ORIGINAL ARTICLE

Randomized Controlled Trial between Conventional Fractionation Radiotherapy and Accelerated Hyperfractionation Radiotherapy in the Elderly with Locally Advanced Non-small Cell Lung Carcinoma

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ABSTRACT

Objective: *This study aimed at observing and discussing the curative effect of conventional fractionation radiotherapy and accelerated hyperfractionation radiotherapy in the elderly with locally advanced non-small cell lung carcinoma (NSCLC).*

Methods: *The study group consisted of 72 patients with locally advanced NSCLC (partly IIIA or IIIB stage) who were admitted between January 2009 and December 2010. They were divided randomly into two groups: 36 in the observation group and 36 in the control group. The control group was treated by conventional fractionation radiotherapy, while the observation group received accelerated hyperfractionation radiotherapy. After three months, six months and one year, at follow-up visits, the comprehensive curative effect was evaluated, and the data on disease-free survival and radiation toxic reaction were acquired. Sixty-four samples were included in this research after excluding patients with distant metastasis and other internal medicine diseases.*

Results: *The remission rate (complete remission + partial remission) in the observation group was 75.0% (24/32) while that in the control group was 62.5% (20/32). The remission rate in the observation group was significantly higher than that in the control group (*$p < 0.05$*). The progression-free survival (PFS) in the observation group at three months, six months and one year was 81.3% (26/32), 31.2% (10/32) and 18.7% (6/32), respectively. The corresponding data in the control group was 6.2% (18/32), 28.1% (9/32) and 15.6% (5/32), respectively. The three-month PFS in the observation group was significantly higher than that in the control group (*$p < 0.05$*). There was no statistically significant difference in myelosuppression, radiation oesophagitis and radiation pneumonitis (*$p > 0.05$*).*

Conclusion: *Compared with conventional fractionation radiotherapy in treating locally advanced NSCLC, accelerated hyperfractionation radiotherapy showed better short-term decentralized control effect. The toxic effects were similar in the two therapies.*

Keywords: Accelerated hyperfractionation radiotherapy, conventional fractionation radiotherapy, the elderly, phase III non-small cell lung carcinoma, short-term effects

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Ensayo controlado aleatorizado entre la radioterapia de fraccionamiento convencional y la radioterapia de hiperfraccionamiento acelerado en los ancianos con carcinoma de pulmón de células no pequeñas localmente avanzado

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RESUMEN

Objetivo: *Este estudio estuvo dirigido a observar y discutir el efecto curativo de la radioterapia de fraccionamiento convencional y la radioterapia de hiperfraccionamiento acelerado en los ancianos con carcinoma de pulmón de células no pequeñas localmente avanzado (CPCNP).*
Métodos: *Setenta y dos pacientes con CPCNP localmente avanzado (parcialmente en etapa IIIA ó IIIB) ingresados entre enero de 2009 y diciembre de 2010, formaron el grupo de estudio. Fueron divididos aleatoriamente en dos grupos: 36 en el grupo de observación y 36 en el grupo de control. El grupo de control fue tratado mediante radioterapia de fraccionamiento convencional, mientras que el grupo de observación recibió radioterapia de hiperfraccionamiento acelerado. Después de tres meses, seis meses y un año, en las visitas de seguimiento, se evaluó el efecto curativo general, y se obtuvieron los datos sobre la supervivencia libre de enfermedad, y la reacción tóxica radiactiva. En la investigación se incluyeron sesenta y cuatro muestras, luego de excluir pacientes con metástasis distante y otras enfermedades de medicina interna.*
Resultado: *La tasa de remisión (remisión completa + remisión parcial) en el grupo de observación fue 75.0% (24/32), mientras que en el grupo de control fue 62.5% (20/32). La tasa de remisión en el grupo de observación fue significativamente más alta que la del grupo de control (*$p > 0.05$*). La supervivencia libre de progresión (SLP) del grupo de observación a los tres meses, seis meses, y un año fue 81.3% (26/32), 31.2% (10/32), y 18.7% (6/32) respectivamente. Los datos correspondientes al grupo de control fueron 6.2% (18/32), 28.1% (9/32), y 15.6% (5/32), respectivamente. La SLP de tres meses en el grupo de observación fue significativamente mayor que en el grupo de control (*$p < 0.05$*). No hubo diferencia estadística significativa en la mielosupresión, la esofagitis por radiación, y la neumonía por radiación (*$p > 0.05$*).*
Conclusión: *A diferencia de la radioterapia de fraccionamiento convencional en el CPCNP, la radioterapia de hiperfraccionamiento acelerado mostró un mejor efecto de control descentralizado a corto plazo. Los efectos tóxicos son similares en las dos terapias.*

Palabras claves: Radioterapia de hiperfraccionamiento acelerado, radioterapia de fraccionamiento convencional, carcinoma de pulmón de células no pequeñas de fase 3, efectos a corto plazo

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INTRODUCTION

Lung cancer is one of the most common human malignancies. Its prevalence and incidence increase yearly and has been a major public health issue (1). In China, lung cancer has the highest mortality rate among other cancers. Non-small cell lung carcinoma (NSCLC) is the most common type of lung cancer as it accounts for about 80% of all types of lung cancer. Nowadays, the major treatment for NSCLC involves surgery, chemoradiotherapy and molecular targeting (1). Radiotherapy is most commonly used in treating NSCLC when patients are found to have advanced lung cancer. The conventional fractionation radiotherapy pattern with 1.8–2.0 Gy/time pattern is mostly used.

Previous work found that cancer cells accelerated their proliferation after irradiation, with an extended treatment course and a declined tumour control rate (2, 3). However, accelerated hyperfractionation radiotherapy can cut down the total curative time without affecting the curative effect (4). Many scholars have affirmed

the advantage of accelerated hyperfractionation radiotherapy in treating head and neck cancer (5, 6), as well as oesophageal cancer (7). Fowler and Chappel found NSCLC to be a rapid proliferation tumour (8), with a doubling time of 3–3.5 days. The accelerated proliferation of cancer cells in the radiotherapy course and extended treatment course significantly affected the final result (9, 10). Radiation Therapy Oncology Group (RTOG) 8311 experiment showed that accelerated hyperfractionation radiotherapy (1.2 Gy, 2 times/day, total dose 69.6 Gy) had a good curative effect on locally advanced NSCLC (11). In view of this result, 72 elderly patients with locally advanced NSCLC who were admitted between January 2009 and December 2010 were studied. They were treated by conventional fractionation radiotherapy and accelerated hyperfractionation radiotherapy, respectively, with a one-year follow-up visit.

SUBJECTS AND METHODS

General data

Seventy-two elderly patients with locally advanced NSCLC who were admitted between January 2009 and December 2010 and received radiotherapy were studied. Inclusion criteria were: (a) NSCLC confirmed by pathological biopsy, Clinical Phase III stage confirmed by combining computed tomography (CT), MRI, thoracoscope and PET-CT examination, including IIIB and partly IIIA; (b) aged from 65 to 80 years; (c) in good physical state with an ECOG score of 0–2; (d) complete case history and continuous follow-up visits for informed subjects. Exclusion criteria were: (a) patients with severe anaemia; (b) combined serious heart and lung function insufficiency.

For the observation group, there were 15 men and 17 women, aged between 65 and 79 years, with an average age of 72.5 ± 8.4 years. Nineteen patients were in phase IIIB and 13 patients in phase IIIA. For the control group, there were 14 men and 18 women, aged between 65 and 80 years, with an average age of 71.8 ± 8.9 years. Twenty patients were in phase IIIB and 12 patients in phase IIIA. There was no statistically significant difference ($p > 0.05$) in gender, age and neoplasm staging. This study was approved by our hospital's ethics committee and proceeded under patients' informed consent.

Therapeutic method

All patients were treated by electron linear accelerator 6MV-X intensity modulated radiation therapy (IMRT) system (Varian, America). The calculation model was done by an analog machine to set the treatment. The head, neck and shoulder were fixed to conduct a first position, assuring good repeatability. A 3D laser red line sign was marked on the body. Enhanced located CT scanning was performed on the chest, and the image was sent to our treatment planning system (TPS). Then, the staff sketched the gross tumour volume using TPS, and extended a further 0.5 cm into the clinical target volume. Planning target volume was then obtained by adjusting the position and error of tumour mobility during breathing. Finally, protected organs and normal circumference were sketched, which laid the foundation for the planned radiotherapy dose. The setting dosage, design, calculation and optimization of intensity-modulated radiation field were carried out by the physicists. Then the optimum result of the dose-volume histogram was obtained. The radiation therapist confirmed the plan and patients restoration. Laser rays were then labelled again. A combination of irradiation and radiotherapy technology was performed in set-up radiotherapy.

Control group: conventional fractionation radiotherapy. Exposure dose: 60 Gy/30 times/6 weeks.

Observation group: accelerated hyperfractionation radiotherapy. Exposure dose: 56.25 Gy/45 times/6 weeks (1.25 Gy/3 times/day).

Two sets of normal organ defined dose: lung V20 < 28%, lung V5 < 50%, heart V50 < 45%, spinal cord < 42 Gy, oesophagus < 58 Gy.

Observation target and therapeutic effect criterion

After three months, six months and one year, at follow-up visits, the comprehensive curative effect was evaluated, and the data on disease-free survival and radiation toxic reaction were acquired.

Therapeutic effect criterion: response evaluation criteria in solid tumors (RECIST).

Evaluation of targeted focus:

Complete remission (CR): all targeted focus disappeared.
Partial remission (PR): compared with base line, the sum of longest diameter in targeted focus decreased by at least 30%.

Progression disease (PD): the sum of longest diameter in targeted focus increased by 20%, compared with minimum sum of longest diameter at the start of therapy. Another evaluation method was the appearance of one or more new foci.

Stable disease (SD): the status between partial remission and progression disease.

Classification of side-effects in this research was performed according to the RTOG radio-reaction evaluation criterion (12).

Statistical method

Clinical and test data were input as SPSS database form. Analysis was performed using SPSS 19.0 statistical software. Chi-square test was employed to compare intergroup data. Results were expressed in percentage. Significance test level was defined as $p < 0.05$.

RESULTS

Comparison of short-term effects in the two groups

The remission rate (CR + PR) in the observation group was 75.0% (24/32) while that in the control group was 62.5% (20/32). The remission rate in the observation group was significantly higher than that in the control group ($p < 0.05$) (Table 1).

Comparison of progression-free survival of the two groups at three months, six months and one year

The three-month progression-free survival (PFS) in the observation group was significantly higher than that in the control group ($p < 0.05$). However, there was no statistically significant difference in PFS at six months and one year between the two groups (Table 2).

Comparison of radiation toxic reaction in the two groups

There was no statistically significant difference in episodes of myelosuppression, radiation oesophagitis and radiation pneumonitis ($p > 0.05$) (Table 3).

DISCUSSION

Nowadays, the major treatment for NSCLC involves surgery, chemoradiotherapy and molecular targeting. Radiotherapy is most commonly used in treating NSCLC when patients are found to have advanced lung cancer. The conventional fractionation radiotherapy pattern with 1.8–2.0 Gy/time pattern is mostly used (13, 14). The primary cause of failure in treating local NSCLC lies in the accelerated proliferation of cancer cells in conventional fractionation radiotherapy (8–10). With the development of radiology, many unconventional fractionation therapies have been explored. Based on the radiotherapy time, dose and fraction frequency (15–17), accelerated hyperfractionation radiotherapy has been found to be advantageous in terms of curative effect and time reduction (18, 19).

Accelerated hyperfractionation radiotherapy is a method that uses fraction dose in patients with a frequency of two or three times per day. For patients who have an acute radiation injury (20), it shortens the total treatment time without affecting the curative effect. Besides, scholars have gained much experience in treating head and neck cancer, as well as oesophageal cancer. Partial control rates could be seen in previous work (5–7). In this study, 32 elderly patients with locally advanced NSCLC were treated with accelerated hyperfractionation radiotherapy, while the others received conventional fractionation radiotherapy. Statistical analysis showed that short-term effects at three-month PFS were more acute in patients who were treated with accelerated hyperfractionation radiotherapy than patients who received conventional fractionation radiotherapy. Many scholars have obtained positive results in treating NSCLC with accelerated hyperfractionation radiotherapy (21–25), indicating the role of interdisciplinary co-operation in increasing curative effect.

The lung is an organ with poor tolerance. Radiation pneumonitis, radiation oesophagitis and other radio-reaction from radiotherapy seriously impact the survival quality and cure schedule of acromegaly (26, 27). For the elderly, the function and physique of their lungs are worse. Thus, a strict dosage restriction is needed. However, Luguang found that the efficacy and tolerance of accelerated hyperfractionation radiotherapy in the elderly with cancer of the oesophagus were not significantly inferior compared with the young (28). Our study

Table 1: Comparison of short-term effects in the two groups

Group	n	CR	PR	SD	PD	Remission rate
Observation group	32	13	11	4	4	75.0%
Control group	32	8	12	7	5	62.5%*
χ^2						2.974
p value						< 0.05

*A significant difference of $p < 0.05$

Table 2: Comparison of progression-free survival of the two groups at three months, six months and one year (%, n)

Group	n	Three-month PFS	Six-month PFS	One-year PFS
Observation group	32	81.3% (26)	31.2% (10)	18.7% (6)
Control group	32	56.2% (18)*	28.1% (9)	15.6% (5)
χ^2		4.654	0.075	0.109
p value		< 0.05	< 0.05	< 0.05

*A significant difference of $p < 0.05$

Table 3: Comparison of radiation toxic reaction in the two groups

Group	n	Myelosuppression		Radiation oesophagitis		Radiation pneumonitis	
		Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Observation group	32	4	2	12	4	6	4
Control group	32	4	2*	14	3	5	5
χ^2		0.096		0.062		0.000	
p value		> 0.05		> 0.05		> 0.05	

*A significant difference of $p < 0.05$

showed that accelerated hyperfractionation radiotherapy and conventional fractionation radiotherapy were equal in severity in causing myelosuppression, radiation oesophagitis and radiation pneumonitis. Besides, there was no significant difference in the two therapeutic patterns. Thus, the results indicated that the tolerance in the elderly with locally advanced NSCLC was fair in aspect of accelerated hyperfractionation radiotherapy and conventional fractionation radiotherapy.

In conclusion, compared with conventional fractionation radiotherapy in treating locally advanced NSCLC, accelerated hyperfractionation radiotherapy showed better short-term curative effect and reduced the total treatment time. The toxic effects were similar in the two therapies. Further research is needed in the area of the elderly with locally advanced NSCLC radiotherapy treatment.

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