ORIGINAL ARTICLE

Exploration of optimal time for initiating adjuvant chemotherapy after surgical resection: A retrospective study in Chinese patients with stage IIIA non-small cell lung cancer in a single center

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Abstract

Background: Adjuvant chemotherapy (ACT) can reduce the risk of recurrence and improve survival after surgical resection in non-small cell lung cancer (NSCLC) patients. We explore the optimal time from surgery to initiation of ACT in Chinese patients with stage IIIA NSCLC.

Methods: Patients pathologically diagnosed with IIIA NSCLC who underwent radical surgery were included in this study. The cut-off point of time to initiation of adjuvant chemotherapy (TTAC) was determined by maximally selected log-rank statistics. Patients were divided into two groups according to the TTAC cut-off point. Propensity score matching (PSM) was used to eliminate confounding variables, and Kaplan–Meier analysis was used to analyze the impact of TTAC on disease-free survival (DFS).

Results: The cut-off time was 46 days from surgery to the first ACT. Prior to PSM, baseline characteristic variables were balanced with no statistical difference between the groups, except for pathologic subtype and smoking history. No difference in DFS was found between the two groups prior to PSM ($P = 0.529$); after PSM, the median DFS was consistent between the two ($P = 0.822$). N2 lymph node station involvement was an independent factor associated with poor survival compared with patients with N0 lymph node involvement. Moderate differentiation and postoperative radiotherapy could improve survival; however, TTAC was not significantly correlated with DFS. Subgroup analyses showed no significant correlation between DFS and different TTAC programs.

Conclusion: No survival difference was obtained as to when ACT was initiated for patients with stage IIIA NSCLC.

Introduction

Lung cancer is the most common cause of cancer-related death worldwide. Some studies have reported that patients with stage II-IIIA non-small cell lung cancer (NSCLC) could benefit from cisplatin-based adjuvant chemotherapy (ACT) after surgical resection.[1,2] A population-based study reported that the two-year survival rate in patients who received ACT was significantly higher than those who were treated with surgery alone (82.0% vs. 64.4% for stage II NSCLC; 76.4% vs. 57.5% stage IIIA NSCLC).[2] In these trials, ACT was usually initiated within approximately four to eight weeks after surgery.[3–5] However, few studies have reported the optimal time for initiating ACT after surgery.

Several clinical studies on breast and colorectal cancer have demonstrated an association between the interval from surgical resection to the initiation of ACT and long term survival.[6–9] One meta-analysis involving colorectal cancer reported that initiation of ACT more than eight weeks after surgery was associated with a poorer overall survival (OS) (hazard ratio [HR] 1.20; 95% confidence interval [CI] 1.15–1.26).[7] A large population-based breast cancer registry demonstrated that a delay of ACT of more than three months was associated with increased disease-specific (HR 1.69; 95% CI

1.31–2.19) and overall mortality (HR = 1.46; 95% CI 1.21–1.75).[9] There is currently no defined optimal interval specific to NSCLC patients to receive ACT. The objective of the present study is to explore the optimal interval from surgical resection to ACT in patients with stage IIIA NSCLC.

Patients and methods

Patients

The study was approved by the Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences (Beijing, China). Details of all patients who received surgical resection and postoperative ACT at the Cancer Hospital between January 2003 and December 2013 were collected from the hospital database. Finally, 454 Chinese patients who were pathologically confirmed as having stage IIIA NSCLC and received ACT after surgical resection met the inclusion criteria. All patients received ACT after radical surgery for, at most, four cycles. Disease recurrence was assessed by computed tomography (CT) scan, magnetic resonance imaging (MRI), bone scanning, and tumor markers. All staging procedures were carried out using the 7th Union for International Cancer Control tumor node metastasis (TNM) classification. The date from surgery to ACT, gender, age, smoking status, pathologic subtype, degree of differentiation, lymphovascular invasion, performance status, adjuvant radiotherapy, and comorbidities were collected. Lymph node invasion was defined according American Thoracic Society criteria.[10] Performance status was defined according to the Eastern Cooperative Oncology Group (ECOG) performance scale.[11] Comorbidities were recorded when patients had preoperatively diagnosed cardiovascular, cerebrovascular or pulmonary diseases, or diabetes mellitus.[12]

The time to initiation of adjuvant chemotherapy (TTAC) was defined as the duration of time from a curative operation to the initiation of ACT. Disease-free survival (DFS) was defined as the duration from surgery to recurrence (local, regional, and/or distant) or death from any cause.[12] By the end of October 2015, data obtained from multiple sources including clinical letters, follow-up scans, hospital computer information systems, and telephone calls were entered into our database for analysis.

Statistical analysis

Continuous and categorical variables from 10% of random samples of the 454 included patients were used as a training set to find the TTAC cut-off point. The optimal TTAC cut-off point (measured in days) was calculated using maximally selected log-rank statistics (validated by maxstat package from R, http://mirrors.opencas.cn/cran/src/contrib/maxstat_0.7-23.tar.gz). The remaining 90% of patients were divided into two groups according to cut-off time. Baseline

characteristics were described as frequencies and percentages for categorical variables, and means and standard deviations for continuous variables. Differences in baseline characteristics between the two groups were analyzed using the Chi square test. Kaplan–Meier curves and log-rank tests were used to compare DFS between the two groups. The Cox proportional hazards regression model was used to identify risk factors independently associated with DFS. Gender, age, lymph node invasion, clinical stage, performance status, adjuvant radiotherapy, Charlson comorbidity score, and World Health Organization performance score were considered as covariates in multivariate analysis.

To reduce the impact of the potential confounding factors in our retrospective study, we performed rigorous adjustment for baseline differences by propensity score matching (PSM).[13] Matched-pairs analysis was performed according to the propensity score in the remaining 90% of patients using an appropriate ratio, and a caliper width of 0.20. After PSM, baseline covariates were balanced and comparable between the two groups. Subgroup analyses were conducted with a forest plot to determine whether TTAC provided survival benefits in terms of gender, age, smoking status, pathologic subtype, differentiation, lymph node invasion, clinical stage, performance status, adjuvant radiotherapy, and Charlson comorbidity score.

Predictors were considered statistically significant at $P < 0.05$, and all statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA) and R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

General characteristics

Data of 45 (10%) patients was selected by random sampling to perform preprocessing calculation of the cut-off point with maximally selected log-rank statistics. The optimal time from surgery to the first AC was 46 days (Fig 1). With the sample of 45 patients deducted, the matching process resulted in a cohort of 409 patients who finally constituted the population of the study: 81.9% patients underwent postoperative ACT within 46 days (median TTAC 34 days [range: 25–45]) and 18.1% patients underwent postoperative ACT in more than 46 days (median TTAC 53.5 days [range: 46–228]). Patient characteristics are summarized in Table 1. The median follow-up period was 429 days (range: 53–2789). Patients who received postoperative ACT for longer than 46 days had higher rates of smoking history ($P = 0.035$) and squamous subtype ($P = 0.004$). When propensity matching was used, 270 patients were included and were well matched by a 4:1 ratio, without showing significant differences in baseline characteristics.
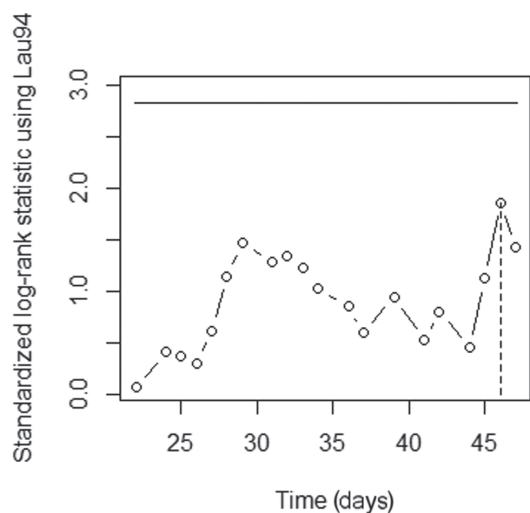
Figure 1 Calculation of the cut-off point with maximally selected log-rank statistics.

Risk factors for disease-free survival (DFS)

The results of the Cox model are shown in Table 2. Univariate analysis showed that compared with squamous cell carcinoma, adenocarcinoma and other subtypes of histology were risk factors affecting patient survival (HR 1.331, 95% CI 1.010–1.752, $P = 0.041$; HR 2.293, 95% CI 1.141–4.605, $P = 0.019$). Compared with N0 lymph node involvement, N2 lymph node involvement was associated with a poorer survival rate (HR 2.425, 95% CI 1.141–5.154, $P = 0.02$), while patients with moderate differentiation had improved survival compared with those with poor differentiation (HR 0.700, 95% CI 0.522–0.938, $P = 0.016$). Multivariate analysis showed that the moderate differentiation subtype was associated with better survival compared with the poor differentiation subtype (HR 0.662, 95% CI 0.490–0.894, $P = 0.007$). Patients who underwent postoperative radiotherapy (PORT) had longer DFS (HR 0.621, 95% CI 0.469–0.821, $P = 0.001$) than those who were not treated with PORT. In contrast, patients

Table 1 Patient characteristics

Characteristics	Unadjusted			Adjusted		
	Group 0 < 46 days (*n* = 335)	Group 1 ≥ 46 days (*n* = 74)	*P* value	Group 0 < 46 days (*n* = 216)	Group 1 ≥ 46 days (*n* = 54)	Adjusted *P* value
Age (mean ± SD)	55.72 ± 8.81	57.51 ± 8.77	0.115	55.69 ± 9.13	57.63 ± 8.86	0.163
Gender, (*n*, %) female	143 (42.69)	23 (31.08)	0.069	77 (35.65)	19 (35.19)	0.949
Smoking history, (*n*, %) Yes	163 (48.66)	46 (62.16)	0.035	119 (55.09)	31 (57.41)	0.721
Pathology, *n* (%)						
Squamous cell carcinoma	76 (22.69)	31 (41.89)	0.004	72 (33.33)	18 (33.33)	1.000
Adenocarcinoma	245 (73.13)	39 (52.70)		136 (62.96)	35 (62.96)	
Adenosquamous	6 (1.79)	2 (2.70)				
Others	8 (2.39)	2 (2.70)		8 (3.70)	2 (3.70)	
Differentiation, (*n*, %)						
Poor	84 (25.07)	20 (27.03)	0.967	58 (26.85)	15 (27.78)	0.955
Moderate to poor	100 (29.85)	25 (33.78)		61 (28.24)	16 (29.53)	
Moderate	124 (37.01)	24 (32.43)		80 (37.04)	18 (33.33)	
Well to moderate	13 (3.88)	2 (2.70)		9 (4.17)	2 (3.70)	
Well	5 (1.49)	1 (1.35)		2 (0.93)	1 (1.85)	
Unknown	9 (2.69)	2 (2.70)		6 (2.78)	2 (3.70)	
Lymphatic invasion (*n*, %)						
N0	11 (3.28)	3 (4.05)	0.072	8 (3.70)	3 (5.56)	0.329
N1	26 (7.76)	12 (16.22)		21 (9.72)	7 (12.96)	
N2	298 (88.96)	59 (79.73)		187 (86.57)	44 (81.48)	
Performance status (ECOG) (*n*, %)						
0	50 (14.93)	15 (20.27)	0.172	33 (15.28)	8 (14.81)	0.746
1	284 (84.78)	58 (78.38)		182 (84.26)	45 (83.33)	
2	1 (0.30)	1 (1.35)		1 (0.46)	1 (1.85)	
Radiotherapy, (*n*, %) Yes	85 (25.37)	21 (28.38)	0.593	52 (24.07)	15 (27.78)	0.583
Charlson comorbidity index (*n*, %)						
0	239 (71.34)	51 (68.92)	0.869	157 (72.69)	39 (72.22)	0.791
1	70 (20.90)	18 (24.32)		39 (18.06)	11 (20.37)	
2	22 (6.57)	4 (5.41)		17 (7.87)	4 (7.41)	
3	4 (1.19)	1 (1.35)		3 (1.39)	0 (0.00)	

ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

Table 2 Risk factors for DFS in stage IIIA NSCLC patients

Characteristics	Univariate analysis				Multivariate analysis			
	P value	HR	HR 95% CI		P value	HR	HR 95% CI	
Group 1 (vs. 0)	0.529	0.907	0.669	1.229				
Age	0.136	0.990	0.977	1.003				
Smoking history Yes (vs. no)	0.536	0.931	0.741	1.169				
Pathology								
Adenocarcinoma (vs. squamous cell carcinoma)	0.041	1.331	1.010	1.752	0.113	1.285	0.942	1.753
Adenosquamous (vs. squamous cell carcinoma)	0.103	1.912	0.877	4.167				
Others (vs. squamous cell carcinoma)	0.019	2.293	1.141	4.605	0.051	2.213	0.994	4.930
Differentiation								
Moderate to poor (vs. poor)	0.176	0.816	0.607	1.096				
Moderate (vs. poor)	0.016	0.700	0.522	0.938	0.007	0.662	0.490	0.894
Well to moderate (vs. poor)	0.263	0.708	0.387	1.297				
Well (vs. poor)	0.380	0.638	0.234	1.742				
Unknown (vs. poor)	0.939	1.028	0.497	2.126				
Lymph node invasion								
N1 (vs. N0)	0.181	1.773	0.766	4.104				
N2 (vs. N0)	0.021	2.425	1.141	5.154	0.021	2.490	1.145	5.416
Performance status (ECOG)								
1 (vs. 0)	0.919	1.017	0.730	1.417				
2 (vs. 0)	0.311	2.081	0.503	8.605				
Radiotherapy Yes (vs. No)	0.083	0.748	0.539	1.040	0.001	0.621	0.469	0.821
Charlson comorbidity index								
1 (vs. 0)	0.692	0.945	0.712	1.253				
2 (vs. 0)	0.190	0.712	0.428	1.183				
3 (vs. 0)	0.164	0.373	0.093	1.500				

CI, confidence interval; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NSCLC, non-small cell lung cancer.

with N2 lymph node involvement had poorer survival rates than those with N0 lymph node involvement (HR 2.490, 95% CI 1.145–5.416, $P = 0.021$). Both univariate and multivariate analyses showed that TTAC was not significantly associated with DFS.

DFS in different times to initiation of adjuvant chemotherapy

The median DFS in patients receiving TTAC within 46 days and those receiving TTAC longer than 46 days was 467 (95% CI 420–552) and 474 days (95% CI 400–623), respectively, showing no statistically significant difference ($P = 0.775$), as indicated by Kaplan–Meier analysis prior to PSM. After PSM, the 216 patients in the 46 day group and the 54 patients in the longer time group were well matched. The median DFS was 438 (95% CI 379–494) and 457 days (95% CI 369–566), respectively, and Kaplan–Meier results were consistent with the prior outcome ($P = 0.822$). There was no significant interaction between TTAC and DFS (Fig 2).

Subgroup analysis

We conducted an exploratory analysis to determine whether TTAC provided survival benefits to stage IIIA NSCLC

patients in terms of gender, age, smoking status, pathology subtype, differentiation, lymph node invasion, clinical stage, performance status, adjuvant radiotherapy, and Charlson comorbidity score subset. Unfortunately, there was no significant difference in any subgroup of patients (Fig 3).

Discussion

The five-year survival rate of IIIA NSCLC patients was 23%, despite radical surgery, which was quite disappointing.[14,15] It has been reported that postoperative ACT could reduce the risk of recurrence and prolong OS. Compared with stage II NSCLC patients, multidisciplinary management is the optimal strategy for stage IIIA NSCLC patients to reduce local recurrence and distant metastasis.[2,16,17] It is important, for both patients and medical oncologists, to determine how to integrate these therapies to obtain the longest possible survival. Some studies concerning TTAC in breast cancer and colorectal malignancy have demonstrated that TTAC could affect DFS.[6–9] We initially presumed that ACT should be initiated within eight weeks after surgery in NSCLC patients, but some analyses have shown that this was not the case. There are two similar studies of TTAC in patients with NSCLC. One evaluated the impact of time to treatment in patients with stage II NSCLC by comparing the risk of recurrence between
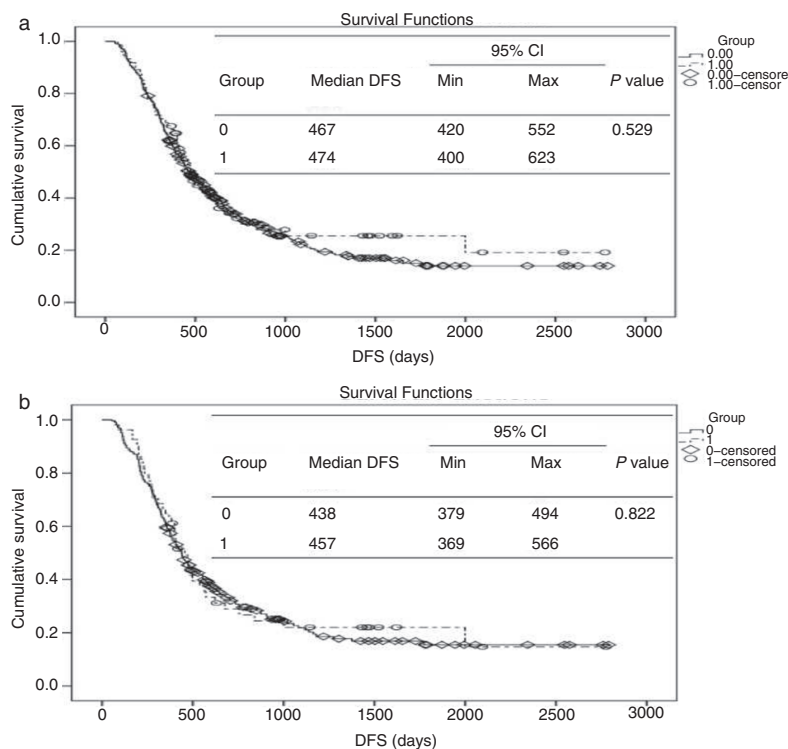
Figure 2 Survival curves: disease-free survival (DFS) of patients with stage IIIA non-small cell lung cancer who received adjuvant chemotherapy between 2003 and 2013. (**a**) Before propensity score matching (PSM); (**b**) after PSM. CI, confidence interval.

groups initiating ACT within 6 weeks, 6–8 weeks, 8–10 weeks, and after 10 weeks, and found that the duration of time did not seem to be associated with survival.[18] Christopher *et al.* conducted a retrospective population-based study and reported that there was no statistically significant difference in stage I-IV NSCLC patients who received ACT within 10 weeks and those who received ACT for longer intervals.[19]

Why delayed TTAC is associated with poorer survival in colorectal and breast cancer patients, but not in NSCLC patients, must still be determined. Is there a defined optimal interval specific for NSCLC patients to receive ACT? Is TTAC for stage IIIA NSCLC consistent with the previous results of all stages of NSCLC, particularly stage II NSCLC? We attempted to determine an optimal TTAC that could deliver better survival rates. Unfortunately, although we succeeded in averting confounding by PSM, the outcome was coincident with the previous conclusion about stage II and I-IV NSCLC, in that TTAC was not associated with survival. Whether there is an optimal TTAC to predict a significant survival benefit in patients with NSCLC remains undetermined.

Compared with previous reports, our study has some distinct features. First, we used DFS as the primary endpoint instead of OS. As the incidence of epidermal growth factor receptor (EGFR) active mutations and anaplastic lymphoma kinase rearrangement is high in Chinese populations,

OS might be affected by targeted therapy in further treatment.[20–22] EGFR-tyrosine kinase inhibitors (EGFR-TKIs) showed high antitumor activity and provided symptom relief in patients with advanced NSCLC previously treated with first or second line chemotherapy.[23,24] Second, in previous studies on breast and colorectal cancers, the TTAC cut-off point was presumed according to the clinical practice of the researchers concerned with identifying the relationship between TTAC and survival.[8,9,18,19] In our study, maximally selected rank statistics were used logically to estimate the optimal TTAC cut-off point, which provide stronger evidence to predict better survival. Finally, our study might be the first study to explore the optimal time from surgery to initiation of AC in Chinese NSCLC patients, by focusing on stage IIIA NSCLC.

Both univariate and multivariate analyses in our study demonstrated that patients with N2 lymph node involvement had inferior survival compared with N0 lymph node involvement, and the moderate subtype of differentiation was associated with better survival compared with poor differentiation. Survival in patients who received PORT was improved compared with patients who did not receive adjuvant radiotherapy, similar to results obtained from a previous meta-analysis, which showed that survival was prolonged in patients with IIIA disease who received PORT.[25] Although controversy remains over whether elderly NSCLC patients

Subgroup	Patients (%)	Hazard Ratio	HR	95% CI	P value
Overall	270(100)				
Gender					
Male	174(64)		1.009	(0.650,1.566)	0.968
Female	96(36)		0.897	(0.475,1.693)	0.737
Smoke					
No	120(44)		0.81	(0.452,1.449)	0.477
Yes	150(56)		1.031	(0.644,1.651)	0.899
Pathology					
Squamous and Other cell carcinoma	100(37)		1.423	(0.778,2.603)	0.252
Adenocarcinoma	170(63)		0.409	(0.409,1.048)	0.078
Differentiation					
Poor	73(27)		0.855	(0.435,1.682)	0.649
Moderate to poor	77(29)		0.677	(0.324,1.415)	0.299
Greater	120(36)		0.9	(0.900,2.919)	0.592
PS					
0	41(15)		0.409	(0.086,1.944)	0.261
1 and 2	229(85)		1.055	(0.721,1.544)	0.076
Lymph_node					
N0 and N1	39(14)		2.802	(0.928,8.459)	0.067
N2	231(86)		0.818	(0.554,1.207)	0.31
Radiotherapy					
No	203(75)		1.008	(0.676,1.504)	0.967
Yes	67(25)		0.737	(0.334,1.625)	0.449
Charlson					
0	196(73)		0.894	(0.592,1.350)	0.599
1, 2 and 3	50(18)		1.215	(0.595,2.480)	0.593

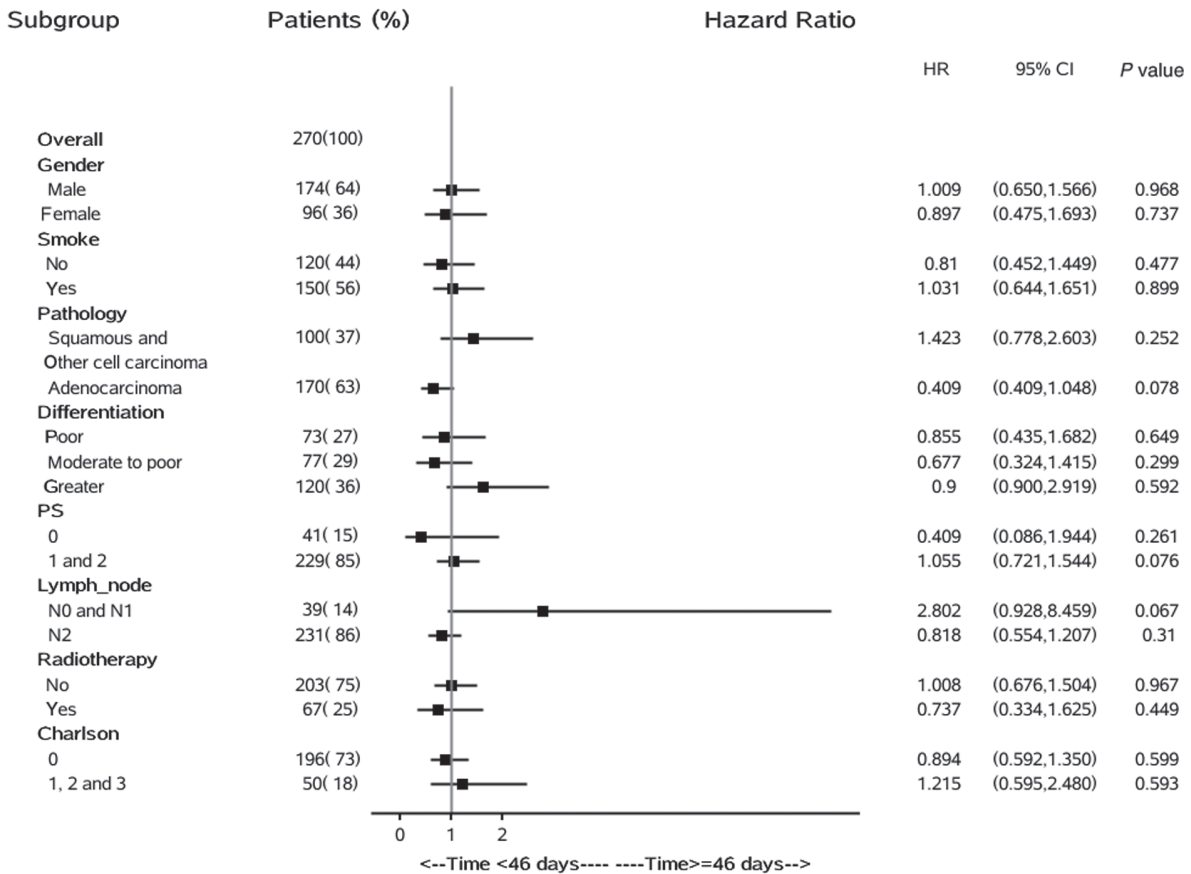<--Time <46 days---- ----Time>=46 days-->

Figure 3 Forest plot of the different subgroups influencing disease-free survival (DFS) between the two groups. A hazard ratio (HR) > 1 corresponds to poorer DFS; HR < 1 corresponds to a better DFS. CI, confidence interval.

should be excluded from ACT based on age, we did not determine any differences between age groups in terms of DFS benefit.

Contrary to the finding that delayed delivery of ACT had a negative effect on survival in breast and colorectal cancer patients, our study found no significant correlation between TTAC and survival in NSCLC patients.[6–9] Although we did not address the issue of whether the optimal time of postoperative ACT was associated with better survival, some findings were noteworthy in our observation. More than 80% of our patients selected to receive ACT within 46 days, and the result of our analysis did not show any reduction in the risk of recurrence in this group of patients. Therefore, we could conclude that it is unnecessary to restrict ACT within a certain limited time for patients with stage IIIA NSCLC, and it is possible to wait until the general condition of the patient is good enough to tolerate chemotherapy, although delayed TTAC may prolong their postoperative hospital stay and increase hospitalization cost. For NSCLC patients with co-existing diseases and poor general condition, delayed TTAC could not only provide them with the same survival benefit but reduce non cancer-related death resulting from ACT.

Compared with other studies on other solid tumors, we failed to identify a significant correlation between ACT and survival in patients with stage IIIA NSCLC. The simplest reason is that there is indeed no correlation between TTAC and survival in NSCLC. Another reason may be that the increased risk of death from competing causes is offset by the survival benefit of early initiation of ACT.[19] The relatively the small sample size of our study in a single cancer center might result in a selection bias. Multicenter studies with larger sample sizes are required to verify the conclusion drawn from this study. Although we performed multivariate analysis and PSM to reduce the selection bias as much as possible, the retrospective nature of the present study and other factors, such as the chemotherapy regimen and the dose of agents, gene mutation, and chemotherapy-related toxicities, may confound the result. Finally, most Chinese patients are prone to start ACT as soon as possible after surgery, partly because of a lack of knowledge about ACT.

Conclusion

With covariates eliminated in the two groups with PSM, TTAC did not seem to be associated with survival in NSCLC patients. The optimal time of postoperative ACT must still be determined. Further research is needed to explore the interaction between TTAC and survival in larger samples.

Acknowledgments

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Disclosure

No authors report any conflict of interest.

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