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Clinical observation of platinum-based combined with concurrent three-dimensional conformal radiotherapy in patients with locally advanced non-small cell lung cancer

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Abstract ***Objective:*** The aim of our study was to explore the short-term efficacy of platinum-based combined with concurrent chemoradiotherapy for locally advanced non-small-cell lung cancer (NSCLC). ***Methods:*** Between 2006 to 2010, 78 cases of locally advanced NSCLC were enrolled into this trial. All patients were given platinum-based chemotherapy combined with concurrent three-dimensional conformal radiotherapy (3-DCRT). Chest CT scans were obtained during end-expiratory and end-inspiratory pauses when performing positioning. Image fusion was done after the image data was transferred to treatment plan system (TPS). The target volume was delineated on the fusion images. The chemotherapy was given on the first day of radiotherapy. Comprehensive examinations were conducted 4–6 weeks after concurrent chemoradiotherapy to assess short-term efficacy. ***Results:*** Complete remission (CR) was achieved in 8 cases and partial remission (PR) in 54 cases. The efficiency rate reached 79.5%. Grade III–IV radiation esophagitis occurred in 11.5%. No exit and death cases during treatment. ***Conclusion:*** Concurrent chemo-radiotherapy could significantly improve the short-term efficacy and prolong survival of stage III NSCLC, meanwhile the adverse reactions could be tolerated.

Key words cisplatin; chemo-radiotherapy; non-small-cell lung cancer; three-dimensional conformal; image fusion

In recent years, the incidence of lung cancer increased year by year, and has become the first cause of death for cancer in our country. Short-term and long-term efficacy of chemotherapy and radiotherapy are not satisfied [1], mainly due to the difficulties of local control and distant metastases. For patients with lung cancer of operable stages III–IV, combining radiotherapy and chemotherapy become the primary means of comprehensive treatment. And 3-dimensional conformal radiation therapy (3-DCRT) has been widely used in clinical practice. Between July 2006 to July 2010, 78 patients who with locally advanced non-small cell lung cancer (NSCLC) in our department (Department of Oncology, Renmin Hospital of Wuhan University, China) were randomized to platinum-based two-drug regimen concurrent chemo-radiotherapy and achieved good effect.

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Patients and methods

Patients

A total of 78 NSCLC patients (aged 38–70 years; median 56 years) confirmed by pathology or cytology were included. Among them, 42 cases were males, 36 cases were females, PS score ≤ 2 points, the expected survival time > 3 months, installments by 2009 IASLC staging. Patients characteristic were shown in Table 1.

Chemotherapy regimens

Patients were treated with perfect pre-treatment assessment before chemotherapy, and the tumors were measured at baseline. The chemotherapy was given on the first day of radiotherapy. All patients received platinum-based chemotherapy (NP, TP or GP), 21-day cycle. Each patient was completed two cycles of chemotherapy. During the treatment, blood routine examination was monitored once a week, liver and kidney function, drug-related toxicity assessment were monitored in all of the patients before and after treatment. Chemotherapy regi-

Table 1 Patient characteristics

Characteristics	No. of patients
Sex	
Male	42
Female	36
Installments	
IIIA	26
IIIB	52
Pathology	
Squamous cell carcinoma	38
Adenocarcinoma	40
Position	
Central	47
Peripheral	31

Table 2 Chemotherapy regimens

Regimen	Usage	The total cycle	*n*
NP	NVB 25 mg/m^2 d1, 8 DDP 80 mg/m^2 d1	78	39
TP	TXL 140 mg/m^2 d1 DDP 80 mg/m^2 d1	56	28
GP	GEM 1000 mg/m^2 d1, 8 DDP 80 mg/m^2 d1	22	11

mens were listed in Table 2.

Radiotherapy regimens

3-DCRT was taken in all the patients. The patient in supine position, with hands catch the plate column by crossing the head, and body fixed by vacuum mould. Spiral CT chest scans, both during end-expiratory and end-inspiratory pauses second scan, slice thickness was 5 mm, 3 mm reconstruction. Image fusion was done after the image data was transferred to treatment plan system (TPS). Deputy chief physician sketch the target areas and surrounding organs in the fused image produced by TPS. Because they were end-expiratory and end-inspiratory secondary scan fusion images (Fig. 1 and 2), the target areas were set as internal gross target volume (IGTV) and another extension of 6–10 mm for the planning target volume (PTV). The dose of the thoracic radiotherapy was 64–68 Gy / 32–34 / 6.2–6.4 W.

Evaluation criteria

Comprehensive examinations were conducted 4–6 weeks after concurrent chemo-radiotherapy to assess short-term efficacy. According to CT examination tumor flinch case before and after treatment, response evaluation criteria in solid tumors (RECIST) as evaluation criteria [2]. The curative effects of the treatment in patients was divided into four categories: complete remission (CR), partial remission (PR), stable disease (SD) and progressing (PD). Response rate (RR) was calculated by CR plus and PR. Quality of life scores by Eastern Cooperative Oncology Group (ECOG) and PS score. Adverse reactions by NCI-CTCAE standards are divided into 0–IV grade. Esophagitis and radiation pneumonitis were evaluated by Radiation Therapy Oncology Group (RTOG) / European Organization for Research and Treatment of Cancer (EORTC) classification standard evaluation.

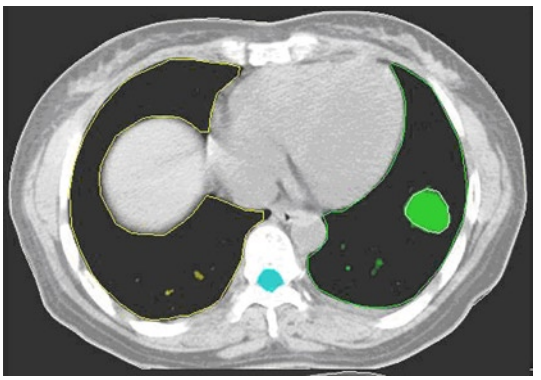

Fig. 1 The images of end-inspiratory

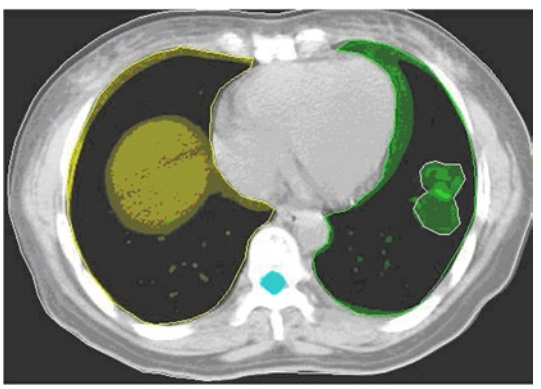

Fig. 2 The fusion images of end-expiratory and end-inspiratory

Results

Short-term effects

Grades III–IV radiation esophagitis occurred in 11.5%. No exit and death cases during treatment. The whole group CR, PR, SD, PD and RR was 8%, 54%, 9%, 7% and 79.5%, respectively.

Adverse reactions

Common adverse reactions were myelosuppression and gastrointestinal reactions. Grades III–IV neutropenia occurred in 33.3%, gastrointestinal reactions occurred in 12.8%, radiation esophagitis occurred in 11.5%, and grades III–IV radiation pneumonitis occurred in 0% (Table 3).

Table 3 Adverse reactions (*n*)

Adverse reactions	Toxicity grade					Incidence of III and IV
	0	I	II	III	IV	
Nausea, vomiting	4	19	45	10	0	12.8%
Neutropenia	6	18	28	21	5	33.3%
Thrombocytopenia	16	26	28	8	0	10.3%
Renal dysfunction	69	9	0	0	0	0
Liver dysfunction	53	18	10	0	0	0
Radiation esophagitis	19	36	14	9	0	11.5%
Radiation pneumonitis	45	17	6	0	0	0

Discussion

Lung cancer is a common clinical malignant cancer, which accounts for about 80% of NSCLC, 30%–40% of patients are diagnosed with locally advanced [3]. Currently NSCLC drug regimen containing platinum has formed a consensus, but not more than 40% efficient [4]. Radiotherapy has certain advantages in locally advanced NSCLC. Compared with the surgical treatment, radiotherapy can adapt to a wider range. Clinical study showed that compared concurrent chemo-radiotherapy and radiotherapy alone, the former improves the survival rate and reduce the rate of distant metastasis, but no change in the rate of local control. The leading cause of treatment failure is local control failure, and the reason is that the limitation of lung tissue tolerated dose [5].

Patients using end-expiratory and end-inspiratory image fusion for target area after the second scan sketch, and the advantages is that irradiated volume is smaller than conventional 3-DCRT target. It was estimated by TPS, which depending on different tumor sites and the size of target volume, and the conventional 3-DCRT target fusion target volume than the second scan images sketched increases 19.17%–45.7% [6].

Currently chemotherapy treatment model has become increasingly mature. Japanese scholars study showed that the 5-year survival rates of concurrent chemo-radiotherapy and sequence chemo-radiotherapy of stage III NSCLC were 15.8% and 8.9% respectively, with a median survival 16.5 months and 13.3 months. We concluded that chemo-radiotherapy can improve local control rate and the survival rate. 3-DCRT is a therapy technique which conforms three dimensional shape volume of high dose radiation to target area and improves enhancement of the therapeutic effects effectively [7]. The advantages of 3-DCRT included: (1) precise target location and target delineation, enabling high-dose region concentrated; (2) accurate calculation of normal tissues around the dose received, minimizing exposure to normal tissues and improvement the local control rate for locally advanced NSCLC. A set of data showed that simple 3-DCRT efficiency is 57.2% in Chinese Academy of Medical Sciences Cancer Hospital [8]. The group of 78 cases of stage III NSCLC patients concurrent chemo-radiotherapy total effective rate was 79.5%, and the results showed that concurrent chemo-radiotherapy significantly increased than 3-DCRT in effective rate, consistent with reports in the literature [9].

Cisplatin is a cell-cycle non-specific drugs, which inhibits the protein synthesis, and cisplatin can also act on hypoxic cells and non-proliferating cells, making tumor cells stay in the G2 phase [10], preventing radiation damage repairing and re-oxygenation. So the effects of radiation therapy, which is sensitive to G2, M phase cells, are promoted.

The advantages of concurrent chemo-radiotherapy were as follows: (1) chemotherapy drugs can improve the sensitivity of tumor cells to radiation, radiation therapy can also enhance cytotoxic chemotherapy drugs, and resulting synergies, improved tumor control rate; (2) chemotherapy killing distant subclinical lesions to achieve control of distant metastases; (3) double whammy on the DNA chain, the tumor cells were difficult to repair; (4) hypoxic tumor cells can be reduced oxygenation; (5) tumor cell apoptosis, G0 phase of the cell contributes to the proliferation of transformed; (6) concurrent chemo-radiotherapy shortening the general treatment.

During the treatment, we observed adverse reactions in patients increased than 3-DCRT. The major limiting toxicity of concurrent chemo-radiotherapy with advanced NSCLC is radiation esophagitis [11]. Esophagitis is one of the main complications of radiotherapy for NSCLC [12]. Meta-analysis [13] have showed that concomitant chemo-radiotherapy significantly increased grade 3 to 4 esophagitis as compared with sequential chemoradiotherapy, from 4% to 18% with a relative risk of 4.9. But meta-analysis of data shows 3-DCRT combination chemotherapy with 3-DCRT in aspects of causing radiation esophagitis, radiation pneumonitis and in the degree of myelosuppression had no significant difference [14]. The incidence of III–IV grade radiation esophagitis is 11.5%, with reports in the literature have some discrepancy. Target delineation after the second scan can decrease the esophagus irradiated volume to some extent.

In summary, concurrent chemo-radiotherapy for locally advanced NSCLC term effect is positive. Compared with sequential chemo-radiotherapy, concurrent chemo-radiotherapy could significantly improve the short-term efficacy and prolong survival of stage III non-small-cell lung cancer, meanwhile the adverse reactions could be tolerated.

The group has different chemotherapy regimens and fewer cases, so there no calculation of long-term efficacy and survival rate. Hospital conditions, target delineation after the second scan image fusion can minimize the amount of normal tissue, reducing the incidence of

complications, improve the local control rate for locally advanced NSCLC.

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