Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage:www.elsevier.com/locate/apjtm

Document heading

Effect analysis of chemoradiotherapy after operation in patients with stage ⅢA non-small cell lung cancer

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ARTICLE INFO

Article history:
Received 15 July 2012
Received in revised form 27 August 2012
Accepted 28 September 2012
Available online 28 October 2012

Keywords:
Non-small cell lung cancer
Chemoradiotherapy
Survival rate

ABSTRACT

Objective: To investigate the effect of chemoradiotherapy after surgery on ⅢA stage non-small cell lung cancer (NSCLC). **Methods:** A total of 156 NSCLC patients undergoing total pneumonectomy or pulmonary lobectomy were included in this study. The chemotherapy group (n=75) received the protocol of cisplatin (DDP) + gemcitabine (GEM) / docetaxel (DOC) / vinorelbine (NVB); the radiotherapy + chemotherapy group (n=81) received sequential chemoradiotherapy. The response rate, local control rate in 1 to 2 years, overall survival (OS), progression-free survival (PFS) and adverse reactions were evaluated. **Results:** The overall response rate was obviously higher in radiotherapy + chemotherapy group (79.4%) than in chemotherapy group (56.8%) (P<0.01). The 1 year local control rates for chemotherapy group and radiotherapy + chemotherapy group were (69.1±7.9)% and (77.8±8.2)% respectively and the difference reached statistical significance (P<0.001). The 2 year local control rates were (42.1±6.1)% and (61.5±6.9)% respectively (P<0.001). The difference in median follow-up time between the two groups did not reach statistical meaning (P>0.05), while the median PFS of two groups were 10.8 months and 16.9 months respectively (P<0.001). 1-year and 3-year survival rates were obviously higher in radiotherapy + chemotherapy group than in chemotherapy group, and the difference reached statistical significance (P<0.05 or P<0.01). The adverse reactions manifested as hematological toxicity and digestive tract reaction in the two groups. In the radiotherapy + chemotherapy group, incidences of radiation-induced esophagus injury and lung injury were 24.7% and 34.6% respectively, all occurring within 2 to 6 weeks after the start of radiation and both below grade 2. **Conclusions:** Chemoradiotherapy after surgery can improve local control rate and reduce or prevent distant metastasis, but there are still many controversies. In clinical work, we should carefully evaluate each patient's age, lung function, basic physical condition scoring and complications to choose a therapeutic schedule that is suitable for the patient.

1. Introduction

Non-small cell lung cancer (NSCLC) accounts for 75% of the total number of lung cancer. Up to now, excision is still the only potential treatment approach for NSCLC and has become a "standard therapy" for NSCLC. After complete resection, the five-year survival rate is about 15%[1]. Though the methods for resection have improved continually in recent years, for most patients, they have been in locally advanced stage or with distant metastasis at the time of diagnosis, not suitable for receiving surgical treatment, or local and regional lymph node recurrence and/or metastasis after surgery. These are all the main reasons for therapy failure. Nearly 30% of patients had local recurrence and regional lymph node metastasis within 5 years after surgery. Even after complete resection, there were still a large number of patients dying of tumor recurrence and metastasis. A large number of studies and meta analysis showed that radiotherapy after surgery could improve the local tumor control rate, but did not increase or decrease the mortality risk of stage Ⅲ NSCLC patients[2-4]. Therefore, there are some controversies on radiotherapy after surgery in clinic. During the period of January 2007 to June 2011, our hospital carried out surgery + chemotherapy and surgery + chemoradiotherapy respectively for stage ⅢA NSCLC patients with total pneumonectomy or pulmonary lobectomy. We have summarized some experience and now it is reported as follows with the purpose of providing reference for clinical practice.

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2. Materials and methods

2.1. Enrolled patients

9The study enrolled 156 stage ⅢA NSCLC patients treated at the department of thoracic surgery of our hospital with complete follow-up data during the period of January 2007 to June 2011. All the patients were diagnosed as having NSCLC pathologically, and received total pneumonectomy or pulmonary lobectomy. Before treatment, Chest CT, abdomen CT, cranial MRI, bone ECT and other checks were carried out to exclude distant metastasis; routine blood tests, biochemical examination and electrocardiography were carried out o exclude chemotherapy contraindications. Eastern Cooperative Oncology Group performance status scoring was 0-1 and predicted lifetime >12 weeks. The hospital's ethics committee approved all the study methods and all the enrolled patients had signed informed consent form.

2.2. Grouping methods

One hundred and fifty-six patients were divided into chemotherapy group and radiotherapy + chemotherapy group according to treatment methods after operation. The clinical characteristics of the two groups were shown in Table 1. There was no statistical difference in clinical characteristics between the two groups (P>0.05).

Table 1
Clinical characteristics of patients in the two groups (*n*).

Characteristic		Chemotherapy group (*n*=75)	Radiotherapy+ chemotherapy group (*n*=81)
Gender	Male	52	54
	Female	23	27
Age (years)	Range	42-75	45-72
	Median	65	68
ECOG performance	0	19	22
status scoring	1	56	59
Histology	Adenocarcinoma	39	37
	Squamous cellcarcinoma	26	27
	Adenosquamous carcinoma	8	12
	Others	2	5
Location	Center	23	26
	Periphery	52	55
T stage	T1	9	8
	T2	41	46
	T3	25	27
N stage	N1	12	14
	N2	63	67
Surgical modality	Total pneumonectomy	29	31
	Pulmonary lobectomy	96	100
Chemotherapy	GP	7	9
protocol	NP	56	59
	DP	12	13

GP = gemcitabine (GEM) + cisplatin (DDP); NP = vinorelbine (NVB) + DDP; DP = docetaxel (DOC) + DDP.

2.3. Therapeutic methods

The chemotherapy group received the protocol of cisplatin (DDP) + gemcitabine (GEM)/docetaxel (DOC)/vinorelbine (NVB); the radiotherapy + chemotherapy group received sequential chemo-radiotherapy.

2.3.1. Chemotherapy

DDP 60-75 mg/m^2, used in 2 to 3 days, also combined with GEM/DOC/NVB. GP protocol: GEM 800-1 000 mg/(m^2·d), d1, d8; DP protocol: DOC 60-75 mg/m^2, d1; NP protocol: NVB 20-25 mg/(m^2·d), d1, d8. Twenty-eight days was used as one chemotherapy cycle. All the patients received chemotherapy for 4 cycles. The chemotherapy group received chemotherapy after surgery; the radiotherapy + chemotherapy group did 2 to 4 chemotherapy cycles, then 1 cycle of radiotherapy, chemotherapy was continued after radiotherapy and 4 treatment cycles would be completed in total.

2.3.2. Radiotherapy

CT scanning range was set from mandible's lower border to the level below the diaphragm, including adrenal gland. The target volume included involved area of mediastinal lymph node and lymphatic drainage area where the pathology was negative after operation, but highly skeptical before operation, or lymph node dissection not completely deemed by surgery. For the patients whose right middle or left lobe, left lower lobe suffered lesion and mediastinal lymph node was invaded, subcarinal lymph node was encased in clinical target volume (CTV); for left upper lobe, if mediastinal lymph node and subcarinal lymph node were invaded, the aortic window lymph node would be encased in CTV; for the patients whose subcarinal lymph node or mediastinal lymph node were invaded, the homolateral hilus of lung would be encased in CTV. The planned target volume (PTV) was CTV expanded 1.0 cm. The evaluation of radiotherapy plans was optimized by dose volume histogram (DVH). Pulmonary tissue (V20) was below 25%, the heart tissue (V40) was below 45%, while the spinal cord required the maximum dose point was below 40 Gy, and the maximum dose point of the esophagus was below 60 Gy. It was planned to use VARIAN 23EX linear accelerator, 6 MV-X beam irradiation, conventional fraction, irradiation dose 2.0 Gy/time, 5 times/week, total dose 60 Gy[5].

2.4. Observed indicators

Short-term effect: The effects were evaluated after treatment in the two groups. According to solid tumor short term therapeutic effect evaluation criteria set by WHO, it was divided into complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), response rate, RR=(CR+PR)/total cases×100%. Long-term effect: local control rate in 1 to 2 years: it was evaluated as the disappearance of tumor on CT, tumor having residue after treatment and the residue was stable or shrinking which maintained above 2 month. Overall survival (OS): it was calculated from the first time of treatment to the last follow-up or the death of patient, if the follow-up was lost, it was

calculated according to the record's last time; progression-free survival (PFS): it was calculated from the patients beginning to receive treatment to the last follow-up of the progressive or non-progressed disease. Adverse reactions were evaluated using Radiation Therapy Oncology Group (RTOG) criteria.

2.5. Statistical processing

All the data were analyzed by SPSS 17.0. The χ^2 test was used for enumeration data and comparison of rates between the two groups. The measurement data was expressed as mean ± SD, and the t test was adopted for the mean comparison. $P<0.05$ was defined as having statistical difference.

3. Results

3.1. Short-term effects

As Table 2 shows the overall response rate was 79.4% in radiotherapy + chemotherapy group, which was obviously higher than that in chemotherapy group (56.8%). The difference reached statistical significance ($\chi^2=10.627$, $P<0.01$).

Table 2
Short-term effect.

Group	CR	PR	SD	PD	RR
Chemotherapy	13	29	18	15	56.0 (42/75)
Radiotherapy + chemotherapy	29	36	9	7	79.4 (65/81)

3.2. Long-term effect

3.2.1. Local control rate

One-year local control rates were (69.1±7.9)% and (77.8±8.2)% for chemotherapy group and radiotherapy + chemotherapy group respectively and the difference had statistical significance ($t=8.6459$, $P<0.001$). Two-year local control rates were (42.1±6.1)% and (61.5±6.9)%, respectively ($t=23.8599$, $P<0.001$).

3.2.2. OS and PFS

Follow-up was carried out for all the patients till February 2012, the follow-up period were 4.2 months to 58.7 months, the median follow-up time was 25.6 months. The median OS for chemotherapy group and radiotherapy + chemotherapy group were 32.2 months and 33.4 months respectively, and the difference did not reach statistical significance ($P>0.05$). But the median PFS was 10.8 months and 16.9 months respectively in the two groups and the difference had statistical significance ($t=6.9150$, $P<0.001$).

3.2.3. Survival rate

As Table 3 shows, 1-year and 3-year survival rates were obviously higher in radiotherapy + chemotherapy group than in chemotherapy group, and the difference had statistical significance ($\chi^2=5.88$, $P<0.05$, or $\chi^2=7.192$, $P<0.01$). While 2 years rate had no significant difference ($\chi^2=0.161$, $P<0.05$).

Table 3
Survival rate [n(%)].

Group	Survival rate		
	1 year	2 years	3 years
Chemotherapy	58 (77.3)	43 (57.3)	18 (24.0)
Radiotherapy + chemotherapy	74 (91.4)	49 (60.5)	36 (44.4)

3.3. Adverse reactions

As Figure 1 shows, the adverse reactions manifested as hematological toxicity and gastrointestinal reactions in the two groups. Hematological toxicities included mainly leukopenia and anemia; gastrointestinal reactions included mainly nausea and vomiting; hematological toxicity, gastrointestinal reactions and incidence of abnormal liver function showed no obvious difference between the two groups ($P>0.05$). In the radiotherapy + chemotherapy group, incidence of radiation-induced esophageal injury was 24.7% (20/81) and incidence of radiation-induced lung injury was 34.6% (28/81), all occurring within 2 to 6 weeks after the start of radiation and both being below grade 2. Imaging reexamination was carried out 6 months after the end of radiation for radiation-induced lung injury, 22 patients were found to have imaging change and the incidence was 27.2%.

Table 4
Adverse reactions.

Toxic and adverse effects	Chemotherapy group (n=75)					Radiotherapy + chemotherapy group (n=81)					χ^2	P
	0	Ⅰ	Ⅱ	Ⅲ	incidence(%)	0	Ⅰ	Ⅱ	Ⅲ	incidence(%)		
Leukopenia	29	35	8	3	61.3	29	35	12	5	64.2	0.137	>0.05
Thrombocytopenia	66	7	2	0	12.0	66	9	5	1	18.5	1.271	>0.05
Anemia	54	15	4	2	28.0	57	18	4	2	29.6	0.050	>0.05
Nausea	20	42	10	3	73.3	19	45	15	2	76.5	0.214	>0.05
Vomiting	27	39	7	2	64.0	26	42	10	3	67.9	0.264	>0.05
Abnormal liver function	66	6	3	0	12.0	65	10	6	0	19.8	1.739	>0.05
Radiation-induced lung injury	–	–	–	–	–	53	22	6	0	34.6	–	–
Radiation-induced esophageal injury	–	–	–	–	–	61	15	5	–	24.7	–	–

4. Discussion

At present, surgery, chemotherapy and radiotherapy are still three major treatment methods for NSCLC, but for most patients they have already been in locally advanced stage or had distant metastasis at the time of diagnosis, the effect of surgery alone for stage ⅢA NSCLC is not ideal[6]. The main reason is distant or recurrent metastasis. At the time of clinical diagnosis, more than 50% of patients are not suitable for receiving surgical treatment. Even after complete resection of the tumor, there are still a large number of patients died of tumor recurrence and metastasis. Patients with stage Ⅲ NSCLC accounts for about 40%, while patients with stage ⅢA who have potential surgical opportunity are few, and most of them are at stage ⅢB, who can not tolerate surgery[7]. There are still controversies on how to carry out treatment, especially for stage ⅢA(N2) NSCLC.

Previous study[8] revealed that the estimated median survival time was 19.3 months with the treatment of F-18-FDG-PET confined radiotherapy on locally advanced NSCLC with concomitant chemotherapy. The radiotherapy and chemotherapy after surgery could effectively prolong patients' survival time. Another study[9] revealed that in the patients receiving radiotherapy after surgical resection of lung cancer invading the aorta or the superior vena cava (SVC), the five-year survival rate was 30.7% for the cases with aortic invasion and 11% for the ones with SVC involvement. The retrospective study of Wu *et al*[10] suggested that for the patients with the stage of N2, the effects of surgical treatment alone was not ideal and the five-year survival rate was only 20%-25%. Therefore, the radical surgery alone has limited benefit. Scholars from home and abroad advocate mainly multimodality therapy. At present, it is believed that the patients with the stage of N2 or T3-4 N1 after radical surgery need to carry out planned clinical study (including radiotherapy and chemotherapy). After surgery, as a local treatment method, the purpose of radiotherapy is to destroy the residual tumor and local subclinical lesions to reduce recurrence rate. Three dimensional conformal radiation therapy (3-D CRT) can make clear the treatment volume, optimize dose distribution, so as to reduce lung and heart's irradiated volume and irradiation dose. The main purpose of chemotherapy is to destroy the already happened tiny subclinical distant metastasis, or prevent and reduce distant metastasis. Therefore, chemoradiotherapy is expected to improve the therapeutic effect theoretically.

Shen *et al*[11] explored the effect of "dose-dense" pemetrexed plus carboplatin/radiotherapy for locally advanced NSCLC, the results showed that thirteen of sixteen patients had in field local regional response, and the actuarial median OS was 28.6 months in the all patients and 34.7 months (estimated) in the stage Ⅲ patients. Uitterhoeve *et al*[12] used concomitant chemoradiotherapy, sequential chemoradiotherapy and radiotherapy respectively for the treatment of patients with medically inoperable or with irresectable NSCLC, the results showed that the 1, 2, and 5 year actuarial OSs were 46%, 24%, and 15%, respectively. In this study, the median OS was 32.2 months and 33.4 months respectively in chemotherapy group and radiotherapy + chemotherapy group and the difference reached no statistical significance, while the median PFS was 10.8 months and 16.9 months respectively in the two groups and the difference reached statistical significance. The above results indicate that chemoradiotherapy after operation could prolong PFS and control the progress of the disease to a greater extent, but the prolongation of the OS did not present obvious improvement, which needs to be confirmed by long-term follow-up and increasing sample amount. The One-year, 2-year and 3-year survival rates were 77.3%, 57.3% and 24.0% respectively in chemotherapy group and 91.4%, 60.5% and 44.4% respectively in the radiotherapy + chemotherapy group. The median OS and survival rates were similar to those reported by above-mentioned literatures.

The adverse reactions of lung cancer radiotherapy manifested mainly as radiation-induced lung injury and esophageal injury. Though theoretically, 3D-CRT can obviously reduce high dose of radiation volume for normal lung tissue compared with conventional radiotherapy, the radiation-induced lung injury caused by it should not be neglected[13,14]. What is different from conventional radiotherapy is that we can predict the possibility of radiation-induced lung injury according to MLD, V20, V30, NTCP and other parameters of lung irradiation dose, and a large number of studies on V20, NTCP and others are regarded as the prediction parameters for lung injury caused by 3D-CRT's treatment for NSCLC. Different studies have different results for their respective relations with radiation-induced lung injury. About the factors resulting in radiation esophagitis, there are different results from different research directions and contents, but the result on esophageal maximum dose has been basically confirmed.

The findings of recurrence and progress of disease are different from each other, which included metastasis types and incidence[15,16]. Distant metastasis is still the main reason for treatment failure of stage ⅢA NSCLC or death of patients, the next is local recurrence. Patients have already had subclinical metastasis at the time of surgery or at the time of auxiliary radiotherapy and chemotherapy; The chemotherapy has larger limitations; Local radiotherapy can not prevent the migration, bloodstream or lymph node metastasis, of residual tumor cells; Chemoradiotherapy after operation further decreases the body's immune ability, which is suitable for the growth of tumor cells[17]. In this study, we were not able to make detailed analysis on disease progress in the two groups. In the future, we will focus on it, so as to further discuss the long-term effect of

radiochemotherapy after operation.

In recent years, multimodality therapy based on operation for stage ⅢA NSCLC has received more and more attention. Radiotherapy before operation and/or neoadjuvant chemotherapy can shrink tumor lesion and create conditions for radical surgery, while radiotherapy after operation can improve local control rate and chemotherapy can reduce or prevent distant metastasis. Based on the results of this study, we think that the postoperative adjuvant therapy for stage ⅢA NSCLC after operation shoulders heavy responsibilities and there are more controversies. In clinical work, we should choose a therapeutic schedule that is suitable for the patient according to each patient's age, lung function, basic physical condition and complications. Particularly for the selection of sensitive drugs and radiation dose, we will not pursue combined application of wide variety of modalities to avoid excessive treatment. We will do our best to improve the patient's survival rate and life quality.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgements

The authors would wish to acknowledge all the patients who participated in this study for their excellent cooperation. We would also like to acknowledge Wenli Guo, Xiaojuan Xu, Third Party Medicine International Publishing Group Co., limited, and Fengqing Ji, Department of Thoracic Surgery, Huai'an First People's Hospital, Nanjing Medical University for their valuable suggestions and help in language editing.

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