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Early tumor shrinkage served as a prognostic factor for patients with stage III non-small cell lung cancer treated with concurrent chemoradiotherapy

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Abstract

Background: Lung cancer is the most common cause of cancer death. About 80% of patients are diagnosed at stage III in the non-small cell lung cancer (NSCLC). It is extremely important to understand the progression of this disease which has low survival times despite the advancing treatment modalities. We aimed to investigate the relationship between early tumor shrinkage (ETS) after initial concurrent chemoradiotherapy (C-CRT) and survival outcome in patients with stage III (NSCLC).

Methods: A retrospective review of 103 patients with stage III NSCLC who had received C-CRT from January 2006 to October 2011 was performed. Patients were treated with systemic chemotherapy regimen of Cisplatin/Vp-16 and concurrent thoracic radiotherapy at a median dose of 66 Gy (range 60–70 Gy). All patients received a computed tomography (CT) examination before treatment. Also subsequently, chest CT scans were performed with the same imaging parameters at approximately 5 weeks after the initiation of treatment. ETS is here stratified by a decrease in tumor size ≥30% and <30% in the longest dimension of the target lesion within 5 weeks.

Results: Of the 103 patients, 59 ones showed a 30% decrease in tumor size, and the rest displayed a decrease of <30%. ETS showed no significant correlation with age, T classification, N classification, histological classification, smoking status, G classification, EGFR status, or acute pulmonary toxicity. In the current retrospective clinical study, Kaplan–Meier curves showed that patients with ETS ≥ 30% had a better progression-free survival and overall survival. The univariate and multivariate Cox regression analyses indicated that ETS < 30% was associated with a significantly increased risk of cancer-related death ($P < .05$) in stage IIINSCLC.

Conclusions: ETS may be served as a useful prognostic factor to predict the outcome of stage III NSCLC patients treated with CCRT.

Abbreviations: 3D-CRT = three-dimensional conformal radiotherapy, C-CRT = concurrent chemoradiotherapy, CT = computed tomography, ETS = early tumor shrinkage, GTV = gross tumor volume, IMRT = intensity-modulated radiotherapy, NSCLC = non-small cell lung cancer, OS = overall survival, PFS = progression-free survival, RR = relative risks.

Keywords: concurrent chemoradiotherapy, early tumor shrinkage, non-small cell lung cancer

1. Introduction

Lung cancer is one of the most common malignant tumors with the highest incidence and mortality rates worldwide,[1] whereby non-small cell lung cancer (NSCLC) accounts for 75% to 80%. Commonly, approximately one-third of the patients with NSCLC are usually clinical diagnosed only after their condition is locally advanced.[2] Surgical and radiotherapy are the main effective treatments for the operable locally advanced NSCLC, resulting in the similar median survival and 5-year survival.[3] However, the outcome of concurrent chemoradiotherapy (C-CRT) for inoperable locally advanced NSCLC is better than that of sequential chemotherapy and radiotherapy.[4] Generally, three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) always applied in radiotherapy was paralleled with etoposidec cisplatin or paclitaxel carboplatin usually applied in chemotherapy.[5] The latest evidence sets a clear mandate for C-CRT as the current standard of care for inoperable stage III NSCLC patients with good performance status and minimal co-morbidities.[6,7] Significantly, the prognosis could be different for locally advanced NSCLC treated with the same therapy. Currently, TNM stage, clinical stage, as well as epidermal growth factor receptor (EGFR) are all considered as important factors. In addition, many other factors, such as tumor tissue type, age, smoking status, radiation dose and treatment mode, also have an influence on the outcome of prognosis. A handful of clinical settings demonstrate that some patients have relatively good survivals if there was tumor shrinkage within the

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first few weeks after the initial C-CRT, which was recognized as early tumor shrinkage (ETS) in the present paper. Here, we hypothesized that the ETS was associated with improved overall survival (OS) for locally advanced NSCLC. In this study, we firstly analyzed the correlation between ETS and clinical characteristics in stage III NSCLC, and the relationship between the survival outcomes and ETS. Subsequently, we analyzed the potential prognostic factors in stage III NSCLC, and identified if ETS could be an independent factor for poor prognosis.

2. Materials and methods

2.1. Patients

From January 2006 to October 2011, 103 inpatients diagnosed pathologically or cytologically with stage III NSCLC were recruited. Therein, 56 (54%) of the patients were males. The median age of the patients at diagnosis was 60 years (range, 36–75 years). The Kanofsky score was >70. According to UICC TNM staging criteria issued in 2002, 66 patients were stage III A and 37 were stage III B, 23 for squamous cell carcinoma, 73 for adenocarcinoma, and 7 for other histology classification. None of the patients had previously been treated with radiotherapy or chemotherapy. All patients provided written informed consent.

2.2. Treatment and assessments of ETS

Concurrent EP regimen[8] consisted of cisplatin 20 mg/m^2 and Vp-16 50 mg/m^2 on days 1 to 5 and 29 to 33, respectively. All of the patients underwent 3D-CRT or IMRT. The prescribed dose was 60 to 70 Gy in 2.0 to 2.2 Gy daily fractions. Five fractions a week were usually applied. All patients received a computed tomography (CT) examination before treatment, and subsequently, chest CT scans were performed with the same imaging parameters at approximately 5 weeks after the initiation of treatment. Two independent reviewers measured the longest diameter of the tumor at baseline imaging and subsequent scans. ETS is stratified by a decrease in tumor size ≥30% and <30% in the longest dimension of the target lesion within 5 weeks.

2.3. Clinical characteristics

Clinical characteristics including age, TNM classifications, histology classification, smoking status, G classification, EGFR status, and acute pulmonary toxicity were evaluated. According to every local policy, each case was followed-up to evaluate tumor response using a CT scan 3 months after completing radiotherapy. This was followed by chest radiographs once every 3 months and an annual CT scan.

2.4. Statistical analyses

All statistical analyses were performed using the SPSS 20.0 statistical software package. The χ^2 test was performed to assess a correlation between early decreases in tumor size and clinicopathological characteristics. Progression-free survival (PFS) was calculated as the time that elapsed between the date of treatment and the date of relapse or progressive disease. OS was analyzed from the day of diagnosis until death or the last follow-up. Survival curves were plotted using Kaplan–Meier survival analysis and compared by log-rank test. Relative risks (RR) of death associated with ETS and other variables were estimated using unvaried and multivariate Cox proportional hazards model. In the current analyses, a RR of 1.000 was set as a baseline for factors including age (≤60 years), T_1+T_2, N_0+N_1, lack of smoking, EGFR no mutation and ETS < 30%[9] Multivariate survival analysis was performed on all the significant characteristics measured by univariate survival analysis through the Cox proportional hazard regression model. In all statistical analyses, $P < .05$ was considered significant.

Table 1

Correlation between ETS and clinical characteristics in stage III NSCLC.

Patient characteristics	Earlier decrease in tumor size		
	ETS ≥30%	ETS < 30%	*P* value
Age, years			
≤60	28	21	.978
>60	31	23	
T classification			
T_1+T_2	16	7	.177
T_3+T_4	43	37	
N classification			
N_0+N_1	25	20	.755
N_2+N_3	34	24	
Histology classification			
Squamous carcinoma	13	10	.735
Adenocarcinoma	41	32	
Others	5	2	
Smoking			
No	31	28	.260
Yes	28	16	
G classification			
G1	20	9	.285
G2	19	15	
G3	20	20	
EGFR status			
No mutation	29	22	.932
Mutation	30	22	
Acute pulmonary toxicity			
G1–2	36	32	.215
G3–4	23	12	

EGFR = epidermal growth factor receptor, ETS = early tumor shrinkage, NSCLC = non-small cell lung cancer.

3. Results

3.1. Correlation between ETS and clinical characteristics in stage III NSCLC

Of the 103 patients, 59 showed equal or more than 30% decrease in tumor size and the rest displayed < 30% decrease. The possible correlations between ETS and clinical characteristics in stage III NSCLC were examined. Analyses of 103 stage III NSCLC cases indicated that ETS showed no significant correlation with age, T classification, N classification, histological classification, smoking status, G classification, EGFR status, or acute pulmonary toxicity, respectively (Table 1).

3.2. The relationship between the survival outcomes and ETS

To further confirm the relationship between survival outcomes and ETS, we evaluated the PFS and OS times when ETS ≥ 30% and ETS < 30%. As depicted in Fig. 1A and B, Kaplan–Meier curves showed that patients with ETS ≥ 30% had longer PFS (median, 13 months) and OS (median, 24 months), whereas patients with ETS < 30% showed much shorter periods of PFS (median, 11 months) and OS (median, 18 months). The

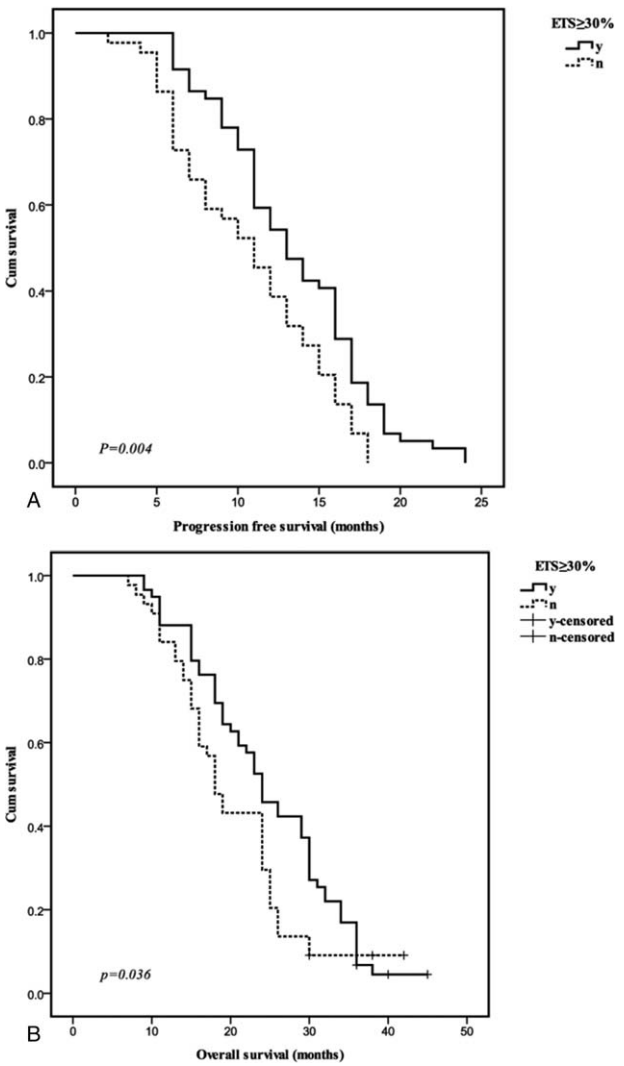

Figure 1. The PFS and OS times were evaluated using Kaplan–Meier curves stratified by ETS ≥ 30% and ETS < 30%. (A) Patients with ETS ≥ 30% have better PFS than those with ETS < 30% ($P < .01$). (B) Patients with ETS ≥ 30% showed better OS when compared with those with ETS < 30% ($P < .05$). ETS = early tumor shrinkage, OS = overall survival, PFS = progression-free survival.

cumulative 2-year survival rate was 45% (26 of 59) for patients with ETS ≥ 30%, whereas the survival rate dramatically dropped to 28% (12 of 44) for patients with ETS < 30% (Fig. 1).

3.3. OS analyses stratified ETS levels with clinicopathological characteristics

To further analyze the impact of clinicopathological characteristics on OS time, the OS curves stratified by ETS ≥ 30% and ETS < 30% were calculated. Clinicopathological characteristics consisted of T classifications, N classifications, histological classification, smoking status, and EGFR status. The survival curve of patients with ETS ≥ 30% or < 30% in smoking panel was different from that in non-smoking panel (Fig. 2A and B). The survival curve in EGFR mutation panel ($P = .496$) showed no obvious difference between patients with ETS ≥ 30% and <30% while that in EGFR no mutation panel ($P = .009$) had significant discrepancy (Fig. 2C and D). In addition, the OS of patients with ETS ≥ 30% and <30% showed no evident distinction in squamous (Fig. 2E, $P = .08$) and adenocarcinoma (Fig. 2F, $P = .151$) panels as well as G1 (Fig. 2G, $P = .104$) and G2 + G3 (Fig. 2H, $P = .165$) panels. Furthermore, the results revealed that patients with ETS ≥ 30% showed better OS in $T_1 + T_2$ (Fig. 2I, $P < .001$) than those in $T_3 + T_4$ (Fig. 2J, $P = .254$). Meanwhile, the results showed that patients with ETS ≥ 30% had longer survival time in $N_0 + N_1$ group (Fig. 2K, $P = .048$) but no significant difference in group $N_2 + N_3$ (Fig. 2L, $P = .412$).

3.4. Cox regression analyses of potential prognostic factors

To determine if ETS < 30% could be served as a useful clinical risk factor, the OS of patients with ETS < 30% was examined using Cox regression proportional hazard analyses. As shown in Table 2, the univariate Cox regression analyses indicated that ETS < 30% was associated with a significantly increased risk of cancer-related death in stage III NSCLC ($P = .049$). The RRs indicated that smoking ($P = .047$) and EGFR no mutation ($P = .003$) were predictors for worse outcomes. The RRs showed no obvious differences when other clinical parameters were considered as the independent factors, such as age, T classification, N classification, G classification, and acute pulmonary toxicity. Subsequently, to further validate the potent prognostic factors, the multivariate Cox regression model was applied for clinicopathological diagnosis analyses. As summarized in Table 3, the results indicated that ETS < 30% ($P = .023$) and EGFR no mutation ($P = .015$) could predict for poor OS, while smoking had no evident impact on patients' survival ($P = .966$).

4. Discussion

With the continuous development of 3D-CRT, IMRT, and stereotactic body radiation therapy, the clinical effects of radiotherapy on NSCLC have been significantly improved in recent years.[10–12]

Mounting evidence indicates that the majority of lung cancers show regression during radiotherapy. Kupelian et al[13] have reported that an average stable daily regression was determined in gross tumor volume (GTV) of 1.2% according to megavoltage computed tomography scanning. In the current experiment, CT for image capture was here applied to further assess the dynamic changes in tumor volume of patients with NSCLC during radiotherapy. The longest diameter of tumor decreased by 30% under the condition of 50 Gy irradiation, where it was considered as ETS. Results showed that there existed significant heterogeneity in the changes of tumor volume among different patients. Some patients presented EST but others did not. Of the 103 patients, 59 had a 30% decrease in tumor size and the rest displayed a decrease of <30%. ETS had no evident association with age, T classification, N classification, histological classification, smoking status, G classification, EGFR status, or acute pulmonary toxicity. These conclusions are consistent with the relevant researches. For example, Siker et al[14] found no obvious connection between tumor regression and chemotherapy, pathology, or original tumor volume. Woodford et al[15] also reported that tumor regression rate had no important connection with original tumor volume, duration of radiotherapy, pathological patterns and staging, or tumor density. Specifically, there was no connection between changes in the volume of primary tumors and relevant properties of patients and the tumor itself.

The dose of radiotherapy has always been an issue of concern for clinical treatment of locally advanced NSCLC. However,

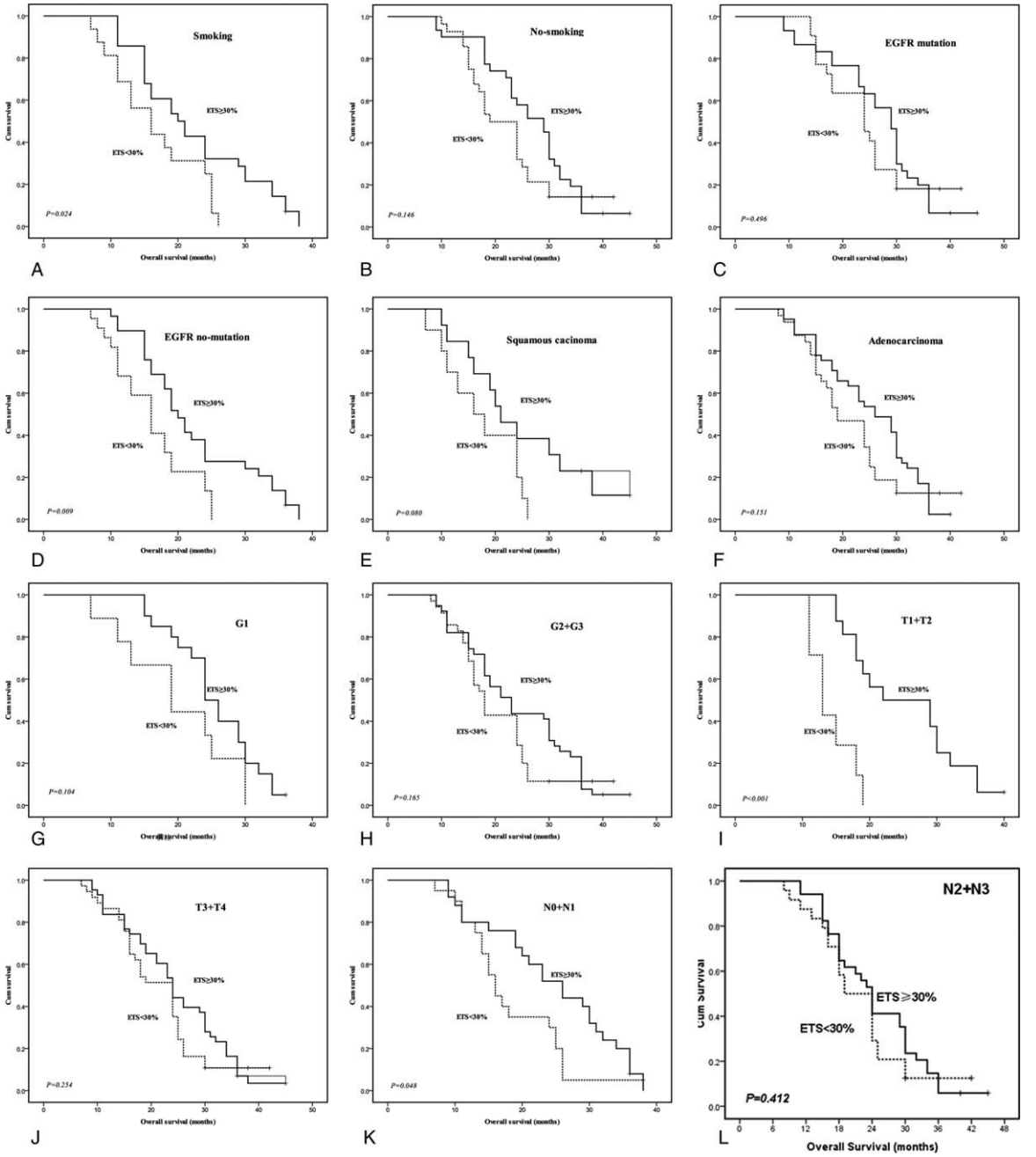

Figure 2. OS analyses stratified ETS levels with clinicopathological characteristics, consisting of T classifications, N classifications, histological classification, smoking status, and EGFR status. (A, B) The survival curve of patients with ETS ≥ 30% or < 30% in smoking was different from that in nonsmoking. (C, D) The survival curve in EGFR mutation panel ($P = .496$) showed no obvious difference between patients with ETS ≥ 30% and < 30% while that in EGFR no mutation panel ($P = .009$) had significant discrepancy. (E, F) The OS of patients with ETS ≥ 30% and <30% showed no evident distinction in squamous ($P = .08$) and adenocarcinoma panels ($P = .151$), as well as (G, H) G1 ($P = .104$) and G2 + G3 ($P = .165$) panels. (I, J) Patients with ETS ≥ 30% showed better OS in $T_1 + T_2$ ($P < .001$) than those in T3 + T4 ($P = .254$). K, L) Patients with ETS ≥ 30% had longer survival time in group $N_0 + N_1$ ($P = .048$), but no significant difference in group $N_2 + N_3$ ($P = .412$). ETS = early tumor shrinkage, EGFR = epidermal growth factor receptor, OS = overall survival.

there is still no clear consensus regarding dose regulation. The RTOG 93-11 experiments on dose-limiting toxicity for NSCLC, which cannot be excised surgically in 3D-CRT, have shown that the radiotherapy dose for patients with lung V20 < 25% can reach 83.8 Gy, while those with V20 of 26% to 36% could reach 77.4 Gy.[16] It is estimated that the dose used to eliminate NSCLC tumors with a diameter of 5 cm should be 80 to 90 Gy, or even 100 Gy. Some studies have considered the obvious dose effect on the radiotherapy of lung cancer. For example, Rengan et al[17] reported that tumor volume was considered as the principal factor to influence the prognosis of NSCLC patients and it was related to the total dose received by the patients. In his work, the median survival among 72 NSCLC patients whose tumor volume $>100\,cm^3$ was 15 months for the group whose radiotherapy dose ≤64 Gy, which was markedly less than that for patients in the >64 Gy group (20 months). The differences were statistically significant. They found that increasing the dose by 10 Gy could reduce local failure by 36.4%. Another example is that Belderbos

Table 2

Univariate Cox regression analysis of potential prognostic factors for stage III NSCLC.

Patient characteristics	RR (95% CI)	*P* value
Age, years		
≤60	1.000	
>60	0.761 (0.509–1.138)	.184
T classification		
T_1+T_2	1.000	
T_3+T_4	0.897 (0.557–1.446)	.656
N classification		
N_0+N_1	1.000	
N_2+N_3	0.891 (0.595–1.333)	.574
Histology classification		
Squamous cacinoma	1.000	
Adenocarcinoma	0.872 (0.534–1.424)	.583
Smoking		
No	1.000	
Yes	1.507 (1.006–2.258)	.047
G classification		
G1	1.000	
G2	0.939 (0.558–1.578)	.811
G3	1.091 (0.666–1.788)	.729
EGFR status		
No mutation	1.000	
Mutation	0.543 (0.361–0.816)	.003
Acute pulmonary toxicity		
G1–2	1.000	
G3–4	0.777 (0.503–1.200)	.255
Earlier tumor size decrease		
ETS < 30%	1.000	
ETS≥30%	0.658 (0.434–0.997)	.049

EGFR = epidermal growth factor receptor, ETS = early tumor shrinkage, RR = relative risk, NSCLC = non-small cell lung cancer.

et al[18] found that performing large-dose radiotherapy on small-volume tumors could increase the local control rate and survival of patients. In addition, Kong et al[19] conducted a study of 106 stage I-III NSCLC cases by 3D-CRT and found that the 5-year overall survival rate of patients with 63 to 69, 74 to 84, and 92 to 103 Gy dose was 4%, 22%, and 28%, respectively, while patients with ≥74 Gy dose survived longer. However, the results varied from different studies. Willner et al analyzed 135 cases of NSCLC and found no difference in local control rate between dose >60 Gy and ≤60 Gy in the subgroup of patients with GTV > 100 cm.[3,20] In patients with GTV < 100 cm^3, long-term local control dose could be achieved more than 70 Gy. It was not clear whether large-volume lung cancer could benefit from incremental radiotherapy. Increasing the dose of radiotherapy within limits plays an extremely important role in improving the prognosis of NSCLC. Repeated CT scanning simulation and points in time at 50 Gy were selected for balance for the fact that the sub-clinical lesion has achieved sufficient dose at this time. Additionally, the dose of irradiation in the target area of primary lesion was enough high to observe the response of tumor volume. According to these responses, a suitable treatment plan could be made to determine whether the promotion of the dose in the target area and protection of normal tissue could be maintained at the end of the treatment.[21]

Table 3

Multivariate Cox regression analysis of potential prognostic factors for stage III NSCLC.

Patient characteristics	RR (95% CI)	*P* value
Smoking		
No	1.000	
Yes	0.987 (0.540–1.802)	.966
EGFR status		
No mutation	1.000	
Mutation	0.495 (0.270–0.906)	.023
Earlier tumor size decrease		
ETS < 30%	1.000	
ETS≥30%	0.586 (0.381–0.902)	.015

EGFR = epidermal growth factor receptor, ETS = early tumor shrinkage, RR = relative risk, NSCLC = non-small cell lung cancer.

Our results indicated that ETS had predictive value in clinical effects. The relationship between ETS and prognosis was more significant in patients with T_1+T_2, N_0+N_1, a history of smoking, and no EGFR mutations. In these patients, PFS and OS were both markedly extended, and ETS can translate into long-term clinical benefits. In addition, univariate and multivariate Cox regression analyses indicated that ETS < 30% are associated with a significantly increased risk of cancer-related death ($P < .05$) in stage III NSCLC. Given this, patients with ETS have better prognosis. It is here suggested that a timely change in treatment plan be made when tumor volume varies dramatically, in order to reduce dose and volume parameters, cut down the probabilities of toxic and adverse effects, or employ higher doses to achieve better effects when needed.

In contrast, patients who do not experience ETS have poor prognosis. Tumor volume showed no visible changes, and incremental radiotherapy was not beneficial. It was not effective to reduce the dose of irradiation and volume parameters of normal lung tissue. Similarly, it was not appropriate to increase the dose of irradiation. Based on the probability of toxic and adverse effects caused by continuous increases in dosage, such as radiation pneumonia, resetting and promoting dosage is not recommended for these patients.

Taken together, our results demonstrated that the relationship between ETS and prognosis was more significant in patients with T_1+T_2, N_0+N_1, a history of smoking, and no EGFR mutations. This implies that ETS exerts predictive value in clinical effect. Hence, ETS may be served as a useful prognostic factor to predict the outcome of stage III NSCLC patients treated with C-CRT.

Author contributions

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Writing – review & editing: Jun Cai.

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