

Efficacy and safety of CT-guided ¹²⁵I brachytherapy in elderly patients with non-small cell lung cancer

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Abstract. Non-small cell lung cancer (NSCLC) has become the most common cancer type and the leading cause of cancer-associated mortality worldwide. The aim of the present retrospective study was to evaluate the efficacy and safety of computed tomography (CT)-guided ¹²⁵I brachytherapy alone in elderly patients with NSCLC. A total of 26 elderly patients with NSCLC stage I-III who had an inoperable lesion or progressive disease following radio-chemotherapy were treated with CT-guided ¹²⁵I seed implantation for lung lesions and included in the present study. The prescribed dose of ¹²⁵I brachytherapy was 80-140 Gy, and dosimetric verification was performed immediately after the procedure. The response rate (RR) and local control rate (LCR) were analyzed according to the Response Evaluation Criteria in Solid Tumors (version 1.1). Survival was estimated using the Kaplan-Meier method. Safety and complications were also documented. All patients were aged 65-85 years (median age, 77 years) and successfully completed the procedure, and the median follow-up time was 9.4 months (range, 3-31 months). After a 6-month follow-up, for pulmonary lesions, complete response (CR) was achieved in 11 (42.3%) cases, partial response in 9 (34.6%) cases, stable disease in 4 (15.4%) cases and progressive disease in 2 (7.7%) cases. The 6-month RR and LCR were 76.9 (20/26) and 92.3% (24/26), respectively. The mean overall survival (OS) time was 11.7±7.6 months and the 0.5- and 1-year OS rates were 90.1 and 73.3%, respectively. Tumor-related symptoms in patients were significantly alleviated following the procedure. No severe complications occurred during and after the procedure of ¹²⁵I seed implantation. In conclusion, CT-guided ¹²⁵I brachytherapy is a feasible, effective and safe therapy and may be considered as an alternative option to surgery and radiotherapy for elderly patients with NSCLC.

Introduction

In recent years, lung cancer has become the most commonly diagnosed cancer type (11.6% of the total cases) and the leading cause of cancer-related death (18.4% of the total cancer deaths), worldwide (1). According to statistics, China accounted for one-third of the global lung cancer deaths (2). In addition, with an aging world population, the proportion of elderly patients with lung cancer has increased concomitantly (2). Furthermore, the average risk of death from lung cancer increases by 62% for every 5 years of age (2). Non-small cell lung cancer (NSCLC) accounts for 80-85% of lung cancer cases (3). Surgery, external beam radiotherapy (EBRT) or chemotherapy used alone or in combination are the standard treatments recommended for patients with NSCLC (4). ¹²⁵I brachytherapy performed by implantation of ¹²⁵I radioactive seeds in the tumors can induce extensive necrosis of tumors and improve the quality of life of patients (5). Previous studies have demonstrated that iodine-125 (¹²⁵I) seed implantation brachytherapy exhibits good clinical results as a minimally invasive and effective treatment for a variety of tumors, such as pancreatic or liver cancer and gynecologic malignancies (6-8). Recently, ¹²⁵I brachytherapy has been used for the treatment of lung cancers; however, most of these studies focused on assessing the effectiveness of ¹²⁵I brachytherapy combined with chemotherapy or radiotherapy (3,5,9,10).

Patients aged ≥60 years are considered to be elderly patients according to the World Health Organization (11). Elderly patients with lung cancer develop various chronic diseases and multiple organ dysfunctions such as those of the heart, lung, kidney and liver, which may increase the risk of treatment-related death (12). As such, these patients are more likely to experience an intolerance to conventional antitumor treatments such as surgery, chemotherapy and radiotherapy (12,13). The treatment of elderly patients with lung cancer remains a challenge.

¹²⁵I seed brachytherapy may provide a novel and effective treatment for elderly patients with lung cancer. To the best of our knowledge, no studies have investigated the effectiveness of CT-guided ¹²⁵I brachytherapy alone in elderly patients with NSCLC to date. Thus the present study aimed to analyze the data of 26 elderly patients with NSCLC treated with ¹²⁵I seed implantation alone and determine the feasibility, efficacy and complications of the technique.

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Materials and methods

Patients and eligibility. This study was approved by the Ethics Committee of Hebei General Hospital (Shijiazhuang, China). The ethics committee waived informed patient consent due to the retrospective nature of this study. All patient records were anonymized prior to analysis.

The present study retrospectively analyzed the data of 26 elderly (≥ 60 years as defined by the WHO) patients treated with ¹²⁵I seed brachytherapy between January 2015 and August 2017. All patients were diagnosed histopathologically using bronchoscopy or transthoracic needle biopsy and staged according to the manual of the American Joint Committee for Cancer Staging, 7th edition.

The inclusion criteria were as follows: i) Age ≥ 60 years; ii) histopathological diagnosis of NSCLC; iii) maximum diameter of the lesion ≤ 8 cm; iv) Karnofsky performance status score ≥ 50 ; v) expected survival ≥ 3 months; vi) patients in early stages of the disease who were not candidates for surgery because of co-morbidities; or in the advanced stages with stable metastases and recurrence or progression of primary lung lesions after chemotherapy or radiotherapy; or patients who refused the aforementioned treatments; vii) patients who did not receive radiotherapy or chemotherapy within 6 months prior to the brachytherapy; viii) epidermal growth factor receptor/anaplastic lymphoma kinase/ROS proto-oncogene 1 receptor tyrosine kinase/ROS proto-oncogene mutations were not detected; and ix) patients provided individual signed informed consent for ¹²⁵I brachytherapy and publication. The exclusion criteria were as follows: i) Severe cardio-pulmonary dysfunction, such as higher than grade III cardiac function (New York Heart Association grading) (14), malignant arrhythmia or active tuberculosis; ii) platelet count $< 20.0 \times 10^9/l$; iii) abnormal coagulation function.

Materials. Radioactive ¹²⁵I seeds (Jinan Xinke Pharmaceutical Science and Technology Co., Ltd.) of type 6711-99, with a length of 4.5 mm and a diameter of 0.8 mm were used. The ¹²⁵I seeds produced gamma-rays (5% of 35 keV, 95% of 28 keV) with an incipient rate of 7 cGy/h, activities of 0.5-0.8 mCi, half-life of 59.6 days, half-value thickness of 0.025 mm of lead and penetration of 17 mm. Seed activities were verified using a radioisotope dose calibrator CRC-25R (CAPINTEC, Inc.; <http://www.lejiesh.com>) prior to operation. Anisotropic factor ϕ was used in the dose calculation equation of the brachytherapy planning system to perform average anisotropy correction. The treatment planning system (TPS) was Prowess Panther Brachy v.5.0 (Prowess Inc.). Mick 200-TPV Needle Applicators (implantation gun) and 18-gauge seed implantation needles were purchased from Mick Radio-Nuclear Instruments, Inc. The 3D-printed template was provided from Beijing Unicorn Science and Technology Ltd. (<http://www.bjunicorn.com>). A vacuum cushion was produced by Tianchang Hengsheng Medical Devices Co., Ltd.

Radiation dosimetry and implant planning. A contrast-enhanced CT scan of the entire lung with a 5-mm slice thickness was performed in all patients 1 week prior to the seed implantation. Continuous axial images were transferred to the TPS. The gross tumor volume (GTV) and the

surrounding organs at risk (OARs) including the spinal cord, heart and esophagus, were carefully delineated in each CT slice. Dosimetric evaluation parameters included the dose delivered to 90 (D90) or 100% (D100) of the clinical target volume (CTV) and the percentage of CTV receiving 90 (V90), 100 (V100) or 150% (V150) of the prescription dose. The dosimetric goal was to achieve a prescription dose of 80-140 Gy, D90 $\geq 90\%$ and V90 $\geq 90\%$. For patients who had received prior radiotherapy, the prescription dose was appropriately reduced according to the tolerated dose of OARs. The matched peripheral dose of OARs was limited according to the recommendations of the American Brachytherapy Society (15) and the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) criteria (16) as follows: Large vessels, < 80 Gy; heart, < 45 Gy; esophagus, < 60 Gy; and spinal cord, < 45 Gy. Two patients were prescribed a dose of 80 Gy due to the tumor reappearing within 6 months after radiotherapy adjacent to the spinal cord. Seeds with low activity (0.5-0.6 mCi) were used in the tumor target area adjacent to the OARs. The implanted seed spacing was 0.5-1 cm, and the needle spacing was 1 cm. TPS was used to calculate the direction and depth of needles, as well as the number and distribution of implanted seeds (Fig. 1A-C and E), and to generate dose-volume histograms (DVH) and isodose curves of different percentages (Fig. 1D and F). Post-operative chest CT scans were obtained immediately after seed implantation, and the images were transferred to TPS to calculate postoperative DVH for the dosimetric verification (Fig. 2B and D). In three patients, treatment was guided using a 3D-printed template. The skin contour of patient, needle coordinates and puncture holes were reconstructed in TPS, and a 3D printing output file was generated. A stereolithography-600 3D printer (Beijing Unicorn Science and Technology Ltd.) was used to print the 3D template.

¹²⁵I implantation. Following intramuscular injection of 10 mg diazepam, patients were fixed on the CT table with the vacuum cushion in the same position. CT scans (SOMATOM Force, Siemens.; <https://www.siemens-healthineers.com/computed-tomography/dual-source-ct/somatom-force>) were used to determine the tumor site and layers of seeds implantation. Next, in most patients of freehand implantation (without template-guided), the puncture points of the needles, according to the preplan, were marked on the surface of the body of the patient with the help of the CT laser. In the 3D-printed template-guided patients, the 3D template was fixed according to the marks on the body surface. Local infiltration anesthesia combined with intercostal nerve block anesthesia with 1% lidocaine was supplied to the puncture range following disinfection. Using CT-imaging guidance, 18-gauge needles were inserted into the farthest edge of tumors and were spaced at a distance of 1.0 cm in a parallel array according to the preplan (Fig. 2A and C). Precautions were taken to avoid puncturing the surrounding large blood vessels, bronchi, ribs, scapula or spinal cord. The ¹²⁵I seeds were implanted into the tumor through each needle and were released while drawing back the needles from deep to shallow. The space between seeds was kept at 0.5-1.0 cm. Post-operative CT

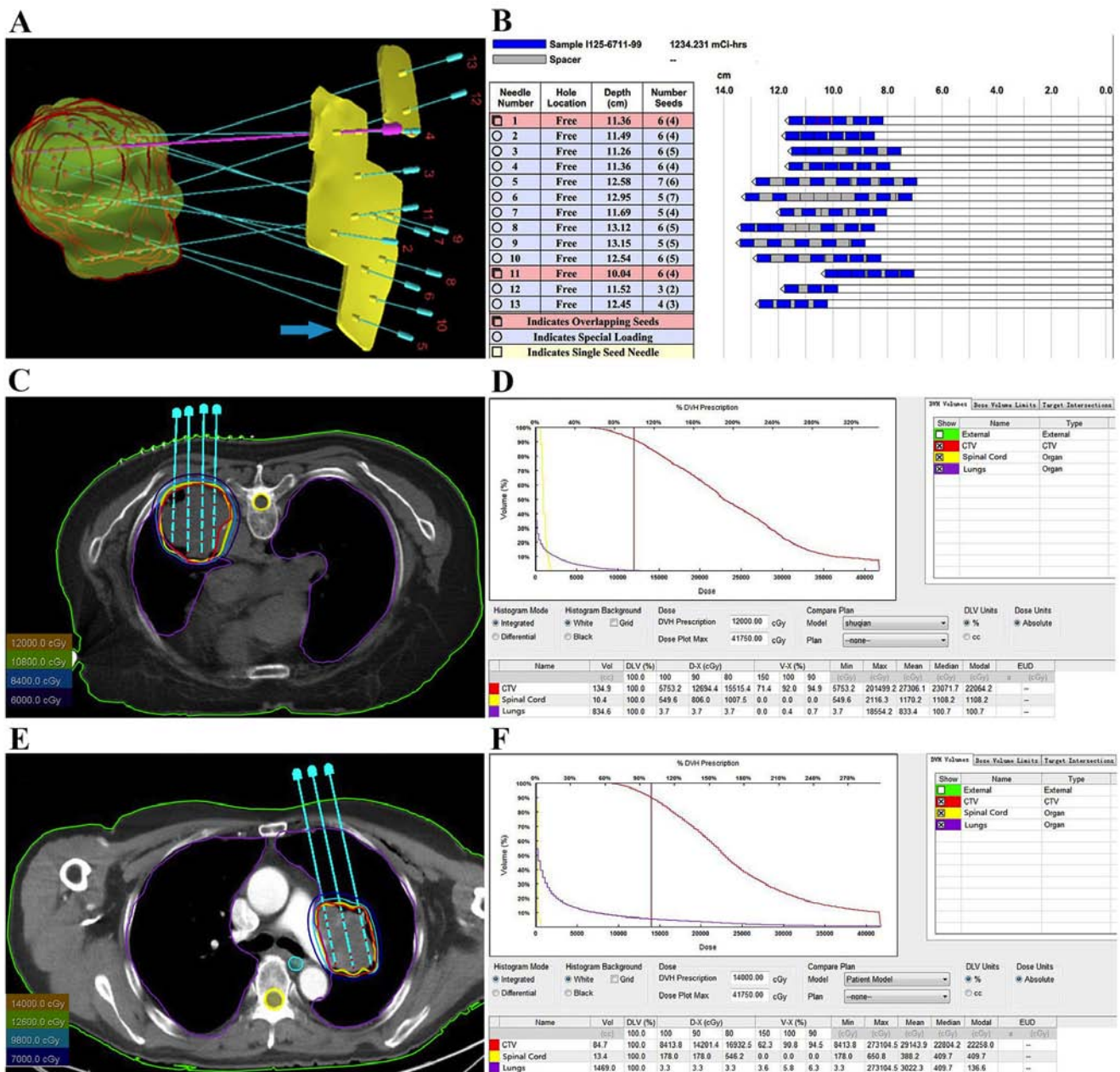


Figure 1. Preoperative planning and DVH of two patients with NSCLC. (A) TPS displaying 3D image of CTV and the direction of needles. (B) TPS displaying the depth of needles and the number and distribution of seeds. (C) Radiation oncologist outlined external contour (outer contour of the body, green line), CTV (red line) and OARs, including the spinal cord (yellow line) and the lungs (purple line). TPS drew the isodose curve and displayed needles and seeds in one of the patient. (D) Preoperative DVH presenting dose distribution in CTV and OARs in one of the patient. (E) The external contour (green line), CTV (red line), spinal cord (yellow line), lungs (purple line), and the isodose curve in another patient. (F) Preoperative DVH of another patient. TPS, treatment planning system; DVH, dose-volume histogram; CTV, clinical target volume; OARs, surrounding organs at risk; NSCLC, non-small cell lung carcinoma.

scans were performed immediately after the implantation procedure to confirm that the seed distribution was correct and to exclude any implantation-related complications such as pneumothorax, pulmonary hemorrhage or seed migration. The vital signs of all patients were monitored during and after the procedure.

Follow-up. CT or positron-emission tomography/CT scans were performed monthly to evaluate the therapeutic effects for the first 3 months, and then every 3 months following implantation. Postoperative symptoms and treatment-related complications were recorded during follow-up.

Endpoints. Efficacy and safety of CT-guided ¹²⁵I brachytherapy were the primary endpoints of the present study. Efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors v.1.1 (17) and classified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The response rate (RR) was confirmed in cases with CR and PR. The local control rate (LCR) was confirmed in cases with CR, PR and SD. Clinical complications were assessed from the beginning of the implantation procedure. The acute and late radiation toxicities were assessed in accordance with the toxicity criteria of RTOG and EORTC (16). The secondary endpoint was the overall survival

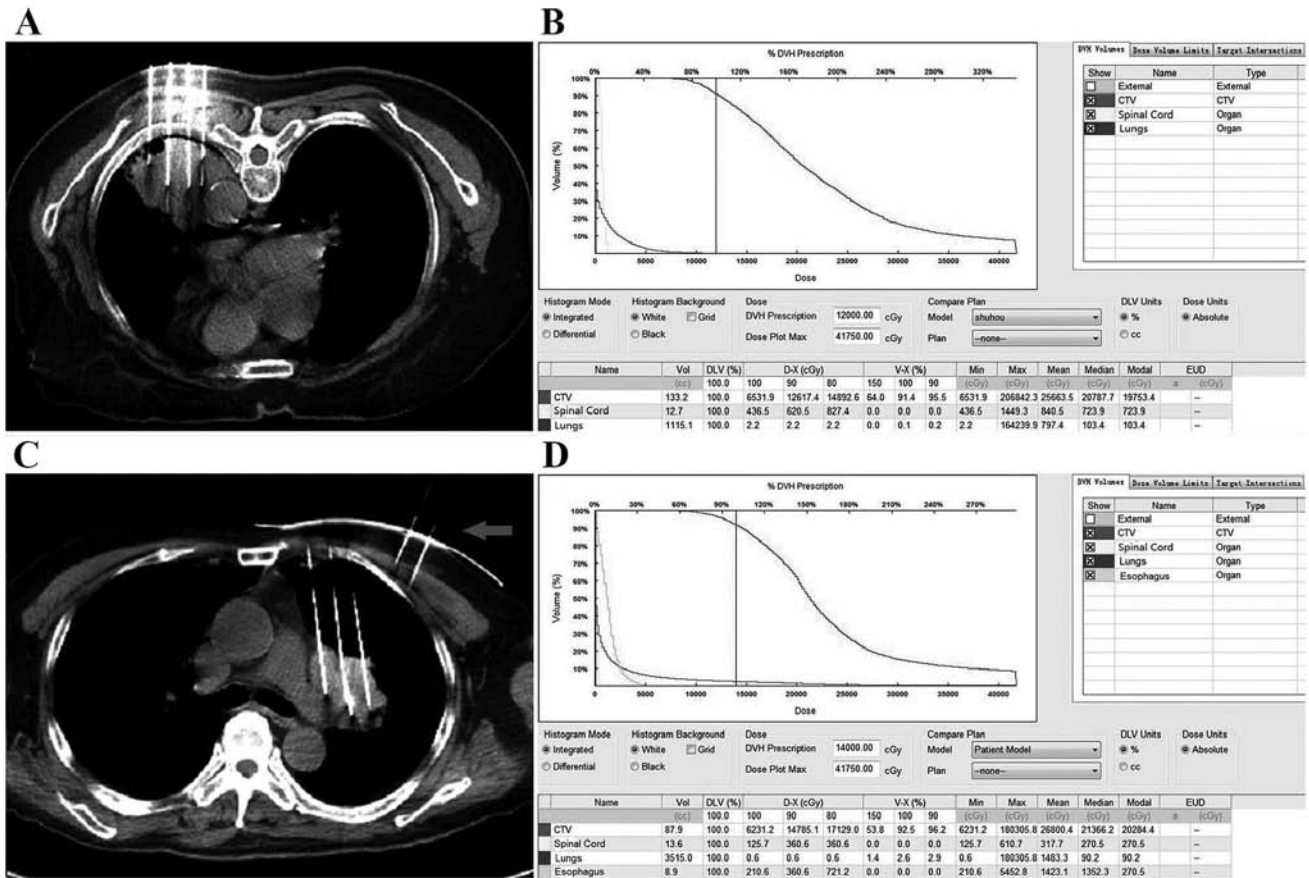


Figure 2. Postoperative DVH and intraoperative CT scan in 2 patients with NSCLC. (A) Freehand ¹²⁵I seed implantation. (B) Post-operative DVH of freehand implantation. (C) 3D-printed template (arrow) guided ¹²⁵I seed implantation. (D) Post-operative DVH of 3D-printed template guided implantation. DVH, dose-volume histogram; NSCLC, non-small cell lung carcinoma.

(OS). OS time was defined as the interval between the date of implantation and the date of death from any cause.

Statistical analysis. Statistical analyses were performed using SPSS 19.0 (IBM Corp.) software. The characteristics of patients were expressed as continuous variables and/or categorical variables. Continuous data were expressed as the mean ± SD, and categorical data were expressed as the median and interquartile range. RR and LCR were expressed based on the number and percentage of patients. OS was analyzed using Kaplan-Meier curves. Deaths from any cause were scored as events when calculating survival rate.

Results

Patient characteristics. Of the 26 patients who enrolled in the present study, 14 (53.8%) were men and 12 (46.2%) were women. The median age was 77 years (age range, 65–85 years). A total of 14 patients presented central type and 12 presented peripheral type tumors (Table I). The median size of tumors was 5.8 cm (range, 2.0–7.7 cm). In this group, ¹²⁵I seed brachytherapy was used as a radical treatment for 17 inoperable stage I and II (T1–3, N0–1) patients, six of whom were received salvage treatment for recurrence after radiotherapy. All patients with stage III had received prior chemotherapy, and six different patients had received prior radiotherapy. ¹²⁵I seed implantation was used as a salvage treatment for patients with

stage III progressive primary lesions following radiotherapy and chemotherapy. Patient characteristics are presented in Table I.

Efficacy of ¹²⁵I seed implantation. All patients successfully underwent ¹²⁵I seed implantation, among whom three patients received 3D-printed template guided implantation (Figs. 1A and 2C) and the rest were treated with freehand implantation. The median number of seeds implanted was 57 (range, 14–100) and the median number of needles was 5 (range, 2–18). Postoperative dosimetric measurements demonstrated that the actual D90 ranged between 79 and 148 Gy (mean D90, 113 Gy; Table SI). All 26 patients were able to provide follow-up data. The median follow-up time was 9.4 months (range, 3–31 months). Following the 6-month follow-up period, for all pulmonary lesions, CR was achieved in 11 (42.3%) cases, PR in 9 (34.6%) cases, SD in 4 (15.4%) cases and PD in 2 (7.7%) cases. The 6-month RR and LCR were 76.9% (20/26) and 92.3% (24/26), respectively (Table II). Furthermore, the results demonstrated that two patients remained CR at 8 and 12 months of follow-up, respectively (Fig. 3A–D). The symptom of coughing was significantly relieved in 16/19 (84.2%) cases, asthma was markedly relieved in 6/10 (60%) cases, and chest pain was relieved in 7/7 (100%) cases within 4 weeks of implantation (Table II).

Six patients died during the follow-up period: One patient died of respiratory failure caused by bilateral lung infection

Table I. Demographic and clinicopathological features of patients with NSCLC (n=26).

Characteristics	Cases, n (%)
Sex	
Male	14 (53.8)
Female	12 (46.2)
Age, median years (range)	77 (65-85)
KPS	
<80	14 (53.8)
≥80	12 (46.2)
Histology	
AC	11 (42.3)
SCC	14 (53.8)
ASC	1 (3.8)
Clinical stage (AJCC)	
I	5 (19.2)
II	12 (46.2)
III	9 (34.6)
Tumor location	
Central	14 (53.8)
Peripheral	12 (46.2)
Maximum tumor diameter, cm	
≤3	5 (19.2)
3-8	21 (80.8)
Concomitant illness	
COPD	3 (11.5)
Emphysema or bulla	8 (30.8)
Prior history of chemotherapy	10 (38.5)
Prior history of EBRT	11 (42.3)

KPS, karnofsky performance status; AC, adenocarcinoma; SCC, squamous cell cancer; ASC, adenosquamous carcinoma; COPD, chronic obstructive pulmonary disease; EBRT, external beam radiotherapy; NSCLC, non-small cell lung carcinoma; AJCC, American Joint Committee on Cancer.

4.2 months following implantation; two died of widespread metastases at 6.8 and 17 months, respectively, following implantation; two died of cardiovascular disease, one of which died of arrhythmia at 6.5 months after implantation, and the other died of acute myocardial infarction at 12.1 months after implantation; and one died of upper gastrointestinal hemorrhage caused by esophageal and gastric varices at 3.3 months after implantation. None of these deaths were related to the brachytherapy. The mean OS time was 11.7±7.6 months, and the 0.5- and 1-year OS rates were 90.1 and 73.3%, respectively (Fig. 4).

Complications. No severe complications occurred during the follow-up period (Table III). Pneumothorax occurred in six patients (23.1%) (Fig. 5A); five of these patients had unilateral lung volume compression of <10% (lung surface retraction ≤2 cm) without any symptoms, and the lung gradually

Table II. Clinical efficacy of ¹²⁵I brachytherapy and symptoms associated with non-small cell lung cancer.

Local control efficacy	Cases, n (%)
CR	11 (42.3)
PR	9 (34.6)
SD	4 (15.4)
PD	2 (7.7)
RR = CR + PR	20 (76.9)
LCR = CR + PR + SD	24 (92.3)
Symptom	
Cough	16/19 (84.2)
Asthma	6/10 (60.0)
Chest pain	7/7 (100.0)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate; LCR, local control rate.

recovered without specific treatment. Unilateral lung volume compression of ~30% (lung surface retraction between 2 and 4 cm) with mild chest tightness was experienced by one patient, and the pulmonary re-expansion was satisfactory within 72 h after immediate treatment with closed thoracic drainage. One patient (3.8%) developed subcutaneous emphysema and recovered 3 days after closed drainage. Hemoptysis was developed by four patients (15.4%), who recovered following conservative hemostasis treatment with a total bleeding volume of 5-10 ml (Fig. 5B). Hemothorax was experienced by one patient (3.8%) during the operation and was immediately treated with closed drainage and hemostasis treatment (Fig. 5C). No active bleeding was confirmed by chest CT examination on the 3rd day after operation and a total of 150 ml of blood was drained. Seed migration (n=2) occurred in one patient during the operation by CT scan who survived without any symptoms at the end of the 20-month follow-up (Fig. 5D). Radiation pneumonitis and myelosuppression were not observed.

Discussion

Surgery, radiotherapy and chemotherapy are standard treatments for lung cancer (4). However, elderly patients with lung cancer are often limited by their own pathological and physiological characteristics, such as multiple other diseases (particularly cardiovascular and pulmonary dysfunction) as well as organ and immune dysfunction, which increase the risks of surgery and systemic chemotherapy (12). In addition, the survival benefits of chemotherapy alone are low and are hampered by potential toxicity such as nausea and vomiting, myelosuppression, liver and kidney function damage, cardiotoxicity and hair loss (12,13). This suggests that clinicians should not make treatment strategies based only on the tumor stage. Therefore, it is important to choose a suitable treatment for elderly patients.

Radiotherapy is an important local treatment for lung cancer. Radiation dose must reach a certain level to destroy malignant tumor cells (18-20). Numerous studies have confirmed that

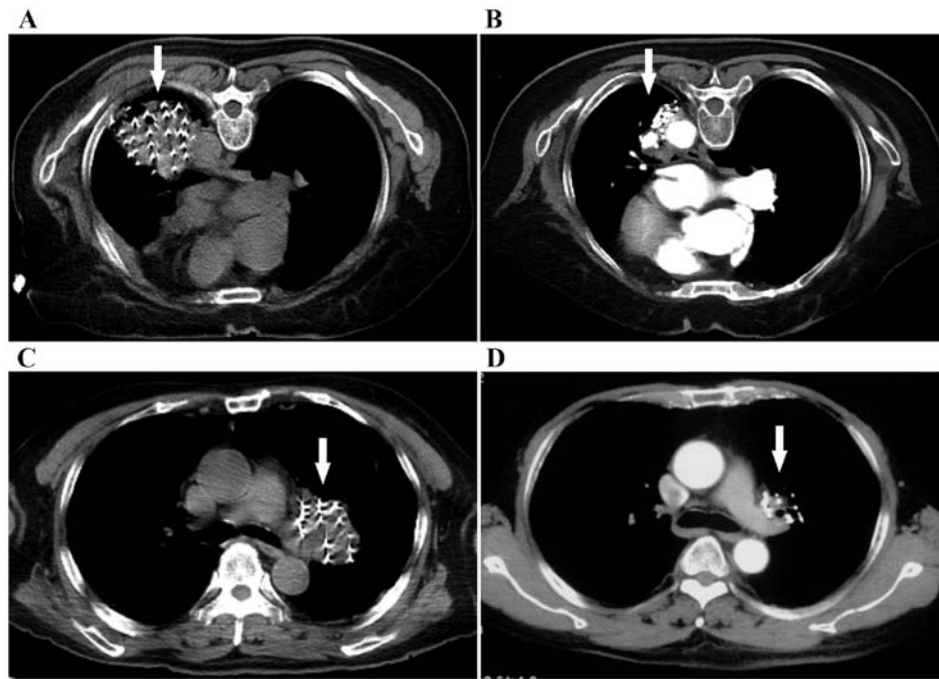


Figure 3. Therapeutic effect of ^{125}I seed brachytherapy in two patients with NSCLC. (A) CT image immediately post-operative showed ^{125}I seeds distributed within the target lesion (arrow) in one of the patients. (B) The target lesion completely disappeared 8 months following implantation. (C) Post-operative CT scan showed ^{125}I seeds distributed within the mass (arrow) in another patient. (D) CT scan indicated a complete response of the lesion 1 year following implantation. NSCLC, non-small cell lung carcinoma.

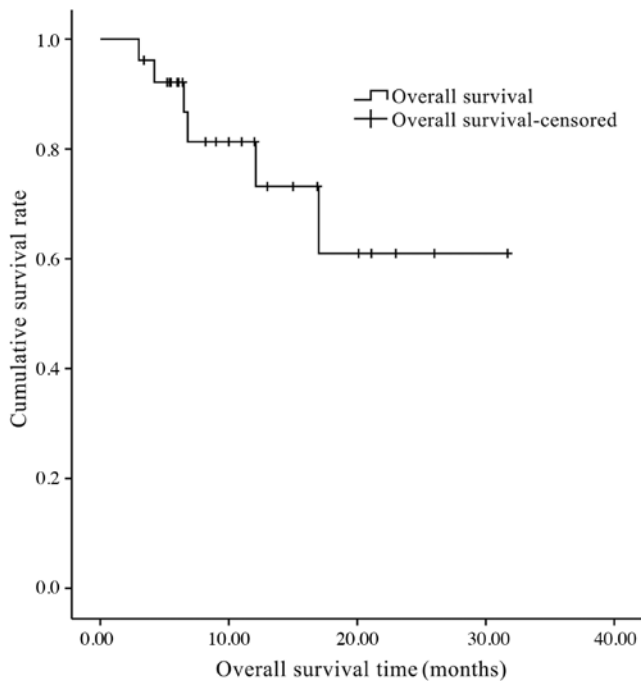


Figure 4. Kaplan-Meier analysis of overall survival of 26 elderly patients with non-small cell lung cancer.

increasing the radiation dose can significantly improve LCR. In a phase I dose-escalation study by Rosenzweig *et al* (18), the 2-year OS rate for patients with stage I-II disease who received <80 Gy was 60% compared with 66% for patients who received >80 Gy ($P<0.05$), with a median survival time of 25.0 months and 53.6 months, respectively. In a randomized trial from China (19), 5-year LCR and 2-year OS rate

improved significantly in patients with stage III lung cancer treated with a total dose of 68-74 Gy compared with those treated with 60-64 Gy (LCR, 51 vs. 36%; $P=0.032$; OS, 39.4 vs. 25.6%, $P=0.048$). However, dose escalation in the RTOG 0617 trial (20) failed to improve survival, which may be related to the following reasons: i) More than half of the patients used 3D conformal radiotherapy (3DCRT), whereas those who used intensity-modulated radiotherapy (IMRT) only accounted for $\sim 45\%$. Physically, IMRT achieved improved dose distribution compared with 3DCRT. A higher dose led to greater side effects (especially cardiac and pulmonary), offsetting the survival advantage of incremental radiotherapy (21). Underestimation of the severe toxicity of high-dose radiotherapy may be the main reason behind the failed improvements of survival rates (21,22). ii) The RTOG 0617 study included locally advanced patients with stage III. The treatment failure or death of locally advanced NSCLC was mainly related to distant metastasis (20,22). The increase in the LCR caused by incremental radiotherapy failed to translate into an increase in survival (20,22). It has been reported that the lowest biologically effective dose (BED) to kill lung cancer cells may exceed 100 Gy (22,23). However, it is difficult to administer a radical radiation dose to tumors due to the poor tolerance to radiation for OARs, even with advanced technology including image-guided radiotherapy and IMRT. Using these modern techniques, current radiotherapy applying a uniform prescription dose of 60 Gy or slightly higher generates LCRs of $<50\%$ and a 5-year OS rate of 10-15% for locally advanced NSCLC tumors (22,23). Stereotactic body radiation therapy (SBRT) involving extreme hypofractionation with high-dose radiation to the target volume and low doses to the surrounding normal tissues is considered superior compared with EBRT. However, SBRT is most suitable for small lesions

Table III. Complications in elderly patients with NSCLC following ^{125}I implantation.

Complications	Cases, n (%)
Pneumothorax	6 (23.1)
Mild	5 (19.2)
Moderate	1 (3.8)
Subcutaneous emphysema	1 (3.8)
Hemothorax	1 (3.8)
Hemoptysis	4 (15.4)
Seed migration	1 (3.8)

According to the distance from the compressed lung surface to the pleura, pneumothorax was graded mild (lung surface retraction, ≤ 2 cm) or moderate (measured lung surface retraction, 2-4 cm) (36).

(typically < 5 cm), and the accuracy and reproducibility of treatments are essential (24,25). In addition, SBRT is contraindicated for lesions within 2 cm from the bronchial tree, and a marked prevalence of complications such as pulmonary toxicity and rib toxicity have been reported (24,25).

^{125}I seed implantation is a minimally invasive treatment for tumors that has been rapidly developed in the past decade and has been listed as a treatment for prostate cancer (26). ^{125}I seeds are implanted into tumors and continuously generate low-energy gamma-rays to kill tumor cells in a similar manner to multiple hyperfractionated radiotherapy, which can prevent the accelerated repopulation of tumor cells (27,28). In addition, low radiation dose rates can induce reoxygenation and increase blood flow in hypoxic tumors, thus producing a radiation-induced bystander effect to kill tumor cells, which can overcome uneven distribution of radiation doses (27,28). Of note, the dose distribution around ^{125}I seeds obeys an inverse-square law; the radiant energy decreases rapidly as the distance from the seed increases (29). Therefore, ^{125}I brachytherapy can target the entire irradiation dose to the target tumor volume, while providing a very low dose to adjacent normal tissues, thus improving local efficacy and reducing the incidence of side effects (27,28). Zhang *et al* (30) reported ^{125}I seed implantation in localized advanced pulmonary carcinomas and demonstrated that the LCR was 78.1% at the 2-month follow-up, with a 1-year survival rate of 65.0%. In the present study, the 6-month RR and LCR were 76.9 and 92.3%, respectively. The mean OS was 11.7 ± 7.6 months and the 0.5- and 1-year OS rates were 90.1 and 73.3%, respectively. The present study demonstrated an improved RR, LCR and 1-year OS compared with that of Zhang *et al* (30) due to the patients in the present study having early-stage NSCLC. These studies have demonstrated the good results of ^{125}I seed implantation for NSCLC (30-32). However, these studies all involved combination therapies of ^{125}I brachytherapy with chemotherapy or EBRT. To the best of our knowledge, no previous studies have investigated the efficacy of ^{125}I brachytherapy alone in elderly patients with NSCLC. The results of the present study indicated that ^{125}I brachytherapy may be used alone to improve the LCR, relieve the symptoms and prolong the OS time. Li *et al* (31) performed CT fluoroscopy-guided ^{125}I seed implantation for patients with stage T1-3N0M0 NSCLC and reported that at the median follow-up

of 31.5 months, the LCR was 78.6% and the 1-, 2- and 3-year OS rates were 95.8, 78.0 and 55.0%, respectively. Another study reported that ^{125}I brachytherapy combined with chemotherapy was an effective treatment for inoperable stage III/IV NSCLC. The RR was 88.5%, and the 1- and 2-year OS rates were 82.8 and 37.1%, respectively (32). These studies demonstrated a more positive outcome compared with the results of the present study. This was likely because a combination of treatments was not performed in the present study, and the patients were elderly with various other medical conditions. In the present study, 60-100% of patients with symptoms of cough, asthma and chest pain had a significant alleviation within 4 weeks after implantation, which directly improved the quality of life.

In addition, the present study used the BED equation (33) to compare doses between ^{125}I brachytherapy and EBRT. The prescription dose of 80-140 Gy used in the present study, which was equivalent to 68-118 Gy of EBRT, contributed to a satisfactory local control without radiation damage to the surrounding normal tissues. In the present study, during the follow-up period, two cases recurred at the edge of the target area, and the possible causes were analyzed. It may be due to the insufficient peripheral doses of target volume. Most studies of ^{125}I implantation only delineated GTV as target areas (34). However, a number of microtumor infiltrative lesions usually occur outside the edge of the primary tumor and are difficult to observe by CT scan (31). Therefore, it is recommended to extend the GTV by 0.5 cm to form CTV as the target volume for ^{125}I seed implantation (31). PTV involves organ movement and daily placement error, which is a concept of EBRT and is rarely considered in ^{125}I seed implantation (31,34). Furthermore, in order to avoid the insufficient peripheral dose, the expert consensus requires $\text{D}_{90} \geq 90\%$ prescription dose (34). Due to the short penetration distance and rapid dose drop around the seed, dose cold spots are prone to occur in and around the target area. It is important to perform intraoperative TPS verification during implantation to provide real-time guidance to replant the seeds in the cold zone (35).

The most common complications of ^{125}I brachytherapy are related to the implantation operation and include pneumothorax, pulmonary hemorrhage and hemoptysis, which can be relieved by timely treatment (36). A previous study demonstrated that the incidence of pneumothorax and hemorrhage in ^{125}I seed implantation was 12.5-31.0 and 9.2-46.9%, respectively (31). In the present study, the incidences of pneumothorax, hemoptysis and hemothorax were 23.1, 15.4 and 3.8%, respectively. In addition, the incidence of pneumothorax was slightly higher compared with the previous aforementioned study, as elderly patients with lung cancer usually suffer from chronic obstructive pulmonary disorder and emphysema, especially bulla, which are more likely to contribute to the development of pneumothorax during the puncture procedure. Pneumothorax is more likely to occur in central compared with peripheral type lung cancer, as more lung tissue is passed through during implantation (36). In addition, rib obstruction and respiratory movement may affect the implantation, resulting in repeated punctures and increased risk of lung injury (36). In the present study, 3D-printed templates were used in three patients, which improved the accuracy and safety of implantation, lowered the difficulty of puncture, shortened the operation time and reduced radiation exposure from repeated CT scans. However, respiratory movements may cause changes in the relative tumor location, rendering the 3D

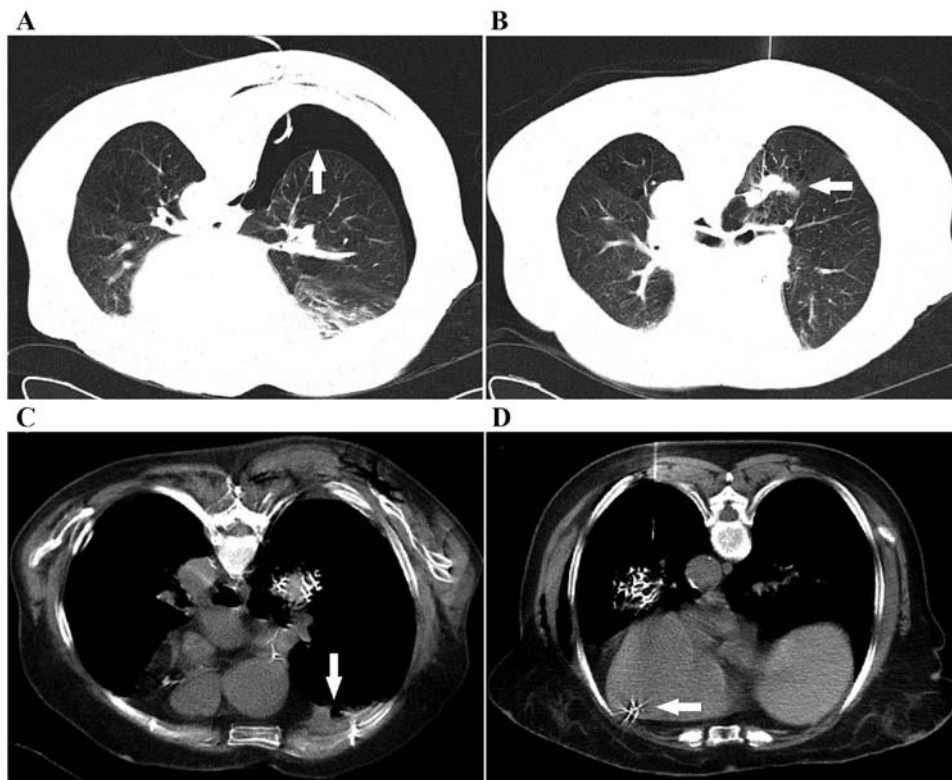


Figure 5. Images of the complications of ^{125}I seed implantation in patients with NSCLC. (A) Pneumothorax (arrow), (B) pulmonary hemorrhage (arrow), (C) hemothorax (arrow) and (D) seed migration (arrow).

templates unusable. In addition, following seed implantation, the relative position of the seeds changes with the change of tumor volume, resulting in changes in the actual exposure dose of the target volume and OARs (37). If the tumor volume shrinks too fast, the dose parameters such as D90 and V90 may significantly increase, potentially leading to complications (37). Our previous study revealed that when the tumor volume shrank at a rate of 15-20% per month, it did not cause a significant change in dose (37). The shrinkage rate of tumor depends on its radiosensitivity (37). In the current study, small cell lung cancer with high radiosensitivity was not included; therefore, the effect of the dynamic dose on the target area was not significant. In order to reduce the incidence of complications, low activity seeds were used in the tumor target areas adjacent to OARs such as the bronchi, esophagus, heart and blood vessels. In addition, an increased risk of treatment-related toxicity was observed in tumors directly abutting the proximal bronchial tree, termed 'ultra-central' tumors. For these tumors, there was no consensus regarding the ^{125}I seed implantation regimen. According to our experience, the distance between the seeds and the bronchial tree should be >1 cm, and low activity seeds are preferred (37). In order to reduce the risk of hemorrhage and hemoptysis in the present study, firstly, contrast-enhanced CT was performed prior to operation to determine the location of blood vessels inside and around the tumor, and the preplan of the current study was designed to avoid puncture injury of blood vessels. Secondly, it was necessary to fully evaluate and discontinue anticoagulant drug treatments, such as aspirin and warfarin prior to operation. In the present study, two seeds were observed to migrate through the blood vessels to the heart during the operation in one patient. In addition, ^{125}I seeds have been reported to migrate

to the lung and heart in the brachytherapy for prostate cancer and hepatocellular carcinoma without serious symptoms (8,38). No cardiac symptoms were observed in this patient during the follow-up period of the present study, although potential adverse effects were reported when seeds migrated to the heart, such as acute myocardial infarction (39). The long-term effects of seed migration have not been monitored. Accurate placement of seeds and care to avoid punctures into blood vessels may reduce seed migration. There were also reports of small amounts of radiation pneumonitis around the implanted seeds, which have no effect on lung function (40). Additionally, in the present study, no radioactive complications such as radiation pneumonitis, radiation esophagitis, cardiotoxicity and tracheal necrosis were observed after ^{125}I brachytherapy.

The present study has several limitations, such as its retrospective design, the relatively small sample size from a single institution, heterogeneous patients and a short follow-up period. Therefore, large-scale prospective studies with long-term follow-up are required to verify the findings of the present study. Furthermore, future clinical trials need to focus on the efficacy of ^{125}I brachytherapy compared with other radiation techniques such as SBRT in early stages of NSCLC or combined with systemic treatment in advanced NSCLC. In the future, the combination regimen and the dosage of brachytherapy and EBRT should be investigated.

In conclusion, the present study preliminarily demonstrated that CT-guided ^{125}I seed brachytherapy was an effective and safe treatment for elderly patients with NSCLC. CT-guided ^{125}I seed brachytherapy led to favorable local control, fewer side effects, good symptomatic relief and an improved quality of life. ^{125}I seed brachytherapy may be an alternative or a

complementary treatment option to surgery and radiotherapy for elderly patients with NSCLC.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

JZ and JW conceived and designed the present study. JZ, HZ, JXZ, KX and ZL performed most of the experiments. JZ, ZZ, YD, CM and AS drafted the initial manuscript and analyzed the data. All authors have read and approved the manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Hebei General Hospital (Shijiazhuang, China). The ethics committee waived informed patient consent due to the retrospective nature of this study. All patient records were anonymized prior to analysis.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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