

# Efficacy and Safety Aiming at the Combined-Modality Therapy of External Beam Radiotherapy (40Gy) and Iodine-125 Seed Implantation for Locally Advanced NSCLC in the Elderly

**LiJun Tian**

Binzhou Medical College Affiliated Hospital

**HongZhi Liu**

Binzhou Medical College Affiliated Hospital

**Qiang Zhang**

Binzhou Medical College Affiliated Hospital

**Dian-Zhong Geng**

Binzhou Medical College Affiliated Hospital

**Yu-Qing Huo**

Binzhou Medical College Affiliated Hospital

**Shou-Jian Xu**

Binzhou Medical College Affiliated Hospital

**YanZhang Hao** (✉ [byfyzly@163.com](mailto:byfyzly@163.com))

Binzhou Medical College affiliated Hospital

---

## Research

**Keywords:** Iodine-125 seed implantation, external beam radiotherapy, combined therapy, NSCLC, the elderly

**Posted Date:** September 8th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-62265/v1>

**License:**  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

# Abstract

## Background

Our retrospective study aimed to evaluate the efficacy and safety of the combined-modality therapy for tumor invading the chest wall of locally advanced non-small-cell lung cancer (NSCLC) in the elderly.

## Methods

We retrospectively enrolled 21 elderly patients (aged  $\geq 60$  years) with locally advanced NSCLC diagnosed as tumor invading the chest wall. The prescription dose of the primary tumor adopting external beam radiotherapy (EBRT) was given 40 Gy which was supplemented with iodine-125 seed implantation, meanwhile the lymph nodes of mediastinum undergoing EBRT was given 60 Gy. Follow-up was conducted every 3 months postoperatively. The related analytic parameters were the change of tumor size, the objective response rate (ORR), the disease control rate (DCR), the degree of pain relief, the improvement of physical status and the toxicity.

## Results

The combined-modality therapy could significantly inhibit the local growth of tumor (from  $7.84 \pm 1.20$  to  $4.69 \pm 1.90$  cm) ( $P < 0.0001$ ), indicating a better validity with an ORR of 71.4% and DCR 90.5%, respectively at 1 year. The cancer-related pain was significantly relieved ( $P < 0.05$ ) and the physical status were also significantly improved ( $P < 0.05$ ). There was no procedure-associated death or grade  $> 2$  irradiation-related adverse effect in our study.

## Conclusions

The combined-modality therapy of EBRT with 40 Gy and permanent iodine-125 seed implantation is an efficacious and safe option and may be recommended as a treatment pattern for the elderly of locally advanced NSCLC with tumor invading the chest wall.

### 1. Background

At present, lung cancer has become a major problem which greatly threatens to human health, and the prevalence of lung cancer is increasing year by year(1, 2). According to an official authoritative data published in 2018, there has been about estimated 2,090,000 newly diagnosed lung cancer patients in the world and about estimated 1,760,000 people may die of lung cancer in the same year(1). The mortality of lung cancer is the highest among all kinds of tumors and more than half of it takes place in Asia (1). In addition, it is more common in the elderly and the incidence is increasing with age(1). Approximately 20% of patients are suitable for curative resection and the remaining patients categorized as advanced non-

small-cell lung cancer (NSCLC) may lose the chance to undergo operation when diagnosed in the hospital at first(3). Therefore the mainstream treatment patterns are external beam radiotherapy (EBRT) and/or chemotherapy for locally advanced NSCLC patients without positive EGFR mutation or ALK-positive status according to related guidelines and criterions(4). In the real world, given the appreciable toxicity and low effectiveness of chemotherapy, patients may be reluctant to choose it as an optimal treatment, especially for the elderly (5). For the sake of avoiding damage to the surrounding normal tissues, it is far from satisfactory to deliver an insufficient irradiation dose to tumor lesions by EBRT, especially when the volume of lung receiving at least 20 Gy (V20) is > 30%(6).

The WHO divided old age into three layers in chronological order as follows: middle aged (45–59 years old), elderly (60–74 years old), and advanced age (75 years or older) (7). Consequently, people over the age of 60 are classified as the elderly who are characterized by poor physical health and may prefer to choose the treatment without side effects or with slight side effects. For elderly patients with accompanying poor general condition, they are more vulnerable to the side effects caused by chemotherapy or EBRT, such as myelosuppression, gastrointestinal reaction, radiation pneumonitis, radiation esophagitis. Under the circumstances, iodine-125 seed implantation, as a form of brachytherapy, is getting more and more attention from all the world(2, 8–10). What is more, there is a growing interest in focusing on the quality of life (QOL) in the elderly with locally advanced NSCLC among the doctors, no matter what treatment patient will adopt(11).

The iodine - 125 seed particle is characterized by small size: 0.5 mm diameter and 3.0 mm long, and the half-life decay time is 59.43 days. It can continuously release low energy radiation which may fall off rapidly within 1.0 cm(12). Similar to EBRT, iodine-125 seed implantation is a form of radiotherapy. But different from EBRT, it is a form of brachytherapy which is deemed to deliver a high radiation dose (100-140Gy) to tumor lesions without obviously damaging the adjacent normal tissues(2). In addition, the introduction of computed tomography (CT) scanner has greatly improved the accuracy of implantation. Generally speaking, the procedure of iodine - 125 seed implantation is no more than 30-45 minutes(13). Additionally, the incidence of severe irradiation-related adverse effects is significantly reduced and the slight complications could disappear soon with supportive care(8). Because of the mentioned advantages, patients including the elderly, have showed great interest and good compliance(14–17).

In our retrospective study, we aimed at clarifying the efficacy and safety of the combined-modality therapy, namely EBRT (40 Gy) and iodine - 125 seed implantation assisted by CT guidance, for locally advanced NSCLC with chest wall invasion in the elderly. What is more, we would investigate the degree of pain relief caused by tumor invading the chest wall and the improvement of QOL.

## **2. Materials And Methods**

### **2.1 Patients**

Eligible patients between January 2016 and February 2019 diagnosed as locally advanced NSCLC with chest wall invasion who received EBRT (40 Gy) supplemented with iodine - 125 seed implantation at the Binzhou Medical College Affiliated Hospital were enrolled in this retrospective study. The pathological diagnosis of all patients was confirmed by bronchoscopy or needle biopsy according to the third edition of the World Health Organization guidelines. All patients underwent enhanced-CT scanner or positron emission tomography-CT (PET-CT), brain enhanced magnetic resonance imaging (MRI) and bone emission computed tomography (ECT). According to the American Joint Committee on Cancer seventh Edition, we organized three experienced physicians to perform TNM staging(18). The inclusion criteria were as follows: patients must have met lung V20 > 30% when the prescription dose was delivered 60 Gy (Fig. 1) and V20 < 30% when the prescription dose was 40 Gy; patients were diagnosed as locally advanced NSCLC (stage-III A/III B); patients were aged  $\geq$  60 years with a Eastern Cooperative Oncology Group (ECOG) performance scores  $\leq$  3 (19); patients could not receive radiotherapy previously; primary tumor lesions invaded the chest wall which also caused cancer-related pain; the tumor measuring  $\leq$  7 cm; the estimated lifespan of patients was no shorter than 3 months; patients should have normal coagulation, hepatorenal function and sufficient hematopoietic function; patients were resistant to undergo surgery. The exclusion criteria were as follows: patients were accompanied with severe cardiopulmonary diseases or a mental disorder; the interval between EBRT and iodine - 125 seed implantation was longer than one week; patients could not agree with the combined-modality therapy; the tumor size could not be measured in the lung; patients could not cooperate with the puncturing treatment. The study was approved by the Ethics Committee of Binzhou Medical College Affiliated Hospital All the patients could promise participating in this study and signing the written informed consent.

## **2.2 External beam radiotherapy (EBRT)**

At first, accompanied by treatment planning system (TPS), the planning target volume (PTV) of all the tumor lesions was designed to deliver a prescription dose of 60 Gy using the intensity-modulated radiation therapy (IMRT), including the primary tumor with chest wall invasion and the lymph nodes of mediastinum. If the lung met the standard of V20 > 30%, we would enroll the patient. When patients finished EBRT of 40 Gy, we would perform iodine-125 seed implantation for the primary tumor lesions and continue EBRT for mediastinal lesions according to the prior schedule. Hence the prescription dose of 60 Gy was formulated to aim at the mediastinal lesions, and the dose of the primary tumor with chest wall invasion was the sum of 40 Gy and the dose of iodine-125 seed implantation.

## **2.3 Procedure of iodine-125 seed implantation**

### **2.3.1. Preoperative planning**

Firstly, when the prescription dose of EBRT reached 40 Gy, all patients afresh underwent CT scanner (Siemens Somatom Sensation 64 CT Scanner). Subsequently, all obtained data would be transmitted to a brachytherapy treatment planning system (BTPS; Linke, China) to finish the preoperative plan design. The procedures were as follows: delineating the tumor target volume (GTV) and adjacent organs at risk

(OARs); formulating the prescription dose of PTV; ascertaining the pathway of seed implantation, such as the direction, depth and distribution; computing the quantity of iodine - 125 seeds; calculating the standardized dose constraints of OARs (e.g. lung V20  $\leq$  30%, heart V30 < 40%). We defined 90% of the dose to the GTV (GTV D90) to meet the prescription dose. Because of adopting the combined-modality therapy, the prescription dose was recommended  $\geq$  60 Gy according to American Brachytherapy Society guidelines (20).

## 2.3.2 Iodine-125 seed implantation

We adopted local infiltration anesthesia for all patients to relieve puncturing pain and patients would put on clothes made from lead ahead of time. With the guidance of real-time CT, the procedures of puncturing and seed implantation were assured to be accurate and two experienced physicians participated in the whole process at the same time. According to the preoperative designed plan, the predetermined pathway, depth and distribution of each needle, the procedure was finished within about 30–45 minutes. After the implantation, all patients would undergo CT scanner repeatedly to ascertain whether to evenly distribute of iodine-125 seeds and whether the complications correlated to the implantation had occurred.

## 2.3.3 Postoperative dose verification

Postoperative CT scanner images would be transmitted to the BTPS to evaluate the postoperative dosimetry. The physicist would use D90 to calculate the tumor target dose. We defined the OARs of thoracic tumors as the lung, esophagus, heart and spinal cord. The treatment procedure is shown in Fig. 2.

## 2.4 Tumor efficacy and safety evaluation

With respect to our study, the corresponding index of local control rate, including the objective response rate (ORR) and the disease control rate (DCR), was our primary observation as well as the toxicity. According to the Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 (21), the evaluation of efficacy was performed as follows: CR (disappearance of the target lesion and lasting for at least 4 weeks), PR (compared to the baseline, more than 30% decrease in the target lesion volume lasting for 4 weeks), PD (at least 20% increase of the target lesion volume from baseline lasting for 4 weeks) and SD (between PR and PD).  $ORR = (CR + PR) / \text{all cases} \times 100\%$ ;  $DCR = (CR + PR + SD) / \text{all cases} \times 100\%$ . The progression-free survival time (PFS) was defined as the time interval from the beginning of treatment to the occurring disease progression, death or the closure of the study. The overall survival (OS) time was calculated from the time of treatment to death. According to the toxicity criteria of RTOG/EORTC (European Organization for Research and Treatment of CANCER), we evaluated the irradiation-related acute and late adverse effects. Based on the ECOG performance status, we classified performance status of patients into five grades: 0 point stood for normal activity; 1 point stood for undertaking slight physical activity; 2 points indicated patients could move freely more than half the day; 3 points indicated that patients lay in bed more than half the day; 4 points indicated that patients could not take care of themselves; 5 points stood for death (19). The numerical rating scale was applied to calculate the pain

score: 0 point stood for no pain, 1–3 points stood for slight pain, 4–6 points stood for moderate pain and 7–10 points stood for severe pain (22).

## 2.5 Follow up

We would track and follow up all patients at 3 months after the operation, and then subsequently every 3 months for the first 2 years and every 6 months thereafter. During the period, if patients had any uncomfortable symptoms, which were considered to be related to the tumor, we would perform corresponding examination. During the follow-up, we would perform CT scanner, routine laboratory examination (e.g. blood cell count, tumor marker and hepatorenal function), the evaluation of pain score, ECOG performance status and irradiation-related adverse effects.

## 2.7 Statistical analysis

We adopted SPSS version 20 to analyze data. For quantitative data expressed as mean  $\pm$  SD, the difference between before and after treatment was determined by Student t-test. Meanwhile, for the categorical variables, we performed chi-square test.  $P < 0.05$  was regarded statistically significant

## 3. Results

We enrolled 21 eligible patients who met the requirements in our center. The characteristics and general information of all patients were listed in Table 1. As shown in Table 2, at the 6-month follow-up, compared before treatment with after the combined-modality therapy, not only the maximum diameter of the tumor ( $4.42 \pm 1.28$  vs.  $2.81 \pm 1.26$  cm) (Fig. 3A) but also the maximum vertical diameter ( $3.42 \pm 0.97$  vs.  $1.89 \pm 0.87$  cm) (Fig. 3B) could significantly inhibit the local growth of tumor (the sum of the two :from  $7.84 \pm 1.20$  to  $4.69 \pm 1.90$  cm) (Fig. 3C)( $P < 0.0001$ ), indicating a better validity with an ORR of 76.2% and DCR 95.2%, respectively. The ORR and DCR was observed 71.4% and 90.5% at 1 year, 33.3% and 47.7% at 3 years, respectively. The OS rates were 62.3% and 23.9% at 1 year and 3 years respectively.

Table 1  
General information of all patients

Characteristic	Patients	Percentage
Sex		
Male	14	66.7
Female	7	33.3
Age (years)	Median 68 (60–79)	
ECOG score	Median 2 (0–3)	
Primary tumor stage		
Stage IIIA	3	14.3
Stage IIIB	18	85.7
Diameter of tumors (cm)		
<5.0	4	19.0
5.0–7.0	17	81.0
Seed radioactivity	Median 0.64 (0.47–0.82)	
Seed number	Median 76.4 (30–135)	
Prescription dose		
<140Gy	10	47.6
≥140Gy	11	52.3
Short-term efficacy		
CR	2	9.5
PR	14	52.4
SD	5	33.3
ECOG: Eastern Cooperative Oncology Group; Short-term efficacy: evaluate at 6 months after the implantation; CR: complete response; PR: partial response; SD: stable disease.		

Table 2

The efficacy of the combined-modality therapy aiming at locally advanced NSCLC with tumor invading the chest wall for the elderly by CT measurement

Groups	Measurement of tumors through CT scan (mean ± SD, cm)		
	Maximum diameter	Maximum vertical diameter	Sum of the two
Before treatment	4.42 ± 1.28	3.42 ± 0.97	7.84 ± 1.20
After treatment	2.81 ± 1.26	1.89 ± 0.87	4.69 ± 1.90
Degree of free	20	20	20
T value	4.118	5.340	5.230
P value	$P < 0.001$	$P < 0.0001$	$P < 0.0001$

NSCLC: non-small-cell lung cancer; CT: computed tomography; SD: standard deviation; cm: centimeter; Sum of the two: the maximum diameter + the maximum vertical diameter.

The cancer-related pain was observed in all the patients enrolled in our center before treatment. (Table 3). The patients achieved complete relief with slight pain ( $n = 3$ ) and 12 of 14 patients bothered by moderate pain achieved the same effect. The partial relief was observed in the remaining two patients, and in four of four patients with severe pain. In this retrospective study, two of three patients with ECOG = 3 could move freely more than half day, and all patients with ECOG = 2 could undertake physical activity or move freely (Table 4). The cancer-related pain was significantly relieved ( $P < 0.05$ ) and the cancer-related symptoms were also significantly improved ( $P < 0.05$ ). The prescription dose of ten patients was delivered  $< 140$  Gy and the remaining 11 patients was delivered  $\geq 140$  Gy. The ORR at 1 year and 3 years for patients with dose  $\geq 140$  Gy were 81.8% and 45.4%. We found that the prescription dose  $\geq 140$  Gy seemed to better inhibit the local growth of tumor, but the difference was not significant because of the low samples size.

Table 3  
Analysis of cancer-pain relief

Group	Pain score				P-value
	0	1-3	4-6	7-10	
Before treatment	0	3	14	4	$P < 0.05$
After treatment	15	1	5	0	

Table 4  
Analysis of physical status score

Group	ECOG score				P-value
	0-1	2	3	4	
Before treatment	3	15	3	0	P < 0.05
After treatment	18	2	1	0	

In terms of complications, there was one patient of grade 1 radiation pneumonitis, and the symptom was a slight dry cough which was relieved soon with supportive care. Two patients suffered from grade 1 radiation esophagitis which did not affect the food-intake. There were two patients suffering from slight pneumothorax which was gradually absorbed without any symptoms. No patients suffered from esophageal or tracheal fistulae and no cases were observed late radiation toxicity. Bloody sputum occurred in two patients which became normal soon with symptomatic treatment. There were four patients of grade  $\geq 1$  radiation myelosuppression, including one patient of grade 2 myelosuppression (Table 5).

Table 5  
Adverse effects

Adverse effects	Cases	Percentage
Radiation pneumonitis (grade 1)	1	4.7
Radiation esophagitis (grade 1)	2	9.5
Pneumothorax	2	9.5
Bloody sputum	2	9.5
Radiation myelosuppression (grade 1)	3	14.3
Radiation myelosuppression (grade 2)	1	4.7
Esophageal or tracheal fistulae	0	0
Late radiation toxicity	0	0

## 4. Discussion

As we know, primary bronchial lung cancer is remarkable for its high morbidity and mortality which threatens the survival of human and results in general panic. It is a pity that most of people are classified as advanced NSCLC with losing the chance to undergo surgical resection. According to the related guidelines and regulations, chemotherapy and EBRT are recommended as palliative treatment strategies for patients without EGFR or ALK gene mutation. Patients, especially the elderly, are unwilling to choose the chemotherapy because of the severe adverse effects, such as fatigue, myelosuppression, nausea and

vomiting, hair loss, cardiotoxicity and hepatorenal function damage. What is more, the low efficacy also hinders patients from adopting to the chemotherapy which brings limited survival benefits. EBRT, as an important local approach, is encumbered by irradiation-related side effects, such as acute radiation pneumonitis, acute esophagitis, and late radiation-induced pulmonary fibrosis which could obviously affect the QOL and survival time (23, 24).

Li et al pointed in his study that it was impossible to deliver enough radiation dose for EBRT aiming at extinguishing tumor without damaging the surrounding normal tissues, especially for tumor measuring > 5 cm (25). However, in clinical practice, physician usually recommend the prescription dose of 60 Gy for primary bronchial lung cancer, when applying EBRT. As a matter of fact, the effective dose of radiotherapy for the diameter of tumor > 5 cm should be more than 100 Gy according to the report of Reveizi (6). As is known to us, radiation pneumonitis is a dose limiting adverse effect which may decline QOL and become life-threatening (26). If patients received so high radiation dose, the adjacent normal tissues would be seriously damaged with increasing the occurrence of severe complications and mortality. In terms of the elderly, they are characterized by poor cardiorespiratory function and physical status. The MILES study had pointed out that QOL was a critical factor for the elderly to decide how to choose a proper treatment (27). Accordingly, it is very necessary to find out proper treatment strategies especially for the elderly which take the QOL evaluation into account.

Fortunately, iodine-125 seed implantation has provided an available approach which can deliver a higher dose (100-170Gy) for doctors. The important point is that the radiation dose could fall off sharply within a short distance, and consequently the adjacent normal tissues would receive a minimal radiation dose, resulting in the reduction of the incidence of irradiation-related pneumonitis and esophagitis (5). Chest wall invasion was defined as soft tissue invasion certified by radiographic evidence and accounted for about 5% in locally advanced NSCLC (28). Owing to the relatively higher mortality of surgical resection for chest wall invasion in perioperative period, many skilled thoracic surgeons suggested it was necessary to look for new strategies(29, 30). Although stereotactic body radiation therapy (SBRT) could deliver a higher radiation dose to tumor lesions, it has been only recommended for small lesions (usually < 5 cm). In addition, patients would suffer from rib fracture or chest wall pain several months after SBRT, especially when tumor lesions were adjacent to the chest wall. Generally speaking, it was improper to perform SBRT for chest wall invasion because of considerable incidence of complications (31, 32). Obviously, the prescription dose of 60 Gy is not sufficient for chest wall invasion and how to improve the dose without damaging to the surrounding tissues has become a hot issue. However, there are few studies about the combined-modality therapy, namely EBRT and iodine-125 seed implantation, applying to the tumor lesions with invading the chest wall. In our study, the data indicated that the combined-modality therapy showed a better local control rate with an ORR of 71.4% and DCR 90.5%, respectively at 1 year, even if there were 15 patients (71.4%) with tumor measuring > 5 cm. What is more, the combined-modality therapy was certified not only to deliver a higher dose for chest wall invasion of NSCLC, but also significantly reduce adverse effect.

There's no denying that iodine-125 seed implantation has its own limitations. Firstly, it is not easy to perform iodine-125 seed implantation aiming at the lesions located in the mediastinum, which may lead to an unsatisfactory disposition of iodine-125 seed. Huang and his colleagues reported that it could carry out artificial pneumothorax for the lymph nodes of mediastinum before seed implantation, which should meet a good cardiorespiratory function. But it also increased the risk of incidence of complications, such as hemoptysis, chest tightness and dyspnea, which was difficult to tolerate for the elderly(10, 32). In addition, when the tumor is larger (especially > 5 cm), the expense of iodine-125 seed implantation will increase which may not be accepted by an ordinary family in developing countries. Therefore, the combined-modality therapy not only had showed superiority in decreasing the expense for tumor measuring > 5 cm, but also provided a new treatment strategy for tumor invading the chest wall.

About 60–90% patients of advanced cancer will suffer from cancer-related pain throughout the process which is a very common clinical issue(20, 33). At the same time, the cancer-related symptoms also bother patients, such as dry cough, hoarseness and hemoptysis. Therefore, how to relieve cancer-related pain and ameliorate cancer-related symptoms to improve QOL has become a critical question for doctors and patients. In our study, all patients suffered from a more or less pain caused by the tumor invading the chest wall. There were 71.4% patients achieving complete pain relief therapy and there were 20 patients, accounting for 95.2%, obtaining evident pain relief after the combined-modality. What is more, patients treated with the combined-modality therapy did not experience rib fracture or intercostal nerve injury in our research which was superior to SBRT (30, 31). After treatment, the cancer-related symptoms of patients were obviously improved, so the ECOG performance scores were pronouncedly improved which was observed in 18 patients in our study. Song et al indicated that iodine-125 seed implantation not only showed noteworthy superiority in ameliorating cancer-related symptoms but also significantly improved QOL of patients diagnosed as advanced NSCLC (34). It is remarkable that the combined-modality therapy was able to significantly relieve cancer-related pain and improve ECOG scores which could contribute to improve QOL.

With respect to severe complications in the research, there was no occurrence, consistent with previous reports(3, 10, 11, 16, 32). Except for grade 2 irradiation-related myelosuppression (1 case), there were no other grade 3 or higher toxicity effects. According to the reports of Jiang et al, there were no evident toxicity effects of grade 3 or higher (35). The incidence of radiation pneumonitis with grade  $\geq 2$  was 7.0 to 32.0% in patients receiving EBRT therapy, while that with grade  $\geq 3$  was 2.6 to 18.0% according to some authorized studies (36–38). Thereby, it is safe to combine EBRT and iodine-125 seed implantation for locally advanced NSCLC.

Due to lacking prospective randomized controlled trials, it is difficult for clinical physicians to formulate standardized prescription dose for iodine-125 seed implantation. Because of different tumor volume, different treatment strategy, and heterogeneity of tumor, it is impossible to obtain effective information about the prescription dose from previous report which varied from 80 Gy to 170 Gy. Ji and his colleague found that the local control was seemingly positively related to the prescribed dose which indicated the higher prescribed dose, the better local control. In their study, they conducted radioactive iodine-125 seed

implantation for solid thoracic malignancies, including the primary lung cancer or metastatic lung cancer. According to their study, the median durations of local control was 11.0 months with the prescription dose < 140 Gy vs. 16.4 months with the dose  $\geq$  140 Gy, but it did not reach significant difference. Based on their study, they strongly suggested the prescription dose should exceed 140 Gy for solid thoracic malignancies and should be as higher as possible, owing to the higher marginal recurrence of primary lung cancer (10). In our study, the ORR with tumor receiving the prescription dose  $\geq$  140Gy seemed better than the other, suggesting that the local control rate should be proportional to the delivered dose to the target lesion. Based on our study and previous other studies, we recommended that the prescription dose for primary lung cancer should exceed 140 Gy, as possible as high, if tolerated. Obviously, the result should be verified by large clinical randomized controlled trial.

## 5. Conclusions

The combined-modality therapy of EBRT and iodine-125 seed implantation, as a safe and effective option, which is accompanied with few severe complications, might be recommended as a favorable treatment for the elderly with chest wall invasion of locally advanced NSCLC. We found that it could relieve cancer-related pain and improve physical status of patients which could contribute to improving QOL, and the prescription dose exceeding 140Gy may result in better local outcomes.

## Abbreviations

locally advanced non-small-cell lung cancer (NSCLC), external beam radiotherapy (EBRT) quality of life (QOL), computed tomography (CT), positron emission tomography-CT (PET-CT), magnetic resonance imaging (MRI), emission computed tomography (ECT), Eastern Cooperative Oncology Group (ECOG), treatment planning system (TPS), planning target volume (PTV), intensity-modulated radiation therapy (IMRT), brachytherapy treatment planning system (BTPS), tumor target volume (GTV), adjacent organs at risk (OARs), objective response rate (ORR), disease control rate (DCR), Response Evaluation Criteria in Solid Tumors (RECIST), overall survival (OS), European Organization for Research and Treatment of CANCER (RTOG/EORTC).

## Declarations

### Ethics approval and consent to participate

All procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki

declaration and its later amendments or comparable ethical standards.

### Consent for publication

Informed consent was obtained from all individual.

## Availability of data and materials

The datasets used or analyzed during the current study were available from the corresponding author on reasonable request.

## Competing interests

None of the authors have any conflicts of interest.

## Funding

This work was not supported by any research fund.

## Authors' contributions

LJT designed the study and drafted the manuscript; HZL interpreted the data and performed statistical analysis; QZ and DZG participated in the coordination of the study; YQH and XSJ helped to perform statistical analysis; YZH supervised the study and helped to draft the manuscript. All authors agreed to be accountable for all aspects of the work.

## Acknowledgements

We thank all participants and patients who participated in this study.

## References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394–424. doi 10.3322/caac.21492.
2. 10.3322/caac.21387  
Siegel RL, Miller KD, Jemal A. Cancer Statistics. 2017. *CA Cancer J Clin* **2017**;67(1):7–30 doi 10.3322/caac.21387.
3. Wu C, Li B, Sun G, Peng C, Xiang D. Efficacy and safety of iodine-125 brachytherapy combined with chemotherapy in the treatment of advanced NSCLC in the elderly. *Onco Targets Ther.* 2018;11:6617–24. doi 10.2147/OTT.S174457.
4. Toschi L, Rossi S, Finocchiaro G, Santoro A. Non-small cell lung cancer treatment (r)evolution: ten years of advances and more to come. *Ecancermedicalscience.* 2017;11:787. doi 10.3332/ecancer.2017.787.
5. Rong B, Zhao C, Gao W, Yang S. Matrine promotes the efficacy and safety of platinum-based doublet chemotherapy for advanced non-small cell lung cancer. *Int J Clin Exp Med.* 2015;8(9):14701–17.
6. Reveiz L, Rueda JR, Cardona AF. Palliative endobronchial brachytherapy for non-small cell lung cancer. *Cochrane Database Syst Rev.* 2012;12:CD004284. doi 10.1002/14651858.CD004284.pub3.

7. Ozcan MF, Altinova S, Atan A. Treatment approaches to small renal masses in patients of advanced age ( $\geq 75$  years). *Turk J Urol*. 2018;44(4):281–6. doi 10.5152/tud.2018.04829.
8. Xiang GL, Zhu XH, Lin CZ, Wang LJ, Sun Y, Cao YW, et al. 125I seed irradiation induces apoptosis and inhibits angiogenesis by decreasing HIF-1alpha and VEGF expression in lung carcinoma xenografts. *Oncol Rep*. 2017;37(5):3075–83. doi 10.3892/or.2017.5521.
9. Cheng J, Ma S, Yang G, Wang L, Hou W. The Mechanism of Computed Tomography-Guided 125I Particle in Treating Lung Cancer. *Med Sci Monit*. 2017;23:292–9. doi 10.12659/msm.898526.
10. Ji Z, Jiang Y, Guo F, Peng R, Sun H, Fan J, et al. Safety and efficacy of CT-guided radioactive iodine-125 seed implantation assisted by a 3D printing template for the treatment of thoracic malignancies. *J Cancer Res Clin Oncol*. 2020;146(1):229–36. doi 10.1007/s00432-019-03050-7.
11. Di Maio M, Perrone F. Quality of Life in elderly patients with cancer. *Health Qual Life Outcomes*. 2003;1:44. doi 10.1186/1477-7525-1-44.
12. Dai F, Wang J, An H, Lei T, Tang K, Ma X, et al. Therapy of (125)I particles implantation inhibited the local growth of advanced non-small cell lung cancer: a retrospective clinical study. *Am J Transl Res*. 2019;11(6):3737–49.
13. Skowronek J. Brachytherapy in the treatment of lung cancer - a valuable solution. *J Contemp Brachytherapy*. 2015;7(4):297–311. doi 10.5114/jcb.2015.54038.
14. Qiu H, Ji J, Shao Z, Wang J, Ma G, Zhang L, et al. The Efficacy and Safety of Iodine-125 Brachytherapy Combined with Chemotherapy in Treatment of Advanced Lung Cancer: A Meta-Analysis. *J Coll Physicians Surg Pak*. 2017;27(4):237 – 45 doi 2597.
15. Huo X, Huo B, Wang H, Wang L, Cao Q, Zheng G, et al. Implantation of computed tomography-guided iodine-125 seeds in combination with chemotherapy for the treatment of stage III non-small cell lung cancer. *J Contemp Brachytherapy*. 2017;9(6):527–34. doi 10.5114/jcb.2017.72605.
16. Chen Y, Li Y, Jia Y, Lei K, Zhang X, Cao Y, et al. Bronchial artery chemoembolization combined with radioactive iodine-125 seed implantation in the treatment of advanced nonsmall cell lung cancer. *J Cancer Res Ther*. 2017;13(4):636–41. doi 10.4103/jcrt.JCRT\_93\_17.
17. Li W, Dan G, Jiang J, Zheng Y, Zheng X, Deng D. Repeated iodine-125 seed implantations combined with external beam radiotherapy for the treatment of locally recurrent or metastatic stage III/IV non-small cell lung cancer: a retrospective study. *Radiat Oncol*. 2016;11(1):119. doi 10.1186/s13014-016-0688-5.
18. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17(6):1471–4. doi 10.1245/s10434-010-0985-4.
19. de Kock I, Mirhosseini M, Lau F, Thai V, Downing M, Quan H, et al. Conversion of Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group Performance Status (ECOG) to Palliative Performance Scale (PPS), and the interchangeability of PPS and KPS in prognostic tools. *J Palliat Care*. 2013;29(3):163–9.

20. Stewart A, Parashar B, Patel M, O'Farrell D, Biagioli M, Devlin P, et al. American Brachytherapy Society consensus guidelines for thoracic brachytherapy for lung cancer. *Brachytherapy*. 2016;15(1):1–11. doi 10.1016/j.brachy.2015.09.006.
21. Watanabe H, Okada M, Kaji Y, Satouchi M, Sato Y, Yamabe Y, et al. [New response evaluation criteria in solid tumours-revised RECIST guideline (version 1.1)]. *Gan To Kagaku Ryoho*. 2009;36(13):2495–501.
22. Licqurish SM, Cook OY, Pattuwage LP, Saunders C, Jefford M, Koczwara B, et al. Tools to facilitate communication during physician-patient consultations in cancer care: An overview of systematic reviews. *CA Cancer J Clin*. 2019;69(6):497–520. doi 10.3322/caac.21573.
23. Matsuoka H, Nishio W, Okada M, Sakamoto T, Yoshimura M, Tsubota N. Resection of chest wall invasion in patients with non-small cell lung cancer. *Eur J Cardiothorac Surg*. 2004;26(6):1200–4. doi 10.1016/j.ejcts.2004.07.038.
24. Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst*. 2011;103(19):1452–60. doi 10.1093/jnci/djr325.
25. Li W, Guan J, Yang L, Zheng X, Yu Y, Jiang J. Iodine-125 brachytherapy improved overall survival of patients with inoperable stage III/IV non-small cell lung cancer versus the conventional radiotherapy. *Med Oncol*. 2015;32(1):395. doi 10.1007/s12032-014-0395-8.
26. Yu H, Wu H, Wang W, Jolly S, Jin JY, Hu C, et al. Machine Learning to Build and Validate a Model for Radiation Pneumonitis Prediction in Patients with Non-Small Cell Lung Cancer. *Clin Cancer Res*. 2019;25(14):4343–50. doi 10.1158/1078 – 0432.CCR-18-1084.
27. Gridelli C, Perrone F, Gallo C, Cigolari S, Rossi A, Piantedosi F, et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst*. 2003;95(5):362–72. doi 10.1093/jnci/95.5.362.
28. Lanuti M. Surgical Management of Lung Cancer Involving the Chest Wall. *Thorac Surg Clin*. 2017;27(2):195–9. doi 10.1016/j.thorsurg.2017.01.013.
29. Powell JW, Dexter E, Scalzetti EM, Bogart JA. Treatment advances for medically inoperable non-small-cell lung cancer: emphasis on prospective trials. *Lancet Oncol*. 2009;10(9):885–94. doi 10.1016/S1470-2045(09)70103-2.
30. Doddoli C, D'Journo B, Le Pimpec-Barthes F, Dujon A, Foucault C, Thomas P, et al. Lung cancer invading the chest wall: a plea for en-bloc resection but the need for new treatment strategies. *Ann Thorac Surg*. 2005;80(6):2032–40. doi 10.1016/j.athoracsur.2005.03.088.
31. Nagata Y, Wulf J, Lax I, Timmerman R, Zimmermann F, Stojkovski I, et al. Stereotactic radiotherapy of primary lung cancer and other targets: results of consultant meeting of the International Atomic Energy Agency. *Int J Radiat Oncol Biol Phys*. 2011;79(3):660–9. doi 10.1016/j.ijrobp.2010.10.004.
32. Huang Q, Chen J, Chen Q, Lai Q, Cai S, Luo K, et al. Computed tomographic-guided iodine-125 interstitial implants for malignant thoracic tumors. *Eur J Radiol*. 2013;82(11):2061–6. doi

10.1016/j.ejrad.2013.05.037.

33. Pan H, Shen P, Shu Q, Lu L, Qian S, Zhou Y, et al. Efficacy and safety of sustained-release oxycodone compared with immediate-release morphine for pain titration in cancer patients: A multicenter, open-label, randomized controlled trial (SOCIAL). *Medicine*. 2019;98(24):e15505. doi 10.1097/MD.00000000000015505.
34. Song J, Fan X, Zhao Z, Chen M, Chen W, Wu F, et al. (125)I brachytherapy of locally advanced non-small-cell lung cancer after one cycle of first-line chemotherapy: a comparison with best supportive care. *Onco Targets Ther*. 2017;10:1345–52. doi 10.2147/OTT.S129903.
35. Jiang Y, Ji Z, Guo F, Peng R, Sun H, Fan J, et al. Side effects of CT-guided implantation of (125)I seeds for recurrent malignant tumors of the head and neck assisted by 3D printing non co-planar template. *Radiat Oncol*. 2018;13(1):18. doi 10.1186/s13014-018-0959-4.
36. Barriger RB, Fakiris AJ, Hanna N, Yu M, Mantravadi P, McGarry RC. Dose-volume analysis of radiation pneumonitis in non-small-cell lung cancer patients treated with concurrent cisplatin and etoposide with or without consolidation docetaxel. *Int J Radiat Oncol Biol Phys*. 2010;78(5):1381–6. doi 10.1016/j.ijrobp.2009.09.030.
37. Phernambucq EC, Spoelstra FO, Verbakel WF, Postmus PE, Melissant CF, Maassen van den Brink KI, et al. Outcomes of concurrent chemoradiotherapy in patients with stage III non-small-cell lung cancer and significant comorbidity. *Ann Oncol*. 2011;22(1):132–8. doi 10.1093/annonc/mdq316.
38. Werner-Wasik M, Paulus R, Curran WJ Jr, Byhardt R. Acute esophagitis and late lung toxicity in concurrent chemoradiotherapy trials in patients with locally advanced non-small-cell lung cancer: analysis of the radiation therapy oncology group (RTOG) database. *Clin Lung Cancer*. 2011;12(4):245–51. doi 10.1016/j.clcc.2011.03.026.

## Figures

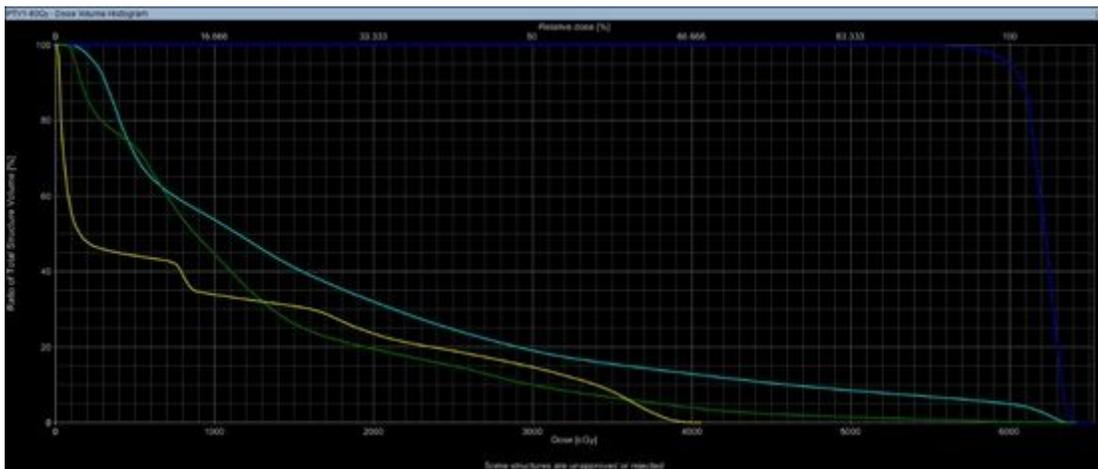
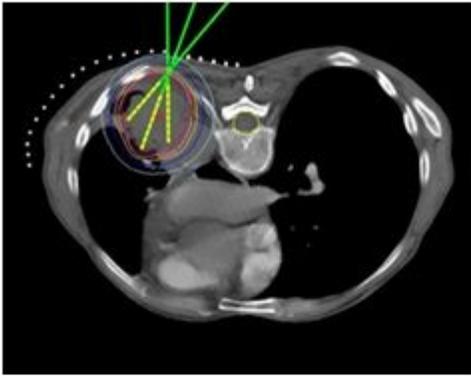


Figure 1

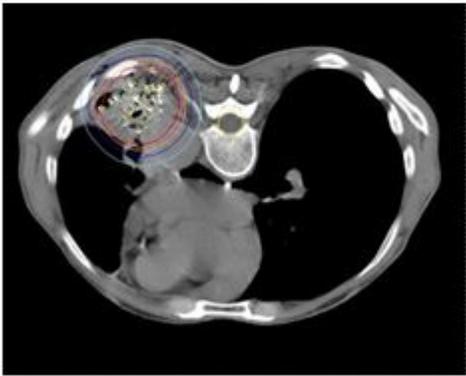
Figure 1



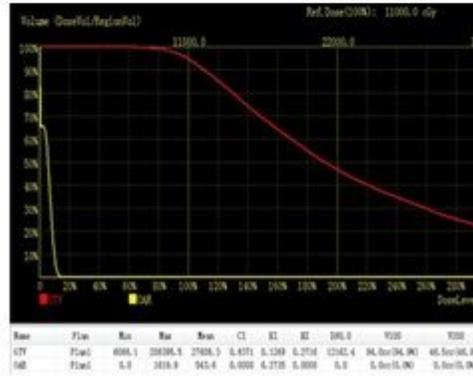
(A)



(B)



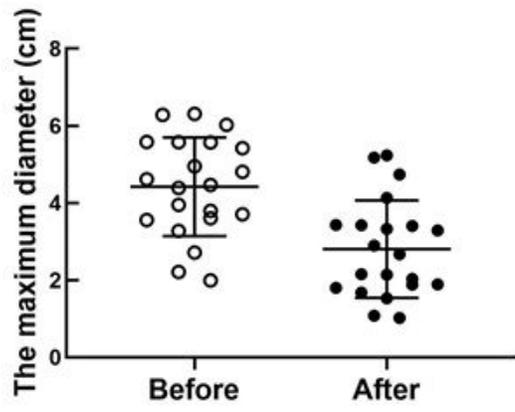
(C)



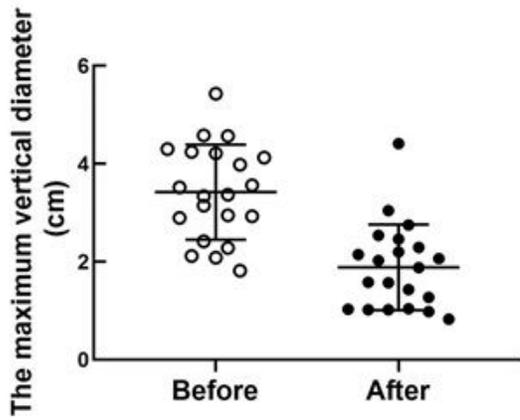
(D)

Figure 2

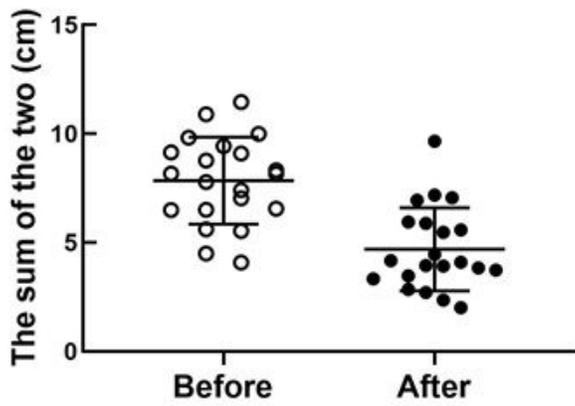
Figure 2



(A)



(B)



(C)

Figure 3

Figure 3