ORIGINAL ARTICLE

Treatment for Patients With Early Stage Adenosquamous Lung Cancer

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ABSTRACT

Introduction: Adenosquamous lung cancer (ASC) is a rare type of NSCLC with poor prognosis. There is no consensus on the necessity of adjuvant chemotherapy and the selection of surgical procedures for patients with early stage lung cancer. Few studies have investigated the treatment for early stage ASC.

Methods: All cases of TNM stage I ASC as per the seventh edition of the American Joint Committee on Cancer staging system were identified from the Surveillance, Epidemiology, and End Results database from 2004 to 2016. The prognostic factors of the primary cohort were identified. Clinical characteristics, first-line treatments, surgical procedures, and survival data, including overall survival and cancer-specific survival, were analyzed.

Results: A total of 1251 patients were included. The mean age of the patients was 70 years (±9.5 y). Male and white patients accounted for larger proportions. There were 656 and 595 patients with stages IA and IB, respectively. The mean tumor size was 26.2 mm (±10.7 mm). With respect to the treatment, 139 patients who received only chemotherapy had the worst prognosis. Similar outcomes were observed in both the surgery and adjuvant therapy groups. Nevertheless, adjuvant chemotherapy could improve survival outcomes of patients with a tumor size of 4 to 5 cm. Of the 1075 patients who underwent surgery, there were 224 cases of sublobar resection, 834 cases of lobectomy, and 17 cases of extended or sleeve lobectomy. The results revealed that patients who underwent lobectomy had better prognosis.

Conclusions: Early stage ASC has a poor prognosis. Adjuvant chemotherapy was found to have no considerable benefit in patients with stage I disease (eighth edition). Lobectomy or other radical surgeries are recommended as they can improve overall survival of patients with ASC.

Keywords: Adenosquamous lung cancer; Adjuvant chemotherapy; Surgery; SEER; Prognosis

Introduction

According to the 2015 WHO histology criteria, adenosquamous carcinoma (ASC) of the lung is categorized as one of the subtypes of NSCLC that is neither adenocarcinoma (AD) nor squamous cell carcinoma (SC). It is defined as a carcinoma containing at least 10% each of AD and SC components.[1-3] It is a relatively rare subtype that comprises only 0.3% to 4.2% of NSCLC.[4-7]

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Some researchers have reported a relatively poor prognosis of patients with ASC, with a 5-year overall survival (OS) rate of only 6.2%.[8] Other studies have indicated that the cumulative postoperative survival rates at 5 and 10 years are 25.4% and 19.2%, respectively.[9] Therefore, the selection of treatment for ASC is crucial for optimizing the survival outcomes of the patients, especially of those with the early stage disease. However, because of its rarity only a small number of studies have reported the clinical and pathologic characteristics of ASC, including some case reports and small-scale retrospective studies.

We have, therefore, sought to find the clinical characteristics of ASC and identify different prognostic factors on the basis of a large sample. Moreover, we have tried to explore optimized treatment for stage I ASC for more benefits and better prognosis.

Materials and Methods

Data Source

The primary cohort of this retrospective study was identified from the Surveillance, Epidemiology, and End Results (SEER) cancer database, which is maintained and managed by the National Cancer Institute (NCI) and represents approximately 28% of the population of the United States.[10]

Inclusive and Exclusive Criteria

Patients diagnosed with primary malignancies at the main bronchus and lung (SEER primary site code, C340–C349) from 2004 to 2016 were identified. The histology code was ASC (8560/3). In this study, the early stage disease was defined as T1a to T2a, N0, and M0 on the basis of the eighth edition TNM staging system of the American Joint Committee on Cancer (AJCC). Patients classified with TNM stages IA to IB in the seventh edition of the AJCC were included in the primary cohort. Those with a tumor size of 4 to 5 cm were also included, though they had been reclassified as T2b and stage IIA in the eighth edition. Patients with missing data on tumor classification or tumor size were subsequently excluded.

Statistical Analysis

The primary outcome was OS. The Kaplan-Meier method and log-rank test were used to reveal survival

Table 1. The Clinical and Pathologic Characteristics of Patients With Adenosquamous Lung Cancer

Clinical Characteristics	Cohort (N = 1251)	Chemotherapy (n = 29)	Surgery (n = 965)	Adjuvant Therapy (N = 110)	Treatment Unknown (n = 147)	*p* Value
Age, y						**<0.001**
Mean (SD)	70.0 (9.5)	75.4 (8.9)	69.8 (9.3)	65.1 (9.0)	74.0 (9.8)	
Sex, no. (%)						0.246
Male	654 (52.3)	19 (65.5)	498(51.6)	64 (58.2)	73 (49.7)	
Female	597 (47.7)	10 (34.5)	467(48.4)	46 (41.8)	74 (50.3)	
Race, no. (%)						0.632
White	1029 (82.3)	24 (82.8)	802 (83.1)	89 (81.0)	114 (77.5)	
Black	104 (8.3)	2 (6.9)	73 (7.6)	12 (10.9)	17 (11.6)	
Asian	60 (4.8)	1 (3.4)	46 (4.8)	6 (5.5)	7 (4.8)	
Other	58 (4.6)	2 (6.9)	44 (4.5)	3 (2.6)	9 (6.1)	
Tumor size, mm						**<0.001**
Mean (SD)	26.2 (10.7)	34.8 (9.0)	25.1 (10.3)	31.8 (11.3)	27.5 (10.8)	
Grade, no. (%)						**<0.001**
Well	26 (2.1)	1 (3.4)	22 (2.3)	1 (0.9)	2 (1.4)	
Moderate	472 (37.2)	3 (10.2)	402 (41.6)	46 (41.8)	21 (14.3)	
Poor	574 (45.9)	12 (41.4)	452 (46.8)	56 (50.9)	53 (36.1)	
Undifferentiated	15 (1.2)	0 (0)	11 (1.1)	2 (1.8)	2 (1.4)	
Unknown	164 (13.1)	12 (41.4)	78 (8.2)	5 (4.6)	69 (46.8)	
Stage, no. (%)						**<0.001**
IA	656 (52.4)	9 (31.0)	543 (56.3)	20 (18.2)	84 (57.1)	
IB	595 (47.6)	20 (69.0)	422 (43.7)	90 (81.8)	63 (42.9)	
Surgery, no. (%)						
No surgery	176 (14.1)	29	0 (0)	0 (0)	147 (100)	
Sublobar resection	224 (17.9)	0 (0)	207 (21.5)	17 (15.5)	–	
Lobectomy	834 (66.7)	0 (0)	745 (77.2)	89 (80.9)	–	
Extended or sleeve	17 (1.3)	0 (0)	13 (1.3)	4 (3.6)	–	
Chemotherapy, no. (%)						
Yes	139 (11.1)	29 (100)	0 (0)	110 (100)	–	
No/unknown	1112 (88.9)	0 (0)	965 (100)	0 (0)	147 (100)	

The bold numbers represent the significant differences of characteristics or proportions among subgroups.

status of the cohort and assess the prognostic differences among various treatments. Univariate and multivariate analyses were performed incorporating sex, age, surgery, stage, adjuvant chemotherapy, and histologic subtypes. Collinear factors were not analyzed in the same Cox model. Cancer-specific survival (CSS) was also analyzed to minimize the influences of other causes of death.

Kaplan-Meier and Cox regressions were performed using SPSS 25 (IBM) and Prism 8 (GraphPad). The hazard ratio and 95% confidence interval were reported. Statistical difference was considered significant when the *p* value was less than 0.05. All tests were two sided.

Results

Clinical Features of Primary Cohort

A total of 1251 patients with stage I ASC were identified in the primary cohort. Among them, there were 656 (52.4%) and 595 (47.6%) patients with stages IA and IB, respectively. The mean age of the cohort was 70.0 (±9.5) years. Male patients accounted for a slightly larger proportion than female patients (654 versus 597, 52.3% versus 47.7%). Most of the patients were of white ethnicity (1029, 82.3%). The mean tumor size was 26.2 (±10.7) mm. Most of the patients were diagnosed as having poor or moderate differentiation (472, 37.2% and 574, 45.9%, respectively), whereas only 26 patients were considered as having high differentiation. A total of 1075 patients had undergone surgery as the primary treatment, including 224 sublobar resections (17.9%), 834 lobectomies (66.7%), and 17 extended or sleeve lobectomies (1.3%); 176 patients had not undergone surgery. A total of 139 patients had received chemotherapy, including 29 as first-line treatment (20.9%) and 110 as adjuvant therapy (79.1%). In the final sample, 147 patients had no data on their primary treatment (Table 1).

Characteristics of Patients With Different Treatments

On the basis of the treatment given, the primary cohort was separated into four subgroups (Table 1). Patients who had received first-line chemotherapy were older than others (75.4 ± 8.9 y). Moreover, their mean tumor size at 34.8 (± 9) mm was also the largest among the subgroups. Male and white patients accounted for a larger proportion (19/29, 65.5% and 24/29, 82.8%, respectively). The number of patients with stage IB was 20, which was 69% of the subgroup cohort and was significantly higher than others.

In the surgery and adjuvant chemotherapy groups, the mean ages were 69.8 years (±9.3 y) and 65.1 years (±9.0 y). Male and white patients had higher proportions in both these groups. Most of the patients were pathologically diagnosed as having moderate and poor

Table 2. The Characteristics of Patients With Operative Adenosquamous Lung Cancer

Clinical Characteristics	Number of Surgery (N = 176)	Sublobar Resection (n = 224)	Lobectomy (n = 834)	Extended or Sleeve (n = 17)	*p* Value
Age, y					**<0.001**
Mean (SD)	74.2 (9.7)	71.9 (9.0)	68.7 (9.3)	66.9 (8.3)	
Sex, no. (%)					0.669
Male	92 (52.3)	112 (50.0)	439 (52.6)	11 (64.7)	
Female	84 (47.7)	112 (50.0)	395 (47.4)	6 (35.3)	
Race, no. (%)					0.239
White	138 (78.4)	195 (87.1)	681 (81.7)	15 (88.2)	
Black	19 (10.8)	13 (5.7)	72 (8.6)	0 (0)	
Asian	8 (4.5)	8 (3.6)	42 (5.0)	2 (11.8)	
Other	11 (6.3)	8 (3.6)	39 (4.7)	0 (0)	
Tumor size, mm					**<0.001**
Mean (SD)	28.7 (10.9)	20.5 (9.0)	26.9 (10.5)	37.3 (8.1)	
Grade, no. (%)					**<0.001**
Well	3 (1.7)	3 (1.3)	20 (2.4)	0 (0)	
Moderate	24 (13.6)	95 (42.4)	348 (41.7)	5 (29.4)	
Poor	66 (37.5)	104 (46.4)	392 (47.0)	12 (70.6)	
Undifferentiated	2 (1.1)	4 (1.8)	9 (1.1)	0 (0)	
Unknown	81 (46.0)	18 (8.1)	65 (7.8)	0 (0)	
Stage, no. (%)					**0.01**
IA	93 (52.8)	134 (59.8)	427 (51.2)	2 (11.8)	
IB	83 (47.2)	90 (40.2)	407 (48.8)	15 (88.2)	
Chemotherapy, no. (%)					
Yes	29 (16.5)	17 (7.6)	89 (10.7)	4 (23.5)	**0.013**
No/unknown	147 (83.5)	207 (92.6)	745 (89.3)	13 (76.5)	

The bold numbers represent the significant difference of numbers or proportions among various operative treatment groups.

differentiation. The surgery group had a smaller tumor size than the adjuvant therapy group (25.1 ± 10.3 versus 31.8 ± 11.3). Furthermore, there were more patients with stage IA in the surgery group than in the adjuvant therapy group (543/834, 56.3% versus 20/110, 18.2%). In the surgery group, 207 patients received sublobar resection, 745 received lobectomy, and 13 received extended or sleeve resection. In contrast, 17, 89, and four patients received sublobar resection, lobectomy, and extended or sleeve resection in the adjuvant chemotherapy group, respectively. Details are given in Table 1.

Characteristics of Patients Who Received Different Surgical Treatments

There were 176 patients who received other treatments and did not undergo surgery. Patients who underwent sublobar resection were older and had a smaller tumor size than the other groups (71.9 ± 9 y and 20.5 ± 9.0 mm). Besides, 134 patients with stage IA underwent sublobar resection, accounting for 59.8% of the cohort. Only 17 patients had received chemotherapy after sublobar resection. Most of the patients with early stage ASC who had undergone lobectomy had a mean age and tumor size of 68.7 (± 9.3) years and 26.9 (± 10.5) mm, respectively. In contrast, more patients who underwent extended or sleeve lobectomy had stage IB (15/17, 88.2%) and larger tumor size (37.3 ± 8.1 mm). No significant difference in ethnicity was observed among these subgroups. There was a significant increasing trend of adjuvant chemotherapy cases from the sublobar resection group to the lobectomy and extended lobectomy groups (17/224, 7.6%; 89/834, 10.7%; 4/17, 23.5%, respectively) (Table 2).

Survival Analysis of Primary Treatments

On the basis of the data from 2004 to 2016 in the SEER database, the 1-, 3-, and 5-year OS rates of patients with stage I ASC were 84%, 63%, and 29%, respectively. In contrast, the OS rates of patients with stage I NSCLC were 86%, 67%, and 41%, respectively. Meanwhile, the OS rates of postoperative patients with stage I NSCLC were 94%, 87%, and 55%, respectively. This result indicates that ASC has a poor prognostic outcome in NSCLC, a result consistent with that of previous studies (Fig. 1).

In the primary cohort of this study, no difference was observed in both OS and CSS between surgery alone and adjuvant chemotherapy groups ($p = 0.5349$ and $p = 0.1698$). Patients who received only chemotherapy had significantly worse prognosis compared with the other groups ($p < 0.0001$). In the subgroup analysis of patients with stages IA and IB, the results were consistent with

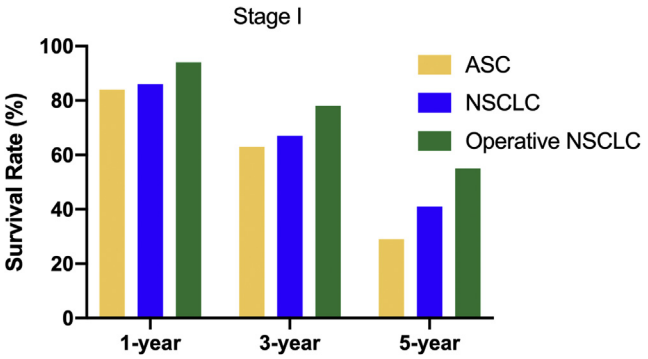

Figure 1. The 1-, 3-, and 5-year survival rates of adenosquamous lung cancer, NSCLC, and operative NSCLC.

those of the primary cohort that patients who received chemotherapy had the worst survival outcomes, whereas patients who underwent surgery alone had similar outcomes to those who received adjuvant therapy (OS: $p = 0.8244$, $p = 0.1149$; CSS: $p = 0.2401$, $p = 0.9212$) (Fig. 2*A–C*) (Supplementary Fig. 1). Although the patients with a tumor size of 4 to 5 cm were classified as stage IIA in the TNM system of the eighth edition of the AJCC, they belonged to stage IB in the seventh edition. Therefore, their survival outcome was also explored. Not surprisingly, it was found that adjuvant chemotherapy could improve survival outcomes in these patients compared with surgery alone ($p = 0.021$) (Fig. 2*D*).

In the univariate and multivariate analyses, age, sex, tumor size, tumor stage, surgery type, and treatment selection were found to be the independent prognostic factors. Specifically, older male patients who had larger tumor size or higher stage had worse prognosis. Nevertheless, those who had undergone radical surgical procedures or adjuvant chemotherapy had better survival outcomes than others (Table 3).

Survival Analysis of Surgical Treatments

The survival outcomes of patients who had undergone sublobectomy or lobectomy were analyzed in different tumor size intervals, including less than or equal to 1 cm (Fig. 3*A*), 1 to 3 cm (Fig. 3*B*), and 3 to 4 cm (Fig. 3*C*). In both OS and CSS analyses, the results concordantly revealed that lobectomy, including extended and sleeve lobectomy, could significantly improve the prognosis of patients with tumor size less than or equal to 4 cm (Fig. 3) (Supplementary Fig. 2).

Discussion

ASC is one of the pathologic subtypes of NSCLC that has both AD and squamous cell cancer contents. It is a rare type of cancer accounting for only 0.3% to 4.2% of NSCLC.[4-7] Owing to its low prevalence, it has

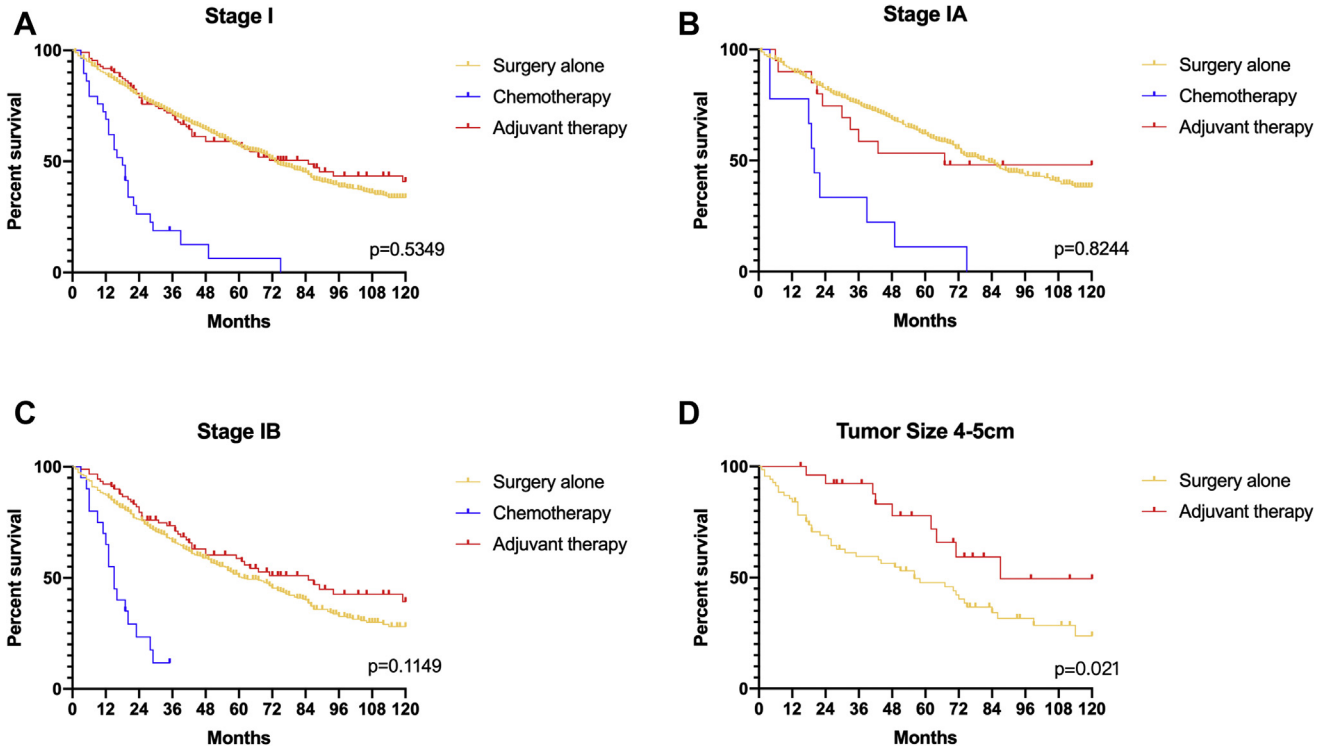

Figure 2. The overall survival (OS) of the primary cohort and patients with different stages of disease. (*A*) The OS of primary cohort; (*B*) the OS of patients with stage IA disease; (*C*) the OS of patients with stage IB disease; and (*D*) the OS of patients with tumor size of 4–5 cm (IB and IIA in the seventh and eighth editions of the American Joint Committee on Cancer, respectively).

received much less attention clinically, and very few articles have been published about it. Besides, with proper treatment, patients with early stage cancer have better prognosis than those with advanced stages. Therefore, this study was performed on a large database to investigate the appropriate treatment for patients with early stage ASC.

Regarding the aggressive clinical features of ASC, Filosso et al.[11] have reported that 48 cases of ASC even in stage I with complete resection had similar 3- and 5-year survival rates compared with those of stage IIIA NSCLC in the same cohort. Nakagawa et al.[8] also reported that 30 patients with ASC with stages IA to IIB had similar survival outcomes as patients with stage IIIA NSCLC.[8] Other studies have reported the 3-year survival rate of ASC ranging from 25% to 35%.[3,5,7,8,12-19] Among them, patients with stage I disease had 62%.[12] However, the 5-year survival rates were rather poor, 0% to 35%. Similar results have been reported in our study, with 63% and 29% and worse than other types of NSCLC.

In our cohort, we noticed that patients who underwent first-line chemotherapy tended to be older and had larger tumor size. It was probable that these patients were not capable of receiving primary surgical treatment because of their physical conditions or other socioeconomic problems. To minimize the influences from other causes of death, we also analyzed the CSS. These patients had the worst survival outcomes both in OS and CSS, indicating that first-line chemotherapy was not an ideal treatment for patients with early stage ASC, at least for those with large tumors.

Although debates on the necessity of adjuvant chemotherapy in stage I NSCLC continue, most oncologists and researchers tend to not administer it to patients with stage I disease. Some previous studies have recommended that adjuvant chemotherapy should be given to patients with poorly prognostic subtypes of NSCLC, such as large cell neuroendocrine lung cancer.[20–22] As ASC is also a pathologic subtype with poor prognosis, some researchers suggest adjuvant chemotherapy is necessary even in those with the stage I disease.

In the primary cohort, patients with large tumors were more likely administered adjuvant chemotherapy. Although we noticed that adjuvant chemotherapy caused no improvement in OS and CSS in the patients with TNM stage IA on the basis of the eighth AJCC, a trend could be seen of slightly improving OS in patients with stage IB ASC. In the patients with a tumor size of 4 to 5 cm, adjuvant chemotherapy was significantly beneficial in terms of OS and CSS.

Lobectomy is considered as a standard surgical procedure in the treatment of early stage NSCLC even in

Table 3. The Univariate and Multivariate Analyses of Stage I Adenosquamous Lung Cancer

		Univariate		Multivariate	
	N	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Age, y	2138	1.044 (1.035-1.053)	**<0.001**	1.034 (1.025-1.043)	**<0.001**
Sex					
Male	1681	1	–	1	–
Female	457	0.807 (0.693-0.940)	**0.006**	0.813 (0.698-0.948)	**0.008**
Race					
White	1947	1	–	–	–
Black	106	0.852 (0.587-1.238)	0.400		
Asian	82	0.770 (0.520-1.141)	0.193		
Unknown	3	0.876 (0.661-1.161)	0.357		
Grade					
Well	28	1	–	–	–
Moderate	25	0.939 (0.548-1.610)	0.820		
Poor	152	1.092 (0.639-1.856)	0.748		
Undifferentiated	58	1.314 (0.583-2.958)	0.510		
Unknown	1857	1.281 (0.731-2.246)	0.387		
Size, mm	2138	1.017 (1.010-1.024)	**<0.001**	1.016 (1.008-1.023)	**<0.001**
Stage					
IA	401	1	–	1	–
IB	472	1.300 (1.117-1.513)	**0.018**	1.128 (1.101-1.501)	**0.001**
Treatment					
Chemotherapy	985	1	–	1	–
Surgery	420	0.217 (0.145-0.324)	**<0.001**	0.262 (0.175-0.391)	**<0.001**
Adjuvant therapy	62	0.199 (0.124-0.319)	**<0.001**	0.255 (0.158-0.413)	**<0.001**
Unknown	671	0.662 (0.430-1.018)	0.06	0.695 (0.451-1.071)	0.099
Surgery					
No.	1027	1	–	1	–
Sublobar resection	401	0.438 (0.344-0.559)	**<0.001**	0.544 (0.424-0.698)	**<0.001**
Lobectomy	332	0.267 (0.218-0.329)	**<0.001**	0.322 (0.261-0.398)	**<0.001**
Extended or sleeve	378	0.537 (0.290-0.995)	**0.048**	0.640 (0.341-1.199)	0.163
Chemotherapy					
Yes	1283	1	–	–	–
No/unknown	855	0.916 (0.725-1.157)	0.463	–	**–**

The significance of independent prognostic factors in univariate and multivariate prediction models were represented in bold numbers.
CI, confidence interval; HR, hazard ratio.

patients with a tumor size less than or equal to 1 cm.[23,24] However, some studies have reported that sublobectomy, including wedge resection and segmentectomy, did not have inferior outcomes compared with lobectomy, although they were less invasive and reserved more normal lung tissues in some cases.[25,26] Regardless of the tumor size, we noticed that patients with stage I ASC who underwent lobectomy had better survival outcomes than those who only underwent sublobectomy in our study.

Some researchers have stated that EGFR mutations were identified in some patients with ASC. Shiozawa et al.[27] found that 24% of patients with ASC (14/59) had EGFR mutations. Sasaki et al.[28] stated that 15% (4/26) had EGFR mutations.[28] Toyooka reported that 27% (3/17) had EGFR-positive mutations in his cohort.[29] They noticed that the mutation frequency in patients with ASC was similar to that in patients with AD. The clinical characteristics of patients with ASC were Asian, female, and nonsmoking patients, which were similar to those in patients with pure AD.[28,30,31] Some case reports and retrospective studies have indicated that EGFR tyrosine kinase inhibitor (gefitinib or erlotinib) was an effective treatment option for patients with mutated ASC in advanced stages and had an objective response rate of 26.5% and a disease control rate of 65.3%.[32]

In our cohort, white ethnicity accounts for the largest proportion. The EGFR mutation rate is less likely as high as in other Asian cohort studies. Although adjuvant EGFR tyrosine kinase inhibitor treatment is reported as one of the effective treatments for postoperative NSCLC, no study had reported its efficacy in patients with postoperative ASC. Besides, clinical genetic testing, surgery, and medicine administration could be related to the economic condition and social status of patients, which lead to uneven access to standard treatments. These may greatly influence the survival of some patients and, therefore, confound the current results.

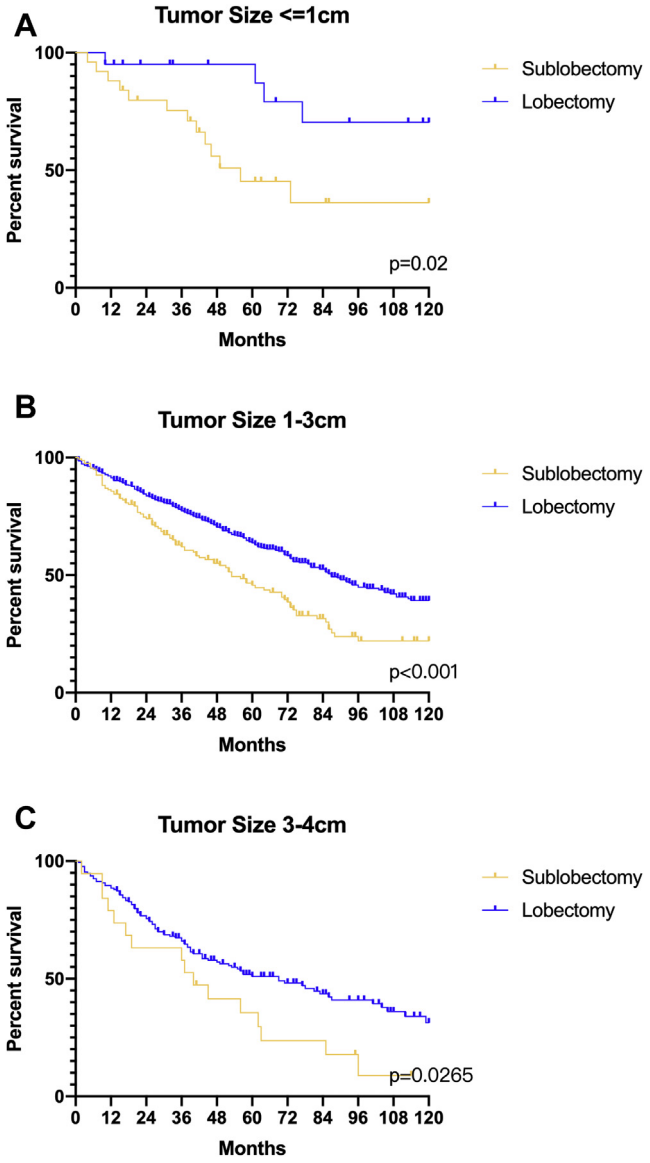

Figure 3. The overall survival (OS) of patients who received different surgical procedures in different tumor size intervals. (*A*) The OS of patients with tumor size less than or equal to 1 cm; (*B*) the OS of patients with tumor size of 1-3 cm; and (*C*) the OS of patients with tumor size of 3-4 cm.

This retrospective study indicates that ASC is a poor prognostic subtype even in the early stage. Lobectomy would be the most ideal surgical procedure in operable patients. Although the efficacy of adjuvant chemotherapy is still unclear, it seems that it could improve survival outcomes of patients with large tumors. More studies are warranted to verify the roles of adjuvant chemotherapy and molecular targeted therapy in patients with early stage ASC.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2020.100021.

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