

Clinical Research on Three-Dimensional Conformal Radiotherapy of Non-Small Cell Lung Cancer

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OBJECTIVE To investigate the clinical efficacy and toxic effect of the 3-dimensional conformal radiation therapy (3DCRT) for non-small cell lung cancer (NSCLC).

METHODS Fifty-two patients with the Stage-I and IV NSCLC were treated with 3DCRT. Cross analysis of the clinical data was conducted in the comparison between the 52 cases with 3DCRT and the other 50 cases with the conventional radiation therapy (CRT). In the 3DCRT group, only the primary tumor and positive lymph-node draining area were included in the clinical target area, setting 4 to 6 coplanar or non-coplanar irradiation fields, with 2 Gy or 3 Gy/fraction, 1 fraction a day and 5 fractions per week. The total dose ranged from a test dose (DT) of 66 Gy to 72 Gy. In the CRT group, the field area contained the primary tumor plus the homolateral hilum of the lung, the mediastinum superior or hol-mediastinum, and opposed anteroposterior irradiation. When the dosage reached DT 36~40 Gy, an oblique portal administered radiation was conducted in order to avoid injuring the spinal cord. The DT was 1.8~2.0 Gy/fraction, 1 fraction a day, 5 fractions per week, with a total dose of 60 Gy to 70 Gy.

RESULTS The therapeutic effect (CR + PR) was 90.4% in the 3DCRT group, and was 72% in the CRT group. There was statistically significant difference between the two groups, $P < 0.01$. There was a clinical symptom improvement attained by 96.5% and 86.4% respectively in the two groups, and there was a statistically significant difference between the groups, $P < 0.01$. The 6-month, 1 and 2-year overall survival rates were 92.3%, 75.0% and 42.3% in the 3DCRT group, and 76%, 60% and 30% in the CRT group, respectively. There was a significant difference in the 6-month overall survival rate between the groups, $P < 0.05$. There was no obvious significant difference in the 1 and 2-year overall survival rates between the two groups, $P > 0.05$. The toxic reaction was 12.5% and 23.7% respectively in the 3DCRT and CRT groups. Acute radioactive esophagitis and leucopenia were markedly lower in the 3DCRT group than in the CRT group. There was a statistically significant difference between the groups, $P < 0.05$. No toxic reaction of Stage-III and over was found in the 3DCRT group during radiation therapy.

CONCLUSION The 3DCRT method has a satisfactory short-term efficacy and improvement of clinical symptoms in treating NSCLC, with a mild toxic reaction and good tolerance in patients. It can be used for enhancing the tumor-control rate and bettering the quality of life.

KEY WORDS: non-small cell lung cancer, radiotherapy, three-dimensional conformal radiotherapy, conventional radiation therapy.

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Introduction

The 3-dimensional conformal radiotherapy (3DCRT) is a new radiotherapeutic technology. From June 2004 to January 2007, 52 patients with non-small cell lung cancer (NSCLC) were treated in our department, using this technology. The data from the 52 patients were analyzed and compared with 50 patients receiving conventional radiation therapy (CRT).

Materials and Methods

Clinical data

A total of 102 eligible patients with NSCLC were randomized into 2 groups (52 and 50 patients). Three cases were diagnosed by CT, or MRI in combination with clinical diagnosis, and the other 99 cases were all confirmed by pathology or cytology. In the group with 52 patients receiving the 3-DRCT, there were 41 males and 11 females, with an age range from 40 to 82 years and an average of 67.5. Among the patients in this group, 38 were 60 years old or older, and 14 were less than 60 years old. Based on the Karnofsky Performance Scale (KPS), the patient's quality of life was rated as 80 or more in 21 of the 52 cases, and less than 80, but at least 60 in the other 31 cases. Among the total 52 cases, squamous cell carcinoma was found in 28, adenocarcinoma in 16, and adenosquamous carcinoma in 3. The other 5 cases were identified to have no pathological typing. Before treatment, the staging was conducted based on the UICC (1997) TNM standards. Among the 52 cases, Stage-I disease was confirmed in 4, Stage-II in 11, Stage-III in 33, and Stage-IV in 4.

In the CRT group of 50 cases, there were 42 males and 8 females, with an age range from 42 to 78 years and an average of 66. Among the patients in this group, 39 were 60 years old or more, and 11 were less than 60. Based on the KPS, the patient's quality of life was identified as 80 or more in 24 of the 50 cases, and less than 80 but at least 60 in the other 26 cases. In the total 50 cases, squamous cell carcinoma was found in 27, adenocarcinoma in 17 and carcinoid in 1. The other 5 cases were not pathologically typed. In the 50 cases, Stage-I disease was confirmed in 5 cases, Stage-II in 12, Stage-III in 29, and Stage-IV in 4. No combined chemotherapy was conducted in any of the cases during the radiation therapy.

Treatment Methods

The 3DCRT group

Postural localization, labeling and CT scan

Fixation of the patient, using a vacuum cushion, or head (or cephalic) mask moulding, was conducted based on the treatment body posture. The π -gage was used to

make 4 to 6 labeling marks on the chest. An enhanced CT scan was conducted, with a layer thickness and a distance each of 5 mm.

Three-dimensional treatment planning

The CT-scan data were transmitted by network to the WIMRT conformal therapy planning system of the TOPSLANE Co. for the three-dimensional image reconstruction. The gross tumor volume (GTV) was confirmed and delineated, so the tumor and the lymph nodes of 1 cm and over could be shown on CT. No preventive radiation of the lymph nodes was conducted in the mediastinum area. The pulmonary lesion was delineated based on the lung window, and mediastinal lymph nodes were outlined in accordance with the mediastinum window. The clinical target volume (CTV), was outlined, i.e. the scope of GTV was outwards extended at a range from 6 mm to 10 mm. The planning target volume (PTV) was finalized, including the limit of the clinical target and the positioning error of organ movement, i.e. generally on the basis of the CTV, the X and Y axes were respectively extended for 10 mm, and the Z axes for 15 mm. The PTV ranged from 4.6 cm³ to 530 cm³, with an average of 184.8 cm³ and layer-to-layer delineation of adjacent sensitive organs such as normal lung, spinal cords and esophagus etc. Four to 6 coplane or non-coplane irradiation fields were set up by the beam's eye view (BEV) and doctor's eye view (DEV), based on the 3-dimensional image of the CTV. A dose weight was set for each field, and at the same time the requirement of the treatment was met, with an histological, heteropical correction of all plans.

Optimization of the three-dimensional treatment plan

A comprehensive assessment of the dose-volume histogram (DVH) and isodose curve was used for optimization, with 95%, or more of the dose administered in more than 95% of the PTV. The prescription dose was calculated based on a 90%~100% isodose line. The exposure dose of the normal lung was assessed by V_{20} , i.e., the percentage of the irradiated volume receiving a 20-Gy exposure dose in the whole lung, in which the V_{20} was no more than 25%~35% in the volume of the total lung, and the maximum dose to the spinal cord and esophagus respectively was less than 45 Gy and 60 Gy.

An exposure dose of a DT of 2~3 Gy/fraction, 5 fractions/week was administered. After irradiation with 36~40 Gy, a CT reexamination was conducted. The scope of irradiation field was altered based on the reduction of the tumors, and the treatment plan was made again, with a total dose of 66~72 Gy.

The CRT group

Localization was performed by the simulating localizer. The irradiation field included the site of the tumor outwards extended for 2 cm, homolateral hilus of the lung. The upper field included the superior mediastinum

(2 cm below the eminence), and the lower and middle field included the whole mediastinum, with an opposed anteroposterior irradiation. After an exposure dose of 36~40 Gy, the irradiation field was adjusted based on the reduction of the tumors. Oblique portal irradiation was used to avoid spinal irradiation, with a DT of 1.8~2 Gy/fraction, 5 fractions/week, and a total dose of 60~70 Gy.

The patients of the two groups who had associated lymph node metastasis in the neck and supraclavicular regions were boosted with an irradiation at the supraclavicular region, with a DT of 60~70 Gy/30~35 fractions.

Assessment of the curative effect and toxic reactions

A cross analysis of thoracic CT outcomes 4 to 12 weeks before and after treatment was performed to evaluate the short-term efficacy, and to observe the clinical situations and toxic reactions in the patients.

Based on the WHO evaluation criteria for the therapeutic effect of solid tumors, the evaluation of the therapeutic effect was divided into complete remission (CR), partial remission (PR), no change (NC) and progression of disease (PD). The CR + PR meant response rate (RR).

Acute reaction in the normal tissue

The Standard of the Radiation Therapy Oncology Group, USA (RTOG) was employed for assessing the radiotherapeutic reaction which occurred 90 days after starting the treatment.

All cases were followed-up until June 2007. Calculation of the survival time began from the start of a treatment until the date of a patient's death, or the last follow-up.

Statistical analysis

Statistical analysis was conducted using the SPSS11.5 package. Rank-sum test and chi-square tests were used.

Results

For the short-term effects, see Table 1.

For the improvement of the clinical symptoms, see Table 2.

For the survival rate, see Table 3.

Table 1. Comparison of the short-term therapeutic effects between the two groups (n, %).

Group	n	CR	PR	NC	PD	RR
3DCRT	52	8 (15.4)	39 (75.0)	5(9.6)	0	47(90.4) *
CRT	50	3 (6.0)	33 (66.0)	11(22.0)	3(6.0)	36(72.0) *

*, $P < 0.01$

Table 3. Comparison of the survival rate between the two groups (n, %).

Group	n	6-month	1-year	2-year
3DCRT	52	48 (92.3)*	39 (75.0)	22 (42.3)
CRT	50	38 (76.0)*	30 (60.0)	15 (30.0)

*, $P < 0.05$; **, $P > 0.05$; ***, $P > 0.05$.

Table 2. Cross analysis of the clinical situations and changes after radiotherapy between the two groups.

Characteristic	3DCRT					CRT				
	n	Vanishing	Palliation	NC	Improvement rate (%)	n	Vanishing	Palliation	NC	Improvement rate (%)
Cough	43	17	24	2	95.4	40	18	16	6	85.0
Short breath	30	15	14	1	96.7	26	10	12	4	84.6
Chest pain	19	15	4	-	100.0	18	13	4	1	94.4
Hemoptysis	14	11	2	1	92.9	11	8	3	0	100.0
Trachyphonia	4	3	1	-	100.0	5	2	1	2	60.0
Superior vena cava syndrome	3	2	1	-	100.0	3	2	-	1	66.7
Total	113	63	46	4	96.5*	103	53	36	14	86.4*

*, $P < 0.01$

Table 4. Comparison of acute adverse reactions between the two groups.

Adverse reactions	3DCRT (n = 52)					CRT (n = 50)					P value
	I	II	III	IV	Incidence (%)	I	II	III	IV	Incidence (%)	
Reaction from alimentary tract	6	3	-	-	17.3	9	4	2	1	32	> 0.05
Radiation esophagitis	8	2	-	-	19.2	10	5	3	1	38	< 0.05
Radiation pneumonia	3	1	-	-	7.7	3	2	2	-	14	> 0.05
Toxic heart reaction	1	-	-	-	1.9	1	1	-	-	4	> 0.05
leukopenia	8	2	-	-	19.2	13	3	2	-	36	< 0.05
Thrombocytopenia	4	1	-	-	9.6	7	2	-	-	18	> 0.05
Total	30	9	0	0	12.5	43	17	9	2	23.7	-

For the acute adverse reactions from radiation therapy refer to Table 4.

In the 3DCRT group, the incidence of toxic reaction was lower than in the CRT group ($P < 0.05$). All the toxic reactions were at the Grade-I and II, and no toxic reaction of Grade-III, or over occurred. Radiation pneumonia of Grade-I and II was found in only 4 cases, showing a significant difference between the groups with radiation esophagitis and with leukopenia, $P < 0.05$. All patients smoothly completed the treatment. In the CRT group, the toxic reaction of Grade-III and over occurred in 11 cases (22%), and radiation pneumonia of Grade-I and III in 7 cases. Treatment was suspended in 5 cases of the group suffering severe toxic reaction. Nevertheless the whole treatment was finished after a pause and symptomatic treatment. No treatment-related death occurred in the 2 groups.

Discussion

NSCLC accounts for approximately 75% or 80% of the total number of lung cancers in China. Advanced NSCLC was found in most patients on their first visit, and distant metastasis occurred in about 40% to 50% of the cases, precluding the opportunity for surgery^[1]. So radiation therapy has become the main therapeutic treatment for middle to late NSCLC. However, the curative effect of CRT is not quite satisfactory, and its 5-year survival rate is only 5%~10%^[2]. Regional proliferation and relapse of the tumor is one of the main reasons for the treatment failure, with a high morbidity of 40% to 75%^[1]. There is a close correlation between the exposure dose and the regional proliferation and tumor relapse.

Because of a limitation of the methods and techniques, CRT fails to effectively concentrate the dose at the target, with a high exposure dose around the target and difficulty of increasing the total dose. Based on Fletcher's basic radiobiological principle^[3], the irradiation dose for eradicating a NSCLC of 5 cm should be 80~90 Gy, or even 100 Gy, and the CRT dose is usually restricted to 60 Gy or so, since overdose may materially increase radiotherapeutic complications. Over the recent years, 3DCRT technology has overcome shortcomings of CRT opposed anteroposterior irradiation, by using precise localization and coplanar/non-coplanar stereotactic conformal radiotherapy. It allows the distribution of high-dose beams to the target area, resulting in the maximum-dose irradiation on the tumor, and less, or no irradiation on the neighboring normal organs and tissues. The technique may even bring about an irradiation of 70~80 Gy, or even a higher dose, at the tumor site. In our study, the α/β value of the tumors was 10 Gy, the biological effective dose attained was 79.2 to 95.6 Gy in the 3DCRT group, resulting in an enhancement of local control of the tumor and the patient's survival rate,

while decreasing complications in the normal tissues.

In most reports, after 3DCRT of the patients with the Stage-I to IV NSCLCs, the 1 and 2-year survival rates were respectively between 67% and 91.67%, and 32.6% and 58%^[4-7]. These rates were respectively 75% and 42.3% in our group. Gao et al.^[8] have conducted a control study of the curative effect for NSCLC between intensity modulation radiated therapy (IMRT) and the CRT. The results showed that the curative effect was significantly higher in the IMRT group than in the CRT group, i.e., 92.3% vs. 53.6%. However, there was no significant difference in the toxic reaction between the 2 groups. Zhang et al.^[9] reported that the total remission was obviously higher in a group with CRT in combination with 3DCRT compared to a group with CRT alone. However there was no significant difference between the 1-year survival rate and the incidence of complications.

Our results are in agreement with those of most reports. After 3DCRT, the near-term effective rate and the improvement rate of clinical symptoms significantly increased compared to the CRT group, $P < 0.01$. However there was no significant difference in comparing the 1 and 2-year survivals between these groups. Nevertheless the incidence of the side effects, such as acute radioactive esophagitis and leukopenia, was lower in the 3DCRT group compared to the CRT group, $P < 0.05$, with occurrence of the Grade-I and II radiation pneumonia in only 4 of the cases. This result does not agree with that of most previous reports, which may be in relation to the fact that the CTV target area included no preventive radiation of the lymph nodes, since a whole-course of 3DCRT was used in the group. It results in minimization of the field area, and a decrease in the injury of adjacent organs, thus lessening the radiotoxic reaction and radiation pneumonia. The necessity of a preventive radiation at the hilum of the lung and the mediastinal lymph-node drainage area remains controversial at present. The irradiation method also varies greatly in China. Usually a 24 Gy to 45 Gy exposure on the mediastinum and tumor before IMRT, or a 35 Gy to 45 Gy IMRT is given before administering a 30 Gy to 40 Gy irradiation on the positive lymph nodes^[5], and a preventive radiation of the negative mediastinal lymph nodes.

Kupelian et al.^[10] reported that the 3-year disease-free survival and local control rates were 44% and 57% in the patients with elective neck irradiation (ENI), and were 31% and 89% in those without ENI. There was no significant difference between the patients of the 2 groups. Shi et al.^[11] conducted a case-control study on the groups with and without the preventive radiation at the nodal drainage area. The results of his study showed that the nodal metastasis runaway rate was 4.5% and 6.3%, and that the incidence of pneumonia was 9.1% and 6.3% in the 2 groups, respectively. There was no statistically significant difference in the survival time between the 2 groups. Our results also indicate that preventive radiation at the hilum of the lung and medi-

astinal lymph nodes is of no additional benefit, and the absence of preventive radiation in the lymph node drainage area will not increase the risk of rapid proliferation. The dosage of GTV can be increased with minimal damage to normal tissues. There is a need for further studies due to the low number of cases examined.

3DCRT can be used to implement an increase in the therapeutic radiation dose to the tumors, but radiation pneumonia is an important consideration for restricting the dose to a lung target. DVH analysis may provide us a criterion, suggesting a possibility and predictability of radiation pneumonia. Graham et al.^[12] insisted that the V_{20} value related to radiation pneumonia. When the V_{20} is < 22 %, 22% to 31% and 31% to 40%, the incidence of radiation pneumonia one year later will be 0, 7% and 13%, respectively. In the 3DCRT group, radiation pneumonia was found in 4 cases (7.7%), and all the pulmonary V_{20} values ranged between 30% and 35%. However, no radiation pneumonia was found in the patients when a V_{20} was less than 20%, indicating that the V_{20} is an important reference value in treatment planning, the preferred value of V_{20} being less than 30%. The radiation dosage should be increased as much as possible without causing radiation pneumonia.

In the literature in relation to 3DCRT for NSCLC, there are only a few reports on Stage-IV NSCLC. In the 3DCRT group of our study, there were 2 Stage-IV patients with brain metastasis. After 3DCRT, a favorable result was achieved in patients with pulmonary and cerebral lesions, with a survival rate of 24 months. We found that as long as the Stage-IV patient was in a good general physical condition, employment of 3DCRT can apparently improve the patient's quality of life and can prolong their survival time.

Our study showed that the near-term efficacy of 3DCRT on NSCLC was satisfactory, with increased tumor control and improvement of clinical symptoms, with less toxic effects. It is a safe and effective radiotherapeutic method, and is applicable in clinical situations. Since our number of cases was limited and the follow-up phase was relatively short, further observation and investigation are needed for evaluating the potential efficacy of NSCLC and injury caused by a late-phase reaction.

References

- 1 Yin WB, Gu XZ. Tumor Radiation Therapy. 3rd eds. Beijing: Chinese Union Medical University Press, 2002: 623–649 (Chinese).
- 2 Wu KL, Jiang GL, Liao Y, et al. Three dimensional conformal radiation therapy for non-small cell lung cancer: a phase I/II dose escalation clinical trial. Zhonghua Fang She Zhong Liu Xue Za Zhi 2003; 12: 10–13 (Chinese).
- 3 Fletcher G. Clinical dose response curves of human malignant epithelial tumors. Br J Radiol 1973; 46: 1–12.
- 4 Onishi H, Kuriyama K, Komiyama T, et al. Clinical outcomes of stereotactic radiotherapy for stage I non-small cell lung cancer using a novel irradiation technique: patient self-controlled breath hold and beam switching using a combination of linear accelerator and CT scanner. Lung Cancer 2004; 45:45–55.
- 5 Zheng MM, Zhao YX, Huang J, et al. Clinical observation of conformal therapy on non-small cell lung cancer in the aged. Zhonghua Yi Xue Cong Kan 2004; 4: 20–22 (Chinese).
- 6 Wang YJ, Wang LH, Wang X, et al. Clinical analysis of three-dimensional conformal radiotherapy on 91 cases with non-small cell lung cancer. Zhonghua Fang She Zhong Liu Xue Za Zhi 2005; 14: 241–244 (Chinese).
- 7 Liu ZH, Wang T, Liu FJ. Clinical observation of three-dimensional conformal radiotherapy on middle-late non-small cell lung cancer. Zhongguo Zhong Liu Lin Chuang 2005; 32: 935–937 (Chinese).
- 8 Gao J, Zhao YF, Cheng GY. Preliminary study on intensity-modulated conformal radiotherapy of non-small cell lung cancer. Lin Chuang Fei Ke Za Zhi 2004; 9: 583–585 (Chinese).
- 9 Zhang L, Liu Q, Ren BY, et al. Clinical research of three-dimensional conformal radiotherapy on local advanced non-small cell lung cancer. Shi Yong Ai Zheng Za Zhi 2006; 21: 384–386 (Chinese).
- 10 Kupelian PA, Komaki R, Allen P. Prognostic factors in the treatment of node negative non-small cell lung carcinoma with radiotherapy alone. Int J Radiat Oncol Biol Phys 1996; 36: 607–613.
- 11 Shi YS, Deng XG, Chen LH. Treatment of non-small cell lung cancer (NSCLC) using CT in combination with a PET examination to minimize the clinical target volume of the mediastinum. Zhongguo Zhong Liu Lin Chuang 2007; 34: 653–656 (Chinese).
- 12 Graham MV, Purdy JA, Emani B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1999; 45: 323.