JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2012;42(3)189–195
doi:10.1093/jjco/hyr188
Advance Access Publication 30 December 2011

Differences Between Squamous Cell Carcinoma and Adenocarcinoma of the Lung: Are Adenocarcinoma and Squamous Cell Carcinoma Prognostically Equal?

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Received August 8, 2011; accepted November 24, 2011

Objective: We analyzed pulmonary squamous cell carcinoma and adenocarcinoma patient survival in our single institution database, to evaluate the relationship of histologic analysis to survival and tumor aggressiveness.
Methods: We reviewed 1856 consecutive patients with surgically resected pulmonary squamous cell carcinoma or adenocarcinoma regarding their clinicopathologic characteristics, overall survival and recurrence-free proportion.
Results: In squamous cell carcinoma patients, there were more elderly male smokers and more patients with T2–4 tumors, moderately/poorly differentiated tumors, lymph node metastasis or vascular invasion than in adenocarcinoma patients. In all patients and in pN0 patients, patients with squamous cell carcinoma showed significantly poorer overall survival than those with adenocarcinoma, but there were no statistically significant differences in the recurrence-free proportion between the two histologic types. There were statistically significantly more lung cancer-specific deaths in patients with adenocarcinoma than in patients with squamous cell carcinoma ($P = 0.001$).
Conclusions: There were no differences in the development of recurrence between squamous cell carcinoma and adenocarcinoma of the lung, but considerable differences in overall survival were observed between the two histologic types. According to the stage grouping strategy of the TNM Classification for Lung and Pleural Tumours, these two histologic types need to be staged differently. This survival difference, however, may reflect the difference in patient background rather than in biologic aggressiveness between the two histologic types.

Key words: histologic type – prognosis – squamous cell carcinoma – adenocarcinoma – TNM classification

INTRODUCTION

Squamous cell carcinoma and adenocarcinoma are the two major histologic types of non-small cell lung cancer. Patients with adenocarcinoma were known to result in poorer prognosis than those with squamous cell carcinoma (1,2). However, a recent increase in the use of computed tomography (CT) has enabled small adenocarcinoma detection on a screening basis, and many of these small adenocarcinomas are relatively dormant bronchioloalveolar carcinomas and have favorable outcome (3). This may be one reason why patients with squamous cell carcinoma are known today to have a poorer prognosis than those with adenocarcinoma following surgical resection (4).

Squamous cell carcinoma mostly develops in smokers, in whom life-threatening co-morbidities often develop, which may also explain the poorer survival rates of patients with

squamous cell carcinoma compared with those with adenocarcinoma. However, differences in biological aggressiveness between squamous cell carcinoma and adenocarcinoma of the lung are not well understood.

In esophageal cancer staging, squamous cell carcinoma and adenocarcinoma are classified differently in the 7th Edition of the Cancer Staging Manual of the American Joint Committee on Cancer (5–7). In lung cancer, however, prognostic differences in histologic types are not taken into consideration in the latest TNM classification (8).

We retrospectively analyzed the survival differences between squamous cell carcinoma and adenocarcinoma of the lung, in an attempt to identify the prognostic impact of histologic difference and to incorporate it in future staging systems, based on our patient database.

PATIENTS AND METHODS

From July 1992 through December 2006, 1856 consecutive patients with pulmonary squamous cell carcinoma or adenocarcinoma underwent complete resection at our institution. We defined complete resection as segmentectomy or greater, with systematic ipsilateral hilar and mediastinal lymph node dissection but with no evidence of residual cancer either macroscopically or histologically. Patients who had induction chemotherapy, radiotherapy or both, patients with evidence of residual tumor at the surgical margin or patients with malignant effusion or distant metastasis verified intraoperatively or by means of postoperative pathologic examination were excluded from this study.

Cases were pathologically staged based on the 7th Edition of the TNM Classification for Lung and Pleural Tumours (8). Histopathologic studies were done according to the World Health Organization criteria (9). We reviewed the medical records of all patients for the following clinicopathologic factors: age, gender, smoking history (never or ever smoker), pathological differentiation, pathological T stage, pathological N stage, vascular invasion and lymphatic permeation.

Student's *t*-test was used to evaluate the relationships between histologic type (squamous cell carcinoma or adenocarcinoma) and age. Fisher's exact test was used to evaluate the relationships between histologic type and other clinicopathologic factors. We compared overall survival and recurrence-free proportion between squamous cell carcinoma and adenocarcinoma in all patients, in pN0 patients, in pT1N0 patients, in pT2N0 patients and in pT3/4N0 patients. When we analyzed recurrence-free proportion, we excluded 249 cases from this study because their recurrence data were incomplete. The survival rates and recurrence-free proportions were calculated using the Kaplan–Meier method, and univariate analyses were performed with the log-rank test. Multivariate analyses were performed by using the Cox proportional hazards model. Zero time was the date of pulmonary resection. The endpoint of overall survival was defined as the date of death from any cause, and the last follow-up observation was censored when the patient was alive or lost to follow-up. The endpoint of recurrence-free proportion was defined as the date when recurrence was confirmed. We examined patients at 3-month intervals for the first 2 years and at 6-month intervals thereafter on an outpatient basis. The follow-up evaluation included physical examination, chest radiography and blood examination including that of pertinent tumor markers. Further evaluations, including CT scans of the chest and abdomen, brain magnetic resonance imaging and bone scintigraphy, were performed on the detection of any symptoms or signs of recurrence. Since 2004, integrated positron emission tomography and CT have also been performed when appropriate. We diagnosed recurrence based on the findings of physical examination and diagnostic imaging and confirmed the diagnosis histologically when clinically feasible. The date of recurrence was defined as the date of cytohistological proof. However, in cases diagnosed on the basis of clinicoradiological findings, the date of recurrence was defined as the date of identification by a physician. The last follow-up observation was censored when the patient was recurrence-free or lost to follow-up. Patients who died from causes other than lung cancer recurrence were also censored on the date of death.

All P values were two-sided, and P values <0.05 were considered to represent statistically significant differences. Survival analyses were performed on SPSS software (Dr SPSS II for Windows, Standard Version 11.0, SPSS Inc., Chicago, IL, USA).

Data collection and analyses were approved, and the need to obtain written informed consent from each patient in this retrospective study was waived, by the institutional review board in June 2010.

RESULTS

Patient Characteristics

The patient characteristics are shown in Table 1. In squamous cell carcinoma patients, compared with adenocarcinoma patients, there were more elderly male smokers and more patients with T2–4 tumors, moderately/poorly differentiated tumors, lymph node metastasis or vascular invasion. In pN0 patients ($n = 1328$), there were more elderly male smokers and more patients with T2–4 tumors, moderately/poorly differentiated tumors or vascular invasion in squamous cell carcinoma patients.

Overall Survival Differences

Patients with squamous cell carcinoma showed significantly poorer overall survival than those with adenocarcinoma in all patients and in pN0 patients (Figs 1A and 2A). The results of multivariate analyses of the statistically significant characteristics listed in Table 1 are summarized in Table 2. Age, smoking history, pathological T classification, vascular

Table 1. Patient characteristics

Patient characteristics	All patients				pN0 patients			
	AD	SQ	*P*-value	Total	AD	SQ	*P*-value	Total
Age								
Median (range)	65 (32–90)	69 (31–88)	<0.001[a]		65 (32–90)	70 (31–88)	<0.001[a]	
Sex								
Men	731 (52)	418 (90)		1149 (62)	521 (51)	263 (89)		784 (59)
Women	662 (48)	45 (10)	<0.001[b]	707 (38)	510 (49)	34 (11)	<0.001[b]	544 (41)
Smoking history								
Never smoker	617 (44)	12 (3)		629 (34)	485 (47)	9 (3)		494 (37)
Ever smoker	776 (56)	451 (97)	<0.001[b]	1227 (66)	546 (53)	288 (97)	<0.001[b]	834 (63)
Pathological T classification								
T1a, T1b	689 (49)	131 (28)		820 (44)	602 (58)	103 (35)		705 (53)
T2a, T2b, T3, T4	704 (51)	332 (72)	<0.001[b]	1036 (56)	429 (42)	194 (65)	<0.001[b]	623 (47)
Pathological N classification								
N0	1031 (74)	297 (64)		1328 (72)	—	—	—	—
N1, N2	362 (26)	166 (36)	<0.001[b]	528 (28)	—	—	—	—
Pathological differentiation								
Well	491 (36)	21 (5)		512 (28)	454 (44)	17 (6)		471 (36)
Moderately/poorly	892 (74)	440 (95)	<0.001[b]	1332 (72)	569 (56)	279 (94)	<0.001[b]	848 (64)
Vascular invasion								
Absent	818 (59)	150 (32)		968 (52)	732 (71)	128 (43)		860 (65)
Present	575 (41)	313 (68)	<0.001[b]	888 (48)	299 (29)	169 (57)	<0.001[b]	468 (35)
Lymphatic permeation								
Absent	964 (69)	320 (69)		1284 (69)	847 (82)	238 (80)		1085 (82)
Present	429 (31)	143 (31)	1.000[b]	572 (31)	184 (18)	59 (20)	0.444[b]	243 (18)
Total	1393	463		1856	1031	297		1328

AD, adenocarcinoma; SQ, squamous cell carcinoma; T/N classification according to the 7th Edition of the TNM Classification for Lung and Pleural Tumours; numbers in parentheses are percentages.
[a]Student's t-test.
[b]Fisher's exact test.

invasion and lymphatic permeation were significant prognostic factors in all patients and in pN0 patients. Pathological N classification was a significant prognostic factor in all patients. Sex, pathological differentiation and histologic type were not significant prognostic factors in any patients or in pN0 patients.

Although patients with squamous cell carcinoma showed significantly poorer overall survival than those with adenocarcinoma in pT1N0 patients and in pT2N0 patients (Fig. 3A and C), no statistically significant differences were observed in pT3/4N0 patients ($P = 0.841$; Fig. 3E).

Recurrence-free Proportion Differences

There were no statistically significant differences in recurrence-free proportion between adenocarcinoma and squamous cell carcinoma in any patients ($P = 0.351$; Fig. 1B) or in pN0 patients ($P = 0.715$; Fig. 2B).

In pT1N0 patients, patients with squamous cell carcinoma showed significantly poorer recurrence-free proportion than those with adenocarcinoma (Fig. 3B). In pT2N0 patients, there was no statistically significant difference in recurrence-free proportion between the two histologic types ($P = 0.098$; Fig. 3D). In pT3/4N0 patients, patients with adenocarcinoma showed significantly poorer recurrence-free proportion than those with squamous cell carcinoma (Fig. 3F).

Causes of Death

There were 638 patients whose causes of death were identified in our cohort. There were significantly more lung cancer-specific deaths in adenocarcinoma patients than in squamous cell carcinoma patients ($P = 0.001$; Table 3).

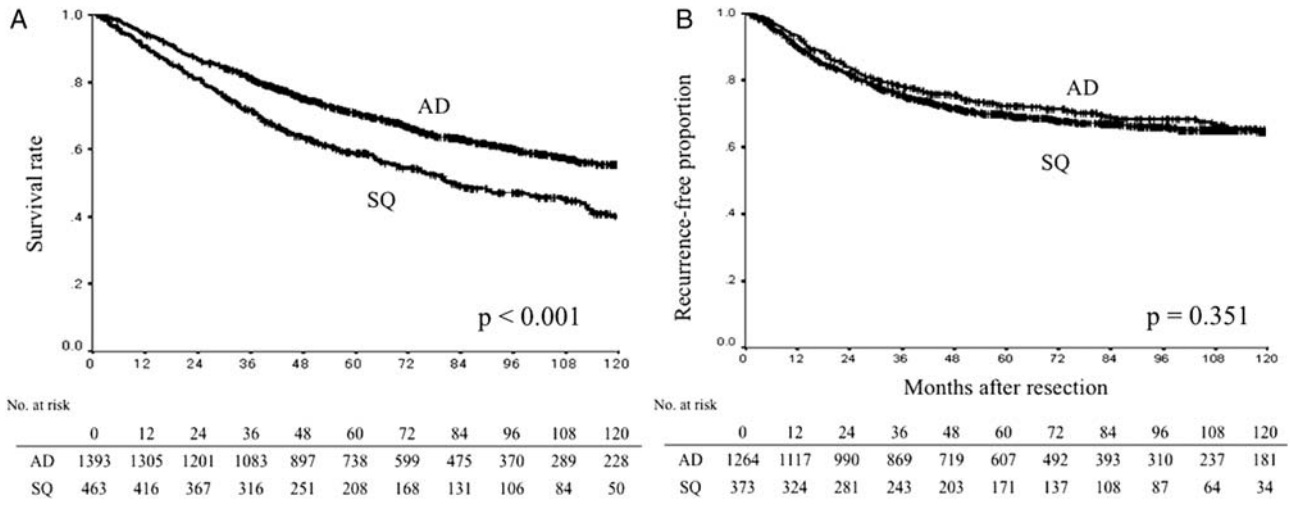

Figure 1. Overall survival and recurrence-free proportion between squamous cell carcinoma and adenocarcinoma in all patients. (A) Overall survival and (B) recurrence-free proportion curves of squamous cell carcinoma and adenocarcinoma in all patients. AD, adenocarcinoma; SQ, squamous cell carcinoma.

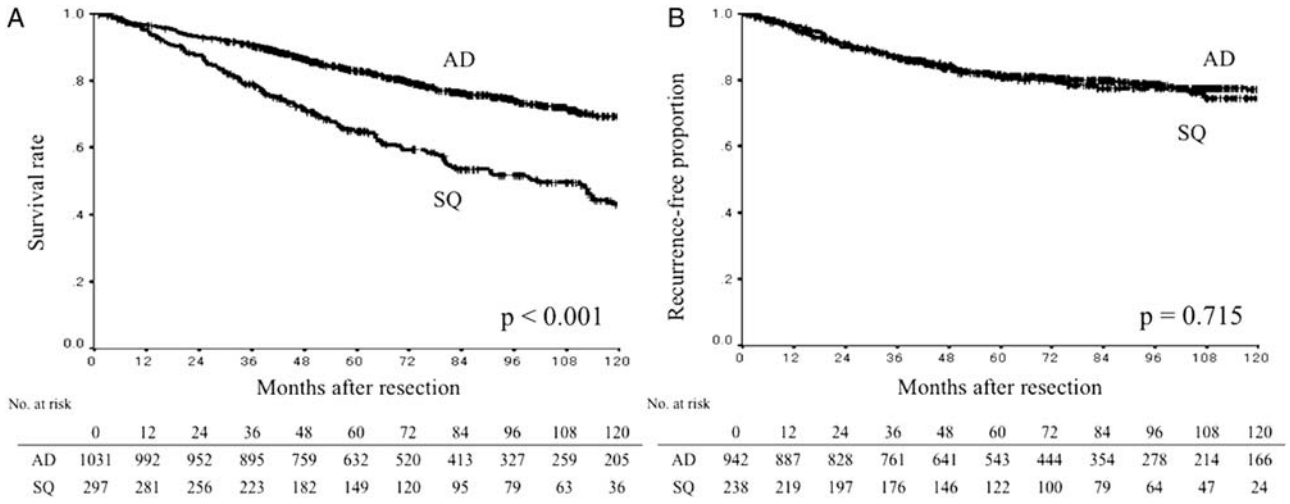

Figure 2. Overall survival and recurrence-free proportion between squamous cell carcinoma and adenocarcinoma in pN0 patients. (A) Overall survival and (B) recurrence-free proportion curves of squamous cell carcinoma and adenocarcinoma in pN0 patients.

Table 2. Multivariate analyses of overall survival

Patient characteristics	All patients		pN0	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (>65/≤65)	1.641 (1.414–1.905)	<0.001	2.152 (1.728–2.680)	<0.001
Sex (men/women)	1.023 (0.805–1.300)	0.853	1.054 (0.768–1.446)	0.744
Smoking history (ever smoker/never smoker)	1.429 (1.104–1.848)	0.007	1.661 (1.166–2.365)	0.005
Pathological T stage (T2 + 3 + 4/T1)	1.988 (1.653–2.391)	<0.001	2.267 (1.772–2.900)	<0.001
Pathological N stage (N1 + 2/N0)	2.182 (1.844–2.582)	<0.001	—	—
Pathological differentiation (moderately + poorly/well)	1.185 (0.943–1.490)	0.145	1.180 (0.888–1.567)	0.255
Vascular invasion (present/absent)	1.572 (1.301–1.900)	<0.001	1.811 (1.426–2.301)	<0.001
Lymphatic permeation (present/absent)	1.352 (1.148–1.592)	<0.001	1.375 (1.092–1.731)	0.007
Histologic type (SQ/AD)	0.875 (0.737–1.039)	0.128	1.095 (0.866–1.385)	0.448

HR, hazard ratio for death; CI, confidence interval.

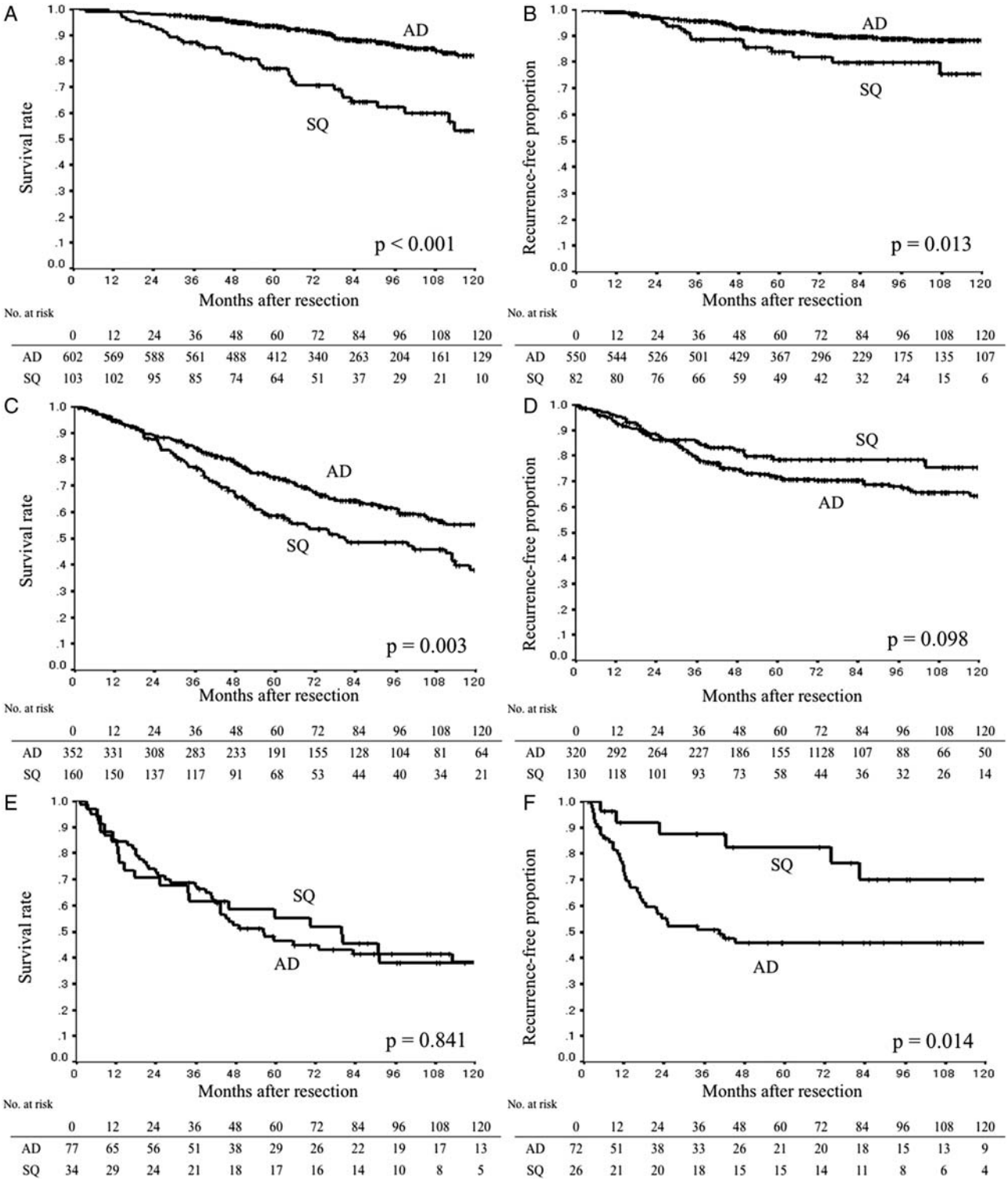

Figure 3. Overall survival and recurrence-free proportion between squamous cell carcinoma and adenocarcinoma in pT1N0 patients, in pT2N0 patients and in pT3/4N0 patients. (A) Overall survival and (B) recurrence-free proportion curves in pT1N0 patients. (C) Overall survival and (D) recurrence-free proportion curves in pT2N0 patients. (E) Overall survival and (F) recurrence-free proportion curves in pT3/4N0 patients.

DISCUSSION

We set out to determine the relationship of histologic analysis to survival and tumor aggressiveness in pulmonary squamous cell carcinoma and adenocarcinoma. Patients with pulmonary squamous cell carcinoma are known today to have a poorer prognosis than those with adenocarcinoma after surgical resection (4). Squamous cell carcinoma mostly develops in smokers

Table 3. Causes of death

Characteristics	Total	AD	SQ	*P* value
Lung cancer-specific deaths	479	355 (79)	124 (66)	
Deaths from other causes	159	96 (21)	63 (34)	0.001[a]
Total	638	451	187	

[a]Fisher's exact test; numbers in parentheses are percentages.

in whom life-threatening co-morbidities also often develop, including atherosclerotic cardiovascular events, chronic obstructive pulmonary disease and cerebral infarction (10), which may explain the poorer survival of patients with squamous cell carcinoma compared with those with adenocarcinoma. In the present study, there were significantly more patients who died of causes other than lung cancer in squamous cell carcinoma than in adenocarcinoma. However, it remains unclear whether biological aggressiveness differs between squamous cell carcinoma and adenocarcinoma of the lung.

In the present study, there were significantly more patients with squamous cell carcinoma than those with adenocarcinoma among smokers. In patients with squamous cell carcinoma, there were significantly more T2–4 patients and patients with lymph node metastases or vascular invasion. There were statistically significant differences in overall survival between adenocarcinoma and squamous cell carcinoma patients in all patients and in pN0 patient cohorts. However, when we analyzed recurrence-free proportion to exclude any possible influence of non-cancer-specific death and to compare biological aggressiveness between squamous cell carcinoma and adenocarcinoma, we found that there were no statistically significant differences in any patients or in pN0 patients. There were significantly more deaths from causes other than lung cancer in patients with squamous cell carcinoma than in those with adenocarcinoma.

These results indicate that although squamous cell carcinoma developed more frequently among smokers and was more advanced and invasive when resected compared with adenocarcinoma, its biological aggressiveness was not significantly different from adenocarcinoma. The poorer overall survival in patients with squamous cell carcinoma than those with adenocarcinoma seemed to be attributable to advanced and invasive cancer status on resection and smoking/age-related co-morbidities.

We also analyzed overall survival and recurrence-free proportion in each pathological T stage in pN0 patients to compare biological aggressiveness between squamous cell carcinoma and adenocarcinoma in each T stage. In pT1N0 patients, the patients with squamous cell carcinoma had significantly poorer survival and recurrence-free proportion than patients with adenocarcinoma. This may partly be explained by the fact that a considerable number of pT1 adenocarcinoma patients had non- or minimally invasive disease, such as bronchioloalveolar carcinoma, thereby resulting in better outcome compared with squamous cell carcinoma patients. In pT3/4 patients, on the other hand, there was no significant difference in overall survival between the two histologic types, but adenocarcinoma patients had significantly poorer recurrence-free proportion than squamous cell carcinoma patients. The poorer recurrence-free proportion of adenocarcinoma patients compared with squamous cell carcinoma patients may be interpreted that adenocarcinoma of this T status has biologically more aggressive nature than squamous cell carcinoma. However, probably because squamous cell carcinoma patients had more smoking/age-related co-morbidities and were more often killed by them than adenocarcinoma patients, there was no significant difference in overall survival.

In the 7th Edition of the TNM Classification for Lung and Pleural Tumours, stage groupings are based on overall survival (8). According to the strategy in this study, and based on our findings, squamous cell carcinoma and adenocarcinoma of the lung need to be staged differently. It is important to note, however, that the difference is likely to be due to advanced and invasive cancer status on resection and smoking/age-related co-morbidities of patients with squamous cell carcinoma, but not to biological tumor aggressiveness of squamous cell carcinoma.

There were several limitations in this study. Although the total number of consecutive patients was large (1856), the study was performed in a single institution using a homogenous Japanese ethnic group. Therefore, a multicenter trial based on various ethnic groups may be valuable. There were more well-differentiated tumors in adenocarcinomas than in squamous cell carcinomas in the present cohort. This may be another reason for the observed better prognosis in adenocarcinoma patients than in squamous cell carcinoma patients.

In conclusion, this study showed that there were no differences in the development of recurrence between squamous cell carcinoma and adenocarcinoma of the lung, but considerable differences in overall survival were observed between the two histologic types in all patients and pN0 patients. According to the stage grouping strategy of the TNM Classification for Lung and Pleural Tumours, these two histologic types need to be staged differently. This survival difference, however, may reflect the difference in patient background rather than the difference in biological aggressiveness between the two histologic types.

Acknowledgements

The authors thank Mr Roderick J. Turner and Prof. J. Patrick Barron of the Department of International Medical Communications of Tokyo Medical University for their review of this manuscript.

Funding

The work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare, Japan.

Conflict of interest statement

None declared.

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