INTRODUCTION

Lung cancer, which continues to be a major global health problem, is the first leading cause of cancer-related mortality for men and women in the world.1 Due to the delayed diagnosis, five-year survival rate accounts for only 15%, most of the patients have distant metastases at the diagnosis.2 Clinical classification distinguishes two groups of primary lung cancer: non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). The treatments include surgery, adjuvant chemotherapy, and radiation therapy; combined modality treatment regimens for advanced lung cancer (stage III and IV) have improved patients’ survival time.3,4 However, these regimens often have been accompanied by more severe early and late side effects.2,5 One of the most distressing symptoms for lung cancer patients is airway obstruction. Therefore, novel approaches are urgently needed to effectively control lung tumors and improve the quality of life for these patients.

Brachytherapy is one of the most efficient methods in controlling the malignant airway obstruction and overcoming difficulties in breathing for the treatment of lung cancer.6,7 In recent years, the technique of iodine-125 radioactive seeds implantation for malignant tumors has been developed rapidly with prostate cancer,8 pancreatic cancer,9 rectal cancer,10 metastatic tumors of the hepatic portal system,11 and gynecologic malignancies;12 and achieved satisfactory clinical therapeutic effects with few complications. Currently, implantation of iodine-125 radioactive seeds in patients with lung cancer are increasing, which makes up for the shortcomings of conventional external radiotherapy and chemotherapy. By placing a radioactive source near or in the tumor, the implanted iodine-125 radioactive seeds can generate a high dose of radiation (140-160 Gy) within target tumor

META-ANALYSIS

The Efficacy and Safety of Iodine-125 Brachytherapy Combined with Chemotherapy in Treatment of Advanced Lung Cancer: A Meta-Analysis

Hui Qiu1, Jiayin Ji2, Zhiying Shao3, Jianshe Wang1, Gaolei Ma2 and Longzhen Zhang1,2

ABSTRACT

The aim of this study was to systematically review the efficacy and safety of iodine-125 brachytherapy combined with chemotherapy in patients with advanced lung cancer. PubMed, MEDLINE, EBSCO, FMJS and Web of Science were searched to obtain randomized controlled trials (RCTs), published in English and Chinese, until February 2016. The evaluating indicators were complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), overall response rate (ORR), disease control rate (DCR), one-year overall survival, two-year overall survival and adverse events. Revman 5.2 software was used for data syntheses and analyses. A total of 296 patients enrolled in 5 RCTs were ultimately included in this study based on our selection criteria, and 150 patients received chemotherapy alone, while another 146 patients received the combination therapy of iodine-125 brachytherapy and chemotherapy. The results showed that iodine-125 brachytherapy combined with chemotherapy was superior to chemotherapy alone in CR (risk ratio [RR] = 3.66, 95% confidence interval [CI]: 2.08 to 6.44, p<0.001), PR (RR = 1.47, 95% CI: 1.16 to 1.86, p=0.001), ORR (RR = 1.85, 95% CI: 1.54 to 2.22, p<0.001), DCR (RR = 1.19, 95% CI: 1.10 to 1.29, p<0.001), one-year overall survival (RR = 1.46, 95% CI: 1.12 to 1.92, p=0.006) and PD (RR = 0.20, 95% CI: 0.09 to 0.43, p<0.001); meanwhile, there was no significant difference in two-year overall survival (RR = 1.30, 95% CI: 0.72 to 2.37, p=0.39). In terms of adverse events, the combination therapy significantly increased the incidence of pneumothorax (RR = 4.93, 95% CI: 1.94 to 12.55, p<0.001); however, no significant differences were found in the incidence of other adverse events. This study indicated that the combination therapy of iodine-125 brachytherapy and chemotherapy could improve the therapeutic efficacy of advanced lung cancer without increasing the incidence of adverse events, except pneumothorax.

focuses to continuously destroy tumor cells, while only a small amount of healthy tissue receives therapeutic dose of radiation. Additionally, with a half-life period of 59.6 days, iodine-125 radioactive seeds implantation can prolong exposure of tumor target to radiation and decrease the local recurrence.

Several randomized clinical trials (RCTs) of combination therapy of chemotherapy and iodine-125 radioactive seeds brachytherapy in the treatment of advanced lung cancer had been carried out in recent years, but this combination therapy is uncommonly used and its efficacy and safety remain unclear. In this study, we comprehensively analyzed the clinical efficacy of the combination therapy of brachytherapy with iodine-125 radioactive seeds and chemotherapy for the treatment of advanced lung cancer by using meta-analysis method.

**METHODOLOGY**

According to guidelines from the Cochrane Collaboration, PubMed, MEDLINE, EBSCO, FMJS and Web of Science were searched to obtain the studies included in this meta-analysis, which cover the period from January 2005 to February 2016. The following Medical Subject Headings (MeSHs) were used: lung cancer, iodine-125 radioactive seeds, brachytherapy, RCTs. The references of the included studies were also screened manually. The publication languages were restricted to Chinese and English.

The inclusion criteria were: (i) studies must be RCTs; (ii) patients must be clinically or pathologically diagnosed with lung cancer in stages III to IV, according to the international union against cancer staging system; (iii) treatment of the control group was chemotherapy alone, and the combination group was iodine-125 brachytherapy combined with chemotherapy; (iv) tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST); (v) chemotherapy adverse events were evaluated according to the Toxicity Criteria of the World Health Organization; radiation adverse events were evaluated according to the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer; (vi) There was no statistical difference between the combination group and the control group on the basic characteristics of the enrolled patients in respects of age, gender ratio, Karnofsky performance status, general vital signs, tumor stages and other general information.

The exclusion criteria were as follows: (i) non-RCTs; (ii) life expectancy of patients shorter than 3 months, patients with a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, severe respiratory failure and uncontrolled hypertension, were excluded for the enrollment; (iii) reviews without original data or lacking control group; (iv) repeated reports.

Two investigators (Hui Qiu, Jiayin Ji) independently selected studies on the basis of the inclusion and exclusion criteria. The selection process is presented in the flow chart (Figure 1) according to the PRISMA guidelines. Another two investigators (Zhiying Shao, Jianshe Wang) conducted data extraction from the included studies, using a standardized data collection form. The data abstracted were: publication details (name of the first author and year of publication), number of patients, age, gender, histology, UICC TNM classification, intervention factors and prescription dose; outcome measurements: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), one-year overall survival rate, two-year overall survival rate and several most frequent adverse events, using CR+PR to calculate overall response rate (ORR), using CR+PR+SD to calculate disease control rate (DCR). Any disagreements that occurred during data extraction were resolved by discussions among the investigators.

The quality of each study was evaluated according to the RCT quality evaluation standards of the Cochrane review manual 5.0.0. Two reviewers (Hui Qiu, Gaolei Ma) independently completed and assessed the methodological quality of the included studies based on: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); (vi) selective reporting (reporting bias); and other biases. All inconsistencies were resolved by discussions among the investigators and a consensus was reached.

The meta-analysis was performed using Review Manager Version 5.2 software (provided by the Cochrane Collaboration, Oxford, UK). Summary measures of efficacy and safety used relative risk ratio (RR), along with its 95% confidence interval (95% CI) for dichotomous variables. The Chi-square test, p-values and I² statistics were used to evaluate the between-study heterogeneity. If there was no significant heterogeneity (p > 0.1 and I² < 50%), the pooled RR value was estimated by the fixed-effects model; if heterogeneity existed, its sources were analyzed and subcategory analysis was adopted for factors that might contribute to the heterogeneity. If there was statistical heterogeneity among the studies without clinical heterogeneity or the difference was not clinically significant, a random-effect model was used. If the heterogeneity between groups was too great, or detailed data from the original trials was not sufficiently available, a descriptive analysis was applied. The publication bias in this study was assessed by a funnel plot. For all tests, p<0.05 was considered statistically significant.

**RESULTS**

A total of 209 potentially relevant references identified in electronic databases were reviewed; of these, 150...
duplicated records were removed, 37 records were excluded after reading title and abstract information. Seventeen full-text articles were excluded because they did not meet the inclusion criteria. Finally, 5 eligible studies with 296 patients were successfully selected for the present systematic review21-25; among them, 146 patients were treated with iodine-125 brachytherapy combined with chemotherapy, and 150 patients were treated with chemotherapy alone. The flow chart of this meta-analysis is shown in Figure 1.

The main characteristics of the included RCTs are summarized in Table I. The general information between the combination group and the control group were similar that indicated the two groups were suitable to compare. Of all the included RCTs, two trials mentioned a specific randomization method (random digital table).24,25 The quality evaluations of the included studies are presented in Figure 2.

The meta-analysis results of short-term therapeutic efficacy are shown in Figure 3.

For CR, there was no significant heterogeneity ($I^2 = 0\%$, $p = 0.98$), RR and 95% CI were calculated by the fixed-effects model. CR in the combination group was significantly higher than control group (RR = 3.66, 95% CI: 2.08 to 6.44, $p<0.001$).

For PR, no significant heterogeneity ($I^2 = 47\%$, $p = 0.11$) was existed among the 5 RCTs, therefore, RR and 95% CI were calculated by the fixed-effects model. The results suggested that the PR in the combination group was significantly higher than control group (RR = 1.47, 95% CI: 1.16 to 1.86, $p=0.001$).

![Figure 1: Flow chart of study selection.](image)

**Table I: Main characteristics of the included studies.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Group</th>
<th>Number of patients</th>
<th>Age range (years)</th>
<th>Male/female</th>
<th>Histology (squamous/adenocarcinoma/other)</th>
<th>Intervention factor</th>
<th>Prescription dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tao Zhang21</td>
<td>2014</td>
<td>Combination</td>
<td>34 (had 67 lesions)</td>
<td>49-85</td>
<td>29/5</td>
<td>20/11/3</td>
<td>125 and Ptxd or Dtxl</td>
<td>100-140 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>35 (had 64 lesions)</td>
<td>46-82</td>
<td>28/7</td>
<td></td>
<td>125 and Ptxd or Dtxl</td>
<td></td>
</tr>
<tr>
<td>Shengchu Zhang22</td>
<td>2011</td>
<td>Combination</td>
<td>24</td>
<td>40-70</td>
<td>20/4</td>
<td>7/14/3</td>
<td>GP</td>
<td>100-140 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>29</td>
<td>40-70</td>
<td>20/9</td>
<td></td>
<td>GP</td>
<td></td>
</tr>
<tr>
<td>Fujun Zhang23</td>
<td>2007</td>
<td>Combination</td>
<td>32</td>
<td>31-73</td>
<td>15/17</td>
<td></td>
<td>GP</td>
<td>100-150 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>30</td>
<td>_</td>
<td>_</td>
<td></td>
<td>GP</td>
<td></td>
</tr>
<tr>
<td>Xiaojuan Yu24</td>
<td>2015</td>
<td>Combination</td>
<td>26</td>
<td>48-72</td>
<td>15/11</td>
<td>9/16/1</td>
<td>GP or CM</td>
<td>90-110 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>26</td>
<td>_</td>
<td>_</td>
<td></td>
<td>GP or CM</td>
<td></td>
</tr>
<tr>
<td>Feng Yu25</td>
<td>2012</td>
<td>Combination</td>
<td>30</td>
<td>63.8 ±5.47</td>
<td>18/12</td>
<td>12/18/0</td>
<td>GP or CM</td>
<td>80 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>30</td>
<td>63.6 ±4.26</td>
<td>18/12</td>
<td>12/18/0</td>
<td>GP or CM</td>
<td></td>
</tr>
</tbody>
</table>

Note: $^{125}$ = iodine-125;  Ptxd = Pemetrexed;  Dtxl = Docetaxel;  GP = Gemcitabine plus cisplatin;  DP = docetaxel plus cisplatin;  CM = Chinese medicine
For ORR, there was no significant heterogeneity ($I^2 = 29\%, p = 0.23$) among the included 5 studies, so the RR and 95% CI were calculated by the fixed-effects model. Our meta-analysis indicated that the ORR in the combination group was significantly higher than control group ($RR = 1.85, 95\% CI: 1.54$ to $2.22, p<0.001$).

For SD, the fixed-effects model was used to calculate RR and 95% CI, because there was no significant heterogeneity ($I^2 = 0\%, p = 0.79$) among the included 5 RCTs. SD in the combination group was significantly lower than control group ($RR = 0.44, 95\% CI: 0.30$ to $0.64, p<0.0001$).

For DCR, there was no significant heterogeneity ($I^2 = 11\%, p = 0.35$) among the 5 RCTs, therefore, the fixed-effects model was used to calculate RR and 95% CI. DCR in the combination group was significantly higher than control group ($RR = 1.19, 95\% CI: 1.10$ to $1.29, p<0.001$).

For PD, no significant heterogeneity was existed among the 5 studies ($I^2 = 24\%, p = 0.26$), hence, RR and 95% CI were calculated by the fixed-effects model. Our meta-analysis suggested that the PD in the combination group was significantly lower than control group ($RR = 0.20, 95\% CI: 0.09$ to $0.43, p<0.001$).

The meta-analysis results of long-term therapeutic efficacy were shown in Figure 4. For one-year overall survival, the fixed-effects model was used to calculate RR and 95% CI, because there was no significant heterogeneity ($I^2 = 0\%, p = 0.98$) among the included 5 RCTs. Our meta-analysis suggested that the 1-year survival...
Figure 3: Meta-analysis results of the short-term efficacy between iodine-125 brachytherapy combined with chemotherapy and chemotherapy alone.
Figure 4: Meta-analysis results of the long-term efficacy between iodine-125 brachytherapy combined with chemotherapy and chemotherapy alone.

Figure 5: Meta-analysis results of the adverse events between iodine-125 brachytherapy combined with chemotherapy and chemotherapy alone.
overall survival in the combination group was significantly higher than control group (RR = 1.46, 95% CI: 1.12 to 1.92, p=0.006).

For two-year overall survival, no significant heterogeneity was existed among the 5 studies (I² = 0%, p = 0.89), hence, RR and 95% CI were calculated by the fixed-effects model. Our meta-analysis suggested that there was no significant difference between combination group and control group (RR = 1.30, 95% CI: 0.72 to 2.37, p = 0.39).

For the safety meta-analysis, we selected the most commonly reported adverse events, including fever (reported in 2 RCTs), nausea and vomiting (reported in 2 RCTs), pneumothorax (reported in 5 RCTs), hemoptysis (reported in 2 RCTs) and leukopenia (reported in 2 RCTs).

In addition to hemoptysis which used a random effects model to calculate RR and 95% CI (I² = 66%, p = 0.09), the fixed-effects model was selected to calculate other RRs and 95% CIs (Figure 5). There was no significant difference between combination group and control group in fever (RR = 0.75, 95% CI: 0.52 to 1.08, p = 0.12), nausea and vomiting (RR = 1.06, 95% CI: 0.84 to 1.35, p = 0.61), hemoptysis (RR = 2.00, 95% CI: 0.59 to 6, p = 0.27), and leukopenia (RR = 1.39, 95% CI: 0.76 to 2.56, p = 0.29). However, the incidence rate of pneumothorax in the combination group was significantly higher than control group (RR = 4.93, 95% CI: 1.94 to 12.55, p <0.001) (Figure 5).

The funnel plots of short-term therapeutic efficacy (Figure 6A), long-term therapeutic efficacy (Figure 6B) and adverse events (Figure 6C) showed a symmetric distribution of studies, indicating no publication bias was existed.

**DISCUSSION**

The majority of lung cancer patients are not diagnosed until the disease is at the relatively late stage. Despite the rapid progress in treatment modalities for lung cancer including surgery, radiotherapy, chemotherapy and biotherapy, the prognosis of patients with advanced lung cancer remains generally poor, and about 60% of those patients will die within one year and 80% will die within two years. Therefore, seeking other more effective therapeutic approaches appears particularly important. With the high-speed development of computerized three-dimensional treatment planning system, more and more physicians shift their attention to CT-guide brachytherapy with radioactive seeds for treating malignant tumors. Iodine-125 radioactive seeds could release continuously low dosage of X-ray and γ-ray, thus effectively improve the dosage distribution ratio between locally radioactive tissues and normal tissues, significantly reduce the regeneration of tumors and cure patients with lung cancer ultimately. In addition, the low radiation dose rate of iodine-125 radioactive seeds could induce the bystander effects, which potentiate the killing action on tumor cells and compensate for the influence of inhomogeneous distribution of radiation dosage on therapeutic outcomes. Iodine-125 radioactive seeds have the advantages including high conformity index and producing high dose in target tumor focuses, thus would have great potential in the treatment of advanced lung cancer.

Meta-analysis is a statistical method which can integrate results from individual studies for a specified outcome. In the present study, 5 eligible RCTs including 358 advanced lung cancer patients were identified by searching several databases. The results of this meta-analysis indicated that, compared with chemotherapy
alone, the combination therapy of iodine-125 brachytherapy and chemotherapy achieved satisfactory clinical efficacies in terms of CR, PR, ORR, DCR and PD (Figure 3). The results show that iodine-125 radioactive seeds have a good local tumor control ability. Moreover, recent studies have indicated that local disease control rate is an important independent prognostic factor for the overall survival of patients with locally advanced lung cancer. The meta-analysis results of overall survival suggested that the treatment modality of iodine-125 brachytherapy and chemotherapy could significantly improve the one-year overall survival in patients with advanced lung cancer, but had no effect on the two-year overall survival (Figure 4).

In terms of safety analysis, the treatment was well tolerated among patients in both groups. Chemotherapy side events, such as fever, nausea and vomiting, leucopenia, were similar between the combination group and the control group (Figure 5). This may be because implantation of iodine-125 radioactive seeds has fewer systemic adverse events. As shown in previous studies, pneumothorax and hemoptysis were the main complications of brachytherapy; and these results indicated that, compared with chemotherapy alone, the combination therapy of iodine-125 brachytherapy and chemotherapy significantly increased the incidence of pneumothorax, but did not increase the incidence of hemoptysis (Figure 5). All patients with pneumothorax and hemoptysis were cured with proper therapy. Moreover, it should be noticed that there were still some deficiencies in this meta-analysis. First, not all RCTs' qualities were high, which may result in the emergence of bias. Second, the usage and dosage of chemotherapy agents and the prescription dose of radiation were not completely equivalent in the eligible studies. Third, the sample size was small, and the follow-up time was not long enough to analyze the three-year or five-year overall survival. Hence, more high-quality, multiple-center, large-sample, and length clinical RCTs should be enrolled to enrich the evidence base and support the widespread implementation of iodine-125 brachytherapy in the advanced lung cancer treatment.

CONCLUSION

This study indicated that the combination therapy of iodine-125 brachytherapy and chemotherapy could improve the therapeutic efficacy of advanced lung cancer without increasing the incidence of adverse events, except pneumothorax.

Acknowledgments: This work was supported by two funds from the National Natural Science Foundation of China (No.81372424 and No.81071831), the Foundation Research Project of Jiangsu Province (No.BK20131131) and Science-education and health development special project of Jiangsu.

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