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Efficacy and safety of iodine-125 radioactive seeds brachytherapy for advanced non−small cell lung cancer—A meta-analysis

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ABSTRACT

PURPOSE: This meta-analysis was conducted to investigate the efficacy and safety of ^{125}I brachytherapy for locally advanced non−small cell lung cancer (NSCLC).

METHODS AND MATERIALS: Trials comparing ^{125}I brachytherapy with chemotherapy in NSCLC were identified. Meta-analysis was performed to obtain pooled risk ratios for an overall response rate (ORR), disease control rate (DCR) and complications, and pooled hazard ratio for overall survival (OS).

RESULTS: Fifteen studies including 1188 cases were included. The pooled result indicated that there were significant differences in ORR, DCR, and OS between ^{125}I brachytherapy combined with chemotherapy and chemotherapy alone, but no statistic differences in gastrointestinal symptoms, leukopenia, myelosuppression, and hemoglobin reduction. Patients treated with ^{125}I brachytherapy combined with chemotherapy have a higher relative risk of pneumothorax, bloody sputum, and pneumorrhagia compared with chemotherapy alone. Seeds migration only occurred in the group treated with ^{125}I brachytherapy. There were significant differences in ORR, DCR, and myelosuppression between ^{125}I brachytherapy alone and chemotherapy.

CONCLUSIONS: ^{125}I brachytherapy combined with chemotherapy can significantly enhance the clinical efficacy and improve the OS of patients with advanced NSCLC without increasing the incidence of complications of chemotherapy. ^{125}I brachytherapy alone can significantly enhance the clinical efficacy and reduce the incidence of myelosuppression compared with chemotherapy. However, ^{125}I brachytherapy may cause lung injury. Large sample and higher-quality randomized controlled trials are needed to confirm the pooled results of complications.

Keywords: Non−small cell lung cancer; Iodine-125; Brachytherapy; Efficacy; Meta-analysis

Introduction

Lung cancer is a major global health problem, which has been the leading cause of cancer death among men and the second leading cause of cancer death (after breast cancer) among women worldwide (1). Surgery is usually the treatment of choice for localized cancers, but most of the patients are not diagnosed until late pulmonary carcinoma, lost the value of treatment, or were inoperable. Only approximately 20% of all patients with non−small cell lung cancer (NSCLC) are candidates for potentially curative resection,

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Authors' contributions: WM and MH contributed to the conception and designed the meta-analysis. WZ and JL collected the data. WZ performed the statistical analysis and wrote the original manuscript. RL and YZ contributed to the modification of content. WM and MH were responsible for the quality control of the study.

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and not all patients with resectable tumors are suitable candidates for surgery due to certain contraindications (2, 3).

For patients who are not candidates for curative surgery, radiotherapy and chemotherapy are commonly used as alternative palliative treatments. However, the effectiveness of traditional chemotherapy treatment to control inoperable tumors is unsatisfactory, and the observed survival continues to be limited (4, 5). External beam radiotherapy is often accompanied by many radiation-related complications such as radiation pneumonia, esophagitis, and myelosuppression. Also, the radiation dose is restricted by the complications of the surrounding normal tissue and vital organs.

Recent years, with the help of image guidance, brachytherapy has been proposed as a strategy to treat medically inoperable tumors. Brachytherapy could deliver a continuous low-dose-rate of radiation to tumor lesions directly over a long period of time while sparing the surrounding normal tissues (6, 7). Iodine-125 (^{125}I) brachytherapy has been increasingly practiced in the clinical treatment of NSCLC since the 1980s (8). ^{125}I radioactive seeds can be implanted into the tumor permanently and release continuous low-dose X- and γ-rays that provide steady irradiation to the tumor cells at all stages of the cell cycle but a lower radiation dose to the normal tissue adjacent to the lesion. The radiation energies of ^{125}I seeds range from 27 to 35 keV, with a half-life of 59.6 days (9−11).

Previous studies have reported that ^{125}I brachytherapy combined with chemotherapy has a higher overall response rate (ORR) as compared to chemotherapy alone for the treatment of NSCLC and could significantly relieve the clinical symptoms for patients with a large tumor and improve the quality of life (12, 13). However, there are few randomized clinical trials carried out in recent years because ^{125}I brachytherapy in the treatment of advanced NSCLC is uncommonly used. A previous study also indicated that there was no significant difference of the overall survival (OS) between the ^{125}I brachytherapy combined with chemotherapy group and the chemotherapy group (14). Therefore, the aim of this study is to systematically collect and summarize the evidence to investigate the efficacy and safety of ^{125}I brachytherapy for advanced NSCLC. We compared the efficacy and safety of ^{125}I brachytherapy combining chemotherapy with chemotherapy alone, as well as ^{125}I brachytherapy alone with chemotherapy alone using meta-analysis, to provide more up-to-date evidence to guide future clinical trials.

Methods and materials

Literature search

PubMed, Web of Science, ScienceDirect, Cochrane Library, China Knowledge Resource Integrated Database, and China Biology Medicine disc were searched to identify relevant studies up to April 2017 without language restrictions. The main keywords used for the search were "Iodine-125 OR I125 OR 125I OR brachytherapy" AND "lung cancer OR lung carcinoma OR NSCLC" AND "chemotherapy".

Studies inclusion and exclusion criteria

The following inclusion criteria were used for the literature: (*1*) The study design was confined to the controlled clinical trials including randomized controlled trials (RCTs) and non-RCTs; (*2*) Patients received ^{125}I brachytherapy (or combined with chemotherapy) in the treatment group and chemotherapy only in the control group for the treatment of NSCLC; (*3*) Patients had stage III or IV NSCLC diagnosed pathologically, Karnofsky Performance Status ≥ 60 and time of survival ≥ 3 months, no chemotherapy contraindication before treatment, and no significant abnormalities in liver, kidney, and heart function; and (*4*) Studies had outcomes of ORR and disease control rate (DCR) defined by World Health Organization criteria or Response Evaluation Criteria in Solid Tumors .

The major exclusion criteria were as follows: (*1*) single-arm studies; (*2*) animal experiments, review, and other irrelevant studies; (*3*) no detailed data about primary outcomes from the literature studies and connection with authors; and (*4*) patients with small cell lung cancer or stage I/II NSCLC, and the treatment of the control group was not intravenous chemotherapy.

Data extraction and quality assessment

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (15), two reviewers (WZ and JL) independently searched potentially relevant articles and conducted the data extraction, and any disagreements between the two reviewers were resolved consensually by involving a third reviewer (WM). The following items were collected from each study: publication details; demographic and clinical information; and outcome measures including ORR, DCR, OS, and complications.

The general methodological quality of the included RCTs was assessed according to the Cochrane Collaboration's Risk of Bias (ROB) criteria of Cochrane handbook (16, 17). The quality of each included RCT was assessed by six items: randomization, allocation concealment, double blinding, integrity of outcome data, selective reporting, and other bias. Every item is given a possible score of 0 for low, 1 for medium, and 2 for high, yielding a total score ranging from 0 to 12 for each study. Low ROB is appointed to trials with a total score from 0 to 4, medium ROB with a total score from 5 to 8, and high ROB with a total score from 9 to 12. The quality assessment of non-RCTs was evaluated with the ROB in Non-Randomized Studies - of Interventions (ROBINS-I) assessment tool (18). Studies were judged for confounding bias, selection bias, bias in classification of interventions, bias in deviation from intended interventions, bias due to missing data, bias in the measurement of outcome, and bias in the selection of the reported results. We will evaluate the ROB as low,