A phase II study of concurrent nab-paclitaxel/carboplatin combined with thoracic radiotherapy in locally advanced squamous cell lung cancer

Kan Wu[1], Lucheng Zhu[1], Jiahao Wang[1], Kaicheng Pan[1], Bing Wang[1], Xin Li[2], Shaoyu Yang[2], Xiao Xu[1], Minna Zhang[1], Xiadong Li[2], Xueqin Chen[2], Shenglin Ma[2], Bing Xia[1,3]

[1]Department of Radiation Oncology, Hangzhou Cancer Hospital, Hangzhou 310002, China; [2]Department of Oncology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou 310002, China; [3]Jiande Second People's Hospital, Jiande 311604, China

Contributions: (I) Conception and design: K Wu, B Xia, S Ma; (II) Administrative support: L Zhu, J Wang; (III) Provision of study materials or patients: K Wu, K Pan, B Wang; (IV) Collection and assembly of data: X Li, M Zhang, S Yang, X Li; (V) Data analysis and interpretation: K Wu, L Zhu, X Chen, X Xu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Bing Xia. Department of Radiation Oncology, Hangzhou Cancer Hospital, 34 Yan-Guan Lane, Hangzhou 310002, China. Email: xb0918@hotmail.com; Shenglin Ma, MD. Department of Oncology, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, 261 Huansha Road, Hangzhou 310006, China. Email: mashenglin@medmail.com.cn.

Background: The development of chemoradiotherapy is urgently needed for locally advanced squamous cell lung cancer due to its poor prognosis and significant toxicity. Carboplatin combined with nab-paclitaxel is a useful choice as first-line therapy in advanced squamous cell lung cancer. This prospective phase II study aimed to explore the efficacy and toxicity of concurrent chemoradiotherapy with nab-paclitaxel, carboplatin, and thoracic radiotherapy in unresectable locally advanced squamous cell lung cancer.

Methods: Patients with unresectable stage III squamous cell lung cancer were eligible. All patients received nab-paclitaxel weekly at a dose of 60 mg/m^2, in combination with carboplatin [area under the plasma concentration time curve (AUC) 2] weekly during concurrent chemoradiotherapy. Thoracic radiation was administered at a dose of 66 Gy/33 fractions. The consolidation chemotherapy consisted of nab-paclitaxel (260 mg/m^2 on day 1) and carboplatin (AUC 6 on day 1) every 21 days was administered in two cycles after the concurrent chemoradiotherapy. The primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety.

Results: Initially, enrollment of 21 patients was planned; however, the trial was prematurely closed due to slow recruitment. Finally, a total of 8 patients were enrolled between January 2012 and July 2015 from one institute. All patients completed concurrent chemoradiotherapy, and 6 patients (75.0%) received consolidation chemoradiotherapy. The ORR was 75%, with complete response (CR) 1 (12.5%), partial remission 6 (62.5%), stable disease 1 (12.5%), progressive disease 1 (12.5%), respectively. After a median follow-up of 15.2 (range, 2.3–51.5) months, 7 patients were dead, and 1 was alive. The median PFS and OS were 12.1 and 15.2 months, respectively. According to Common Terminology Criteria for Adverse Events version 4.0, 6 patients (75.0%) experienced acute radiation esophagitis, 4 (50.0%) were grade 2 (G2), and 2 (25.0%) were G3; 4 patients (50%) experienced acute radiation pneumonitis, 3 (37.5%) were G2, and 1 (12.5%) was G3. No late radiation-induced esophageal and pulmonary toxicity was observed after 1-year follow-up.

Conclusions: Concurrent nab-paclitaxel, carboplatin, and thoracic radiotherapy was shown to be an effective regimen for patients with unresectable locally advanced squamous cell lung cancer; however, further study should exercise caution due to the severe radiation esophagitis.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all cases, and of these, about 30% are squamous cell carcinoma (1,2). The locally advanced disease accounts for more than 25% of all squamous cell carcinoma (3). Concurrent platinum-based doublet chemoradiotherapy is considered the standard treatment for patients with inoperable locally advanced NSCLC with a good performance status (PS) (4,5); however, the current chemotherapy regimens are not ideal due to a poor outcome (6,7) and a high rate of toxicity. In recent phase III trials delivering concurrent chemoradiotherapy with a total dose between 60 and 66 Gy, the incidence of symptomatic esophagitis ranged from 7% to 21%, with corresponding rates of symptomatic radiation pneumonitis ranging from 2.5% to 7% (8,9). Therefore, the development of treatment is urgently needed to improve efficiency and reduce toxicity.

Previous studies suggest that different platinum/third-generation chemotherapy agent combinations have similar efficacy in advanced squamous cell carcinoma (10). Recently, the choice of chemotherapy in non-squamous NSCLC has been influenced by histology. Pemetrexed has favorable efficacy and safety in non-squamous NSCLC but not in the squamous population (11). Most targeted drugs are also effective in non-squamous cell carcinoma (12-14). In locally advanced non-squamous NSCLC, the PROCLAIM trial showed less hematological toxicity for pemetrexed-cisplatin and radiation than etoposide-cisplatin and radiation. Compared with non-squamous NSCLC, treatment breakthroughs for both advanced and locally advanced squamous cell carcinoma are rare.

Albumin-bound paclitaxel is a paclitaxel formulation in which nanoparticles of paclitaxel are bound to human serum albumin. A previous study indicated that nab-paclitaxel increased intratumoral paclitaxel concentrations and antitumor activity more than cremophor based paclitaxel when an equal dose was delivered (15). Combination therapy of carboplatin and nab-paclitaxel is a useful choice as first-line therapy for patients with advanced NSCLC, especially for squamous cell cancer (16,17). Weekly administration of nab-paclitaxel plus carboplatin with concurrent thoracic radiation has been reported to be a safe and well-tolerated regime for locally advanced NSCLC in a phase I study (18). Therefore, this prospective phase II study was conducted to explore the efficacy and toxicity of concurrent chemoradiotherapy with nab-paclitaxel, carboplatin, and thoracic radiotherapy in unresectable locally advanced squamous cell lung cancer.

Methods

Patients

Adults aged 18 years or older were eligible for enrolment if they had histologically/cytologically confirmed diagnosis of squamous cell lung cancer, and unresectable stage IIIA/B disease, excluding those with pericardial, pleural effusion, and those with contralateral hilar or contralateral supraclavicular lymph nodes; an Eastern Cooperative Oncology Group (ECOG) PS score of 0 or 1; a life expectancy of at least 3 months; weight loss ≤5% in the previous six months; adequate organ function; a measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (19); and all detectable tumors could be encompassed by reasonable radiation therapy fields. Patients were excluded for the following reasons: complete tumor resection, recurrent disease, or disease eligible for definitive surgery; previous treatment for lung cancer; previous thoracic radiation therapy; untreated active interstitial lung disease; prior or concurrent malignancy except non-melanomatous skin cancer unless disease-free for 5 years or more; a history or presence of poorly controlled systemic diseases; history of significant neurological or mental disorder, including seizures or dementia; possibly pregnant females or males currently

attempting to produce a pregnancy; or the volume of the whole lung receiving ≥20 Gy (V_{20}) more than 30% or the mean lung dose (MLD) of the whole lung more than 17 Gy. This study protocol was approved by our institution's ethics review board. All patients provided written informed consent before trial participation.

Study design

Patients received nab-paclitaxel weekly at a dose of 60 mg/m^2 on day 1, in combination with carboplatin [area under the plasma concentration time curve (AUC) 2] on day 1 for 6 cycles during concurrent chemoradiotherapy. Thoracic radiotherapy was administered on day 1 at a dose of 66 Gy/33 fractions over 6 weeks, 5 times every week. Two cycles of consolidation therapy with nab-paclitaxel (260 mg/m^2) on day 1 and carboplatin (AUC 6) on day 1 every 21 days were delivered and initiated 4 weeks after the concurrent chemoradiotherapy. Standard chemotherapy dose adjustments applied. Patients were withdrawn from the study of the adverse events failed to resolve after 14-day treatment interruption.

Radiation therapy

Patients were immobilized in the supine position with arms over the head, using a thermoplastic body frame or a vacuum pad. A free breathing contrast-enhanced helical CT scan with 5-mm slice thickness was performed in the treatment position. Use of four-dimensional computed tomography (4D-CT) during the simulation process was not mandatory. The gross tumor volume (GTV) was defined as the visualization of any gross tumor (GTV-P) and lymph nodes involved (GTV-N). If present, atelectasis was not included in the GTV and was facilitated by positron emission tomography/computed tomography (PET/CT) fusion to the planning CT. Elective node irradiation was omitted. With regard to the margin that should be added from GTV to the planning target volume (PTV) to cover the subclinical invasion and trade-off the setup error, a 1.0- to 1.5-cm margin was placed around the GTV-P and GTV-N, respectively. Furthermore, a kV-cone beam CT (CBCT) scan was performed once a week during radiotherapy to verify the patient position. All patients were treated with Elekta Synergy linear accelerator with 6 or 10 MV photons, and both three-dimensional conformal and intensity-modulated radiation therapy were allowed. Ninety-five percent of the PTV received 100% of the prescribed dose, and the maximum dose of the PTV should not have exceeded 107% of the prescription dose. The maximum dose to the spinal cord was 45 Gy, and the dose constraint for the heart was mean heart dose (MHD) ≤30 Gy. For the lungs, the V_{20} and V_5 were limited to 30% and 50%, separately, and the MLD was ≤17 Gy. The dose constraint for the esophagus was the mean dose <34 Gy, V_{50} <40%, and V_{35} <50%.

Baseline and treatment assessments

Baseline tumor assessments were performed within 4 weeks before the start of treatment. Subsequent tumor assessments occurred every 4 weeks during the treatment period, every 6 weeks within 24 weeks, then every 12 weeks until disease progression. Other imaging examinations, including brain magnetic resonance imaging (MRI), were performed when recurrence was suspected.

The response was assessed according to imaging examinations, which were recorded according to the RECIST criteria. The primary endpoint was objective response rate (ORR), which was defined as the percentage of participants with the best confirmed response [complete response (CR) or partial response (PR)]. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. OS was measured from the date of their random assignment to their death from any cause. PFS was defined as the time from the date of random assignment to objective progressive disease or death as a result of any cause. All adverse events and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Statistical analysis

The primary endpoint of this study was the ORR. Simon's optimum two-stage phase II design was used. The study was designed to measure a response rate (CR plus PR) of 85% compared with a minimal, clinically meaningful response rate of 70%, with a one-sided α-error of 0.05 and a β-error of 0.2. The target number of cases required in the first stage was 19 cases. Assuming a lost-to-follow-up rate of 5%, at least 20 patients were needed. For the second stage, an additional 43 patients were enrolled. Therefore, a
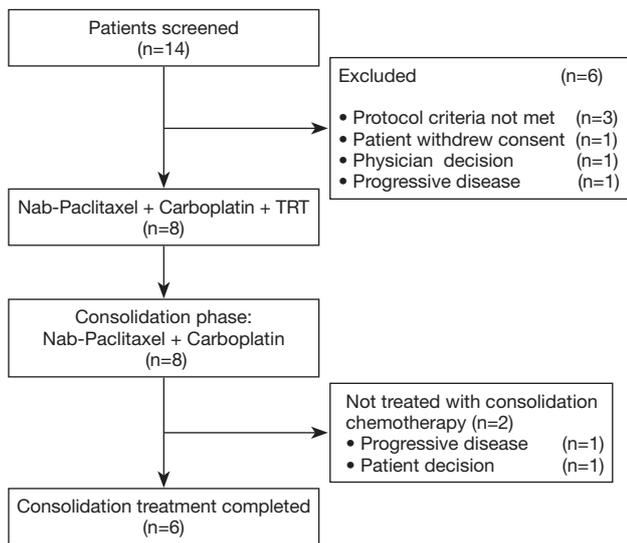
Figure 1 CONSORT diagram of the study. A total of 8 patients completed concurrent chemoradiotherapy, and 6 patients (75.0%) received consolidation chemotherapy according to the protocol. TRT, thoracic radiotherapy.

total of 63 patients was the planned accrual size. The *t*-test was used for the statistical analysis. The survival curves were calculated using the Kaplan–Meier method. Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). All probability values were two-sided and P values <0.05 were considered statistically significant.

Results

Patient characteristics

Initially, the enrollment of 21 patients was planned; however, the trial was prematurely closed due to slow recruitment. Finally, a total of 8 patients were enrolled between January 2012 and July 2015 from 1 institute (*Figure 1*). The characteristics of 8 eligible patients are listed in *Table 1*. The median age was 64 years, with a range from 46 to 75 years. All of the 8 patients were male. PS was 0 in three patients and 1 in five patients. Stage distribution was as follows: IIIA, 3 patients (37.5%); IIIB 5 patients (62.5%).

Treatment administered

All patients completed concurrent chemoradiotherapy, and

Table 1 Patient characteristics

Characteristics	No.	%
No. of eligible patients	8	
Age, y		
Median [range]	64 [46–75]	
Gender		
Male	8	100.0
Female	0	0.0
ECOG PS		
0	3	37.5
1	4	50.0
2	1	12.5
Smoking history		
Absent	2	25.0
Present	6	75.0
Stage (AJCC 7th ed)		
IIIA	3	37.5
IIIB	5	62.5
Location of primary site		
Upper lobe	3	37.5
Middle lobe	2	25.0
Lower lobe	3	37.5

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

6 patients (75.0%) received consolidation chemotherapy according to the protocol. Because of progressive disease (one patient) and refusal of chemotherapy (another patient) after concurrent therapy, 2 patients were unable to complete the scheduled consolidation chemotherapy.

Efficacy

By CT scan criteria, the CR and PR rate were 12.5% and 62.5%, respectively, for an ORR of 75.0%. Stable disease and progressive disease both occurred in 1 patient (12.5%).

The median follow-up time of the patients was 15.2 months (range, 2.3–51.5 months). During follow-up, 7 (87.5%) patients had died at the time of analysis. The median PFS and OS were 12.1 and 15.2 months,

Table 2 Hematological and non-hematological adverse events according to CTCAE v4.0

Toxicity	0	G1	G2	G3	G4	≥ G3 (%)
Hematological toxicities						
Anemia	1	3	2	2	0	25.0
Leukopenia	2	1	1	4	0	50.0
Neutropenia	3	0	3	1	1	25.0
Thrombocytopenia	5	2	0	1	0	12.5
Non-hematological toxicities						
Blood bilirubin increased	7	1	0	0	0	0.0
ALT abnormalities	7	1	0	0	0	0.0
AST abnormalities	8	0	0	0	0	0.0
Creatinine increased	8	0	0	0	0	0.0
Nausea	5	1	1	1	0	12.5
Vomiting	5	1	2	0	0	0.0
Anorexia	3	2	2	1	0	12.5
Diarrhea	6	2	0	0	0	0.0
Fatigue	3	3	2	0	0	0.0
Neuropathy	7	1	0	0	0	0.0
Myalgia	7	1	0	0	0	0.0
Arthritis	6	2	0	0	0	0.0
Radiation pneumonitis	4	0	3	1	0	12.5
Radiation esophagitis	2	0	4	2	0	25.0

CTCAE, Common Terminology Criteria for Adverse Events; ALT, alanine amiotransferase; AST, aspartate transaminase.

respectively. Six (75.0%) patients developed disease progression, 1 patient died unrelated to progression, and 1 (12.5%) patient was free of disease progression as of the latest follow-up. Causes of death included the progression of the primary tumor in 4 patients (57.1%), brain metastasis in 1 patient (14.3%), pericardium metastasis in 1 patient (14.3%), and bacterial pneumonia in 1 patient (14.3%). For the patients who died of bacterial pneumonia, the time from treatment completion to onset of clinical symptoms was 14.2 months, and *Klebsiella pneumoni* was found in the sputum culture.

Toxicity

The acute adverse effects are summarized in *Table 2*. These include main toxicity (grade 3 or greater, %): anaemia 2

(25.0%), leukopenia 4 (50%), neutropenia 2 (25.0%); nausea 1 (12.5%); and anorexia 1 (12.5%). In addition, 6 patients (75.0%) experienced symptomatic acute radiation esophagitis (ARE), 4 (50.0%) were grade 2 (G2), and 2 (25.0%) were G3; 4 patients (50%) experienced symptomatic acute radiation pneumonitis, 3 (37.5%) were G2, and 1 (12.5%) was G3. Most adverse effects were grade 1/2 and well-tolerated with supportive care. No late radiation-induced esophageal and pulmonary toxicity was observed after 1-year follow-up.

Discussion

The issue of how to improve local control while reducing the toxicity remains a challenge in unresectable stage III squamous cell lung cancer. Concomitant treatment with nab-paclitaxel/carboplatin and thoracic 3D conformal/intensity-modulated radiotherapy followed by nab-paclitaxel/carboplatin consolidation chemotherapy has been shown to be an effective regimen. In the current study, the ORR was 75%, and the median PFS was 12.1 months. However, the toxicity incidence, especially the incidence of ARE in the study, was higher than expected. Although toxicity did not affect the treatment completion, the incidence of severe ARE was not acceptable in this single-center study.

The efficacy of nab-paclitaxel/carboplatin has been reported in first-line patients with advanced NSCLC in the previous study (16,20). Nab-paclitaxel is a formulation of paclitaxel which is not dissolved in Cremophor EL. This formulation potentially increases the delivery of paclitaxel into tumor cells by initiating albumin receptor (gp60)-mediated transcytosis across endothelial cells (21) and accumulating drug in tumors due to the binding of albumin to secreted protein acidic and rich in cysteine (SPARC) (22).

Nab-paclitaxel has been demonstrated to be a safe drug for locally advanced NSCLC patients who received chemoradiotherapy in several phase I trials (18,23). However, the incidence of ARE in the current study was high: 6 patients experienced symptomatic ARE, and two-thirds of them were severe cases. The incidence of severe ARE (Radiation Therapy Oncology Group (RTOG) grade 3 or higher) was reported to be about 7–21% in NSCLC patients treated with concurrent chemoradiotherapy, and the differences in ARE risk across studies might be related to different criteria for definition of ARE, population heterogeneity, and differences in treatment (24,25).

The esophagus is a critical dose constraints organ in the definitive radiotherapy of lung cancer (26,27). Once

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Table 3 Dose-volume histogram parameters of esophagus and contralateral esophagus

Characteristics	Patients (n=8) median (range)		P value
	Esophagus	Contralateral esophagus	
Dmax (Gy)	63.05 (57.60–67.94)	59.44 (44.40–64.92)	0.73
V_{45} (cc)	4.90 (0.08–9.67)	2.37 (0–4.60)	0.11
V_{55} (cc)	3.75 (0–7.60)	1.64 (0–3.47)	0.12
V_{60} (cc)	2.91 (0–6.09)	1.19 (0–2.92)	0.12
V_{60} (%)	6.62 (0–12.97)	5.19 (0–10.67)	0.61

Vn, volume of lung receiving at least n Gy of radiation dose.

symptomatic ARE occurs, it typically influences the quality of life and following treatment, possibly leading to poor outcomes. RTOG 0617 showed that maximum esophagitis grade was found to be an independent prognostic factor predicting OS (8). Previous studies have found a correlation between esophagitis and dosimetric parameters. A meta-analysis involving 1,082 locally advanced NSCLC patients who underwent concurrent chemoradiation therapy found that V_{60} of the esophagus was the best predictor of grade ≥2 and grade ≥3 esophagitis (27). Another analysis reported a maximum dose exceeding 55 Gy as predictive. In this study, the incidence of severe ARE was up to 25%. The dosimetric parameters of esophagitis in this study were not satisfactory, as the median maximum dose and V_{60} of the esophagus was 63.05 Gy and 6.62%, respectively (*Table 3*). In fact, the specific histology of enrolled patients may be a critical reason for the high occurrence of esophagitis. Squamous cell lung tumors are usually located close to the esophagus, which may be responsible for the high radiation dose of the esophagus and the high incidence of esophagitis.

Therefore, it is important to devise new strategies for improving esophageal sparing and ultimately minimize the rates of severe ARE in squamous cell lung cancer patients undergoing concurrent chemoradiotherapy. In a recent secondary analysis, the RTOG 0617 group reported that patients treated with intensity-modulated radiotherapy had significantly lower rates of severe pneumonitis and cardiac doses compared with those treated with 3D-conformal treatment (28). It is possible that intensity-modulated radiotherapy may be a fine treatment option for reducing the risk of esophagitis. A recent study (29) applied intensity-

modulated radiotherapy-based contralateral esophageal (CE) (which was defined as the cross-sectional half of the esophagus that was opposite to the gross tumor) sparing technique (CEST), to spare the CE wall in patients with locally advanced lung cancer treated with concurrent chemoradiotherapy; the result demonstrated an improvement in esophageal toxicity with the use of this technique. The CE had more favorable dosimetry in comparison with the whole esophagus with CEST: the median maximum dose to the CE was significantly lower than the maximum dose to the esophagus (62.3 *vs.* 67.5 Gy); the median esophageal V_{60} was higher than the median CE V_{60} (5.3% *vs.* 0.5%). In contrast, there was no statistically significant difference in the median maximum dose (63.05 *vs.* 59.44 Gy, respectively; P>0.05) and median V_{60} (6.62% *vs.* 5.19%, respectively; P>0.05) between the esophagus and CE in the current study, which suggests no steep dose falloff across sections of the esophagus with standard esophageal dose constraints radiotherapy. Furthermore, the suggested CE dose constraints was V55 <0.5 cc when CEST was used (29), which was significantly lower than the dose of CE in this study (*Table 3*). Therefore, we tried to apply this technique to spare the CE wall in a patient who experienced grade 2 ARE, with the goal of decreasing the dose to the esophagus. The maximum dose to the CE was significantly decreased with CEST than with common technique (52.21 *vs.* 64.23 Gy, respectively). Similarly, the maximum dose and V_{60} to the CE was significantly lower than that to the esophagus (52.21 *vs.* 67.74 Gy; 0 *vs.* 4.9%, respectively) (*Figure 2*). It is believed that the improvement in dosimetry of CE may result in a decrease in the incidence of esophagitis. In the future, to decrease the incidence and severity of ARE, CEST may be a promising technique to treat high-risk patients with a central-location tumor.

Conclusions

This study suggests that concurrent nab-paclitaxel, carboplatin, and thoracic radiotherapy is an effective regime in unresectable locally advanced squamous cell lung cancer. However, the incidence of ARE was not acceptable in this study. A prospective trial of concurrent thoracic radiotherapy with CEST and nab-paclitaxel/carboplatin is further needed to validate the safety of this regimen. Moreover, this study is relatively small, and more data from randomized trials are needed in the future.
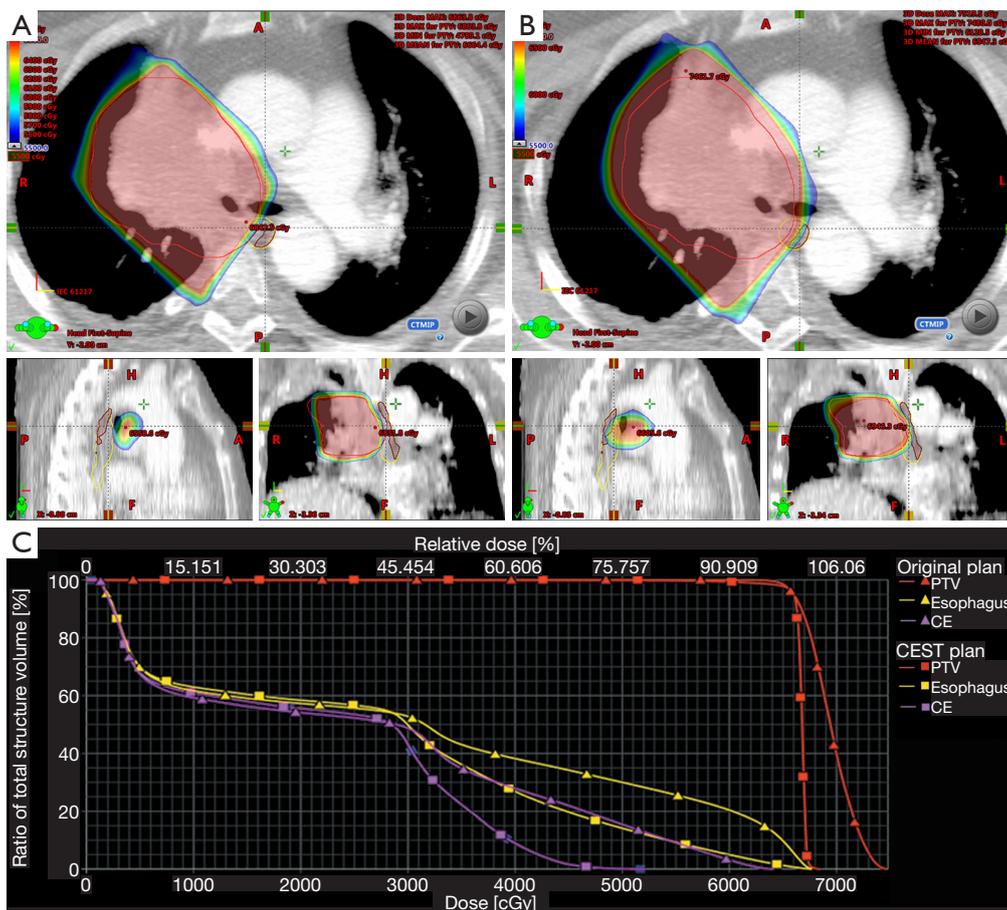
Figure 2 A shows the original plan: the PTV is covered by 66 Gy, and the contralateral esophagus received a high dose; B shows the dose distribution of the same patient using the contralateral esophageal sparing technique: the PTV is well covered by the prescription dose of 66 Gy, and the high isodose lines are shown to effectively bend around the contralateral esophagus. C shows a dose-volume histogram of the two plans. PTV, planning target volume.

Footnote

Conflicts of Interest: The results of this study were presented at the meeting of 17th World Conference of Lung Cancer, December 4-7, 2016, Vienna, Austria.

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 approved by the institutional ethics committee of medical ethics committee of Hangzhou First People's Hospital (No. 2011-1025).

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