–0.828	< 0.001*	0.771	0.673–0.882	< 0.001*
≥4	0.573	0.520–0.631	< 0.001*	0.687	0.603–0.783	< 0.001*
Unknown	0.600	0.513–0.703	< 0.001*	0.909	0.741–1.115	0.361
Tumor size (mm)						
≤10	1			1		
11–20	1.117	1.009–1.237	0.032*	1.154	1.000–1.331	0.049*
21–30	1.300	1.169–1.448	< 0.001*	1.328	1.145–1.540	< 0.001*
SP						
SR				1		
LT	0.806	0.743–0.873	< 0.001*	0.804	0.722–0.895	< 0.001*
* indicates that the difference was statistically significant						
Abbreviations: UD, undifferentiated; LN, lymph node; SP, surgical procedure; SR, sublobar resection; LT, lobectomy; SCC, squamous cell carcinoma.						

Table 3
Multivariate regression analyses for lung cancer specific survival

Adenocarcinoma				Squamous cell carcinoma		
	HR	95% CI	P	HR	95% CI	P
Sex						
Male	1			-		
Female	0.778	0.682–0.887	< 0.001*	-	-	-
Marriage Status						
Married	1			-		
Unmarried	1.336	1.171–1.525	< 0.001*	-	-	-
Others	0.864	0.578–1.291	0.475	-	-	-
Grade						
Well/moderate	1			1		
Poor/UD	1.823	1.582–2.101	< 0.001*	1.148	0.971–1.357	0.107
Unknown	0.935	0.728–1.200	0.597	0.764	0.447–1.307	0.326
Resected LNs						
0	1			1		
1–3	0.776	0.633–0.952	0.015*	0.828	0.636–1.078	0.161
≥4	0.568	0.465–0.693	< 0.001*	0.694	0.553–0.870	0.002*
Unknown	0.556	0.401–0.770	< 0.001*	0.874	0.576–1.328	0.529
Tumor size(mm)						
≤10	1			1		
11–20	1.379	1.098–1.733	0.006*	1.154	1.000–1.331	0.049*
21–30	1.841	1.456–2.329	< 0.001*	1.328	1.145–1.540	< 0.001*
SP						
SR	1			-		
LT	0.992	0.841–1.170	0.920	-	-	-
* indicates that the difference was statistically significant						
Abbreviations: UD, undifferentiated; LNs, lymph nodes; SCC, squamous cell carcinoma; SR, sublobar resection; LT, lobectomy; SP, surgical procedure.						

Survival analyses for overall survival and lung cancer specific survival stratified by tumor size

To investigate the impact of histology on survival in different-sized tumor, the study population was further analyzed. As shown in Supplementary Figs. 1 and 2, for patients with $TS \leq 10$ mm, SR achieved better OS in LUAD (HR = 0.668, 95%CI (0.555, 0.804), $P < 0.001$) but not in LSQCC (HR = 0.799, 95%CI (0.615, 0.036), $P = 0.091$), and similar LCSS in LUAD (HR = 0.866, 95%CI (0.568, 1.320), $P = 0.502$) and LSQCC (HR = 0.987, 95% CI (0.532, 1.833), $P = 0.967$) compared with LT; while for $TS > 20$ mm & ≤ 30 mm, LT yielded better OS (LUAD: HR = 0.645, 95%CI (0.572, 0.726), $P < 0.001$; LSQCC: HR = 0.627, 95%CI (0.542, 0.724), $P < 0.001$) and LCSS (LUAD: HR = 0.738, 95%CI (0.588, 0.927), $P = 0.009$; LSQCC: R = 0.696, 95%CI (0.530, 0.914), $P = 0.009$) in LUAD and LSQCC compared with SR; For patients with $TS > 10$ mm & ≤ 20 mm, LT yielded longer OS (HR = 0.595, 95%CI (0.545, 0.650), $P < 0.001$) and LCSS (HR = 0.738, 95%CI (0.588, 0.927), $P = 0.009$) in LUAD, and better OS (HR = 0.751, 95%CI (0.626, 0.900), $P = 0.002$) but not LCSS (HR = 0.872, 95%CI (0.675, 1.128), $P = 0.297$) in LSQCC.

Due to relative reliable than univariate ones, multivariate analyses were also performed to evaluate outcomes of stage A NSCLC patients. As shown in Tables 4 and 5, in LUAD patients with $TS \leq 10$ mm, LT achieved similar OS (HR = 0.843, 95% CI (0.673, 1.062), $P = 0.149$) and LCSS (HR = 1.074, 95% CI (0.626, 1.843), $P = 0.795$) compared with SR. For adenocarcinoma with $TS > 10$ mm & ≤ 20 mm, LT was associated with better OS (HR = 0.785, 95% CI (0.703, 878), $P < 0.001$) but not LCSS (HR = 0.962, 95% CI (0.766, 1.209), $P = 0.741$); while for LSQCC patients, LT seemed to achieve better OS (HR = 0.864, 95% CI (0.746, 1.005), $P = 0.051$) but not significant. LUAD patients with $TS > 20$ mm & ≤ 30 mm received SR were at a significant risk of reduction of OS (HR = 0.816, 95% CI (0.709, 0.938), $P = 0.004$) and but not LCSS (HR = 0.954, 95% CI (0.732, 1.244), $P = 0.729$); while for LSQCC, patients received LT had a better OS (HR = 0.742, 95% CI (0.624, 0.883), $P < 0.001$) but not LCSS (HR = 0.776, 95% CI (0.563, 1.071), $P = 0.123$).

Table 4
Multivariate regression analyses for overall survival stratified by tumor size

Adenocarcinoma				Squamous cell carcinoma		
	HR	95% CI	P	HR	95% CI	P
Tumor size ≤ 10 (mm)						
Gender						
Male	1					
Female	0.613	0.510–0.736	< 0.001*			
Grade						
Well/moderate	1					
Poor/UD	1.354	1.047–1.750	0.021*			
Unknown	1.129	0.865–1.475	0.371			
Resected LNs						
0	1					
1–3	0.984	0.760–1.274	0.901			
≥ 4	0.555	0.429–0.718	<0.001*			
Unknown	0.735	0.674–1.055	0.136			
SP						
SR	1					
LT	0.843	0.673–1.062	0.149			
10 < Tumor size ≤ 20						
Gender						
Male	1			1		
Female	0.701	0.641–0.768	< 0.001*	1.358	1.056–1.748	0.017*
Grade						
Well/moderate	1			-		
Poor/UD	1.582	1.422–1.761	< 0.001*			

* indicates that the difference was statistically significant

Abbreviations: UD, undifferentiated; SP, surgical procedure; SR,sublobar resection; LT, lobectomy; LNs, lymph nodes.

	Adenocarcinoma			Squamous cell carcinoma		
Unknown	0.997	0.848–1.173	0.972			
Resected LNs						
0	1			1		
1–3	0.756	0.661–0.865	< 0.001*	0.792	0.662–0.948	0.011*
≥ 4	0.577	0.506–0.659	< 0.001*	0.643	0.539–0.767	< 0.001*
Unknown	0.502	0.400–0.631	< 0.001*	0.693	0.525–0.914	0.009*
Marriage status						
Married	1					
Unmarried	1.259	1.147–1.381	< 0.001*			
Others	1.199	0.940–1.529	0.144			
Race						
White	1					
Black	1.080	0.877–1.329	0.470			
Others	0.842	0.694–1.021	0.080			
SP						
SR	1			1		
LT	0.785	0.703–0.878	< 0.001*	0.864	0.746–1.005	0.051
20 < Tumor size ≤ 30						
Gender						
Male	1			1		
Female	0.669	0.599–0.747	< 0.001*	0.828	0.727–0.944	0.005*
Grade						
Well/moderate	1					
Poor/UD	1.422	1.262–1.602	< 0.001*			
Unknown	0.895	0.715–1.120	0.331			

* indicates that the difference was statistically significant

Abbreviations: UD, undifferentiated; SP, surgical procedure; SR,sublobar resection; LT, lobectomy; LNs, lymph nodes.

Adenocarcinoma				Squamous cell carcinoma		
Resected LNs						
0	1			1		
1–3	0.664	0.552–0.799	< 0.001*	0.686	0.540–0.872	0.002*
≥ 4	0.553	0.463–0.660	< 0.001*	0.644	0.513–0.809	< 0.001*
Unknown	0.685	0.527–0.894	0.005*	1.309	0.943–1.818	0.107
Marriage status						
Married	1					
Unmarried	1.316	1.175–1.473	< 0.001*			
Others	0.826	0.585–1.165	0.275			
Race						
White	1					
Black	1.012	0.795–1.289	0.921			
Others	0.763	0.614–0.948	0.015*			
SP						
SR	1			1		
LT	0.816	0.709–0.938	0.004*	0.742	0.624–0.883	0.001*
* indicates that the difference was statistically significant						
Abbreviations: UD, undifferentiated; SP, surgical procedure; SR,sublobar resection; LT, lobectomy; LNs, lymph nodes.						

Table 5
Multivariate regression analyses for lung cancer specific survival stratified by tumor size

Adenocarcinoma				Squamous cell carcinoma		
	HR	95% CI	P	HR	95% CI	P
Tumor size ≤ 10 (mm)						
Gender						
Male	1					
Female	0.527	0.346–0.802	0.003*			
Grade						
Well/moderate	1					
Poor/UD	2.073	1.253–3.429	0.005*			
Unknown	0.787	0.375–1.652	0.527			
Resected LNs						
0	1					
1–3	0.746	0.407–1.367	0.343			
≥ 4	0.524	0.321–0.855	0.010*			
Unknown	0.888	0.391–2.017	0.776			
SP						
SR	1					
LT	1.074	0.626–1.843	0.795			
10 < Tumor size ≤ 20						
Grade						
Well/moderate	1					
Poor/UD	1.951	1.590–2.394	< 0.001*			
Unknown	1.014	0.721–1.425	0.936			
Resected LNs						
0	1					

* indicates that the difference was statistically significant

Abbreviations: UD, undifferentiated; SP, surgical procedure; SR, sublobar resection; LT, lobectomy; LNs, lymph nodes.

	Adenocarcinoma			Squamous cell carcinoma		
1–3	0.853	0.646–1.126	0.263			
≥ 4	0.617	0.468–0.813	< 0.001*			
Unknown	0.390	0.231–0.661	< 0.001*			
Marriage status						
Married	1					
Unmarried	1.179	0.988–1.406	0.067			
Others	0.906	0.529–1.552	0.720			
Race						
White	1					
Black	1.215	0.817–1.805	0.336			
Others	0.657	0.424–1.017	0.060			
SP						
SR	1					
LT	0.962	0.766–1.209	0.741			
20 < Tumor size ≤ 30						
Grade						
Well/moderate	1					
Poor/UD	1.680	1.358–2.078	< 0.001*			
Unknown	0.882	0.576–1.349	0.562			
Resected LNs						
0	1			1		
1–3	0.679	0.482–0.956	0.027*	0.845	0.535–1.335	0.470
≥ 4	0.516	0.370–0.719	< 0.001*	0.771	0.497–0.991	0.045*
Unknown	0.659	0.403–1.079	0.108	1.519	0.818–2.822	0.185
SP						

* indicates that the difference was statistically significant

Abbreviations: UD, undifferentiated; SP, surgical procedure; SR, sublobar resection; LT, lobectomy; LNs, lymph nodes.

	Adenocarcinoma			Squamous cell carcinoma		
SR	1					
LT	0.954	0.732–1.244	0.729	0.776	0.563–1.071	0.123
* indicates that the difference was statistically significant						
Abbreviations: UD, undifferentiated; SP, surgical procedure; SR, sublobar resection; LT, lobectomy; LNs, lymph nodes.						

Additionally, we found that advanced tumor grade was strongly associated with worse OS (Multivariate: TS $\leq$ 10 mm: HR = 1.354, 95% CI (1.047, 1.750), $P = 0.021$; TS > 10 mm & $\leq$ 20 mm: HR = 1.582, 95% CI (1.422, 1.761), $P < 0.001$; TS > 20 mm & $\leq$ 30 mm: HR = 1.422, 95% CI (1.262, 1.602), $P < 0.001$) and LCSS (Multivariate: TS $\leq$ 10 mm: HR = 2.073, 95% CI (1.253, 3.429), $P = 0.003$; TS > 10 mm & $\leq$ 20 mm: HR = 1.951, 95% CI (1.590, 2.394), $P < 0.001$; TS > 20 mm & $\leq$ 30 mm: HR = 1.680, 95% CI (1.358, 2.078), $P < 0.001$) in LUAD patients; however, in LSQCC patients, the difference not observed in both OS (Univariate: TS $\leq$ 10 mm: HR = 1.116, 95% CI (0.847, 1.470), $P = 0.436$; TS > 10 mm & $\leq$ 20 mm: HR = 1.088, 95% CI (0.966, 1.225), $P = 0.164$; TS > 20 mm & $\leq$ 30 mm: HR = 0.932, 95% CI (0.817, 1.062), $P = 0.291$) and LCSS (Univariate: TS $\leq$ 10 mm :HR = 1.423, 95% CI (0.763, 2.653), $P = 0.268$; TS > 10 mm & $\leq$ 20 mm: HR = 1.291, 95% CI (1.000, 1.658), $P = 0.050$; TS > 20 mm & $\leq$ 30 mm: HR = 0.994, 95% CI (0.782, 1.264), $P = 0.964$) (Data shown in Supplementary table 3 and 4).

Moreover, multivariate analyses demonstrated that a larger number of resected LNs predicted favorable OS and LCSS in LUAD with TS $\leq$ 30 mm and LSQCC with TS > 10 mm & $\leq$ 30 mm (Data shown in Tables 4 and 5); while in LSQCC, the differences were not significant in TS $\leq$ 10 mm (Univariate: OS: “1–3” vs “0”: HR = 0.833, 95%CI (0.573, 1.210), $P = 0.337$; “ $\geq$ 4” vs. “0”, HR = 0.843, 95%CI (0.626, 1.134), $P = 0.258$; LCSS: “1–3” vs “0” HR = 1.446, 95%CI (0.601, 3.476), $P = 0.410$; “ $\geq$ 4” vs. “0”, HR = 1.205, 95%CI (0.564, 2.577), $P = 0.630$) (Data shown in Supplementary table 3 and 4).

Discussion

In present study, we investigated the impact of histology on prognosis of elderly patients with surgically resected IA stage LUAD and LSQCC. Univariate analyses showed that LT closely was associated with better OS (HR = 0.647, 95% CI (0.606, 0.689), $P < 0.001$) and LCSS (HR = 0.834, 95% CI (0.731, 0.951), $P = 0.007$) in A stage LUAD patients; while in LSQCC, LT yielded better OS (HR = 0.706, 95% CI (0.649, 0.769), $P < 0.001$) but not better LCSS (HR = 0.884, 95% CI (0.740, 1.055), $P = 0.171$). Multivariate analyses demonstrated that LT achieved better OS (HR = 0.806, 95% CI (0.743, 0.873), $P < 0.001$) but not LCSS (HR = 0.992, 95% CI (0.841, 1.170), $P = 0.920$) in LUAD patients compared with SR. In LSQCC patients, LT was associated with better OS (HR = 0.804, 95% CI (0.722, 0.895), $P < 0.001$) in patients compared with SR.

Recently, numerous studies pointed out that LSQCC and LUAD patients are significantly different in many prognostic factors, including age, sex, pathological and clinical TNM stage, smoking status, tumor

location, tumor differentiation grade and visceral pleura invasion[4, 18–20]. However, the prognosis of the two types of lung cancer had mixed results. Previous studies suggested that LSQCC had a favorable survival compared to LUAD[21, 22]. Some researchers found that there was no significant difference in prognosis between LSQCC and LUAD[23, 24]. However, recent studies demonstrated that LUAD was associated with better survival compared to LSQCC[5, 6, 25]. Although more and more people came to realize that two types of lung cancer should be separately analyzed, few studies focused on investigating whether the different types of histology could have an impact on outcome of elderly patients with early-stage NSCLC. Furthermore, the question whether the limited resection is suitable for early-stage NSCLC remains to be investigating, and lobectomy is still the standard treatment for early-stage NSCLC according to National Comprehensive Cancer Network (NCCN) guidelines. However, there is emerging evidence from retrospective studies supporting that sublobar resection suitable for certain early-stage NSCLC[26–29]. In our study, we found that SR yielded similar OS compared to LT for LUAD patients with $TS \leq 10$ mm, and for LSQCC patients with $TS \leq 20$ mm, LT didn't show superior OS compared to SR. For LUAD patients with $TS > 10$ mm & ≤ 30 mm, LT achieved better OS compared to SR; while for LSQCC patients with $TS > 20$ mm & ≤ 30 mm, LT achieved better OS compared to SR. However, LT yielded similar LCSS in both elderly LUAD and LSQCC patients with $TS \leq 30$ mm. These results suggested that SR maybe acceptable for elderly LUAD patients with $TS \leq 10$ mm and LSQCC patients with $TS \leq 20$ mm. As mentioned, elderly patients were likely to have declined cardiopulmonary reserve and a limited life expectancy, and limited resections reduced lung function impairment and might reduce morbidity. The high-quality randomized controlled trials, including the Japan Clinical Oncology Group/West Japan Oncology Group (JCOG0802/WJOG4607L) and the Cancer and Lymphoma Group (CALBG 140503), were ongoing. Our results need to be verified in the future.

In addition, we found that advanced tumor grade was significantly associated with poorer OS and LCSS in elderly LUAD patients; while in LSQCC, the difference was not significant. We speculated that early stage LSQCC was likely to have less metastasis tendency than LUAD. Consistent with our speculation, Wang et al[5]. pointed out that LSQCC was mostly found in stage II and IIIA, whereas LUAD was mostly found in stage I. They speculated that LUAD patients tended to have an earlier clinical T status than LSQCC patients but have stronger metastasis tendency. The reason for that may be the different mechanisms of metastasis. Cao et al. [30] found that a larger number of resected regional LNs predicted better LCSS and OS rates compared with less regional LN dissection. Moreover, we also observed that a larger number of resected lymph nodes (LNs) was strongly associated with better OS and LCSS, and, however, the difference was not observed in LSQCC patients with $TS \leq 10$ mm, which may support our speculation that early stage LSQCC was likely to have less lymph nodes metastasis tendency than LUAD. For LSQCC patients with $TS > 10$ mm and LUAD patients, mediastinal lymph nodes evaluation should be paid attention.

The limitations of this study include the lack of targeted therapy information and immunotherapy information as well as the nature of retrospective studies. The impact of the former factor is limited because of the lower chance for these early stage patients to receive such treatments; while that of the latter is inevitable. Multivariate analyses were conducted to remove biases as could as possible. There is

no detailed information about pure ground-glass opacity (GGO), mixed GGO, and pure solid adenocarcinoma as well as lack of information regarding the status of tumor component; thus, we could not take these factors into consideration. In addition, micropapillary was recently reported as an important prognostic factor that was closely related to the spread of lung cancer tumor cells into air spaces in the lung parenchyma adjacent to the main tumor[31]. However, the information about micropapillary couldn't be obtained in SEER database. Thus, our conclusions still need to be further verified in future large randomized cohort studies.

Conclusions

In conclusion, we found that LUAD patients with age > 70 had superior OS and LCSS compared to that of LSQCC. We also observed that a larger number of resected LNs was associated with favorable OS and LCSS in LUAD with TS ≤ 30 mm and LSQCC with TS > 10 mm & ≤ 30 mm. Our study demonstrated that SR achieved similar OS in LUAD patients with TS ≤ 10 mm and LSQCC patients with TS ≤ 20 mm compared to LT, which suggested that SR maybe acceptable for elderly LUAD patients with TS ≤ 10 mm and LSQCC patients with TS ≤ 20 mm.

Abbreviations

LUAD, lung adenocarcinoma; LSQCC, lung squamous cell carcinoma; NSCLC, non-small lung cancer; SEER, Surveillance, Epidemiology, and End Results; OS, overall survival; LCSS, lung cancer-specific survival; TS, tumor size; LT, lobectomy; SR, sublobar resection; SP, surgical procedure; HR, hazard ratio; CI, confidence interval; LN, lymph node.

Declarations

Acknowledgements

We acknowledged the SEER database for providing clinical data.

Author contributions

BH: Study design, data analysis, manuscript preparation, and final approve of manuscript

HJF: Study design, data analysis and revision of the manuscript.

XXW: Study design, data analysis and revision of the manuscript.

LZ: Data analysis and revision of the manuscript.

ZLL: Data analysis and revision of the manuscript.

BHL: Data analysis and revision of the manuscript.

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HM: Data analysis and revision of the manuscript.

TF: Data analysis and revision of the manuscript.

WYJ: Data analysis and revision of the manuscript.

QG: Study design, data analysis, revision of the manuscript and final approve of manuscript

Funding

The work was funded by the National Natural Science Foundation of China (grant no. 81700093 and 81770095). The funding bodies had no role in the design of the study, the collection, analysis, or interpretation of the data, or writing the manuscript.

Availability of data and materials

All data in the present study is available in the SEER database (<https://seer.cancer.gov/data/>).

Ethics approval and consent to participate

Not applicable

Consent for publication

All authors approved for publication of the manuscript for the journal.

Declaration of Competing interest

All of the authors declare no conflicts of interest for this paper.

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Figures

Figure 1

Postoperative overall survival curves between sublobar resection (SR) and lobectomy (LT).

Figure 2

Postoperative lung cancer specific survival curves between sublobar resection (SR) and lobectomy (LT).

Supplementary Files

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