A modified Phase I trial of radiation dose escalation in 3D conformal radiation therapy with concurrent vinorelbine and carboplatin chemotherapy for non-small-cell lung cancer

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The Radiation Therapy Oncology Group reported a maximum tolerated dose of 74 Gy for patients with non-small cell lung cancer (NSCLC); however, it was unclear whether this dose could be safely administered to Asian patients due to differences in their physique compared to Western patients. We therefore conducted a modified Phase I trial to determine whether 70 Gy could be safely delivered to Chinese patients with NSCLC undergoing 3D-conformal radiation therapy (3D-CRT) with concurrent chemotherapy. Previously untreated NSCLC patients received 3D-CRT (2 Gy/day, 5 fractions per week). Three dose levels were examined: 62, 66 and 70 Gy. Two cycles of concurrent chemotherapy (vinorelbine and carboplatin) were started on the first day of radiation therapy. Dose-limiting toxicity (DLT) was defined as severe or life-threatening side effects that altered the continued implementation of chemoradiotherapy. Among the 19 patients recruited in this study, most of the haematologic and non-haematologic toxicities were mild to moderate and clinically manageable. Only one patient, in the 70 Gy cohort, experienced a DLT of Grade 3 radiation-induced pneumonia. The overall response rate was 77.8% (14/18). The median progression-free survival (PFS) was 12 months, and the 1-year PFS was 37.6%. Our results support both the feasibility of incorporating 3D-CRT with concurrent vinorelbine and carboplatin and a dose escalation to 70 Gy for Chinese patients with NSCLC, based on the acceptable toxicity and encouraging overall response and survival rates. A further evaluation of this regimen in a prospective Phase II trial is ongoing.

Keywords: non-small-cell lung cancer; 3D conformal radiation therapy; dose escalation; concurrent chemoradiotherapy

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for about 80% of all lung cancer cases. For most NSCLC patients, radical surgical resection is not an option since by the time the disease is clinically diagnosed it is often at an advanced stage [1]. Thus, radiotherapy alone has been the standard treatment modality for locally advanced NSCLC in patients not eligible for surgical resection. According to the guidelines originally elaborated by the Radiation Therapy Oncology Group, USA (RTOG), 60 Gy conventional fractionated radiotherapy was considered to be the standard radiotherapy dose; however, these patients had a median survival time of only 10 months, and the 5-year survival rate was only about 5% [2]. Subsequent studies showed that a combination of radiotherapy and chemotherapy was better than radiotherapy alone [3], while the findings of recent clinical trials and of a meta-analysis supported concurrent...
chemoradiotherapy over sequential chemoradiotherapy [4–5]. Therefore, concurrent chemoradiotherapy has become the standard treatment for NSCLC. Following a report that increasing the radiotherapy dose within a certain range could enhance the tumour control rate and hence improve survival [6], the RTOG conducted radiotherapy dose escalation trials involving 3D-conformal radiation therapy (3D-CRT) and concurrent chemotherapy, reporting that the radiotherapy dose of concurrent chemoradiotherapy could be safely escalated to 74 Gy [7]. Nonetheless, the escalation trial was carried out on Western patients and, given the differences in the physique of Asian patients, it is unclear whether the results are applicable to them.

In the CALGB9431 trial, there was no significant difference either in the response rates or in the 3-year overall survival (OS) rates of patients receiving concurrent chemoradiotherapy in which a combination of cisplatin and vinorelbine, paclitaxel, or gemcitabine was administered. However, treatment-related toxicities were milder in the cisplatin and vinorelbine group [8]. To the best of our knowledge, radiotherapy dose escalation in patients receiving concurrent vinorelbine and carboplatin chemotherapy (VC) for NSCLC has not been evaluated. Thus, to determine whether 70 Gy could be safely delivered to Chinese patients with NSCLC undergoing 3D-CRT with concurrent chemotherapy, the VC regimen was concurrently applied in a modified Phase I trial of radiotherapy dose escalation.

**MATERIALS AND METHODS**

**Eligibility**
The eligibility criteria for study entry were: cytological or histological confirmation of a previously untreated NSCLC evaluative lesion and no other severe internal diseases that required patient hospitalisation. Only patients with Stage III–IV (UICC, 1997) disease or a medically unresectable tumour of any stage, or those who had refused surgery for personal reasons, were included in the study. Stage IV patients were recruited because, for cultural and economic reasons, there are few patients in China who are willing to accept concurrent chemoradiotherapy and who can afford it. Some patients with relatively mild disease, who met the conditions for chemoradiotherapy for Stage IV disease, were also included to accelerate completion of the Phase I trial. The literature contains similar reports of Phase I trials of concurrent chemoradiotherapy in which patients with Stage IV disease were recruited [9, 10].

Additional inclusion criteria were: age ≥18 years and ≤75 years, Karnofsky performance status ≥70, and a life expectancy >3 months. The required laboratory findings were: 2.0 × 10⁹ neutrophils/l; ≥100 × 10⁹ platelets/l; ≥100 g haemoglobin/l; and serum creatinine, aspartate aminotransferase, alanine aminotransferase, and total serum bilirubin levels below the upper limits of normal.

Patients with any of the following conditions were excluded: Stage IIIb disease with effusion; multiple metastatic lesions in the brain or bones; interstitial pneumonia; superior vena cava syndrome; pregnancy or lactation; a history of other malignancies, with the exception of carcinoma in situ of the cervix, non-melanomatous skin cancer, and cancer from which the patient had been disease-free for 5 years; or a general medical condition that prevented combined modality therapy. Patients being treated with another concurrent antineoplastic therapy (such as cancer immunotherapy, targeted therapy, etc.) during concurrent chemoradiotherapy rather than cytotoxic drug therapy) were also excluded.

This modified Phase I study was approved by the Ethics Committee of Hebei Medical University and was performed in accordance with the ethical standards of human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. All patients provided written informed consent prior to study enrolment.

**Pretreatment evaluation**
A pretreatment evaluation carried out ≤2 weeks before treatment initiation consisted of the following: an assessment of the patient’s medical history; a complete physical examination; chest, abdominal and brain helical computed tomography (CT) scans with intravenous (IV) contrast; electrocardiography; bronchoscopy; bone marrow scans (if clinically indicated); a complete blood count; and a biochemical profile. The patients also underwent weekly physical examinations and blood counts (or more often if necessary). A biochemical profile was obtained and electrocardiography was performed before every chemotherapy cycle.

**Study design**
This modified Phase I trial was designed as an open-label, non-randomised dose-escalation study. The primary endpoint was safe escalation of the 3D-CRT dose from 62 Gy to 70 Gy when delivered concurrently with vinorelbine and carboplatin. The secondary endpoints were response rate and progression-free survival (PFS). Groups of at least three patients received a sequentially increasing dose of radiation concurrently with VC, as outlined in Table 1.

All patients were administered 3D-CRT while in a supine position, with their hands on their heads and their fingers interlocked. A vacuum pad was used to fix the patient’s body position and appropriately limit respiratory movement. Contrast spiral CT (GE LightSpeed Plus 4) was performed by acquiring 5-mm slices, with input of the image data into the 3D therapeutic planning system (VENUS 5014 software, Shanghai Tuoneng Co.) used to design the radiation plan. The convolution algorithm was that of the 3D therapeutic planning system. The target volume was delineated using the standard method for
Table 1. Concurrent chemoradiotherapy schema

| Concurrent chemoradiotherapy schema | Dose Escalation |
|------------------------------------|-----------------|
| RT regimen: Weeks 1–7: 2 Gy/f, 1 f/d, 5 f/w | Level 1: |||
| Week | Level 2: |||
| RT | Level 3: |||
| 1 | |
| 2 | |
| 3 | |
| 4 | |
| 5 | |
| 6 | |
| 7 | |

Chemotherapy: NVR (25 mg/m²) d1, d8; CBDCA AUC = 5 mg/m1.min on d8, repeated every 28 d

NSCLC [11], delineating the primary lesion in the pulmonary window (1600, –600 HU) and mediastinal lymph nodes in the mediastinal window (400, 20HU). An involved field radiation regimen was adopted, without the delivery of prophylactic radiation to the lymph drainage field. The target volume was defined as follows: gross tumour volume (GTV) = primary lesion plus lymph nodes with a shortest diameter >1 cm; clinical target volume (CTV) = GTV + a 6-mm margin for squamous cell carcinoma, large cell cancer or metastatic lymph nodes, or an 8-mm margin for adenocarcinoma; planning target volume (PTV) = CTV plus a 10- to 15-mm margin according to the respiratory movement observed under the X-ray simulator in the direction of the head and feet, and 10 mm in all directions. The GTV was confirmed by two radiation oncologists and one diagnostic imaging physician. The outlines of the vital organs and body surface were drawn by a medical physicist. Three to six coplanar or non-coplanar fields were adopted for the conformal radiation. The therapeutic plan was optimised using dose-volume histograms, determining the dose according to an isodose curve that encompassed at least 95% of the PTV. Restrictions put in place to protect the organs at risk were as follows: the percentage of the total lung volume that received 20 Gy (V20) was set at ≤30% for both lungs (‘both lungs’ when the two lungs minus the PTV was used to calculate V20); for the spinal cord, 0% should receive >45 Gy; ≤10 cm of the oesophagus should receive >60 Gy and 0% should receive >70 Gy; and for the heart, V40 ≤ 40%. All patients were irradiated using a SIEMENS PRIMUS PLUS linear accelerator delivering 6-MV X-rays and equipped with a 27-pair multi-leaf collimator (Topslane®_M, Shanghai Tuoneng Co.). CT scans were repeated after the total delivered dose had reached 50 Gy. Radiation was continued as planned until completion unless obvious shrinkage of the target volume was determined, in which case the irradiated field was reduced based on another contrast CT scan obtained with the patient in the original body position. All lesions were included in the same target field whenever possible; a second field was defined if there was a large margin between the lesions. Radiotherapy was administered with conventional fractionation on the first day of Week 1. Patients were treated with five daily fractions of 2.0 Gy per week. Treatment with a combination of X-rays and electron rays at a total dose of 60–70 Gy was adopted in patients with supraclavicular nodular metastasis.

Chemotherapy

Two cycles of concurrent chemotherapy during radiotherapy were started on the first day of radiation. Vinorelbine (NVR) was administered in a single dose of 25 mg/m² as a 15 min IV infusion on Day 1 (d1) and d8, and carboplatin (CBDCA) in a single dose with an area under the curve (AUC) of 5 mg/ml per min as a 30 min IV infusion on d8, repeated every 28 days thereafter. Patients received a maximum of four cycles of consolidative chemotherapy after the concurrent chemoradiotherapy. The consolidative chemotherapy regimen was the same as the concurrent chemoradiotherapy regimen. Anti-vomiting, white blood cell/platelet promotion, and other supportive medical care were used if clinically indicated.

Dose escalation and definition of DLT

The radiation dose was escalated using a modified Fibonacci sequence [10], whereas the chemotherapy doses were fixed. Based on the results of the RTOG escalation trial and our previous escalation trial for oesophageal carcinoma [7, 10], 62 Gy was chosen as the initial radiation dose, with a 4 Gy escalation step. Every cohort contained at least three patients. If no dose-limiting toxicity (DLT) was observed after a patient had completed full-dose radiotherapy and concurrent two-cycle chemotherapy, the next dose level was administered; however, repeated administration to the same patient was not allowed. Thus, if one of three patients treated at a particular dose level experienced a DLT, three additional patients were treated at the same level. If a second patient experienced the same DLT, the escalation was stopped and the maximum tolerated dose (MTD) was defined as the dose below the one that caused the DLT. Toxicity was monitored continuously as each patient was accrued, and each patient was evaluated for acute DLT during the first 90 days after the start of radiotherapy.

The MTD of the RTOG escalation trial was 74 Gy, and one iatrogenic death was reported [7]. In our previous oesophageal carcinoma escalation trial involving Asian patients, the MTD value was different from the one obtained in Western patients in the RTOG85-01 trial [10]. Specifically, the MTD of concurrent chemoradiotherapy in Chinese patients was about 70% of that in Western patients.
Although no such discrepancy has been reported in other studies, in clinical practice, we found that the tolerance of Asian patients to concurrent chemoradiotherapy is much lower than that of Western patients. This could also affect the limitations placed on the dose delivered to normal tissue during thoracic radiotherapy in Chinese and other Asian patients. Although there is no direct evidence that the normal tissue of Chinese people has a lower radiation tolerance than that of Western patients, the strict limitations applied in virtually all Chinese studies include a V20 ≤30% for normal tissue: and a maximum dose to the spinal cord of ≤45Gy [9, 12]. In Western studies, the corresponding values are V20 ≤37–40% and ≤50 Gy [13, 14]. To the best of our knowledge, the study described herein is the first radiotherapy dose escalation trial of concurrent chemoradiotherapy with an Asian patient population. Given our concern that overly aggressive concurrent chemoradiotherapy could result in side effects that might threaten patient safety, 70 Gy was set as the target dose. This method of presetting the target dose follows the convention employed in the literature. When the University of North Carolina carried out the first radiotherapy dose escalation study of concurrent chemoradiotherapy for NSCLC, there were no previous data on high-dose concurrent chemoradiotherapy. To address concerns regarding the side effects of treatment, they selected a preset target dose of 74 Gy. Although no DLT occurred at that dose, it was retained as the target dose in a subsequent Phase I trial [15]. The same rationale was used in the dose escalation study of Wu et al. [16]; although none of their three subgroups showed DLT, dose escalation was stopped to avoid the risk of side effects due to higher-dose radiotherapy [16]. Similarly, in this study, the preset target dose was limited to 70 Gy and there was no further dose escalation even in the absence of a DLT. As this design was somewhat different from the traditional design of Phase I trials, it is better designated as a ‘modified Phase I trial’, according to the convention employed in the literature [15]. The purpose of this modified Phase I trial was to determine whether 70 Gy is tolerated by Chinese patients with NSCLC who are concurrently undergoing chemotherapy. Thus, three dose levels were examined in this trial: 62, 66 and 70 Gy. The dose escalation schema is provided in Table 2.

Treatment-related toxicities were assessed according to NCI/NIH CTCAE version 3.0 and were evaluated weekly during concurrent chemoradiotherapy. DLT was defined as severe or life-threatening side effects that influenced the continued implementation of chemoradiotherapy: Grade 3 febrile neutropenia or any Grade 4 neutropenia; Grade 3–4 thrombocytopenia; Grade 3–4 anaemia; Grade 3–4 non-haematologic toxicities except for Grade 3 nausea, vomiting, fatigue and weight loss; or any Grade 5 toxicity.

### Dose attenuation

Dose modifications were based on the most serious toxicities that occurred on any day after treatment according to the plan.

According to the rules of the study, the irradiation dose could not be modified. However, radiotherapy was delayed in patients who suffered Grade 3 or higher toxicity until it resolved (except for Grade 3 nausea, vomiting or weight loss). Radiotherapy was continued but chemotherapy was withheld in patients in whom Grade 3 or higher toxicities unrelated to radiotherapy occurred, for example, peripheral neuritis. Chemotherapy was resumed when these toxicities resolved.

The chemotherapeutic doses were modified as follows: in the presence of Grade 3–4 thrombocytopenia, Grade 3–4 anaemia, Grade 4 neutropenia or Grade 3–4 non-haematologic toxicities (except Grade 3 nausea, vomiting or weight loss), both radiotherapy and chemotherapy were withheld until the toxicities resolved. If this did not occur within 2 weeks, the patient was withdrawn from the study. The NVR and CBDCA doses of the next chemotherapy cycle were thus reduced by 25%, and prophylactic recombinant-human granulocyte colony stimulating factor (GCSF) was administered concurrently with chemotherapy and in all subsequent chemotherapy cycles. If Grade 3 neutropenia or Grade 2 thrombocytopenia alone occurred, chemotherapy was withheld but radiotherapy was continued. The NVR and CBDCA doses of the next chemotherapy cycle were the same as those of the original regimen and GCSF was administered prophylactically.

### Response

Patients were re-evaluated within 4 weeks of completion of the concurrent chemoradiotherapy regimen. Thoracoabdominal spiral CT images were evaluated with respect to the short-term efficacy of the treatment according to the Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST1.1) for tumour response [17]. Response was evaluated as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The response rate (RR) was defined as CR + PR.

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**Table 2. Radiation dose escalation schema**

| Dose level | 3D-CRT (Gy) | Cases |
|------------|-------------|-------|
| 1          | 62          | 3     |
| 2          | 66          | 3     |
| 3          | 70          | 13*   |

*Thirteen patients were in level 3, including one who eventually withdrew from the study.
Follow-up and statistical analysis
After treatment completion, the patients were followed up every 3 months for 2 years and then every 6 months thereafter. All analyses were performed using the SPSS13.0 software package. Survival data were estimated using the Kaplan-Meier model. Survival time was measured from the start date of the concurrent chemoradiotherapy until death from any cause or until the last follow-up. Only the first treatment failure was taken into account. PFS was defined as the duration of survival without local regional recurrence or distant metastases.

RESULTS

Patient characteristics
Between June 2008 and July 2010, 19 patients with previously untreated histologically or cytologically proven NSCLC were enrolled in this trial. The patients’ characteristics are listed in Table 3. One patient who completed only one cycle of chemotherapy during radiotherapy withdrew from the trial for personal reasons. The toxicities and responses of the other 14 men (77.8%) and four women (22.2%) were assessable. The median age was 67 years (48–75), and the median Karnofsky performance status was 80. One patient had clinical Stage IIA disease and had refused surgery for personal reasons, four had Stage IIIA disease, ten had Stage IIIB disease, and three had Stage IV disease with metastatic disease in a thoracic vertebra (one patient), in the brain (one patient) and in the left adrenal gland (one patient). The median GTV was 84.85 cm$^3$ (mean, 87.58 cm$^3$; range, 18.25–200.28 cm$^3$), while the median PTV was 249.70 cm$^3$ (mean, 250.19 cm$^3$; range, 91.61–436.04 cm$^3$).

Compliance
Three dose levels were examined. The respective cohorts comprised 3, 3 and 13 patients receiving 62, 66 and 70 Gy. All patients completed the planned radiotherapy and all, except the one who withdrew from the study for personal reasons, received at least two cycles of concurrent chemotherapy. After they had completed concurrent chemoradiotherapy, the 16 patients with non-PD were administered consolidative chemotherapy. The median number of chemotherapy cycles was four (range, 1–4).

Actual radiation dose for PTV and organ at risk
The dosimetric parameters for PTV are listed in Table 4. The actual radiation doses for the lungs and oesophagus were a mean dose for both lungs of 1498.21 ± 217.47 cGy, V20 = 25.56 ± 4.43%, and a mean dose to the oesophagus of 3464.73 ± 1108.94 cGy.

| Characteristic | No. of patients | Percent |
|----------------|-----------------|---------|
| Gender         |                 |         |
| Male           | 14              | 77.8    |
| Female         | 4               | 22.2    |
| Age            |                 |         |
| Median         | 67              |         |
| Range          | 48–75           |         |
| Karnofsky performance status | |         |
| Median         | 80              |         |
| Range          | 70–90           |         |
| Histology      |                 |         |
| Squamous cell carcinoma | 9 | 50.0 |
| Adenocarcinoma | 8              | 44.4    |
| Large cell carcinoma | 1               | 5.6     |
| Stage          |                 |         |
| IIA            | 1               | 5.6     |
| IIIA           | 4               | 22.2    |
| IIIB           | 10              | 55.6    |
| IV             | 3               | 16.7    |
| Weight loss    |                 |         |
| ≥5%            | 5               | 27.8    |
| <5%            | 13              | 72.2    |
| GTV            |                 |         |
| Median         | 84.85 cm$^3$    |         |
| Range          | 18.25–200.28 cm$^3$ |     |
| PTV            |                 |         |
| Median         | 249.70 cm$^3$   |         |
| Range          | 91.61–436.04 cm$^3$ |     |

Haematologic toxicities
Table 5 describes the haematologic toxicities experienced by the patients according to the dose cohort. Haematologic toxicities were common in the whole study population. The rates of neutropenia, thrombocytopenia and anaemia were 94.4% (17/18), 50.0% (9/18) and 38.9% (7/18), respectively. However, they were were mild to moderate and none of the patients had Grade IV or Grade V haematologic toxicities. Grade 3 non-febrile neutropenia occurred in only 11.1% (2/18) of the patients. Both of them were in the 70
Gy cohort and the duration was less than 7 days in each case. All episodes of thrombocytopenia and anaemia were Grade I or Grade II. Therefore, none of the hematologic toxicities was considered to be a DLT.

**Non-haematologic toxicities**

The Grade 1–3 non-haematologic toxicities experienced by the patients are listed in Table 6. Despite the appearance of common toxicities, the therapy was well tolerated. Most toxicities were mild and manageable. Nausea occurred in 88.9% (16/18) of the patients, with most of the episodes being of Grade I or Grade II and not requiring special medical care other than routine anti-emetic treatment. Vomiting was not common, and all cases were Grade I or Grade II. Most patients experienced weight loss and fatigue, but only a few required support with temporal fluid replacement. The frequency of radiation oesophagitis was 77.8% (14/18); however, there were no Grade III or worse toxicities. All cases of Grade I or Grade II radiation oesophagitis were clinically manageable, and neither a feeding tube nor intravenous hyperalimentation was needed. The planned therapy was not stopped or delayed because of nausea, vomiting, fatigue, weight loss or radiation oesophagitis in any case.

At a dose level of 70 Gy, one of the initial three patients developed Grade III radiation pneumonia 4 weeks after the completion of radiotherapy. It was controlled by corticosteroid therapy using the following regimen: 40 mg methylprednisolone (IV; 1–7 days followed by 50 mg prednisone tablets (oral; 1/day). Depending on the disease condition of the patient, the prednisone dose was reduced to 5–10 mg every 1–2 weeks until the minimum effective

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**Table 4.** Radiation dose of PTV

| Group | D100 (cGy) | D90 (cGy) | V100 (%) | V90 (%) |
|-------|------------|-----------|----------|---------|
| 62 Gy | 5334.79 ± 270.58 | 5943.43 ± 239.81 | 91.83 ± 3.24 | 99.86 ± 1.79 |
| 66 Gy | 5679.38 ± 245.73 | 6381.35 ± 298.64 | 91.02 ± 3.97 | 99.38 ± 2.02 |
| 70 Gy | 6017.83 ± 406.13 | 6806.82 ± 267.57 | 90.76 ± 6.12 | 99.14 ± 1.84 |

**Table 5.** Haematologic toxicity

| Toxicity     | 62 Gy Case | 66 Gy Case | 70 Gy Case | Total (%) |
|--------------|------------|------------|------------|-----------|
| Neutropenia  | 1 1 4      |            |            | 17 (94.4) |
|              | 2 2 5      |            |            |           |
|              | 0 0 2      |            |            |           |
| Thrombocytopenia | 0 1 4    |            |            | 9 (50.0)  |
|              | 1 0 3      |            |            |           |
| Anaemia      | 1 1 3      |            |            | 7 (38.9)  |
|              | 0 0 2      |            |            |           |

**Table 6.** Non-haematologic toxicity

| Toxicity                      | 62 Gy Case | 66 Gy Case | 70 Gy Case | Total (%) |
|-------------------------------|------------|------------|------------|-----------|
| Radiation pneumonia           | 1 1 3      |            |            | 11 (61.1) |
| Radiation oesophagitis        | 1 1 4      |            |            | 14 (77.8) |
| Radiation dermatitis          | 0 1 2      |            |            | 6 (33.3)  |
| Nausea                        | 1 0 0      | 1 2 9      | 0 1 2      | 16 (88.9) |
| Vomiting                      | 0 0 2      | 1 1 2      |            | 6 (33.3)  |
| Anorexia                      | 1 0 3      | 2 1 5      | 0 2 3      | 17 (94.4) |
| Fatigue                       | 0 1 3      | 1 1 3      | 1 0 3      | 13 (72.2) |
| ALT                           | 1 1 3      | 1 1 3      | 1 0 3      |           |
| AST                           | 1 0 2      | 3 16.7     | 3 16.7     |           |
| Cr                            | 1 0 2      | 3 16.7     | 3 16.7     |           |

ALT = alanine aminotransferase, AST = aspartate aminotransferase, Cr = serum creatinine.
dose was maintained. Maintenance therapy was carried out for at least 3 months. After the patient’s disease condition was judged as stable based on the physical examination and a review of the chest CT study, hormone therapy was stopped. Grade III radiation pneumonia was defined as the first DLT. At that point, three additional patients were enrolled in the 70 Gy dose level and there was no further DLT. To examine the safety of the 70 Gy dose level, six additional patients were included; there was no case of DLT. From these results, we concluded that 70 Gy can be safely delivered to Chinese patients with NSCLC who are undergoing concurrent chemoradiotherapy. According to the trial design, the target dose of 70 Gy was achieved.

Response
The clinical responses of the irradiated target lesions of 18 patients were assessable. The RR was 77.8% (14/18); specifically, 27.8% (5/18) of the patients achieved CR, 50.0% (9/18) achieved PR, 11.1% (2/18) achieved SD and 11.1% (2/18) achieved PD.

Survival
As the follow-up time was relatively short, survival data were not yet available at the time of writing. The median follow-up time was only 9.5 months (range, 4–18 months). The median PFS was 12 months, and the probability of PFS at 1 year was 37.6% (Fig. 1). The median survival and 1 year overall survival (OS) were not reached. Ten patients experienced disease recurrence or progression; in three patients the progression was local, restricted to within the radiation field. One patient suffered local progression within the radiation field and distant progression (brain metastases), while six had only distant progression (liver metastases in two patients, brain metastases in two patients, bone metastases in one patient and adrenal metastases in one patient).

DISCUSSION
Radiotherapy is one of the most important treatment modalities for NSCLC. According to Fletcher, a dose of 80–100 Gy is required to cure lung cancer [18]. This was confirmed in a clinical trial of stereotactic body radiotherapy, in which the survival rate of patients who received a biologically effective dose (BED) of at least 100 Gy was significantly higher than that of patients who received a BED of less than 100 Gy [19]. However, due to the limitations imposed by the need to protect normal tissues and organs, this high radiotherapy dose cannot be applied using conventional radiotherapy techniques.

3D-CRT is able to deliver a high-dose of radiation to the tumour target area while minimising the irradiation dose administered to the surrounding tissues, thus allowing, e.g., an increase in the radiotherapy dose for NSCLC. The RTOG9311 study applied 3D-CRT in a dose escalation trial of radiotherapy alone and reported that with this approach the radiotherapy dose could be safely increased to 83.8 Gy [20]. In a dose escalation trial after 42 Gy conventional radiotherapy (3 Gy increments), Fudan University Cancer Hospital administered 3D-CRT to a group of patients and determined that 78 Gy was tolerable [16]. Dong et al. reported that at V20 <25%, the radiotherapy dose could be safely increased to 82 Gy, and the resultant radiation injuries were acceptable [21].

Furuse et al. confirmed that concurrent chemoradiotherapy significantly improved the survival rates of patients with locally advanced NSCLC compared to radiotherapy alone [4]. Based on their findings, the RTOG initiated a dose escalation trial of concurrent chemoradiotherapy in which a radiotherapy dose of 74 Gy was determined to be the MTD [7]. Likewise, an American multi-centre clinical trial identified the same MTD for concurrent chemoradiotherapy involving weekly paclitaxel and carboplatin [13]. Currently, the RTOG is assessing radiotherapy at a dose of 74 Gy in a multi-centre Phase III clinical trial of concurrent chemoradiotherapy for NSCLC.

Numerous studies have evaluated concurrent chemoradiotherapy for NSCLC in China. However, they differed with respect to radiotherapy devices, delivered dose, irradiation area and radiotherapy regimen, such that currently there is still no standard regimen. Moreover, it is very difficult to compare the efficacy and side effects of the various regimens since the examined radiotherapy doses ranged from 60 Gy to 70 Gy [22–24]. To the best of our knowledge, radiotherapy dose escalation for concurrent chemoradiotherapy has yet to be examined in a Phase I trial. To increase the tumour control rate and improve survival, the
maximal radiotherapy dose within the tolerable range should be administered.

Due to the differences in physique between Asian and Western patients, it was unclear whether the dose of 74 Gy recommended by the RTOG Phase I trial could be safely used to treat Chinese patients. Before this modified Phase I trial for NSCLC we have carried out a dose escalation trial of concurrent chemoradiotherapy for oesophageal carcinoma using the chemotherapy regimen similar in design to the RTOG85–01 trial. Although the radiation field was significantly smaller than in the RTOG trial, the MTD was significantly lower [10]. Therefore, it was important to conduct a dose escalation trial in Chinese patients with NSCLC, with the goal of delivering the high radiotherapy dose used in concurrent chemoradiotherapy.

Paclitaxel is a third-generation chemotherapeutic agent with improved effectiveness in chemoradiotherapy alone and in chemoradiotherapy for patients with NSCLC. The RTOG thus examined the utility of paclitaxel and carboplatin in a Phase I trial. We selected vinorelbine and carboplatin regimens for the following reasons. First, the CALGB9431 study examined the utility of concurrent chemoradiotherapy involving cisplatin combined with vinorelbine, paclitaxel, or gemcitabine, with no significant difference in the RR or the 3-year OS rate among the three groups; however, treatment-related toxicities were milder in the vinorelbine group. The frequency of Grade III/IV neutropenia was significantly lower in the vinorelbine group than in the paclitaxel and gemcitabine groups, as were the frequencies of vomiting and weight loss [8]. Second, in weekly paclitaxel regimens dexamethasone is required to prevent allergic reactions, but a large dose of dexamethasone could increase the incidence of relevant side effects. Third, large doses of cisplatin have the disadvantages of stronger emetic effects and the need for increased hydration. In addition, we replaced cisplatin with carboplatin to reduce further the frequency of gastrointestinal side effects, as confirmed by the results of this modified Phase I trial.

In radiotherapy dose escalation trials, the RTOG and NCCTG0028 determined the same MTD of 74 Gy [7, 13] and dose-related deaths occurred during the dose escalation process. Taking into consideration the differences in physique between Asian and Western patients and the results of dose escalation studies of oesophageal carcinoma, the target dose in our study was 70 Gy; that is, the dose would not be increased beyond 70 Gy even in the absence of DLT. As demonstrated in our modified Phase I trial, dose escalation of 3D-CRT to 70 Gy is possible for Chinese patients with NSCLC, with acceptable toxicity. The overall incidence of radiation pneumonitis was 61.1%, mostly Grade I/II. There was one case of Grade III radiation pneumonitis, controlled by corticosteroid treatment, in the 70 Gy group; this patient died due to disease progression and his death was not associated with radiation pneumonitis. Radiation oesophagitis was common, developing in 77.8% of the patients. Since in this study the involved field irradiation regimen and active intervention measures were used, all episodes of radiation oesophagitis were Grade I/II and did not significantly influence the implementation of radiotherapy. The incidence of neutropenia was as high as 94.4% but in the 70 Gy group the frequency of Grade III neutropenia was only 11.1% (2/18). Since the duration of the neutropenia was less than 7 days and no patient had Grade III febrile neutropenia, these two cases of Grade III neutropenia were not considered as DLT. None of the other haematologic toxicities, such as thrombopenia and anaemia, were serious, whereas due to the administration of concurrent chemoradiotherapy, there was a high incidence of gastrointestinal side effects. The incidences of nausea, fatigue and weight loss were 88.9% (16/18), 72.2% (13/18) and 94.4% (17/18), respectively, with only three cases of Grade III fatigue whereas all of the others were Grade I/II. Vomiting occurred in only 33.3% (6/18) of the patients and all of these cases were Grade I/II; thus no case was of Grade III or higher. Only a few of the patients required a short peripheral intravenous infusion; none required nasal feeding or intravenous hyperalimentation support. It was therefore concluded that concurrent chemoradiotherapy involving 3D-CRT combined with vinorelbine and carboplatin has mild gastrointestinal side effects and is easy to manage clinically. Moreover, this concurrent chemoradiotherapy strategy produces a high tumour RR. The RR determined in this study was 77.8% (14/18), in line with the 62.5–86.5% of previous studies [8, 22–24] and supporting the use of this treatment regimen to achieve a good local control rate for tumours. Although survival data were not the main endpoint of this modified Phase I trial, the median PFS of 12 months and the 1 year PFS of 37.6% were encouraging, given that 72.2% of patients had Stage III/IV or IV disease. Due to the relatively short follow-up period, the overall survival data cannot be evaluated yet.

In summary, the integration of high-dose 3D-CRT with concurrent vinorelbine and carboplatin is feasible in Chinese patients, and dose escalation of thoracic radiotherapy to 70 Gy is possible, producing acceptable toxicity. The overall response and PFS data of this study are encouraging. Based on this modified Phase I trial, a Phase II trial has been initiated to evaluate further the safety and efficacy of this therapeutic strategy.

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