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Swedish Lung Cancer Radiation Study Group: Predictive value of histology for radiotherapy response in patients with non-small cell lung cancer

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ABSTRACT

The aim of the present study was to evaluate the potential predictive value of histology in non-small cell lung cancer (NSCLC) treated with curatively intended radiotherapy. In a collaborative effort among all the Swedish Oncology Departments, clinical data were collected for 1146 patients with a diagnosed non-small cell lung cancer subjected to curatively intended irradiation ($\geqslant$50 Gy) during the years 1990 to 2000. The included patients were identified based on a manual search of all medical and radiation charts at the oncology departments from which the individual patient data were collected. Only patients who did not have a histological diagnosis date and death date/last follow-up date were excluded (n = 141). Among the 1146 patients with non-small cell carcinoma eligible for analysis, 919 were diagnosed with either adenocarcinoma (n = 323) or squamous cell carcinoma (n = 596) and included in this study. The median survival for the 919 patients was 14.8 months, while the 5-year survival rate was 9.5%. Patients with adenocarcinoma had a significantly better overall survival compared with patients with squamous cell carcinoma (p = 0.0062, log-rank test). When comparing different stages, this survival benefit was most pronounced for stages IIA–IIB ($p < 0.0001$, log-rank test). The difference in survival between the two histological groups was statistically significant in a univariate Cox analysis (p = 0.0063) as well as in two multivariate Cox analyses including demographic and treatment variables (p = 0.037 and p = 0.048, respectively). In this large population based retrospective study we describe for the first time that patients with adenocarcinoma have a better survival

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after curatively intended radiation therapy in comparison with squamous cell carcinoma patients, particularly those with clinical stages IIA–IIB.

1. Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, killing approximately 12,00,000 people annually.[1] In Sweden, 3500 people died of the disease in 2006 making it the most lethal cancer in both men and women.[2] In clinical practice, lung carcinomas are categorised into two categories; small cell lung carcinomas (SCLC) or non-small cell lung carcinomas (NSCLC). NSCLC represents 80% of all lung cancer and is composed of several histological types, including squamous cell carcinomas (SCC), adenocarcinomas (AC) and undifferentiated large cell carcinomas. In Sweden, the average five-year overall survival rate is only 10–15% taking all clinical stages together.[3] Patients with stage I or II disease, who are physically able to tolerate surgical intervention, display a 5-year survival of around 50%[4] after surgical resection. Adjuvant chemotherapy is generally indicated for patients with resected stages IIA through IIIA NSCLC, and an improvement of 5–10% in 5-year survival rates has been reported with cisplatin-based regimens.[5] Patients with localised, inoperable, non-small cell lung cancer are usually treated with radiotherapy. Conventional curatively intended radiotherapy (defined as $\geqslant$50 Gy)[6–8] in locally advanced, non-resectable NSCLC results in a median survival of 10 months and a 5-year survival rate of around 5%.[3] Cisplatin-based induction chemotherapy along with radiotherapy seem to lead to a modestly better survival rates than radiotherapy alone.[9] Given these poor results, it would be most valuable to predict the small subgroup of patients that could benefit from a particularly powerful localised treatment initiative with radiotherapy. Although histology has not been considered a prognostic factor in NSCLC, it has recently emerged as a potential predictive factor for the outcome of patients with advanced NSCLC treated with chemotherapy or EGFR inhibitors.[10,11] To the best of our knowledge there has been no investigation of the predictive value of histology on the outcome of patients treated with curatively intended radiotherapy. The aim of this study was to retrospectively investigate patients with lung cancer who have undergone curatively intended radiotherapy or postoperative radiotherapy and to elucidate whether the histology of the tumours could predict the response to treatment.

2. Materials and methods

The present study is a collaboration among all the Swedish Oncology Departments. The study includes detectable patients with a diagnosed non-small cell lung cancer of either that have been subjected to irradiation with a curative intent ($\geqslant$50 Gy) during the time period of 1990 to 2000. The study was reviewed and approved by the research ethical committee (Dnr 2005: 025). The included patients were identified based on a manual search of all radiation charts from which the individual patients were selected and their medical charts retrieved. A reference group composed of five oncologists visited all sites and reviewed the charts together with the medically responsible doctor for the treatment of lung cancer at the specific site. In the analyses, all patients were included who had a histological diagnosis date as well as a death date or a last follow-up date. The following variables were collected: gender, age, time period, histology (defined as squamous cell carcinoma, adenocarcinoma; other non-small cell histology was excluded from the study), stage according to the TNM 6 classification system (re-evaluated by three of the authors based on available information in the charts as well as based on available X-ray investigations), all given treatment (first-line as well as subsequent treatment), occurrence of relapse and cause of death.

Data were missing for some patients regarding some of these variables. However, these patients were not excluded from the study unless there was lack of data required to estimate survival. This, unfortunately, causes inconsistencies among some of the frequencies accounted for in the results section of this article.

2.1. Statistics

Patients' characteristics at diagnosis are presented using standard descriptive statistics. Overall survival was analysed with Kaplan–Meier product-limit estimates. Survival curves for different categories were compared using the log-rank test. The follow-up time was calculated from the date of diagnosis to death or last follow-up until the end of 2008. Age was defined as age at diagnosis. Overall survival was also analysed using Cox proportional hazards regression models. Univariate and multivariate analyses were performed. The multivariate models were adjusted by gender and age at diagnosis. Results were presented as hazard ratios with 95% confidence intervals (95%CI). In addition p-values were given, where $p < 0.05$ was regarded as statistically significant.

3. Results

3.1. Patient characteristics

A total of 1146 patients with non-small cell carcinoma were eligible for analysis and of these 919 were diagnosed with either adenocarcinoma (n = 323) or squamous cell carcinoma (n = 596) and thus included in this study. Of the patients with adenocarcinoma, 152 (47%) were women as compared with 146 (25%) of the patients with squamous cell carcinoma. The median age was 63 (range 25–84) years for patients with adenocarcinoma and 66.5 (range 32–86) years for patients with squamous cell carcinoma. In patients with adenocarcinoma, 241 (83%) of 289 patients had a relapse while the corresponding value for SCC was 344 (74%) of 466 patients. There were only minor differences between the histological groups

in distribution of stage and radiotherapy given with curative intent. Mean radiation dose for patients with adenocarcioma was 59 (range 50–70) Gy and for patients with squamous cell carcinoma the corresponding value was 58 (range 50–74) Gy. Some patients were operated and received radiotherapy in a postoperative fashion. Of the patients with AC, 86 (33%) had surgery before radiotherapy, whereas the corresponding value for SCC was 112 (23%). First-line chemotherapy was given to a total of 266 (30%) of 893 patients with either AC or SCC; of these 266 patients, 54 (20%) received it concomitantly with radiation treatment and 114 (43%) in a neo-adjuvant setting. Furthermore, 98 (37%) patients were given both concomitant and induction chemotherapy. However, comparing the two histological groups, 149 (26%) of the SCC patients received any type of chemotherapy in the first-line as compared with 117 (37%) of the patients with adenocarcinoma. In the second-line setting, 60 (19%) of 323 patients with adenocarcinoma received chemotherapy against the recurring tumour, whereas the corresponding number of patients with squamous cell carcinoma was 64 (11%) of 596 patients. For the 622 patients, where information concerning cause of death was available, 575 (92%) died from lung cancer while 47 (8%) died due to other causes. For patients with adenocarcinoma the cancer-related mortality was 96% as compared with 91% for patients with squamous cell carcinoma. A summary of patient characteristics, given treatment, occurrence of relapse and cause of death is provided in Table 1.

Table 1 – Patient characteristics, treatment, relapse and cause of death.

Histopathology	Adenocarcinoma	Squamous cell carcinoma
Gender		
Male	171 (53%)	450 (76%)
Female	152 (47%)	146 (25%)
Age		
<55 years	76 (24%)	83 (14%)
55–64 years	111 (34%)	166 (28%)
65–74 years	109 (34%)	241 (40%)
⩾75 years	27 (8%)	106 (18%)
Time period		
1990–1995	140 (44%)	317 (54%)
1996–2000	180 (56%)	272 (46%)
Stage		
Ia	9 (3%)	16 (3%)
Ib	21 (8%)	38 (8%)
IIa	7 (3%)	4 (1%)
IIb	31 (11%)	61 (12%)
IIIa	70 (25%)	104 (21%)
IIIb	132 (48%)	256 (51%)
IV	7 (3%)	25 (5%)
Surgery		
Yes	86 (33%)	112 (23%)
No	178 (67%)	374 (77%)
Any first-line chemotherapy[a]		
Yes	117 (37%)	149 (26%)
No	197 (63%)	430 (74%)
Second-line chemotherapy		
Yes	60 (19%)	64 (11%)
No	263 (81%)	532 (89%)
Relapse		
Yes	241 (83%)	344 (74%)
No	48 (17%)	122 (26%)
Cause of death		
Lung cancer	212 (96%)	363 (91%)
Other	9 (4%)	38 (9%)

[a] Induction and/or concomitant chemotherapy.

3.2. *Histology and survival*

The estimated median overall survival of all 919 patients was 14.8 months (95% CI 14.1 to 16.2 months). The 5-year survival rate was estimated to be 9.5%. The survival for patients with adenocarcinoma and squamous cell carcinoma, respectively, is shown in Fig 1. Patients with adenocarcinoma had a significantly better overall survival compared with patients with squamous cell carcinoma ($p = 0.0062$, log-rank test). When comparing different stages, this survival difference was most pronounced for stages IIA–IIB ($p < 0.0001$, log-rank test), For adenocarcinomas in stages IIA–IIB, the median overall survival was 22.9 months and the 5-year overall survival rate was 18.4%. This is in contrast to squamous cell carcinomas where the median overall survival was 11.2 months and 5-year overall survival rate was 3.1%. The survival for the different histological subtypes and stages is shown in Fig. 2. Estimated median survival and 5-year survival rate for different subgroups are presented in Table 2. The univariate Cox-analyses showed that the variables histology, age at diagnosis, surgery, stage and chemotherapy were statistically significantly associated with survival, while this was not the case for gender and period (Table 3). Four different definitions of chemotherapy use were investigated; any chemotherapy (concomitant *and/or* induction), concomitant, induction and second-line chemotherapy. Each definition showed a statistically significant association with survival. In a multivariate Cox-analysis, where the effect of histology was adjusted by gender and age at diagnosis, this significant relationship with survival for histology was retained ($p = 0.037$). In a second multivariate analysis, where the variables surgery, stage and chemotherapy were added as covariates to the first model,

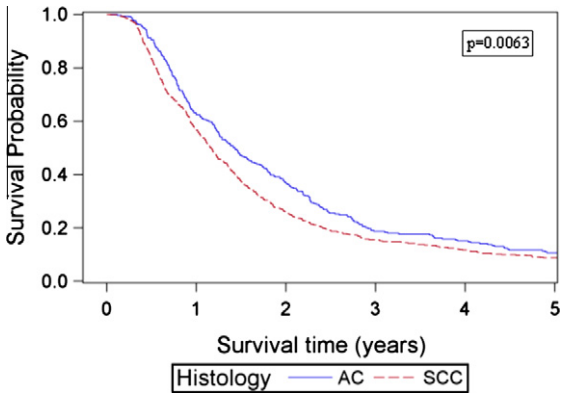

Fig. 1 – Overall survival for patients with adenocarcinoma and squamous cell carcinoma, respectively.

these new variables were all found to be significantly associated with survival. Histology ($p = 0.048$) and age, except for the

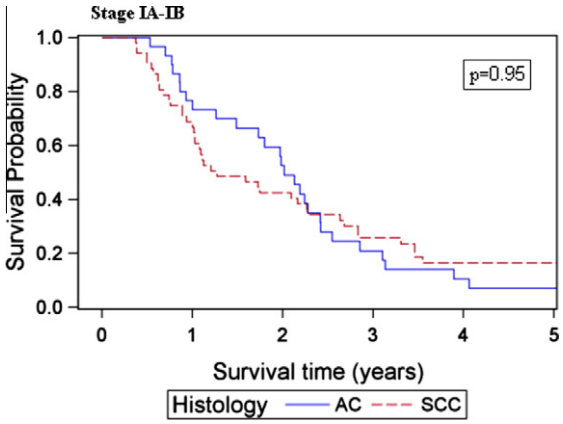

Fig. 2a – Overall survival in stages Ia–Ib for patients with adenocarcinoma and squamous cell carcinoma, respectively.

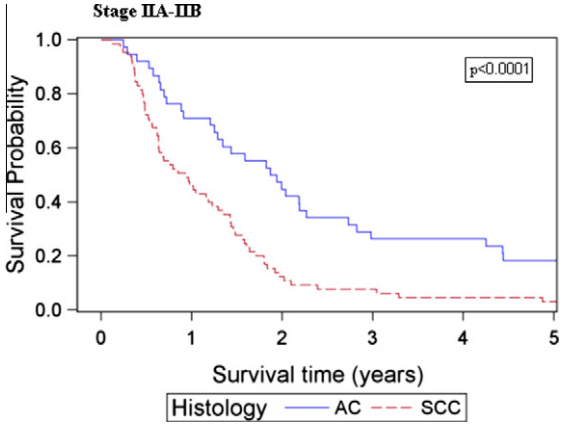

Fig. 2b – Overall survival in stages IIa–IIb for patients with adenocarcinoma and squamous cell carcinoma, respectively.

Fig. 2c – Overall survival in stages IIIa for patients with adenocarcinoma and squamous cell carcinoma, respectively.

oldest age group, were still statistically significantly and independently associated with survival, whereas gender did not show statistically significant results. With data from this study, the increased risk for patients with SCC could be estimated to be around 20% as compared with patients diagnosed with AC.

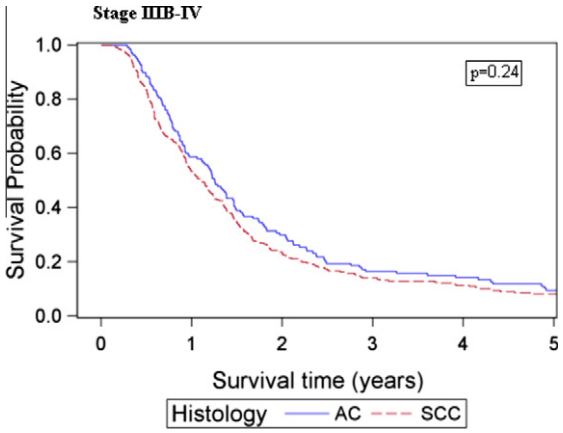

Fig. 2d – Overall survival in stages IIIb–IV for patients with adenocarcinoma and squamous cell carcinoma, respectively.

4. Discussion

During the last decades, patients with non-small cell lung cancer have been given similar treatment, although evidence exists that there is a difference both in terms of survival as well as response towards treatment between the two dominating histological entities, adenocarcinoma and squamous cell carcinoma.[12] In the present study, we show that patients with adenocarcinoma on the whole had a better survival than patients with squamous cell carcinoma after curatively intended irradiation (defined as $\geqslant$50 Gy), especially pronounced in patients with stage IIA–IIB disease. However, there were only 103 patients in stage IIA–IIB in this study, which makes it hard to draw any definitive conclusions about the survival advantage for patients with adenocarcinoma in stages IIA–IIB. The poorer survival in patients with squamous cell histology was statistically significant in both univariate and multivariate Cox analyses. (Table 4)

The present study is unique both in terms of size of the cohort and its population based character, as well as in the review of individual charts with a long follow-up period. All patients diagnosed with non-small cell lung cancer and given curatively intended radiotherapy during 1990–2000 in a well-defined geographical area with a common health care system (Sweden) were included. A reference group composed of five oncologists visited all sites and in collaboration with the medically responsible doctor at the specific site reviewed all charts. A total of 919 patients were included in the present study which makes it one of the largest studies in which individual data have been collected retrospectively in patients receiving curatively intended radiation treatment. The presented data reflect the clinical reality since all identifiable patients who have been localised were included and no obvious selection has been performed. However, there are some limitations with the present study setting. There are well-known

Table 2 – Estimated median survival for different subgroups.

Strata	N	Median survival (95%CI), months	*p*-Value, log-rank test	5-year survival rate,%	Standard error of survival rate
All patients	919	14.8 (14.1–16.2)	–	9.5	0.010
AC	323	17.0 (15.0–19.4)	0.0062	10.7	0.018
SCC	596	14.0 (12.8–14.9)		8.8	0.012
AC – men	171	16.2 (14.2–19.8)	0.029	12.4	0.026
AC – women	152	17.2 (14.7–21.6)		8.6	0.024
SCC – men	450	14.0 (12.5–15.5)		7.7	0.013
SCC – women	146	13.8 (11.5–16.8)		12.3	0.028
AC – Stage Ia + b	30	24.2 (17.9–29.0)	0.95	7.0	0.048
SCC – Stage Ia + b	54	15.3 (12.3–27.2)		16.4	0.055
AC – Stage IIa + b	38	22.9 (15.0–27.2)	<0.0001	18.4	0.063
SCC – Stage IIa + b	65	11.2 (7.6–15.5)		3.1	0.021
AC – Stage IIIa	70	24.0 (15.4–28.5)	0.070	13.2	0.043
SCC – Stage IIIa	104	15.5 (12.6–18.4)		9.5	0.031
AC – Stage IIIb + IV	139	15.0 (12.7–17.6)	0.24	9.5	0.026
SCC – Stage IIIb + IV	281	13.3 (11.4–14.9)		8.2	0.017

Table 3 – Univariate Cox analyses of overall survival.

Variable	Number of patients	Hazard ratio (95% CI)	*p*-Value
Gender	919		
Female (Ref.[a])			
Male		1.11 (0.96 –1.28)	0.17
Age	919		
<55 years (Ref.)			
55–64 years		1.19 (0.97–1.47)	0.10
65–74 years		1.35 (1.11–1.65)	0.0033
⩾75 years		1.32 (1.04–1.67)	0.024
Period	909		
1990–1995 (Ref.)			
1996–2000		1.05 (0.92–1.20)	0.50
Histopathology	919		
AC (Ref.)			
SCC		1.22 (1.06 –1.40)	0.0063
Stage[b]	781	1.10 (1.04–1.16)	0.0008
Surgery	750		
No (Ref.)			
Yes		0.51 (0.43–0.61)	<0.0001
Any first-line chemotherapy[c]	893		
No (Ref.)			
Yes		0.72 (0.62–0.84)	<0.0001
Concomitant chemotherapy	887		
No (Ref.)			
Yes		0.72 (0.59–0.87)	0.0008
Induction chemotherapy	919		
No (Ref.)			
Yes		0.67 (0.57–0.79)	<0.0001

[a] Reference level for the respective variable.
[b] Stages IA, IB, IIA, IIB, IIIA, IIIB and IV were coded 1–7.
[c] Induction and/or concomitant.

Table 4 – Multivariate Cox analysis of overall survival.

Variable	Hazard ratio (95% CI)	*p*-Value
a. Number of observations used = 919		
Histopathology		
AC (Ref.)		
SCC	1.17 (1.01–1.35)	0.037
Gender		
Female (Ref.[a])		
Male	1.03 (0.89–1.20)	0.69
Age		
<55 years (Ref.)		
55–64 years	1.16 (0.94–1.43)	0.17
65–74 years	1.29 (1.06–1.59)	0.013
⩾75 years	1.23 (0.96–1.58)	0.097
b. Number of observations used = 625		
Histopathology		
AC (Ref.[a])		
SCC	1.19 (1.00–1.43)	0.048
Gender		
Female (Ref.)		
Male	0.88 (0.73–1.05)	0.15
Age		
<55 years (Ref.)		
55–64 years	1.32 (1.02–1.70)	0.036
65–74 years	1.41 (1.09–1.82)	0.0088
⩾75 years	1.06 (0.77–1.46)	0.72
Surgery		
No (Ref.)		
Yes	0.55 (0.44–0.67)	<0.0001
Stage[b]	1.09 (1.02–1.16)	0.0081
Any first-line chemotherapy[c]		
No (Ref.)		
Yes	0.75 (0.62–0.91)	0.0040

[a] Reference level for the respective variable.
[b] Stages IA, IB, IIA, IIB, IIIA, IIIB and IV were coded 1–7.
[c] Induction and/or concomitant.

difficulties of accurately subclassifying NSCLC in small diagnostic samples. Some studies showing a diagnostic accuracy for adenocarcinoma of around 59% even in specialists hands[13] and more recently discussed by Stinchcombe et al.[14] Recent studies have suggested that immunohistochemical staining of such small biopsies may improve the accuracy of classification.[15] In addition, not all patients underwent a tissue biopsy for histology but were diagnosed by cytology. In this setting poorly differentiated adenocarcinomas are very difficult to confidently distinguish from non-keratin squamous carcinomas. The specimens that were used at the time for histological classification of the patients in the present study were, regrettably never reviewed for a second opinion and the possibility of wrong subclassification of tumours may have had a confounding effect on the results. Furthermore, the TNM classification was based on the available imaging techniques during different time intervals. Thus, there may be a stage migration with time and more sensitive staging techniques. Another important aspect of the TNM staging is that there were some patients who were wrongly staged at diagnosis and therefore received curatively intended radiotherapy despite having an advanced clinical stage (stage IV or wet IIIb according to the TNM 6 system) at diagnosis, which was not discovered until the treatment had already begun. These patients were retrospectively included in the study anyway as the study aimed to include all patients who received curatively intended radiotherapy, regardless of TNM stage. Moreover, the majority of patients were not autopsied, especially so among the elderly patient population and thus the cause of death might not be thoroughly investigated.

However, the described biological differences between adenocarcinoma and squamous cell carcinoma have shown some inconsistency in the studies published so far. In patients with stage I disease, not receiving any postoperative chemotherapy, the histological subtype has in some trials been described not to be a predictor of risk for recurrence.[16,17] On the contrary, Rena et al. reported a better 5-year survival rate for adenocarcinoma than for squamous cell carcinoma in 436 patients with stage I NSCLC.[18] Concerning curatively intended radiation therapy without chemotherapy in stage I disease, Ishikawa et al. reported that the 5-year primary control rate of squamous cell carcinoma was significantly better than that of adenocarcinoma (SCC = 88.2% versus AD = 53.0%).[19] These data are not in conjunction with the present study in which patients with stage I disease with squamous cell carcinoma seemed to have a poorer overall survival after five years follow-up in comparison with adenocarcinoma.

When reviewing the literature concerning the more advanced stages, the role of histology seems to be a little more complex. In a retrospective study, 134 patients with non-small cell carcinoma of the lung underwent radiation therapy with curative intent.[20] The median survival for patients with squamous cell carcinoma was 11.5 months, the 2- and 4-year survival rates were 21% and 7%, respectively, whereas the median survival for adenocarcinoma was 18 months, 2- and 4-year survival rates were 38 and 23%, respectively; thus a large numerical advantage in favour of the adenocarcinoma group. However, the overall survival experience did not show a significant difference between the two cell types ($p = 0.12$). In a larger study by the same group, data were analysed from 1415 patients treated with curatively intended irradiation alone (part of four Radiation Therapy Oncology Group (RTOG) studies), as well as from 350 patients included in five RTOG studies in which chemotherapy was added to radiation treatment.[21] The authors showed that death with no evidence of progression was significantly more likely to occur in squamous cell carcinoma (35%) than either adenocarcinoma (22%) or large cell carcinoma (24%) ($p < 0.0001$ and $p = 0.0035$, respectively). A couple of small randomised studies displayed even more complex data and no conclusive results could be read out (see Table 5).

5. Conclusion

The role of curatively intended radiation therapy is broadly accepted as the primary treatment for inoperable 'non-small' cell carcinoma of the lung. Several studies have shown significant differences between squamous cell carcinoma and adenocarcinoma in terms of biological behaviour, where patients with adenocarcinoma of the lung seem to have a better response towards certain biological and chemotherapeutical agents.[12,17] Despite these facts, the role of histology has not

Table 5 – Summary of studies of chemoradiation in locally advanced NSCLC.

References	No. of patients	Induction therapy	Concurrent therapy	Consolidation therapy	Median survival time (months)
Kim et al.	29 (AC)	NA	60 Gy + Pac	NA	16.2 (AC)
	52 (SCC)		66 Gy + Carbo + pac	Carbo + pac	19.8 (SCC)
			69.6 Gy + Carbo/pac	Carbo + pac	
Cyjon et al.	17 (AC)	Cis + etopo	45 Gy + Cis	NA	19 (AC)
	27 (SCC)				16 (SCC)
Movsas et al.	63 (AC)	Cis + vin	60 Gy	NA	15.6 (AC)
	63 (SCC)				12.8 (SCC)
	34 (AC)	Cis + vin	60 Gy + vin + etopo		13.4 (AC)
	46 (SCC)				25.7 (SCC)
	75 (AC)	NA	69.6 Gy + vin + etopo		19.7 (AC)
	83 (SCC)				12.7 (SCC)
Segawa et al.	20 (AC)	NA	62.5–70 Gy + Cis + 5-FU	NA	18.6 (AC)
	22 (SCC)				18.7 (SCC)

been implemented in the design of radiation therapy studies/protocols. In this large retrospective study, we describe that patients with adenocarcinoma seem to have a better overall survival after curatively intended radiation therapy in comparison with squamous cell carcinoma patients, particularly in clinical stages IIA–IIB. These data are of importance to consider for future clinical trials involving radiation treatment of patients with non-small cell lung cancer.

Conflict of interest statement

None declared.

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