125I Brachytherapy Combined with Chemotherapy for Advanced Non-Small Cell Lung Cancer Postprint

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Abstract

This study aimed to evaluate the effect of 125I brachytherapy combined with chemotherapy on advanced non-small cell lung cancer (NSCLC). Patients with NSCLC in stages III to IV were divided into two groups: Group A (n=27) received 125I brachytherapy combined with gemcitabine and cisplatin (GP) chemotherapy, and Group B (n=27) received GP chemotherapy only. The results showed that the overall response rate and median progression-free survival time were 78% and 11.5 months in Group A, 41% and 8 months in Group B, respectively ($P<0.05$). For Group A, the 1- and 2-year survival rates were 67% and 37%, respectively, with the median survival time of 16 months, whereas the corresponding data for Group B were 48%, 22% and 11.5 months ($P>0.05$). The interventional complications in Group A included 5 patients with postoperative pneumothorax and 4 patients with hemoptysis. No patients had radiation pneumonia, radiation esophagitis or esophagotracheal fistula. Chemotherapy treatment-related toxicities were not significantly different between the two groups. The relief of tumor-associated symptoms including cough, hemoptysis, chest pain, and shortness of breath was found in both groups, without statistical difference in remission rates between Groups A and B ($P>0.05$). In conclusion, 125I brachytherapy combined with chemotherapy proved to be safe and effective for treating advanced NSCLC with few complications. It improves the local control rate and prolongs the progression-free survival time.

Full Text

Preamble

125I Brachytherapy Combined with Chemotherapy for Advanced Non-Small Cell Lung Cancer

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This study evaluated the efficacy of ^{125}I brachytherapy combined with chemotherapy for advanced non-small cell lung cancer (NSCLC). Patients with stage III–IV NSCLC were divided into two groups: Group A (n = 27) received ^{125}I brachytherapy combined with gemcitabine and cisplatin (GP) chemotherapy, while Group B (n = 27) received GP chemotherapy alone. The results showed that the overall response rate and median progression-free survival time were 78% and 11.5 months in Group A, compared to 41% and 8 months in Group B, respectively ($P < 0.05$). For Group A, the 1- and 2-year survival rates were 67% and 37%, respectively, with a median survival time of 16 months, whereas the corresponding data for Group B were 48%, 22%, and 11.5 months ($P > 0.05$). Interventional complications in Group A included pneumothorax in 5 patients and hemoptysis in 4 patients. No patients developed radiation pneumonia, radiation esophagitis, or esophagotracheal fistula. Chemotherapy-related toxicities were not significantly different between the two groups. Both groups experienced relief of tumor-associated symptoms including cough, hemoptysis, chest pain, and shortness of breath, with no statistical difference in remission rates between Groups A and B ($P > 0.05$).

In conclusion, ^{125}I brachytherapy combined with chemotherapy proved to be safe and effective for treating advanced NSCLC with few complications, improving local control rate and prolonging progression-free survival time.

Keywords: Non-small cell lung cancer, ^{125}I brachytherapy, Chemotherapy
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Introduction

Lung cancer is the leading cause of cancer-related mortality, with non-small cell lung cancer (NSCLC) accounting for approximately 80%–85% of cases [1–3]. While surgery remains the dominant treatment modality, the lack of typical early-stage symptoms means that up to 70% of NSCLC patients present with locally advanced or metastatic disease at diagnosis. Consequently, only one-third of all patients are eligible for curative treatment, resulting in a poor overall prognosis [4,5]. Although radiation therapy can alleviate clinical symptoms in

intermediate and advanced-stage NSCLC to some extent, the overall efficacy remains unsatisfactory [6]. Chemotherapy represents the mainstay of treatment for intermediate and advanced-stage NSCLC, with gemcitabine and cisplatin (GP) serving as the standard regimen [7]. However, the local control rate of chemotherapy and its effect on distant metastases remain suboptimal due to imperfect tissue distribution [8].

Iodine-125 decays with a half-life of $T_1/_2 = 59.6$ days through electron capture into excited tellurium-125, which emits low-energy γ-rays (27–35.5 keV, primarily the 35.5 keV γ-ray and tellurium Kα and Kβ X-rays induced by the 35.5 keV γ-ray). This property enables low-dose-rate brachytherapy by implanting ^{125}I seeds directly into the tumor area. In lung cancer treatment, ^{125}I seeds cause minimal trauma, produce fewer complications, and achieve favorable local control rates [9–11]. This study evaluated the efficacy and feasibility of combining ^{125}I brachytherapy with chemotherapy for advanced NSCLC.

Subjects and Methods

A. Subjects

From February 2010 to January 2012, 54 patients treated at the China-Japan Union Hospital affiliated with Jilin University were enrolled in this study. The inclusion criteria were: (a) histologically confirmed NSCLC in stages III–IV according to the International Union Against Cancer staging system, with ineligibility for surgical resection [12]; (b) Karnofsky performance status of 70 or higher; (c) no severe coagulation disorders; and (d) life expectancy exceeding 3 months.

Exclusion criteria included: (a) pregnancy or lactation; (b) prior anti-tumor treatment such as chemotherapy, radiotherapy, or other therapies within 3 months of study treatment; (c) uncontrolled serious infections; and (d) concomitant serious illnesses such as uncontrolled angina pectoris, myocardial infarction within 3 months, heart failure, uncontrolled diabetes mellitus, severe respiratory failure, uncontrolled hypertension, or severe coagulation disorders.

The 54 patients were divided into two groups: brachytherapy combined with GP chemotherapy (Group A, n = 27) and GP chemotherapy alone (Group B, n = 27). Informed written consent was obtained from all patients, and the study protocol was approved by the Ethics Committee and Institutional Review Board of China-Japan Union Hospital, Changchun, China.

B. ^{125}I Seed Implantation

The ^{125}I seeds (Model BT-125-1, GMS Pharmaceutical Co., Ltd., Shanghai, China) measured (4.5 ± 0.5) mm in length and (0.80 ± 0.05) mm in diameter, with an initial activity of 25.9 MBq. Before implantation, Group A patients underwent Single-Photon Emission Computed Tomography/CT (SPET/CT, Philips Healthcare, WA) scanning to evaluate tumor morphology, volume, and

characteristics. CT images with 5 mm slice thickness were imported into the treatment planning system (TPS) produced by Beijing Flying Zhaoye Technology Co., Ltd. The minimum prescribed dose to the tumor (MPD) was 120 Gy (range 100–140 Gy). Based on the preoperative plan generated by the TPS, the required number and placement of ^{125}I seeds were determined, and needle positions were marked on the patient's body surface. Implantation was performed by professional radiation technicians under CT guidance. Following local anesthesia with 2% lidocaine, one or multiple 18-gauge needles were gradually inserted percutaneously into the tumor, and a turntable implantation gun was used to place ^{125}I seeds into the tumor at 0.5–1.0 cm intervals, with adjacent implantation needles spaced approximately 1 cm apart. The ^{125}I seeds were implanted according to plan, and immediate verification was performed by CT scanning.

C. Chemotherapy

All patients received chemotherapy consisting of gemcitabine (1000 mg/m^2 on Days 1 and 8) and cisplatin (30 mg/m^2 on Days 1, 2, and 3) administered intravenously. The GP chemotherapy regimen was repeated every 3 weeks for a maximum of 4 cycles. Before chemotherapy, patients routinely received 5-HT_3 antagonists for prevention of vomiting. If a patient experienced excessive adverse events, subsequent treatment cycles were delayed until the events had nearly resolved.

D. Follow-up and Evaluation

Before treatment, vital signs and tumor-associated symptoms (cough, hemoptysis, chest pain, and shortness of breath) were recorded. Follow-up CT examinations and clinical hematological tests were performed monthly for the first 3 months and then at 1–3 month intervals.

Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) and classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The overall response rate (ORR) was calculated as the percentage of patients with CR or PR. Clinical treatment efficacy was assessed by ORR, progression-free survival time (PFST), survival time (ST), and treatment-related adverse effects.

E. Statistical Analysis

Statistical analysis was performed using SPSS 19.0 software. Data are presented as mean $\pm$ standard deviation (SD). Differences were evaluated using Student's t-test. Treatment response was analyzed using Pearson's ^{2} test. Survival analysis was performed using the Kaplan-Meier method, and the log-rank test was used for survival comparisons. P-values < 0.05 were considered statistically significant.

Results

A. Patient and Tumor Characteristics

From February 2010 to January 2012, a total of 54 patients with unresectable stage III–IV NSCLC were recruited. Group A (n = 27) received combined ^{125}I brachytherapy and GP chemotherapy, while Group B (n = 27) received GP chemotherapy alone. The median follow-up time was 15 months (range 5–28 months). The average number of chemotherapy cycles was 2.4 ± 0.8 in Group A and 2.7 ± 0.9 in Group B ($P > 0.05$). The verified dose for Group A was (123.4 ± 10.7) Gy, which was consistent with treatment requirements. Patient characteristics are summarized in Table 1 . No statistically significant differences were found between the two groups in age, gender, histology, lesion location, clinical stage, or tumor size ($P > 0.05$).

B. Anti-tumor Efficacy

In Group A, CR, PR, SD, and PD were observed in 5, 16, 4, and 2 patients, respectively. A typical case of complete response in Group A is shown in Fig. 1 [Figure 1: see original paper]. In Group B, CR, PR, SD, and PD were observed in 2, 9, 9, and 7 patients, respectively. The ORR (CR + PR) at 6 months was 78% for Group A and 41% for Group B ($P < 0.05$; Table 2). The median PFST was 11.5 months in Group A and 8 months in Group B ($P < 0.05$; Fig. 2(a) [Figure 2: see original paper]). The median ST was 16 months in Group A and 11.5 months in Group B ($P > 0.05$; Fig. 2(b) [Figure 2: see original paper]). The 1- and 2-year survival rates were 67% and 37% in Group A and 48% and 22% in Group B, respectively. No statistically significant difference in survival rates was found between the two groups ($P > 0.05$), while a significant difference in ORR was observed ($P < 0.05$).

C. Complications

No treatment-related deaths occurred in either group. In Group A, 5 patients developed postoperative pneumothorax during the ^{125}I seed implantation procedure. Among these, 4 patients recovered within 2 hours, while 1 patient with lung compression > 30% required closed thoracic drainage and recovered within 2 days. Four patients with hemoptysis recovered after conservative treatment. None of the patients developed radiation pneumonia, radiation esophagitis, or esophagotracheal fistula during follow-up.

D. Adverse Events of Chemotherapy

Chemotherapy-related toxicities in all patients were classified according to WHO toxicity criteria. Grades 3 and 4 leukopenia, thrombocytopenia, and anemia were observed in 5, 3, and 2 patients in Group A and 6, 2, and 3 patients in Group B, respectively ($P > 0.05$). Grade 3 nausea/vomiting and diarrhea were observed in 3 and 2 patients in Group A and 4 and 1 patient in Group B,

respectively ($P > 0.05$). No Grade 3 or 4 arrhythmia, alopecia, or liver or renal function damage was found in either group.

E. Tumor-Associated Symptoms

Tumor-associated symptoms including cough, hemoptysis, chest pain, and shortness of breath were compared between the two groups before and after treatment. Symptom relief was observed in both groups to varying degrees. The remission rates for cough, hemoptysis, chest pain, and shortness of breath were 60.0% (9/15), 64.3% (9/14), 61.1% (11/18), and 60.0% (12/20) in Group A, and 35.3% (6/17), 36.4% (4/11), 35.0% (7/20), and 38.9% (7/18) in Group B, respectively. No statistically significant difference in remission rates was found between the two groups ($P > 0.05$; Table 3).

Discussion

The mechanism of ^{125}I brachytherapy involves using low-energy γ-rays to damage DNA duplexes and reduce the probability of cancer cell mitosis and proliferation [9,13]. Using an advanced TPS system, we simulated the three-dimensional shape of the tumor and calculated ^{125}I seed distribution and therapeutic dose according to tumor morphology. The ^{125}I seeds were implanted into the tumor under ultrasound, CT, or endoscopic guidance, providing continuous irradiation to tumor cells at all stages of the cell cycle while delivering lower radiation doses to adjacent normal tissues. Several studies have demonstrated the effectiveness of ^{125}I brachytherapy for head and neck cancer, pancreatic cancer, and prostate cancer [14–18]. Chemotherapy remains the mainstay of treatment for advanced NSCLC, with GP serving as a standard regimen [7]. While ^{125}I brachytherapy improves local control rates, chemotherapy has potential effects on distant metastases.

Similar to previous studies [19,20], combined ^{125}I brachytherapy with GP chemotherapy achieved better overall response rates and longer PFST than the control group ($P < 0.05$). The combined treatment also showed better trends in median ST and survival rates, though these results were not statistically significant.

The main complications of ^{125}I brachytherapy were pneumothorax and hemoptysis [21–24]. In the present study, 5 patients developed postoperative pneumothorax and 4 patients experienced hemoptysis during the puncture procedure, all of whom recovered with appropriate treatment. These findings are consistent with previous reports [21–24]. Both groups tolerated treatment well, with no treatment-related deaths. Due to the low-energy spectrum of ^{125}I, minimal radiation damage occurs to neighboring organs. With a median follow-up of 15 months (range 5–28 months), none of the patients developed radiation pneumonia, radiation esophagitis, or esophagotracheal fistula. Chemotherapy-related toxicities were similar between Group A and Group B, indicating that ^{125}I brachytherapy combined with systemic chemotherapy does not increase

chemotherapy toxicities while achieving good local tumor control.

For patients with advanced NSCLC, therapeutic goals include not only improving response rates and prolonging survival but also alleviating symptoms and improving quality of life [25]. Approximately 74% of patients with advanced lung carcinoma experience chest pain [26]. ^{125}I brachytherapy can relieve chest pain, possibly through mechanisms related to decreased pain chemical mediators as radiation treatment shrinks tumors or inhibits tumor cells from releasing pain mediators [27]. Both groups experienced relief of tumor-associated symptoms including cough, hemoptysis, chest pain, and shortness of breath, with no statistically significant difference in remission rates between the groups, likely due to the small sample sizes.

Therefore, further research with larger patient populations is necessary. Additionally, the observation period (median 15 months) was relatively short, and long-term follow-up of curative effects, survival time, and other indicators should be conducted. Finally, ^{125}I seeds are relatively expensive and may not be affordable for all patients.

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Note: Figure translations are in progress. See original paper for figures.