Disparities in survival following surgery among patients with different histological types of N2-III non-small cell lung cancer: a Surveillance, Epidemiology and End Results (SEER) database analysis

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Background: This study aimed to determine the extent to which the survival outcomes of patients with N2-III non-small cell lung cancer (NSCLC) following surgery differ by histological subtype.

Methods: Patients with N2-III NSCLC receiving surgery between 2010 to 2016 were included using the Surveillance, Epidemiology and End Results (SEER) database. Cox proportional hazards models were used to identify risk factors associated with overall survival (OS) and non-cancer mortality. The Kaplan-Meier method with log-rank tests was used to estimate survival. Propensity score matching (PSM) was used. Statistical significance was defined as P<0.05. Statistical analyses were done with IBM SPSS 23.0.

Results: Ultimately, 2,501 patients with stage N2-III NSCLC receiving surgery were included: 1,891 (75.6%) patients had adenocarcinoma (AC), and 610 (24.4%) patients had squamous cell cancer (SCC). The percentages of patients with AC and SCC receiving chemotherapy and postoperative radiotherapy (PORT) were comparable. In multivariate analysis, histology remained a significant predictor for OS and non-cancer mortality after adjusting for other clinical factors (P<0.05). Based on clinical factors, 522 patients with SCC were ultimately matched with 518 patients with AC using PSM. The 5-year OS of SCC patients after matching was much worse than that of AC patients (36.3% *vs.* 41.5%; P=0.018), and the 5-year non-cancer mortality of SCC patients was much higher than that of AC patients (18.8% *vs.* 4.8%; P=0.001).

Conclusions: Among patients with stage N2-III NSCLC following surgery, those with SCC had worse OS than those with AC, due to the higher percentage of patients dying from non-cancer causes.

Keywords: Squamous cell cancer (SCC); adenocarcinoma (AC); overall survival (OS); non-cancer mortality

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Introduction

For patients with operable stage N2-III non-small cell lung cancer (NSCLC), surgery remains the standard treatment. Furthermore, for these patients, adjuvant chemotherapy is routinely recommended, whereas, postoperative radiotherapy (PORT) is not routinely recommended owing to the lack of high level evidence, although it is still often used in clinical practice (1,2). Despite the treatments, the overall survival (OS) of these patients continues to be poor,

with a 5-year OS of less than 25% (3). NSCLC comprises a group of malignancies, such as adenocarcinoma (AC), squamous cell cancer (SCC), neuroendocrine cancer, and large cell cancer, and whether histology should play a role in therapeutic decision making remains controversial. AC and SCC, which have long been considered to be almost similar in both postoperative prognosis and chemoradiotherapeutic response, account for approximately 85% of all NSCLC cases (4,5).

Given the improvement of survival outcomes afforded by chemotherapy and the significant toxicity associated with chemotherapy and PORT, a better evaluation which incorporates the histological subtype of NSCLC may improve clinical decision making (6-8). In addition, chemotherapy responses vary according to different chemotherapy agents for histological subtypes of NSCLC. For instance, it was reported that a chemotherapeutic regimen of cisplatin and gemcitabine was more effective for SCC, whereas, a regimen of cisplatin and pemetrexed was more effective for AC (9). At present, the new agents of target therapy and immune therapy have significantly improved survival and safety profiles of patients with NSCLC (10) and increased the possibility for patients with stage N2-III to receive more aggressive and individualized treatment.

Currently, clinical decisions for NSCLC patients are still based on tumor-node-metastasis (TNM) stage, with no consideration given to histological subtype. Even though Grosu *et al.* reported that among patients with stage I NSCLC, those with SCC had a higher risk of mortality than those with AC taking into account competing risks (11). Whereas, the treatment modalities of patients with stage I NSCLC differ significantly from those with N2-III NSCLC. A randomized phase II trial by Yue *et al.* reported that adjuvant erlotinib improved 2-year disease-free survival in patients with EGFR mutation-positive stage IIIA NSCLC, compared with chemotherapy (81·4% *vs.* 44·6%; P=0.005) (10). Thus, whether histological subtype affects survival for patients with stage N2-III NSCLC receiving surgery remains unclear. While the recurrence rate is comparable between patients with AC and SCC following surgery (12). Our previous study showed that the recurrence pattern was different between patients with N2-IIIA AC and those with SCC, and patients with SCC tend to have mediastinal lymph nodes recurrence, whereas, those with AC tend to have distant metastasis (13). Several studies have reported that patients receiving radical resection with SCC had a poorer OS compared to those with AC (12,14,15). However, whether histological subtype affects survival for patients with stage N2-III NSCLC who receive surgery remains unclear.

The main objective of this study was to determine the extent to which the survival outcomes of patients with stage N2-III NSCLC following surgery differ by histological subtype. To this end, we compared the survival outcomes of patients with AC *vs.* SCC using the data from Surveillance, Epidemiology and End Results (SEER) database. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4357).

Methods

Data source

The data for this population-based, retrospective study was abstracted from the SEER 18 registries research database, comprising information on approximately 30% of the total U.S. population. In the past decade, great advances in tumor management have been achieved. To explore the management and survival outcomes during the modern era and unify the tumor staging, lung cancer patients who were diagnosed between 2010 and 2016 were included in the present study. SEER*Stat Software version 8.3.6 was used to generate the case listing.

Cohort selection

The inclusion criteria were as follows: (I) diagnosed as the first and only malignant cancer; (II) only one primary site; (III) diagnosis not obtained from a death certificate or an autopsy; (IV) aged ≥18 years; (V) having either a lobectomy or pneumonectomy; (VI) American Joint Committee on Cancer (AJCC, 7th edition) stage N2-III; (VII) AC and SCC; (VIII) receiving postoperative external-beam irradiation or no irradiation; (IX) stated number of lymph nodes involved and sampled; (X) stated T tumor stage and laterality; and (XI) applicable cause of death. The exclusion criteria were as follows: (I) stage N0, N1, N3 diseases or unknown nodal status; (II) metastatic disease or unknown T tumor stage; (III) use of radiotherapy as preoperative radiotherapy, intraoperative radiotherapy, or brachytherapy; (IV) having wedge resection or segmentectomy; (V) other histological types apart from AC and SCC (e.g., small cell cancer, neuroendocrine cancer); and (VI) no cause of death listed. The flowchart for the population selection is shown in *Figure 1*.

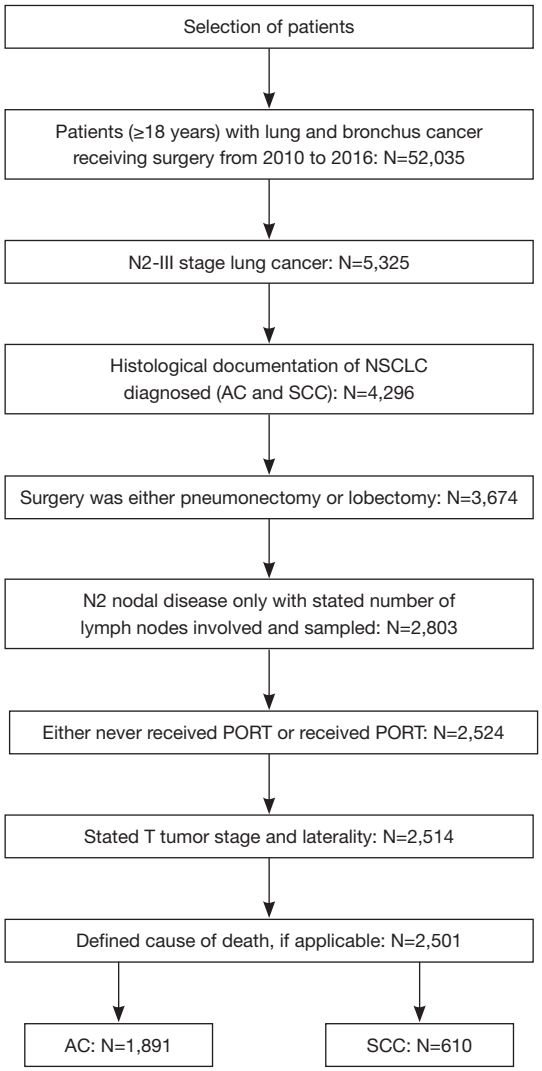

Figure 1 The flowchart for the population selection.

Statistical analysis

OS was defined as the time from the date of diagnosis to the date of death or last follow-up. For time to death from non-cancer, we used a Cox model to assess the cause-specific hazard associated with the risk factors for death from non-cancer. The Kaplan-Meier method was used to estimate survival, with log-rank tests used to compare curves. Univariate analysis (UVA) and multivariate analysis (MVA) were done with Cox proportional hazards models. Covariates with P<0.2 in the UVA were entered into the MVA models. A stepwise forward approach (likelihood ratio) was used to obtain the final MVA model. To reduce bias resulting from the retrospective nature of this study and to enhance comparability between groups, propensity score matching (PSM) analysis was used with Stata 14. Chi-square test was used to test the difference between groups. Statistical significance was defined as P<0.05. Statistical analyses were completed with IBM SPSS 23.0 (IBM, Chicago, IL, USA).

Results

Patient characteristics

In all, 2,501 patients with stage N2-III NSCLC receiving surgery were included in the final analysis: 1,891 (75.6%) patients had AC, and 610 (24.4%) patients had SCC. The patient characteristics for the entire cohort are shown in *Table 1*. The median age was 66 years (range, 18–89 years), the majority were White (80.3%), and most patients had early T tumor stage (75.6%). Over a half of the patients had adequately sampled lymph nodes, and 41% patients had no fewer than 4 positive lymph nodes.

The outcomes of univariate and multivariate analysis for overall survival

The median survival time for all patients was 41 months (range, 0–83 months), and the 5-year OS was 38.9%. The results of the UVA and MVA of factors for OS are summarized in *Table 2*. Under UVA, younger age, female, AC, early T stage, fewer positive lymph nodes [1–3], chemotherapy, PORT, and lobectomy were significantly associated with better OS (P<0.05). The factors of interest that were identified from UVA with a P value <0.2 were entered into the MVA models. In the multivariate models for OS, younger age (P<0.001), female sex (P<0.001), AC (P=0.004), early T stage (P<0.001), localization in the left lung (P=0.019), fewer positive lymph nodes [1–3] (P<0.001), chemotherapy (P<0.001), and lobectomy (P=0.018) were significantly associated better OS. However, PORT was not associated with OS (P=0.408).

The outcomes of univariate and multivariate analysis for non-cancer mortality

The results of the UVA and MVA for factors of non-cancer mortality are also summarized in *Table 2*. Under UVA, younger age, female sex, non-White and non-Black race, AC, chemotherapy, and PORT were significantly associated with lower non-cancer mortality (P<0.05). In multivariate

Table 1 The patient characteristics of the entire cohort

Variables	No. of patients [%]
Age (years)	
≤60	742 [30]
60 to 70	899 [36]
>70	860 [34]
Sex	
Male	1,214 [49]
Female	1,287 [51]
Race	
White	2,008 [80]
Black	244 [10]
Other/unknown	249 [10]
Histology	
Adenocarcinoma	1,891 [76]
Squamous cell cancer	610 [24]
T stage	
T1–2	1,902 [76]
T3–4	599 [24]
Laterality	
Right	1,396 [56]
Left	1,105 [44]
No. of nodes sampled	
>10	1,428 [57]
≤10	1,073 [43]
No. of positive lymph nodes	
1 to 3	1,483 [59]
≥4	1,018 [41]
Chemotherapy	
Yes	1,923 [77]
No	578 [23]
Postoperative radiotherapy	
Yes	1,049 [42]
No	1,452 [58]
Type of surgery	
Lobectomy	2,285 [91]
Pneumonectomy	216 [9]

models for non-cancer mortality, younger age (P=0.015), non-White and non-Black race (P=0.038), chemotherapy (P<0.001), and AC (P<0.001) were significantly associated with lower non-cancer mortality. However, sex (P=0.057) and PORT (P=0.958) did not impact non-cancer mortality.

Propensity score matching for patients with squamous cell cancer and adenocarcinoma

The number of patients with AC was twice that of the patients with SCC. Compared with SCC, AC had more young patients, more female patients, fewer White patients, more early T stage patients, and more patients with ≥4 positive lymph nodes. Additionally, SCC had more patients receiving pneumonectomy than AC, possibly due to the higher frequency of patients with centrally localized SCC. The percentage of AC patients receiving chemotherapy and PORT was comparable to that of SCC patients.

To reduce the influence of potential confounders in the comparisons between SCC and AC, PSM based on sex, race, age, PORT, laterality, T stage, number of positive lymph nodes, chemotherapy, and surgery types was used to create well-balanced groups. We ultimately matched 522 patients with SCC with 518 patients with AC (1:1 ratio, caliper 0.001). Characteristics of all eligible cases and PSM pairs are summarized in *Table 3*. The 5-year OS of patients with SCC after matching was much worse than that of AC patients (36.3% *vs.* 41.5%; P=0.018), and the 5-year non-cancer mortality of SCC patients with was much higher than that of AC patients (18.8% *vs.* 4.8%; P=0.001). The Kaplan-Meier curves for OS by histological types are displayed in *Figure 2*.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Discussion

Our findings suggest that the histological subtype of stage N2-III NSCLC was an important prognostic indicator for OS. Patients with SCC had a much higher non-cancer mortality than those with AC, after adjusting for other variables.

For patients with N2-III NSCLC following surgery, the percentage of SCC patients who received chemotherapy and PORT was comparable to that of AC patients. This can be explained by the fact that NSCLC is always treated as a group of malignancies, without accounting for histology.

Table 2 The results of univariate and multivariate analysis of factors for overall survival and non-cancer mortality

Variables	Univariate analysis				Multivariate analysis			
	OS		Non-cancer mortality		OS		Non-cancer mortality	
	HR	P	HR	P	HR	P	HR	P
Age (years)	1.365	<0.001	1.647	<0.001	1.299	<0.001	1.354	0.015
≤60								
60 to 70								
>70								
Sex	1.517	<0.001	1.501	0.025	1.466	<0.001		0.057
Male								
Female								
Race		0.058	0.674	0.03		0.086	0.688	0.038
White								
Black								
Other/unknown								
Histology	1.337	<0.001	2.117	<0.001	1.225	0.004	2.135	<0.001
AC								
SCC								
T stage	1.408	<0.001		0.33	1.32	<0.001		
T1–2								
T3–4								
Laterality		0.156		0.704	0.864	0.019		
Right								
Left								
No. of nodes sampled		0.235		0.255				
>10								
≤10								
No. of positive lymph nodes	1.375	<0.001		0.375	1.418	<0.001		
1 to 3								
≥4								
Chemotherapy	0.549	<0.001	0.274	<0.001	0.576	<0.001	0.3	<0.001
Yes								
No								
PORT	0.795	<0.001	0.615	0.011		0.408		0.958
Yes								
No								
Type of surgery	1.466	<0.001		0.439	1.263	0.018		
Lobectomy								
Pneumonectomy								

PORT, postoperative radiotherapy; OS, overall survival; AC, adenocarcinoma; SCC, squamous cell cancer.

Table 3 Characteristics of all eligible cases and propensity score matching pairs for patients with adenocarcinoma and squamous cell cancer

Characteristics	All eligible cases			Propensity score matching pairs		
	No. of Pt with AC [%]	No. of Pt with SCC [%]	P	No. of Pt with AC [%]	No. of Pt with SCC [%]	P
Total	1,891	610		518	522	
Age [years]			0.006			0.093
≤60	592 [31]	150 [24]		146 [28]	119 [24]	
60 to 70	658 [35]	241 [40]		183 [35]	211 [40]	
>70	641 [34]	219 [36]		189 [37]	192 [36]	
Sex			<0.001			0.586
Male	822 [43]	392 [64]		302 [58]	313 [60]	
Female	1,069 [57]	218 [36]		216 [42]	209 [40]	
Race			0.001			0.622
White	1,495 [79]	513 [84]		427 [82]	440 [84]	
Black	184 [10]	60 [10]		54 [10]	52 [10]	
Other/unknown	212 [11]	37 [6]		37 [8]	30 [6]	
T stage			<0.001			0.657
T1–2	1,471 [78]	431 [70]		400 [77]	397 [76]	
T3–4	420 [22]	179 [30]		118 [23]	125 [24]	
Laterality			0.122			0.228
Right	1,072 [57]	324 [53]		304 [59]	287 [55]	
Left	819 [43]	286 [47]		214 [41]	235 [45]	
No. of positive lymph nodes			0.002			0.178
1 to 3	1,089 [58]	394 [65]		350 [68]	332 [64]	
≥4	802 [42]	216 [35]		168 [32]	190 [36]	
Chemotherapy			0.223			0.137
Yes	1,465 [77]	458 [75]		424 [82]	408 [78]	
No	426 [23]	152 [25]		94 [18]	114 [22]	
PORT			0.263			0.084
Yes	805 [43]	244 [40]		191 [37]	220 [42]	
No	1,086 [57]	366 [60]		327 [63]	302 [58]	
Type of surgery			<0.001			0.432
Lobectomy	1,785 [94]	503 [82]		466 [90]	477 [91]	
Pneumonectomy	109 [6]	107 [18]		52 [10]	45 [9]	

PORT, postoperative radiotherapy; Pt, patients; AC, adenocarcinoma; SCC, squamous cell cancer.

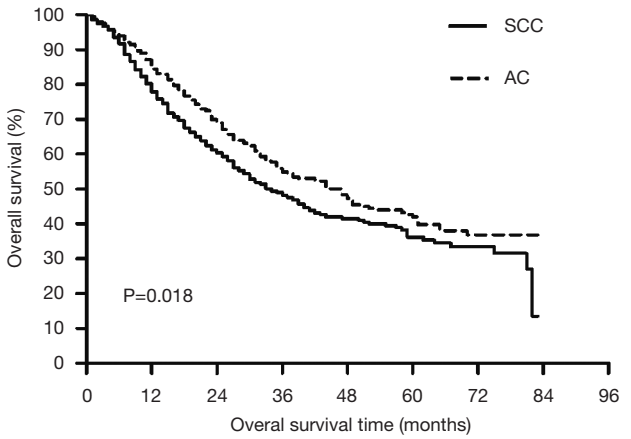

Figure 2 Overall survival of patients with adenocarcinoma (AC) and squamous cell cancer (SCC) who had N2-III stage non-small cell lung cancer receiving surgery.

In addition, the target therapy is not recorded in the SEER database, although a great number of patients with AC who have mutation-driven genes receive target therapy (10). Furthermore, more SCC patients receive pneumonectomy than AC patients do, which may be a result of the higher proportion of patients with SCC located centrally in the mediastinum.

The survival rate results for AC and SCC in patients undergoing complete surgery are mixed. Some research suggests that SCC histology has worse survival than AC histology. In the study by Nakamura *et al.*, 537 NSCLC patients with surgery (AC, 434; SCC, 103) were included, with SCC having a poorer OS compared to the AC histology (12). A study using the SEER database reported that histology was a significant predictor for survival (16). In contrast, several studies have demonstrated that NSCLC patients with SCC had better survival than those with AC (17,18). The Adjuvant Navelbine International Trialist Association (ANITA) trial reported the survival of NSCLC patients with completely resected stage IB-IIIA diseases who were randomly assigned to vinorelbine and cisplatin or to observation (17). The trial yielded a median survival time of 37.3 and 45.5 months for patients with AC and non-AC, respectively, and AC histology appeared to be a poor prognostic factor in patients with resected NSCLC (18). After analyzing 9,137 surgically managed cases with NSCLC, Chansky *et al.* found a small survival advantage for SCC over AC (19). In contrast, the study by Douillard, etc. showed no survival difference between patients with SCC and non-SCC (8).

In this study, after adjusting for other clinical variables, including, sex, race, age, PORT, laterality, T stage, number of positive lymph nodes, chemotherapy, and surgery types, we found that SCC histology had worse OS than AC histology for patients with N2-III NSCLC receiving surgery, which is similar to the results of previously published studies, to some extent (12,14,15,20). After PSM, the 5-year OS for patients with SCC was 5.2% lower than that of AC (P=0.018). This may be attributable to SCC tending to have a greater loco-regional failure rate than AC (HR 1.934, 95% CI: 0.94–3.977, P=0.073) (21), which contributes to worse OS. Unfortunately, recurrence information is not available on the SEER database, so we are not able to compare loco-regional failure between SCC and AC.

To further determine the reasons for the survival differences between SCC and AC, we analyzed the non-cancer mortality as the complementary endpoint for OS. Surprisingly, we found that the non-cancer mortality of SCC was 14% higher than AC (P=0.001). One of the reasons postulated to account for this survival difference is the fact that SCC had higher non-cancer mortality, which contributes to decreased survival. Another reason is the fact that patients with SCC are more likely to be smokers (12,20). Smoking is a risk factor for recurrence (12), which contributes to decreased OS, and is associated with several life-threatening diseases, like emphysema, pneumonia, ischemic heart diseases, cerebrovascular disease, and several malignant tumors including lung cancer, all of which may result in a high risk of non-cancer mortality and decreased OS (12,22,23).

This study is the first to compare the OS and non-cancer mortality of patients with SCC and AC who had N2-III NSCLC following surgery. Our findings revealed that the reason for SCC having a worse OS potentially lies in the fact that more patients with SCC die from non-cancer causes, such as chronic obstructive pulmonary disease, ischemic heart diseases, and cerebrovascular disease, rather than from the tumor itself. To reduce bias in this study, we included patients defined according to the AJCC 7th version guidelin es applied after 2010 to ensure that most patients were treated with relatively consistent and modern modalities.

Our study had several limitations, chief among them was its retrospective nature. Second, the SEER database did not have information on smoking, smoking-related comorbidities and death, other detailed causes of death, and tumor recurrence and related treatment, which limited

our comparison of smoking-caused death and recurrence-related death between patients with SCC and AC. Third, the SEER database did not have information concerning adjuvant therapy, including data on radiation dose, chemotherapy cycles, chemotherapy agents, etc. Fourth, the SEER database did not have information on target therapy, which limited our analysis on the benefits of target therapy for patients with AC. Given these restrictions, further prospective studies are needed in the future.

In conclusion, our study showed that among patients with stage N2-III NSCLC following surgery, the management modalities between SCC and AC histology were similar. Also, those with SCC histology had worse OS than those with AC as result of the higher percentage of patients dying from non-cancer causes. Thus, more aggressive and individualized treatment modalities should be taken to improve the therapeutic efficiency of patients with N2-III SCC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-4357

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-4357). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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