Efficacy of the smaller target volume for stage III non-small cell lung cancer treated with intensity-modulated radiotherapy

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Abstract. The present study reports the local recurrence, distant metastasis, progression-free survival, overall survival and radiation toxicity between two arms of stage III non-small cell lung cancer (NSCLC) treated with intensity-modulated radiotherapy (IMRT); one arm with clinical target volume (CTV) and the other without CTV. The two arms of local recurrence, distant metastasis, progression-free survival, overall survival, grade 3-4 radiation esophagitis and hematological toxicity had no statistical significance. However, the grade 3-4 radiation pneumonia rate of the group without CTV was significantly decreased. This supports the concept that stage III NSCLC treated with IMRT, which omitted CTV, can reduce the occurrence of radiation pneumonia. The aim of the present study was to analyze the feasibility of the smaller target volume for stage III NSCLC treated with IMRT. Data from 105 patients with stage III NSCLC who were hospitalized and received IMRT between January 1, 2008 and November 30, 2012 were retrospectively analyzed. A total of 55 cases were irradiated with target volume without CTV and 50 cases were irradiated with CTV. Dose prescription was 100% PTV at 54-63 Gy/27-35 F/5.4-7 weeks. The two arms of the patient characteristics and treatment deliveries had no statistical significance. The two arms of the patients were compared for local recurrence, distant metastasis, progression-free survival, overall survival and radiation-related toxicity. In the arms without and with CTV, the local relapse and distant metastases rates were 32.7 and 32.0% (P=1.000) and 56.4 and 48.0% (P=0.946), respectively. The median progression-free survival time for the two arms was 9 months (P=0.619). The 1-, 2- and 3-year survival rates of the arms without and with CTV were 74.5, 43.6 and 23.6%, and 70.0, 46.0 and 20.0% (P=0.956), respectively. In the two arms, grade 3-4 radiation esophagitis and hematological toxicity had no statistical significance. However, in the arm without CTV, grade 3-4 radiation pneumonia was only 5.5%, compared with 18.0% in the arm with CTV (P=0.044). In conclusion, the smaller target volume for stage III NSCLC treated with IMRT was feasible.

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Introduction

Currently, lung cancer constitutes the major cause of cancer-associated mortality worldwide (1), accounting for 18% (2,3). Non-small cell lung cancer (NSCLC) accounts for 85% among lung cancer. The majority of patients are stage III, losing the chance of radical surgery (4). At present, the 1st or 2nd cycle of chemotherapy concurrent with chest irradiation has become the standard treatment for stage III NSCLC in the NCCN Guidelines. However, the lung, regarded as a sensitive organ to radiation damage, is inevitably under irradiation. Radioactive pneumonia is the important restriction factor of radiation dose escalation (5). Numerous studies indicated that radiation pneumonia may be a life-threatening complication (6,7), with a mortality rate of ~4% (8). Therefore, to reduce the occurrence of radioactive pneumonia is crucial.

At present, clinical target volume (CTV) is a tissue volume that contains gross tumor volume (GTV) and subclinical microscopic malignant lesions following International Commission on Radiation Units and Measurements (ICRU) 62. To take into account 95% of the microscopic extension, the CTV margin of 8 and 6 mm must be chosen for adenocarcinoma and squamous cell carcinoma, respectively (9). Delineation of CTV is currently the standard for current intensity-modulated radiotherapy (IMRT) for patients with NSCLC. Cai *et al* (10) noted that target volume delineation omitting CTV for limited-disease small cell lung cancer receiving IMRT was feasible, and it did not reduce the local control and survival rates, but significantly reduced the incidence of radioactive pneumonia.

Thoracic radiotherapy omitting CTV for stage III NSCLC reduced the radiation volume, so radiation pneumonia may be controlled. The present study compared one arm of patients with CTV and the other arm without CTV with local relapse, distant metastasis, progression-free survival, overall survival and radiation toxicity. The aim of the study was to analyze the feasibility of the smaller target volume for stage III NSCLC treated with IMRT.

Materials and methods

Study design. In total, 105 patients with stage III NSCLC who were hospitalized and received IMRT were enrolled. A total of 55 cases were irradiated with target volume without CTV, and 50 cases were irradiated with CTV. All the patients included in the study were followed up at regular intervals: Every 3 months for the first 2 years after treatment, and subsequently every 6 months during 3-5 years. The final follow-up time was November 30, 2012. Follow-up examinations included basic laboratory studies, bone emission computed tomography (ECT), CT of the chest, magnetic resonance imaging (MRI) of the brain and ultrasound imaging of the abdomen. The region that was 5 mm inside and outside of the planning target volume (PTV) was defined as relapse in-margin. In and out of the area of relapse in-margin were defined as relapse in-field and out-of-field, respectively. Radiation-related toxicity was scored according to the criteria of Radiation Therapy Oncology Group (RTOG).

Patients. In total, 105 patients were treated in the Department of Radiation Oncology at Peking University Cancer Hospital (Beijing, China) between January 1, 2008 to November 30, 2012. All the patients were proved by cytology or histology and were untreated prior to enrollment. Staging procedures included bone ECT, CT of the chest, MRI of the brain and ultrasound imaging of the abdomen. Stage III NSCLC was defined according to the criteria of the 7th edition of tumor-node-metastasis staging of lung cancer, which was established by the Union for International Cancer Control. Exclusion criteria were receipt of lung cancer resection, recurrence following radiotherapy or metastatic carcinoma.

Treatments. Patients were fixed with a thermoplastic sheet and 5-mm slices were scanned with a conventional CT simulator. The pulmonary extent of the tumor was delineated on pulmonary window (width, 1600 HU; level, -800 HU) and the mediastinal lymph nodes, which were positive on biopsy or positron emission tomography (PET) or were ≥10 mm in the short axis on the chest CT, and were delineated on mediastinal window (width, 400 HU; level, 20 HU).

In the arm with CTV, target volume was delineated according to ICRU 62. GTV contained a clinically detectable tumor according to CT or PET. The CTV margin of 8 mm covered microscopic spread of cancer cells in adenocarcinoma, however, this was 6 mm for squamous cell carcinoma. A margin of 3-15 mm was added to CTV to form the internal target volume (ITV), which was to cover respiratory movement. Respiratory movement was measured on a conventional simulator during patients' free breathing. Considering setup variations, a margin of 5 mm was added to ITV to create PTV. In the same way, GTV, ITV and PTV were delineated in the arm without CTV, but CTV was omitted. The treatment planning system used was the Varian Medical System (Palo Alto, CA, USA), and the dose prescription was 100% PTV for 54-63 Gy/27-35 F/5.4-7 weeks.

Statistical analysis. Statistical analysis was performed with SPSS 17.0 (SPSS, Inc., Chicago, IL, USA). The differences between the two arms were assessed using t-test for the mean of sample and using λ^2 test for the constituent ratio of sample. Overall survival and progression-free survival rates were studied by Kaplan-Meier analysis. Patients alive at the time of last follow-up were allocated that date.

Table I. Patient characteristics.

Characteristics	Arm without CTV	Arm with CTV	P-value
No. of patients	55	50	
Gender, n (%)			
Male	42 (76.4)	40 (80.0)	0.653
Female	13 (23.6)	10 (20.0)	
Age, median years (range)	59 (41-78)	61.5 (44-81)	0.330
≤65 years	38 (69.1)	30 (60.0)	
>65 years	17 (30.9)	20 (40.0)	
ECOG score, n (%)			
0	34 (61.8)	28 (56.0)	0.545
1	21 (38.2)	22 (44.0)	
Weight loss, n (%)			
>5%	3 (5.5)	2 (4.0)	1.000
≤5%	52 (94.5)	48 (96.0)	

CTV, clinical target volume; ECOG, Eastern Cooperative Oncology Group.

Results

Patients. In the study, 105 cases were evaluated, of which 55 cases were irradiated with target volume without CTV and 50 cases with CTV. All the cases were from the Department of Radiation Oncology at Peking University Cancer Hospital between January 1, 2008 to November 30, 2012. Patient characteristics are listed in Table I.

Chemotherapy cycles. The 1st or 2nd cycle of chemotherapy concurrent with chest irradiation was the standard treatment for stage III NSCLC in the NCCN Guidelines. The arm without CTV accepted 1.54±1.51 cycle induction chemotherapy, 0.94±1.00 cycle adjuvant chemotherapy and 0.58±0.91 cycle concurrent chemotherapy; the arm with CTV accepted 1.31±1.60 cycle induction chemotherapy, 0.96±0.94 cycle adjuvant chemotherapy and 0.65±0.95 cycle concurrent chemotherapy. Treatment delivery was as listed in Table II. There were no statistically significant diffences between the two arms.

GTV and PTV volume and dose, and short-term response. The volume and dose of GTV and PTV, and the short-term response of the two arms are as listed in Table III. There was a statistical significance for PTV volume between the two arms.

Relapse and distant metastases rates. In the arms without and with CTV, the local relapse and distant metastases rates were 32.7 and 32.0% (P=1.000), and 56.4 and 48.0% (P=0.946),

Table II. Treatment delivery.

Characteristics	Arm without CTV	Arm with CTV	P-value
No. of patients	55	50	
Treatment schedule, n (%)			
Induction chemo	3 (5.5)	6 (12.0)	0.724
Concurrent chemo	12 (21.8)	10 (20.0)	
Induction + concurrent adjuvant chemo	20 (36.4)	19 (38.0)	
Induction + concurrent chemo	6 (10.9)	5 (10.0)	
Concurrent adjuvant	10 (18.2)	5 (10.0)	
RT alone	4 (7.3)	5 (10.0)	
Induction chemo (cycles), n (%)			
0	26 (47.3)	20 (40.0)	0.828
1	4 (7.3)	3 (6.0)	
2	16 (29.1)	16 (32.0)	
≥3	9 (16.4)	11 (22.0)	
Concurrent chemo (cycles), n (%)			
0	37 (67.3)	35 (70.0)	0.517
1	0 (0)	1 (2.0)	
2	18 (32.7)	14 (28.0)	
Adjuvant chemo (cycles), n (%)			
0	25 (45.5)	26 (52.0)	0.117
1	7 (12.7)	1 (2.0)	
2	23 (41.8)	23 (46.0)	

CTV, clinical target volume; chemo, chemotherapy; RT, radiation therapy.

respectively. Relapse and metastasis sites of the two arms are listed in Table IV.

Toxicities. Radiation and chemo-related toxicities were scored according to RTOG. They are listed in Table V. The only apparent statistical significance between the two arms was for grade 0-2 radiation pneumonia.

Discussion

Once radiation pneumonia occurs during radiotherapy, the radiotherapy must be terminated. Thus, it increases the local relapse and reduces the overall survival rates, influences the patient's quality of life and can even result in fatality. The 1st or 2nd cycle of chemotherapy concurrent with chest irradiation has become the standard treatment for stage III NSCLC in the NCCN Guidelines. It also increases the incidence of radiation pneumonia at the same time as improving the curative effect (11). In the study by Sura *et al* (12), IMRT increased the volume of lung receiving smaller, yet potentially toxic doses of radiation, thus it increased the incidence of radiation pneumonia. Therefore, more attention must be paid to reduce the incidence of radiation pneumonia.

How to reduce the incidence of radiation pneumonia whilst not reducing the radiotherapy curative effect remains to be solved. Cai *et al* (10) noted that target volume delineation omitting CTV for limited-disease small cell lung cancer receiving IMRT was feasible, and it did not increase the local relapse rate or reduce the survival rate, however, it significantly reduced the incidence of radiation pneumonia. Comparing the arm without CTV to the arm with CTV, the local relapse rate

Table III. Volume and dose of GTV and PTV, and short-term response of the two arms.

Characteristics	Arm without CTV	Arm with CTV	P-value
Volume, cm^3			
GTV	168.48±70.40	166.84±75.76	0.909
PTV	370.71±117.94	471.59±154.01	0.000
Dose, Gy			
GTV	61.56±2.34	61.84±3.12	0.607
PTV	58.91±3.46	58.48±3.56	0.533
Short-term response, n			
CR	4	3	0.961
PR	32	29	
SD	19	18	
PD	0	0	

CTV, clinical target volume; GTV, gross tumor volume; PTV, planned target volume; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table IV. Relapse and metastasis sites of the two arms.

Characteristics	Arm without CTV	Arm with CTV	P-value
No. of patients	55	50	
Local relapse, n (%)	18 (32.7)	16 (32.0)	1.000
In field	17 (30.9)	15 (30.0)	
In margin	1 (1.8)	1 (2.0)	
Metastasis, n (%)	31 (56.4)	24 (48.0)	0.946
Brain	6 (10.9)	4 (8.0)	
Bone	7 (12.7)	5 (10.0)	
Liver	7 (12.7)	4 (8.0)	
Lung	3 (5.5)	2 (4.0)	
Mediastina LN	2 (3.6)	3 (6.0)	
Peritoneum LN	0 (0.0)	1 (2.0)	
Supraclavicular LN	1 (1.8)	1 (2.0)	
Adrenal gland	1 (1.8)	1 (2.0)	

CTV, clinical target volume; LN, lymph node.

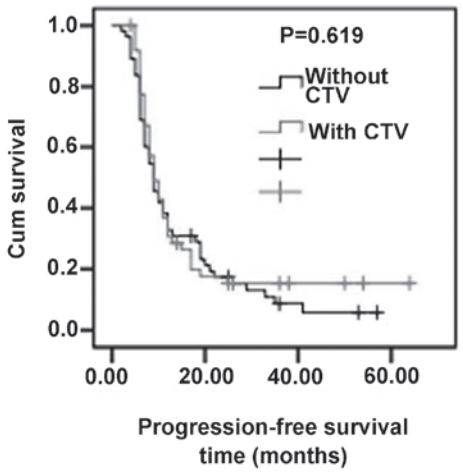

Figure 1. Kaplan-Meier analysis of progression-free survival. The median progression-free survival of the two arms were 9 months (P=0.619). The difference of progression-free survival of the two arms had no statistical significance.

Table V. Radiation and chemo-related toxicities of the two arms.

Toxicities	Arm without CTV, n (%)	Arm with CTV, n (%)	P-value
Hematological toxicity			
0-2	49 (89.1)	42 (84.0)	0.443
3-4	6 (10.9)	8 (16.0)	
Radiation esophagitis			
0-2	50 (90.9)	43 (86.0)	0.430
3-4	5 (9.1)	7 (14.0)	
Radiation pneumonia			
0-2	52 (94.5)	41 (82.0)	0.044
3-4	3 (5.5)	9 (18.0)	

CTV, clinical target volume.

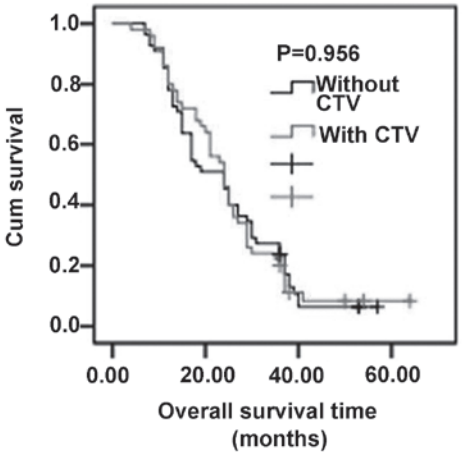

Figure 2. Kaplan-Meier analysis of overall survival. The 1-, 2- and 3-year survival rates of the arm without clinical target volume (CTV) and arm with CTV were 74.5, 43.6 and 23.6%, and 70.0, 46.0 and 20.0% (P=0.956), respectively. The difference of overall survival of the two arms also had no statistical significance.

was 16.7 vs. 17.1% (P=0.586), and distant metastases rate was 42.6 vs. 51.4% (P=0.274). The 1-, 2- and 3-year survival rates of the arm without CTV and arm with CTV were 81.0, 66.2 and 61.5%, and 88.6, 61.7 and 56.6% (P=0.517), respectively. In the arm without CTV and arm with CTV, grade 3-4 radiation pneumonia was 7.4 and 22.9% (P=0.040), respectively. Whether this can be applied to NSCLC is unknown.

To the best of our knowledge, this is the first clinical study reporting target volume omitting CTV in stage III NSCLC treated with IMRT. We were concerned most with whether omitting CTV resulted in a high margin local relapse rate. In the study, the margin local relapse rate was 1.8% in the arm without CTV and 2.0% in the arm with CTV. In the two arms, the major local relapse section was all in-field. The existence of hypoxic cancer cells, which are radiation resistant and require higher irradiation doses to be killed (13), was the possible reason. However, in the arm without CTV, grade 3-4 radiation pneumonia was only 5.5%, compared with 18.0% in the arm with CTV (P=0.044).

The possible reasons for these conclusions were as follows. First, the radiation dose is one of the important prognostic factors. Omitting CTV can reduce the radiation target volume and make it easier for GTV to receive an efficient radiation dose, which can reduce the local relapse (14-16). GTV could receive a higher radiation dose, which can eliminate the hypoxic cancer cells, whilst simultaneously protecting the normal tissue. Therefore, a smaller target volume and higher GTV radiation dose may be the future research direction. Second, the subclinical lesions that were scattered on the edge of the GTV had a lower tumor burden and were in an oxygen enrichment condition. Therefore, their radiation sensitivity was better (17). In radiotherapy, the incidental dose to the ipsilateral hilus pulmonis, the mediastinal and paratracheal nodes could be <40-50 Gy when these regions were not in the radiotherapy target volume (18). The subclinical lesions received enough to

be eliminated by the incidental dose. As 100% PTV irradiation was the prescription dose in the present study, a ≥8 mm range between PTV and GTV would accept at least half of the total radiation dose. Third, NSCLC was not radiation sensitive, but had easy local relapse and distant metastases compared with SCLC (19). The main cause of treatment failure was local recurrence and distant metastasis, however, the main cause of fatality was always organ failure lead by distant metastasis (20). In the present study, the distant metastasis rate of the two arms was significantly higher compared with the local recurrence rate. Therefore, a perfect local control rate is insignificant if the higher distant metastasis rate cannot be reduced.

In conclusion, the smaller target volume for stage III NSCLC treated with IMRT was feasible. It did not increase the local relapse rate and reduce survival rate, but significantly reduced the incidence of radiation pneumonia. However, the study is not a randomized controlled study, and further research and validation is necessary.

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