

RESEARCH ARTICLE

Chemotherapy and Late Course Three Dimensional Conformal Radiotherapy for Treatment of Patients with Stage III Non-small Cell Lung Cancer

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Abstract

Objective: To compare the efficacy and complications of chemotherapy and late course three-dimensional conformal radiotherapy (3DCRT) in treating patients with stage III non-small cell lung cancer (NSCLC). **Patients and Methods:** All patients were divided into two groups: to receive chemotherapy and late course 3DCRT (3DCRT group), or chemotherapy and conventional fraction radiation (control group). In the 3DCRT-group, patients were given 6~15 MV X-rays with a total dose of 40 Gy, followed by 3DCRT, 2.5 Gy~3.0 Gy per fraction, 1 fraction/every day, total 68 Gy~70 Gy; in the control group, with conventional fraction radiation the total dose was 64~66 Gy. The chemotherapy regimen in both cases was EP (VP-16 and DDP). **Results:** Sixty four patients with stage III NSCLC were divided into two groups: 32 patients into 3DCRT, 32 into the control group. One and 2-year survival rates in 3DCRT and control group were 87.5%, 56.3% and 65.6%, 34.4%, respectively ($P < 0.05$); local control rates were 90.6%, 81.3% and 65.6%, 53.1%, respectively ($P < 0.05$). **Conclusion:** Chemotherapy and late course 3DCRT is associated with improved survival rate in patients with stage III NSCLC with good tolerability.

Keywords: Non-small cell lung cancer - chemotherapy - radiotherapy - three dimensional conformal radiotherapy

Asian Pacific J Cancer Prev, 14 (4), 2663-2665

Introduction

Approximately 75% of lung cancer, a leading cause of cancer-related death worldwide, is non-small cell lung cancer (NSCLC) (Ferlay et al., 2001). Most patients in China present with locally advanced stage III or IV disease. Although current practice for treatment includes several newer generation agents, e.g. vinorelbine, gemcitabine, paclitaxel or docetaxel with a platinum agent, no combination is a gold standard (Non-Small Cell Lung Cancer Collaborative Group, 1995; Schiller et al., 2002). For inoperable NSCLC, radiotherapy is a treatment option, but 5-year survival rate is less than 10%; local-regional failure and distant metastasis are main reasons for treatment failure. In order to improve treatment efficacy of stage III NSCLC, we designed a comparative study: one group received chemotherapy plus concurrent late course conformal radiotherapy, another group received chemotherapy plus concurrent conventional radiotherapy.

Materials and Methods

Patient

Eligible patients were aged 18 years or older, with histologically or cytologically confirmed, unresectable

locally advanced (stage IIIB with pleural or pericardial effusion) or metastatic NSCLC (stage IV), and were hospitalized. Patients had to have a life expectancy of more than 3 months and a Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2 , and adequate organ function [serum bilirubin ≤ 1.5 times the upper normal limit (UNL); AST and ALT ≤ 2.5 UNL in the absence of perceptible liver metastases, or ≤ 5 UNL in the presence of liver metastases; serum creatinine ≤ 1.5 times the UNL; neutrophils $\geq 1.5 \times 10^9/L$, and platelets $\geq 100 \times 10^9/L$]. Patients with known, symptomatic central nervous system metastases were ineligible. Other eligibility criteria were: absence of active infection, history of significant cardiac disease (unstable angina, congestive heart failure, myocardial infarction within the previous 6 months, ventricular arrhythmias) or malnutrition (loss of $\geq 20\%$ of the original body weight). All patients provided written informed consent before chemo- or radiotherapy.

Treatment

All patients were divided into two groups: to receive chemotherapy and late course 3DCRT (3DCRT group), or to receive chemotherapy and conventional fraction radiation (control group). Before radiotherapy, every patient was examined by chest CT or MRI, color Doppler

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Table 1. Comparison of Treatment-related Adverse Reactions (n)

Adverse reactions (Grade)	3DCRT group					Control group				
	0	1	2	3	4	0	1	2	3	4
Nausea and vomiting	7	10	13	2	0	5	11	14	2	0
Leukopenia	7	12	10	3	0	6	9	12	4	1
Thrombocytopenia	26	4	2	0	0	23	7	2	0	0
Hemoglobin decrease	24	5	3	0	0	22	6	4	0	0
Radiation esophagitis	9	15	6	2	0	5	17	7	3	0
Radiation pneumonia	19	9	3	1	0	16	12	2	2	0

ultrasound and other tests to exclude distant metastasis. All patients were given with 6/15 MV X-ray conventional external radiotherapy at first. If the primary tumor located in upper lobe, target volume included primary tumor, ipsilateral hilar and upper mediastinal lymphatic drainage area. While the primary tumor was detected in lower lobe, target volume included primary tumor, ipsilateral hilar and all mediastinal lymphatic drainage area. All patients were given with front and rear irradiation DT 40 Gy/20 f, and then conformal group exposed to stereotactic body radiation therapy holder and three-dimensional treatment planning system (TPS). At first, patients should be placed in simulator machine with negative-pressure bag, and arms placed overhead. Using comfortable supine position before vacuum fixing. Under quiet respiration, chest CT was used to check the upper and lower boundary of the tumor; in the same treatment position, using spiral CT with enhanced scanning, scanning thickness was 5mm, and images were transmitted by the network to the TPS; three or more physicians delineated GTV commonly in lung window. CTV was GTV plus a 5-10 mm, and a 15-20mm setup uncertainty margin was added to form the PTV. Using 4-6 fields, more than 90% isodose line packaging PTV, 2.5 Gy~3.0 Gy per fraction, one fraction per day, the total dose of 68 Gy~72 Gy. In contrast, the conventional radiotherapy targeting primary tumor and metastatic lymph nodes in reduced fields was used by the control group, the total dose of 64 Gy~66 Gy; in addition, patients with lymph node metastasis in collarbone area, supraclavicular metastatic side should be irradiated. Using 6-15MeV β ray and escalating to DT 60 Gy~65 Gy. Chemotherapy in both groups was EP regimen: VP-16 100 mg/m² IV d1-3, DDP 20 mg/m² IV d1-5) concurrent with radiotherapy.

Response and toxicity

The objective response of radiotherapy was assessed by WHO solid tumor criteria after treatment within 2 months. The National Cancer Institute Common Toxicity Criteria (version 2) were used to report and grade acute toxicity.

Statistical method

Using Kaplan - Meier method to calculate the survival rate and local control rate. We have enough experience in conducting medical research, and have published results elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Gao et al., 2011; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011;

Zhang et al., 2011; Gong et al., 2012; Li et al., 2012; Yu et al., 2012).

Results

From October 2009 to August 2011, 64 patients with stage III NSCLC were recruited, and were divided into two groups: 32 patients received chemotherapy and late course 3DCRT (3DCRT group), including 21 squamous cell carcinoma, 9 adenocarcinoma, 2 adenosquamous carcinoma, of which 24 males and 8 females, age from 47 to 76 years, with a median age of 62 year; other 32 patients received chemotherapy and conventional fraction radiation (control group), including 23 squamous cell carcinoma, 9 adenocarcinoma, of which 22 males and 10 females, age from 45 to 78 years, with a median age of 63.2 year. Clinical staging by UICC stage in 1997, including 38 patients with stage IIIA, 26 with IIIB, karnofsky \geq 70.

Sixty four patients were followed up for more than 2 years, of which 2 patients were lost, and the follow-up rate was 96.9%. All patients had chest CT examination to assess the efficacy within 2 months after radiation therapy, and the recent response rate of 3DCRT and control group was 87.5% and 75.0%, respectively. One and 2-year survival rates in 3DCRT and control group were 87.5%, 56.3% and 65.6%, 34.4%, respectively; local control rates were 90.6%, 81.3% and 65.6%, 53.1%, respectively. Toxic reactions were shown in Table 1.

Discussion

Chemoradiotherapy is a treatment option for unresectable stage III NSCLC, and is better than chemo- or radiotherapy alone. Radiotherapy is a local treatment, while chemotherapy is a systemic one. It is hypothesized that chemo- or radiotherapy combined could be synergistic. Sensitivity of radiotherapy is different in cell cycle, and most sensitive in G2/M phase, followed by late G1, S and G0 phase. Moreover, hypoxia within tumor cell could cause resistance to radiotherapy. However, chemotherapeutic agents could suppress tumor cell in S phase, and even transfer hypoxic cell into oxygen-rich one.

For a long time, conventional fractionated radiotherapy is a treatment option for unresectable stage III NSCLC, but the efficacy is disappointing; the main reason is tumor recurrence and distant metastases, which is considered to be related to insufficient irradiation dose. It is reported that for tumor with a diameter of 3 to 4cm, to achieve a local tumor control rate of 50 % to 80%, 100Gy irradiation dose is needed, but tolerated dose

for lung during conventional radiotherapy was about 65Gy (Emami et al., 1997). In addition, after four weeks of conventional radiotherapy, tumor stem cells could experience accelerated repopulation. However, 3DCRT provides a mode to solve this problem, which enhances local tumor dose, and greatly reduces exposure of the normal tissue. Therefore, we adopt the EP regimen plus late course conformal radiotherapy, and concurrent chemotherapy, in order to control micrometastases and prevent distant metastasis. Our result suggested that response rate of 3DCRT and control group was 87.5% and 75.0%, respectively. One- and 2-year survival rates in 3DCRT and control group were 87.5%, 56.3% and 65.6%, 34.4% ($P<0.05$), respectively; the local control rates were 90.6%, 81.3% and 65.6%, 53.1% ($P<0.05$), separately. This result is similar to what Li Jianbin reported; The main adverse reactions are leucopenia, gastrointestinal reaction and radiation esophagitis; no significant difference was detected between two groups. In order to further improve the efficacy and reduce the toxicity, we suggest further study to be conducted to confirm whether: regional lymph nodes should be considered as a target for prophylactic irradiation; for patients whose tumor is larger than 5cm in diameter and with atelectasis, sequential chemoradiotherapy be more beneficial to reduce radiation pneumonitis; after treatment, consolidated therapy be encouraged.

In conclusion, this study suggests that 3DCRT combined with chemotherapy is associated with improved survival rate in patients with stage III NSCLC with good tolerability.

Acknowledgements

Dr. Xin-En Huang is supported in part by a grant from Jiangsu Provincial Administration of Chinese Medicine (LZ11091), and in part from a special research fund of Organization Department of Jiangsu Provincial Party Committee, Talent Work Leading Group of Jiangsu Province (333 High-level Talents Training Project).

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