Clinical outcome of whole-body gamma-knife combined with pemetrexed concurrent chemoradiotherapy in elderly patients with locally advanced lung adenocarcinoma

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Abstract
Objective: Currently, concurrent chemoradiotherapy has become the standard treatment for locally advanced non-small cell lung cancer, but it is often difficult for elderly patients to tolerate. In this study, we evaluated the curative effect, acute radiation reaction, and clinical application of stereotactic radiotherapy with whole-body gamma-knife combined with pemetrexed treatment in elderly patients with locally advanced lung adenocarcinoma.

Methods: A total of 37 elderly patients with lung adenocarcinoma from Hubei Provincial Armed Police Corps Hospital from 2 January 2013 to 30 December 2015, who were treated with stereotactic radiotherapy with super-gamma-knife, were included in the study. The radiotherapy plan was made according to the patient’s physical condition, tumor location and size, and therapeutic purpose. A dose of 3.5–5 Gy was administered by 50–70% isodose curve, with a total dose range of peripheral irradiation 35–45 Gy. In the same period, pemetrexed was administered at 500 mg/m², the first day of chemotherapy (d1), intravenous drip, with 21 days as one cycle, and the number of cycles was more than two.

Results: The median follow-up duration was 18 months, and the 1-, 2-, and 3-year follow-up rates were 86.49% (32/37), 59.46% (33/37), and 21.62% (8/37), respectively. There were no missing cases. After 2–3 months of treatment, computed tomography showed that 13 patients (35.14%) had complete remission, 22 patients (59.46%) had partial remission, one patient (2.70%) achieved a stable status, and one patient (2.70%) still had progression, and the total response rate was 94.59%. The 1-year local control rate was 67.57%. The 1-, 2-, and 3-year overall survival rates were 86.49%, 45.45%, and 25.00%, respectively. The median overall survival time was 17.0 months (95% CI 14.5–21.3 months); the progression-free survival time was 12.0 months (95% CI 11.6–12.8 months). Multivariate analysis showed that lymph node stage N ≥2 and radiotherapy biological effective dose <60 Gy were the adverse prognostic indicators of overall survival (P = 0.016 and P = 0.032, respectively). The 1-year local control rate and median survival time were 62.50% and 71.43%, and 19 and 17 months in the gross tumor volume ≥120 cm³ subgroup and gross tumor volume <120 cm³ subgroup, respectively. There was no significant statistical difference (P = 0.061 and P = 0.400, respectively). The incidence rates of grade 3–4 neutropenia and thrombocytopenia were 10.81% (4/37) and 5.41% (2/37), respectively, during the period of concurrent chemoradiotherapy. The incidence of grade 2 radiation-induced pneumonitis and esophagitis was 13.51% and 16.22%, respectively. No grade >2 acute or late lung and esophagus toxicity was observed.
1 | INTRODUCTION

Recently, concurrent chemoradiotherapy has become a standard treatment for locally advanced non-small cell lung cancer (LA-NSCLC), but it is difficult for elderly patients to tolerate. When a double scheme with platinum-based drugs becomes the first-line treatment for LA-NSCLC, the improvement in prognosis in chemotherapy is within the platform period, and that in radiotherapy is also within the bottleneck area. Therefore, there is no satisfactory standard treatment for elderly patients with lung cancer.

Based on three-dimensional conformal radiotherapy or intensity-modulated radiotherapy, proton therapy improved the 2-year survival rate to 57% in patients with stage III NSCLC. Increasing the dose of local irradiation seems to reduce the incidence of late adverse reactions. However, because the normal tissue in front of the proton still has a high dose of irradiation and the treatment is expensive, the technology still has some challenges, so it is not suitable for most patients with LA-NSCLC.

The whole-body gamma-knife has been used in China for >20 years, and has been used to treat a large number of patients with cancer. In the present study, we retrospectively analyzed 37 elderly patients with locally advanced lung adenocarcinoma, who received whole-body gamma-knife stereotactic body radiotherapy (SBRT) combined with pemetrexed concurrent chemotherapy in Hubei Provincial Armed Police Corps Hospital, which had good clinical effect.

2 | METHODS

2.1 | Patient and characteristics

We selected 37 elderly patients with locally advanced lung adenocarcinoma who received whole-body gamma-knife (super-gamma-knife SGS-I; Haibo Science & Technology co. LTD, Shenzhen, China) SBRT combined with pemetrexed concurrent chemotherapy in Hubei Provincial Armed Police Corps Hospital from 2 January 2013 to 30 December 2015, with 20 men and 17 women. The age range was 65–84 years, and the median age was 71 years. All patients refused or were unable to undergo surgery for medical reasons. Blood routine examination, liver and kidney function test, and electrocardiography findings were basically normal, and there were no serious cardiovascular disease, previous history of diabetes, gastrointestinal ulcer, and other malignancies before radiotherapy. There were four, eight, 11, 11, and three patients with Karnofsky Performance Scale scores of 60, 70, 80, 90, and 100, respectively. There were 21 cases of peripheral type, and 24 cases of central type lung cancer. According to the 2009 Union for International Cancer Control TNM staging standard, 14 patients had stage IIIA, including four patients with T4N0, three patients with T3N1, five patients with T2N1, and two patients with T1N2, and 23 patients had stage IIIB, including two patients with T1N3, six patients with T2N3, five patients with T3N3, eight patients with T4N2, and two patients with T4N3.

This study was approved by the institutional review board of Hubei Provincial Armed Police Corps Hospital, and all the patients provided voluntary informed consent to participate in the study.

2.2 | Whole-body gamma-knife treatment system

The whole-body gamma-knife, also called super gamma-knife, which was developed by Haibo Science & Technology (Shenzhen, China), can be used to treat head and body tumors. The system consists of radiation sources, collimator, and treatment bed. 18Co60 radiation sources were distributed on the curved collimator, and the 18 beams of gammaray were focused by collimators of different pore sizes (Figure 1a). Collimators used for body therapy include four apertures with diameters of 15 mm, 25 mm, 40 mm, and 55 mm. The 18 beams focus on the target area and can rotate 360° around the human body (Figure 1b). By moving in X, Y, and Z directions, the therapeutic bed can deliver the tumor in any part of the human body to the focal point of the emitter device for focused radiation.

The patients were placed in a fixed position with a vacuum bag, lying on the three-dimensional coordinate stereotactic positioning bed. Each patient underwent slow computed tomography (CT) simulation at 10 s/slide with a CT slide thickness of 5 mm and CT slide interval of 5 mm. Then, the coordinate parameters of the patient’s body surface repeat location, N shape scale coordinate value, and CT scanning parameters were recorded. Subsequently, the image data and related data were transferred to the treatment planning system, and body outlines, normal and sensitive organs, therapeutic targets, and lung lesions were delineated, and the gross tumor volume (GTV) was outlined with the lung window. Mediastinal lymph nodes were delineated by the mediastinal window combined with CT, magnetic resonance imaging, and positron emission tomography/CT before treatment for three-dimensional reconstruction. The GTV is automatically calculated by the treatment planning system, the size ranges from 42.6 to 596.2 cm³.
and the median value is 123 cm³. The planned target volume was delineated out of GTV to avoid the sensitive organs, such as the spinal cord, esophagus, and pericardium, 1 and 2 cm outside, up, and down, respectively. According to the patient’s physical condition, the treatment purpose, tumor location, target volume, and radiotherapy plan was formulated, and the dose distribution was adjusted for optimization. The 50%–70% of prescription dose curve covered a planned target volume >95%. The dose-volume histogram, three-dimensional dose distribution, and the peripheral sensitive tissue dose limited the plan. The single prescription dose was 3.5–5.5 Gy, the median value was 3.8 Gy, the fractionated treatment was 8–12 times, and the median was 10 times, five times a week. The treatment duration was 12–18 days, and the median duration was 15 days. The total dose of peripheral treatment was 35–45 Gy, the median dose was 38 Gy, and the biological effective dose (BED) was converted using the linear quadratic formula. The critical organ dose limit (BED10) was 47.25–85.25 Gy, and the median dose was 56 Gy. The maximum BED10 in the spinal cord was <30 Gy, V20 in both lungs was <20%, and V30 was <15%. The dose in the trachea and main bronchus was <60 Gy, the maximum dose in the esophagus was <60 Gy, and the heart V40 was <20%.

On the first days of radiotherapy, 500 mg/m² of pemetrexed disodium (PEM) for injection produced by Jiangsu Hausen Medical was administered through intravenous drip, with 3 weeks as one cycle. After 22 days, consolidation chemotherapy was started, with a total of two to four cycles. Before the first cycles were started after 7 days, 1000 μg vitamin B12 from Shandong Fang Ming Pharmaceutical Group batch number, 20120504) and oral folic acid produced by Jiangsu Yabangipusen Pharmaceutical (batch number, 20110308; Yancheng city, Jiangsu province, China) 400 μg/day, before and after PEM, were administered for 1 day, and regular oral dexamethasone from Guangdong Triple Stone Qi Pharmaceutical. (batch number, 20120923; Zhongshan city, Guangdong province, China) 10 mg was administered during chemotherapy support symptomatic treatment.

2.3 | Observation index and evaluation of curative effect

2.3.1 Short-term efficacy
After 2–3 months of radiotherapy, CT was carried out to evaluate efficacy. The RECIST 1.1 evaluation criteria were used for the short-term efficacy evaluation of solid tumor. Local tumor control was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to CT images. CR + PR is an effective index.

2.3.2 Long-term curative effect
The survival period was followed until 30 June 2016. Overall survival (OS) was defined as the time from the first day of treatment to death of any cause. The period from the first day of treatment to the first occurrence of disease progression or death of any cause is known as the progression-free survival, and the earliest possible time was recorded.

The side-effects were evaluated according to common terminology criteria for adverse events (CTCAE) 3.0 and 1992 Radiation Therapy Oncology Group (RTOG) standard. After treatment, the patients were evaluated at the 1, 3, and 6 months, and every 6 months thereafter, and the end-point of follow up was the death date of the patients.

2.4 | Statistical analysis
SPSS 19 statistical software (IBM Corporation, Armonk, NY, USA) was used for data processing. The corresponding index was used to describe and analyze the counting data. The survival analysis was described using the Kaplan–Meier curve method. The log–rank test was used in the single-factor analysis of the prognosis. The multivariate analysis of prognosis was carried out using the Cox regression model, and the χ²-test was used to compare the count data groups. A P-value <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Curative effect
All patients completed concurrent chemoradiotherapy. There were eight, 18, and 11 patients who completed chemotherapy in four, three, and two cycles, respectively. The median follow-up time was 18 months (95% CI 3–39 months), with a follow-up rate of 100%. Among these, 32 patients were followed for 1 year, 22 patients for 2 years, and eight patients for 3 years. The local control rates of CR, PR, SD, and PD
were 35.14%, 59.46%, 2.70%, and 2.70%, respectively, and the total effective rate (CR + PR) was 94.59%. The local control rate in 1 year was 67.57%. The OS rates in 1, 2, and 3 years were 86.49%, 45.45%, and 25%, respectively. The median survival time was 17 months (95% CI 14.5–21.3 months), and the median progression-free survival time was 12 months (95% CI 11.6–12.8 months). The 1-year local control rate and median survival time of patients with GTV < 120 cm³ and GTV ≥ 120 cm³ were 62.50% and 71.43%, and 19 and 17 months, respectively. There was no statistically significant difference ($\chi^2 = 1.932, 0.527; P = 0.061, 0.400$; Figure 2). In the GTV > 120 cm³ group, there were seven patients with stage IIIA, and nine patients with stage IIIB. In the GTV < 120 cm³ group, eight and 13 patients had stage IIIA and IIIB, respectively. There was no statistically significant difference between the two subgroups in clinical staging ($\chi^2 = 1.521, P = 0.236$).

There were 13 patients with local recurrence (35.14%) and 10 patients with distant metastasis (27.03%). Five patients had both local recurrence and distant metastasis. The single-factor experiment result is shown in Table 1. Karnofsky Performance Scale score, lymph node stage, and BED10 are prognostic factors influencing patient survival time. Multivariate analysis is shown in Table 2. The adverse prognostic factors were lymph node stage N ≥ 2 and BED10 < 60 Gy.

### 3.2 Side-effects

The $V_{20}$ of both lungs in 37 patients were all < 20%; the maximum irradiation BED10 in the esophagus was 52.44 Gy, and the median value was 35.35 Gy. The trachea and main bronchus mean dose was 44.35 + 10.30 Gy. The maximum irradiation BED in the spinal cord was 39.86 Gy, and the median value was 28 Gy. The main adverse reaction during the treatment was a decrease in leukocyte and platelet count, with 10.81% (4/37) and 5.41% (2/37), respectively. The other adverse reactions were radiation-induced esophagitis and pneumonia. Of the patients, 13.51% (5/37) and 16.22% (6/37) had grade 2 and grade ≥ 2 radiation-induced esophagitis and pneumonia, respectively. Radiation-induced esophagitis often develops 1 week after the end of concurrent chemoradiotherapy. Symptoms can be relieved after treatment. No treatment-related death occurred.

### TABLE 1 Relationship between clinical features and prognosis of 37 elderly patients with locally advanced lung adenocarcinoma

| Clinical features | n | MST, months (95% CI) | $\chi^2$ | P-value |
|------------------|---|---------------------|---------|--------|
| Sex              |   |                     |         |        |
| Male             | 20| 18 (16.35–23.67)    |         |        |
| Female           | 17| 17 (10.41–20.20)    |         |        |
| Age (years)      |   |                     |         |        |
| <70              | 19| 19 (10.65–25.73)    |         |        |
| ≥70              | 18| 18 (10.16–18.63)    |         |        |
| KPS score        |   |                     |         |        |
| <60              | 14| 14 (19.24–29.91)    |         |        |
| ≥60              | 23| 23 (11.68–17.87)    |         |        |
| Lymp node stage  |   |                     |         |        |
| <2               | 14| 24 (14.45–34.62)    |         |        |
| ≥2               | 23| 14 (11.68–17.87)    |         |        |
| GTV (cm³)        |   |                     |         |        |
| <120             | 21| 19 (12.81–25.33)    |         |        |
| ≥120             | 16| 17 (11.75–23.46)    |         |        |
| BED10 (Gy)       |   |                     |         |        |
| <60              | 17| 14 (11.55–18.69)    |         |        |
| ≥60              | 20| 24 (19.17–30.18)    |         |        |

### TABLE 2 Multivariate analysis of median survival in 37 elderly patients with locally advanced lung adenocarcinoma

| Prognostic factor | $\beta$ | Wald | HR (95% CI) | P-value |
|-------------------|---------|------|-------------|---------|
| KPS score (≥90 vs <90) | 0.58 | 0.81 | 0.63 (0.30–1.39) | 0.311 |
| Lymp node stage (N <2 vs N ≥2) | -2.74 | 3.63 | 0.57 (0.21–0.86) | 0.028 |
| GTV (≥120 cm³ vs <120 cm³) | 2.35 | 1.92 | 1.59 (0.65–3.36) | 0.076 |
| BED10 (<60 Gy vs ≥60 Gy) | -3.67 | 4.98 | 2.91 (1.44–5.68) | 0.009 |

β regression coefficient; BED10, •••; GTV, gross tumor volume; HR, hazard ratio; KPS, Karnofsky Performance Scale; Wald, test statistic.

### 4 DISCUSSION

NSCLC accounts for approximately 85% of lung cancers, of which 30–40% of patients have locally advanced and inoperable cancer. Approximately 50% of patients with NSCLC are aged > 65 years, and approximately one-third of patients are aged > 70 years. Therefore, the proportion of elderly patients is quite large. Many clinical studies have confirmed that concurrent chemoradiotherapy can effectively improve survival time of patients with LA-NSCLC, However, OS and the tumor local control rate in these patients are unsatisfactory. In elderly patients with lower body function, immunity is significantly lower, and the adverse reaction resistance is poorer. A reduction in the side-effects of chemoradiotherapy and improvement in the quality of...
life are the focus of clinical treatment. PEM is a new kind of multiple target for folic acid-resistant agents, and is important in the clinical treatment of NSCLC, first-line treatment, secondary treatment, and maintenance treatment, and treatment with other chemotherapy drugs, such as molecular target drugs, and radiation therapy plays an important role. Studies confirm that PEM possibly interferes with the balance of nucleic acids in cells by inhibiting adenosine triphosphate synthesis and damage to the accurate replication of DNA, and preventing cell block in radiation-sensitive G1/S phase boundary, joint genome DNA damage caused by radiotherapy, and cell apoptosis, and thus plays a role in radiotherapy sensitization. In the present study, we used whole-body gamma knife SBRT combined with PEM concurrent chemoradiotherapy in the treatment of locally advanced lung adenocarcinoma in elderly patients. The local control rates of CR, PR, SD, and PD were 35.14%, 59.46%, 2.70%, and 2.70% respectively, and the total effective rate (CR + PR) was 94.59%. It is similar to the efficiency (CR + PR) of 91.67% in NSCLC 6 months in the middle and late stage of the treatment using the body gamma-knife, as reported by Ma et al. It is higher than the results of the simultaneous treatment with PEM/carboplatin with a short-term efficiency in LA-NSCLC (CR + PR) of 83.33%, which is higher than the results of 3-D conformal radiation therapy, intensity-modulated radiation therapy, or combined chemotherapy in most studies. The local control rate for 1 year in this group was 67.57%. The total survival rates for 1, 2, and 3 years were 86.49%, 45.45%, and 25%, respectively, which were similar to those reported by most studies using gamma-knife, 3-D conformal radiation therapy, and intensity-modulated radiation therapy or combined chemotherapy in the treatment of LA-NSCLC. The adverse reactions, such as leukocyte count reduction, thrombocytopenia, radiation-induced esophagitis, and radiation-induced pneumonia, are also mild, obviously superior to the results of the same study with other single- or double-drug regimens.

In conventional radiotherapy technology, increasing the radiation dose of the tumor cannot improve the patient’s OS. The present study suggests that this might be related to a single low dose of radiation, prolonged course of radiation, and increased side-effects associated with increased tumor dose. The whole-body gamma-knife, as a special method of SBRT, adopting the high-dose treatment mode to improve the target dose and better protect the normal tissues, simultaneously reducing the number of segmentation, significantly shortens the treatment period, inhibits tumor cell repopulation, and improves local control rate of the tumor. The results of the present study showed that the whole-body gamma-knife SBRT is a good treatment for elderly patients with locally advanced lung adenocarcinoma. Its advantage is that it overcomes the disadvantages of conventional radiotherapy. First, it shortened the 6–7 weeks conventional radiotherapy treatment duration to 2 weeks. It is critical for the elderly patients to actively accept successful complete treatment. More importantly, the treatment was completed within a short period, and there was no accelerated repopulation of tumor cells, which greatly improved the local control rate. Furthermore, gamma-knife SBRT has a higher degree of conformal dose distribution of target, and the radiation center has high doses, allows rapid decrease in the outside dose, and guarantees target therapeutic doses that can effectively reduce the surrounding normal tissue dose, increasing the enhancement ratio. Furthermore, it can selectively reduce lymph node exposure without affecting the efficacy, and is simple and feasible. Finally, the shorter course of SBRT is better combined with chemotherapy to improve patient tolerance.

In the present study, single-factor and multifactor analysis found that N staging and radiotherapy dose are both related to the prognosis. The median survival time of N0-1 patients in this group was 10 months longer than that of N2-3 patients (P = 0.011). Therefore, the higher the N stage is, the greater the invasiveness of the tumor and easier the dissemination. These results are similar to the results of the study by Speicher et al. The 1-year local control rate and median survival time in the GTV > 120 cm³ subgroup were lower than those in the GTV < 120 cm³ subgroup, but the difference was not statistically significant. The results were different from those of patients with GTV > 130 cm³, as reported by Yu et al. Eliminating the interference factors of clinical stages, the difference in the results might be related to more target placement of gamma-knife therapy for large-volume tumors. Because of the multitarget arrangement, if the radiation therapy physiologist is not well controlled in designing the treatment plan, the dose distribution will be uneven, and the cold point will affect the curative effect. The present study agrees with the view that the size of the focus should not be a limiting factor for SBRT. The relationship between the size of GTV and optimal fractional dose, total dose, and treatment course has no definite biological theoretical basis and unified clinical research conclusion.

The whole-body gamma-knife SBRT combined with PEM curative chemoradiotherapy has a significant effect on the prognosis of senile locally advanced lung adenocarcinoma, with minor side-effects. It is a good choice for elderly patients with locally advanced lung adenocarcinoma who cannot or are unwilling to undergo surgery because of medical reasons. The time–dose–fraction model requires a large sample of clinical randomized controlled trials for further study.

CONFLICT OF INTEREST

The authors declare that they have read the article and there are no competing interests.

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How to cite this article: Pang J, Chen Y, Hao G-y. Clinical outcome of whole body gamma-knife combined with pemetrexed concurrent chemoradiotherapy in elderly patients with locally advanced lung adenocarcinoma. *Prec Radiat Oncol*. 2019;3:139–144. https://doi.org/10.1002/pro6.1082