Peer Review File

Article information: https://dx.doi.org/10.21037/tlcr-23-243

Reviewer A

Comment 1: A selection bias potentially influencing the results may be present in the study, since in the SEER cohort surgical treatment was performed only in 24.3% of the patients with LCSIS, while all the patients in the Shanghai hospital cohort underwent surgical treatment.

Reply 1: We gratefully appreciate for your valuable comment. We must acknowledge the potential selection bias in this study. To decease the influence of the selection bias, we divided the LSCIS patients from the SEER database into a surgery group and a non-surgery group and performed further analyses in both groups.

Changes in the text: We performed analyses in the surgery group and the non-surgery group respectively (see Page 6-8, line 191-196, 224-231)

Comment 2: Diagnosis of Squamous cell cancer in situ with CT-scan may be difficult, as this type of tumor is more frequently incidentally found during bronchoscopy. The Authors should report, at least in their series, how a diagnosis was obtained and if surgical treatment was intentionally planned in patients with LSCIS or if this diagnosis (LSCIS vs LSQCC) was obtained only after surgery.

Reply 2: Thank you for your rigorous comment. In this study, all patients from the Shanghai Pulmonary Hospital diagnosed LSCIS with tumor operative specimen. If LSCIS progressing and recurrence after treated with bronchoscopy, surgical resection would be performed for patients in the Shanghai Pulmonary Hospital cohort. In the SEER cohort, all patients histologically diagnosed with LSCIS. Of these patients in the SEER cohort, 340 patients treated without surgery and 109 patients underwent resection. In the non-surgery group in the SEER cohort, 45 patients had been recommended to treat with surgery. These findings indicated that surgical treatment was intentionally planned in some patients with LSCIS and the diagnosis (LSCIS vs LSQCC) was obtained after surgery in some patients and before surgery in the others.

Changes in the text: We have revised our text and added the data of chemotherapy (see Page 5, line 124-127; Page 6, line 180-182)

Comment 3: In line 171 the Authors state that 17.1% of patients with LSCIS received chemotherapy. The reason to perform systemic treatment in such early-stage disease should be reported.

Reply 3: Thanks for your great suggestion on improving our manuscript. Chemotherapy was considered as the preferred treatment for patients with unresected lung cancer. Therefore, we

divided the LSCIS patients in the SEER cohort into surgery and non-surgery groups and found that chemotherapy was performed in the 74 LSCIS patients in the non-surgery group and only 3 of LSCIS patients in the surgery group received chemotherapy (Table S1). Low proportion of resection could be the reason why 17.1% of patients with LSCIS received systemic treatment in such early-stage disease.

Changes in the text: We added some data of chemotherapy (see Page 6, line 183-185)

Table S1 Demographics and clinicopathologic characteristics of the patients with LSCIS in the SEER cohort

Characteristics	Non-surgery, N (%)	Surgery, N (%)	P
Total	340 (100.0)	109 (100.0)	
Age (years)			0.013
≤60	70 (20.6)	27 (24.8)	
>60 to 70	107 (31.5)	47 (43.1)	
>70	163 (47.9)	35 (32.1)	
Gender			0.472
Male	237 (69.7)	80 (70.6)	
Female	103 (30.3)	29 (26.6)	
Race			0.101
White	274 (80.6)	97 (89.0)	
Black	48 (14.1)	7 (6.4)	
Asian/other	18 (5.3)	5 (4.6)	
Primary site			0.335
Main bronchus	36 (10.6)	10 (9.2)	
Upper lobe	174 (51.2)	63 (57.8)	
Middle lobe	15 (4.4)	8 (7.3)	
Lower lobe	95 (27.9)	25 (22.9)	
Unspecific	20 (5.9)	3 (2.8)	
Chemotherapy			<0.001
No	266 (78.2)	106 (97.2)	
Yes	74 (21.8)	3 (2.8)	
Radiotherapy			<0.001
No	241 (70.9)	102 (93.6)	
Yes	99 (29.1)	7 (6.4)	
Reason of non-surgery			
Not recommended	295 (86.8)		
Recommended but not performed	45 (13.2)		

LSCIS, lung squamous cell cancer *in situ*.

Comment 4: Patients who received chemotherapy had significantly worse LCSS (Line 223). Was this related to the fact that chemotherapy was performed only in patients with a systemic recurrence?

Reply 4: Thank you for your rigorous comment. We performed analyses in the LSCIS patients in the SEER cohort and found that chemotherapy was performed in the 74 LSCIS patients

treated without surgery and only 3 LSCIS patients underwent surgery received chemotherapy. These results indicated that relation between chemotherapy and worse LCSS might not be irrelevant to the systemic recurrence after surgery. Some studies have reported that chemotherapy cannot prevent the progression of preinvasive squamous cell carcinoma. Because chemotherapy is not recommended for preinvasive NSCLC patients, LSCIS might be treated with chemotherapy which is the preferred treatment for NSCLC patients who cannot undergo surgery, when the preinvasive tumors develop into an invasive disease in the patients having chemotherapy. This may be the reason why chemotherapy relating to worse LCSS in LSCIS patients.

Changes in the text: We added some data of chemotherapy (see Page 6, line 183-185; Page 12, line 366-374)

Comment 5: Lung cancer specific survival and overall survival of patients with stage IA lung squamous lung cancer was better than in patients with LSCIS (see line 196). This finding should be further discussed, since does not appear to be justified by tumor histology.

Reply 5: Thank you for your rigorous comment. We consider the selection bias could be the reason why there were significant differences between the LSCIS and stage IA LSQCC in the SEER cohort. We divided the LSCIS and LSQCC patients in the SEER cohort into a surgery group and a non-surgery group, and found that in the non-surgery group there were significant differences between the LSCIS and stage IA LSQCC in OS and LCSS, but in the surgery group in the SEER cohort and the Shanghai Pulmonary Hospital cohort, the OS and PFS were comparable between the LSCIS and stage IA LSQCC. Besides, after the adjustment of the confounders in the SEER cohort, the multivariate survival analysis showed the OS and LCSS of the LSCIS patients were comparable to those of the stage IA LSQCC patients.

Changes in the text: We added some data on the comparison of LSCIS and LSQCC (see Page 6-7, line 224-231)

Reviewer B

Comment 1: Squamous cell carcinoma has frequently developed as a fashion of multiple primary tumors, and this finding was explained by the concept of field cancerization. This concept is well adapted to head and neck cancer, but also to lung squamous cell carcinoma. Indeed, multiple LSCIS has been reported in literature. This finding raises the question on the poor prognosis of LSCIS due to this multiple cancer.

Reply 1: We gratefully appreciate for your valuable comment. After consulting many references, we found that prognosis of multiple primary lung cancer is determined by the highest clinical TNM stage, number of lesions, and radiological classification in the multiple tumors in some studies. Besides, multiple primary lung cancer may be associated with a lower resection rate of all incident tumors in LSCIS patient. Therefore, multiple primary tumors could lead to a worse

survival in LSCIS. However, because it is difficult to discrimination between metastasis and multiple primary tumors, and both LSCIS and multiple primary tumors are uncommon tumors, there is lack of data of multiple primary LSCIS in this study.

Changes in the text: We added some findings from other studies and revised (see Page 13, line 408-410).

2. The cohort from the Shanghai Pulmonary Hospital included some diagnoses of LSCIS, which were made with bronchoscopy. Biopsy specimens do not represent the entire lesion, so the patients diagnosed with bronchoscopy should be excluded for analysis.

Reply 2: Thank you for your good suggestion. Although some patients from the Shanghai Pulmonary Hospital diagnoses of LSCIS with bronchoscopy before surgical resection, these patients are diagnosed again with LSCIS after surgery.

Changes: We have modified our text as advised (see Page 5, line 127).

Comment 3: The authors emphasized that LSCIS has a poorer prognosis than that of LAIS. However, adenocarcinoma tends to show better prognosis that squamous cell carcinoma in stage IA. The authors should show the data of stage IA in both histological subtypes and discuss the prognosis of LSCIS based on the findings.

Reply 3: Thanks for your great suggestion on improvement of our manuscript. We add the data of patients with lung adenocarcinoma (LAUD) (Table 1) and performed the analyses with the data of LUAD. We found that LUAD was associated with better survival than LSQCC and LSCIS, and the discussion is performed based on these new findings.

Changes in the text: We added some data and performed analyses (see Page 7, line 200-207 and line 214-220)