



# Efficacy and safety of immune checkpoint inhibitors combined with iodine-125 seed implantation in driver gene-negative non-small cell lung cancer: a retrospective cohort study

Xipeng Tao<sup>#</sup>, Lan Liang<sup>#</sup>, Junjie Xu, Lici Xie, Qing Wen, Xiangdong Zhou, Hu Luo

Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Army Medical University, Chongqing, China

**Contributions:** (I) Conception and design: X Zhou, H Luo; (II) Administrative support: X Zhou, H Luo; (III) Provision of study materials or patients: L Liang; (IV) Collection and assembly of data: X Tao; (V) Data analysis and interpretation: J Xu, L Xie, Q Wen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

<sup>#</sup>These authors contributed equally to this work as co-first authors.

**Correspondence to:** Xiangdong Zhou, MD; Hu Luo, MD. Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Army Medical University, No. 30 Gaotanyan Street, Chongqing 400038, China. Email: xiangdongzhou@126.com; luohucy@163.com.

**Background:** Non-small cell lung cancer (NSCLC) presents the most common type of lung cancer, accounting for 80–85% of cases. Combining immunotherapy with radiotherapy (RT) has emerged as a significant research area in recent years. However, the risk of radiation pneumonitis, especially in lung cancer patients, poses a significant concern. Iodine-125 ( $I^{125}$ ) seed implantation offers a precise, less invasive alternative, minimizing damage to surrounding lung tissues and reducing side effects. This study aims to evaluate the safety and efficacy of  $I^{125}$  seed implantation combined with immune checkpoint inhibitors (ICIs) and chemotherapy (CT) in treating driver gene-negative NSCLC patients.

**Methods:** Retrospective analysis of 95 patients with driver gene-negative NSCLC who presented to the First Affiliated Hospital of Army Medical University was conducted. Among them, 33 cases in the observation group were treated with  $I^{125}$  seed implantation combined with CT and ICIs (ICIs + CT +  $I^{125}$ ), and 62 cases in the control group were treated with extracorporeal RT combined with CT and ICIs (ICIs + CT + RT). The primary observational endpoint was median progression-free survival (mPFS), while the secondary observational endpoints included the 1- and 2-year PFS rate and the incidence of adverse events.

**Results:** mPFS was not reached in the observation group but 11.8 months [95% confidence interval (CI): 9.743–13.857] in the control group, a statistically significant difference ( $P < 0.001$ ). The restricted mean survival time (RMST) was 22.2 (95% CI: 18.257–26.101) and 13.8 (95% CI: 11.912–15.718) months in both groups at 31.7 months, PFS was better in the observation group than in the control group. In the observation group, two cases (6.1%) developed grade 3 pneumothorax or hemorrhage, and in the control group, 16 cases (25.8%) developed grade 3 radiation pneumonitis, which was higher in the control group than in the observation group ( $P = 0.02$ ).

**Conclusions:** Compared to RT in combination with CT and immunotherapy, patients with driver gene-negative NSCLC who received  $I^{125}$  seed implantation had greater advantages with longer survival and fewer adverse effects.

**Keywords:** Non-small cell lung cancer (NSCLC); immune checkpoint inhibitors (ICIs); iodine-125 seed ( $I^{125}$  seed); chemotherapy (CT)

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## Introduction

### Background

Non-small cell lung cancer (NSCLC) presents the most common type of lung cancer, accounting for 80–85% of cases. Immune checkpoint inhibitors (ICIs) are now the first-line standard of care for patients with driver gene-negative advanced and locally advanced lung cancers (1), and combination therapy based on ICIs in combination with chemotherapy (CT) has improved lung cancer patients' survival rates.

Combining immunotherapy with radiotherapy (RT) has emerged as a significant research area in recent years. Radiotherapy can enhance antigen presentation and programmed death 1 ligand 1 (PD-L1) expression in tumor cells, augmenting the efficacy of ICIs. Conversely, ICIs might ameliorate the tumor's hypoxic environment and enhance its radiosensitivity, potentially amplifying radiotherapy's long-term benefits (2,3). Clinical evidence supports the substantial benefits of integrating radiotherapy with immunotherapy (4-7).

However, the risk of radiation pneumonitis, especially in lung cancer patients, poses a significant concern (8). Iodine-125 ( $I^{125}$ ) seed implantation offers a precise, less invasive alternative, minimizing damage to surrounding lung tissues and reducing side effects (9,10). While Wang *et al.*'s study (11) demonstrates the effectiveness and safety

of combining  $I^{125}$  seed implantation with CT in treating advanced NSCLC patients, research on combining CT, ICIs, and  $I^{125}$  seed implantation remains limited (12-14).

### Objective

This study aims to evaluate the safety and efficacy of  $I^{125}$  seed implantation combined with ICIs and CT versus external RT plus CT and ICIs in treating driver gene-negative NSCLC patients, offering insights into potentially safer and more effective treatment options and multidisciplinary approaches to lung cancer therapy. We present this article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-24-1403/rc>).

## Methods

### Setting

Retrospective analysis of 95 patients with driver gene-negative NSCLC who visited the First Affiliated Hospital of Army Medical University between December 2018 and December 2023 was conducted, including 33 patients treated with  $I^{125}$  seed implantation in combination with CT and ICIs (observation group) and 62 patients treated with extracorporeal RT in combination with CT and ICIs (control group).

The criteria for inclusion were: (I) age greater than 18 years; (II) pathologically confirmed NSCLC with negative driver genes; (III) no prior treatment (other than surgery or radiofrequency ablation) regarding this tumor; (IV) Eastern Cooperative Oncology Group (ECOG) score of 0–1; and (V) at least two cycles of ICI therapy. The criteria for exclusion were: (I) concurrent primary malignancy at other sites; (II) concurrent  $I^{125}$  seed implantation and RT during first-line treatment; (III) presence of a serious disease affecting treatment or survival as assessed by the investigator; (IV) incomplete clinical data; (V) participation in an randomized controlled trial (RCT) clinical study; and (VI) combination of symptomatic brain metastases. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Affiliated Hospital of Army Medical University (No. KY2024028). Medical records obtained in previous clinical treatment were collected and analyzed retrospectively, individual consent for this study was waived.

$I^{125}$  seed implantation: complete blood routine,

### Highlight box

#### Key findings

- Compared to radiotherapy (RT) in combination with chemotherapy (CT) and immunotherapy, patients with driver gene-negative non-small cell lung cancer who received iodine-125 ( $I^{125}$ ) seed implantation had greater advantages with longer survival and fewer adverse effects.

#### What is known and what is new?

- Clinical evidence supports the substantial benefits of integrating RT with immunotherapy. Compared to RT,  $I^{125}$  seed implantation offers a precise, less invasive alternative, minimizing damage to surrounding lung tissues and reducing side effects.
- This manuscript evaluated the safety and efficacy of  $I^{125}$  seed implantation combined with immune checkpoint inhibitors and CT in treating driver gene-negative non-small cell lung cancer patients.

#### What is the implication, and what should change now?

- A higher-quality prospective cohort study needs to be established to reduce bias and further enhance the reliability of the results.

coagulation function, and electrocardiogram (ECG) to exclude contraindications. To locate the tumor and identify the surgical site, as well as the direction and depth of needle entry, a preoperative computed tomography scan was carried out. The radioactive particle treatment planning system (TPS) system is used to determine the radiation dose and number of seeds. I<sup>125</sup> seeds are implanted by TPS after a puncture needle is injected into the tumor tissue under computed tomography guidance. The gap between the puncture needles is typically 1 to 1.5 cm. Once all of the tips have reached the tumor's distal edge, the I<sup>125</sup> seeds are implanted by folding the tips back along the same distance or by TPS. Throughout the procedure, closely monitor the patient's heart rate, blood pressure, and oxygen saturation, observe the patient's consciousness, breathing, and symptoms (including pain, cough, or hemoptysis), and treat if necessary (15). After implantation, the entire lung is rescanned to verify the distribution and quantity of I<sup>125</sup> seeds in each plane. Additionally, look for any problems, such as bleeding or pneumothorax, and treat if necessary.

### Study design

#### Evaluation and follow-up

The results of the last imaging test performed before the initiation of treatment served as the baseline. The evaluation included a review of the efficacy and adverse events, and the follow-up data included information from our medical records and publicly available out-of-hospital data. The efficacy was assessed using the RECIST 1.1 criteria, and the results were divided into four grades: complete response (CR), partial response (PR), stable disease (SD), and progression disease (PD).

#### Observational indicators

Progression-free survival (PFS) was the primary observation endpoint, while PFS rate and adverse event rate were the secondary endpoints. PFS was defined as the time from the start of treatment to the first progression of the tumor or death from any cause (censored data were terminated by the last meaningful imaging), and overall survival (OS) was defined as the time from the start of tumor diagnosis to the patient's death (censored data were terminated by the last follow-up). The safety analysis was based on medical records and examination test results, and it was graded using Common Terminology Criteria for Adverse Events (CTCAE) 5.0.

### Statistical methods

Data analysis was conducted using SPSS 26.0 and R 4.2.2. Baseline characteristics between groups were compared using the Chi-squared test (or Fisher's exact test) and the *t*-test (or Mann-Whitney *U* test). Cox regression analysis was applied for survival analysis. The Kaplan-Meier method constructed subgroup PFS curves to compare the PFS rates between groups, with the log-rank test evaluating differences. The restricted mean survival time (RMST) was calculated for both groups. The incidence of adverse events was compared using the Chi-squared test (or Fisher's exact test), considering  $P < 0.05$  as statistically significant.

## Results

### Patient population

As of December 31, 2023, the median follow-up for the observation group was 23.6 [95% confidence interval (CI): 18.792–28.408] months, with 13 cases (39.4%) experiencing an endpoint event (progression after first-line treatment). In contrast, the control group had a median follow-up of 28.5 (95% CI: 24.334–32.666) months, with 52 cases (83.9%) encountering an endpoint event. Fifteen patients were lost to follow-up, including eleven from the control group and four from the observation group. Despite these differences, baseline characteristics between the two groups were comparable and statistically insignificant ( $P > 0.05$ ), as shown in *Table 1*, which outlines the distribution of baseline characteristics.

### Comparison of PFS between two groups

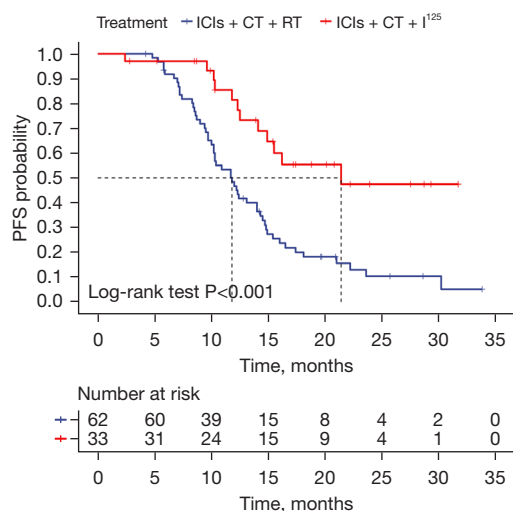
The control group's median PFS was 11.8 months (95% CI: 9.743–13.857), whereas the observation group did not reach a median PFS, indicating a significant difference (log-rank test,  $P = 0.001$ ) as illustrated in *Figure 1*. The observation group demonstrated superior outcomes, with 1- and 2-year PFS rates of 77.3% *vs.* 46.7% and 46.0% *vs.* 10.4%, respectively. Due to the interaction and non-proportionality of the Kaplan-Meier curves between groups, a segmented RMST analysis was conducted.

At the point of intersection (5.3 months), the RMST was 5.2 (95% CI: 5.043–5.382) months for the observation group and 5.3 (95% CI: 5.276–5.308) months for the control group, showing no significant difference ( $P = 0.36$ ). At 31.7 months (the shortest maximum observation period among the groups), the RMSTs were 22.2 (95% CI:

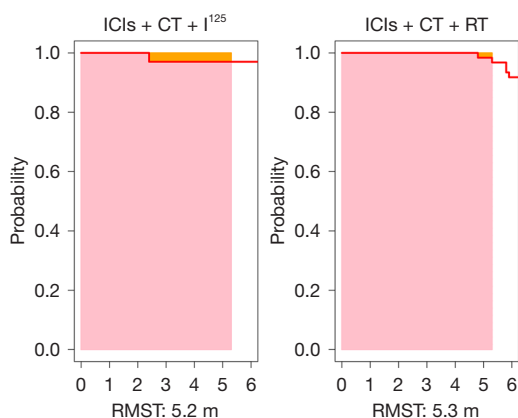
**Table 1** Distribution of baseline characteristics of observation and control groups

Baseline characteristics	Observation group (n=33)	Control group (n=62)	P value
Age (years)	60.18±8.39	60.77±8.47	0.69
Gender			0.19
Male	29 (87.9)	59 (95.2)	
Female	4 (12.1)	3 (4.8)	
Postoperative recurrence <sup>†</sup>			0.35
Yes	3 (9.1)	3 (4.8)	
No	30 (90.9)	59 (95.2)	
T stage			0.34
T1–2	8 (24.2)	19 (30.6)	
T3–4	25 (75.8)	43 (69.4)	
N stage			0.38
N0	8 (24.2)	12 (19.4)	
N1	25 (75.8)	50 (80.6)	
M stage			0.54
M0	15 (45.5)	29 (46.8)	
M1	18 (54.5)	33 (53.2)	
AJCC stage			0.57
Stage I & II	2 (6.1)	3 (4.8)	
Stage III & IV	31 (93.9)	59 (95.2)	
Pathological type			0.23
Squamous carcinoma	25 (75.8)	41 (66.1)	
Non-squamous carcinoma	8 (24.2)	21 (33.9)	
Smoking index (pack-years)			0.59
≤400	9 (27.3)	17 (27.4)	
>400	24 (72.7)	45 (72.6)	
Pulmonary disease			0.55
Yes	12 (36.4)	22 (35.5)	
No	21 (63.6)	40 (64.5)	
Anti-angiogenesis therapy			0.13
Yes	10 (30.3)	11 (17.7)	
No	23 (69.7)	51 (82.3)	

Data are presented as mean ± standard deviation or number (%). <sup>†</sup>, refers to the primary lesion's surgical excision and recurrence following systemic therapy. AJCC, American Joint Committee on Cancer.



**Figure 1** Kaplan-Meier curves and log-rank test for the observation group (ICIs + CT + I<sup>125</sup>) versus the control group (ICIs + CT + RT). ICIs, immune checkpoint inhibitors; RT, radiotherapy; CT, chemotherapy; I<sup>125</sup>, iodine-125; PFS, progression-free survival.

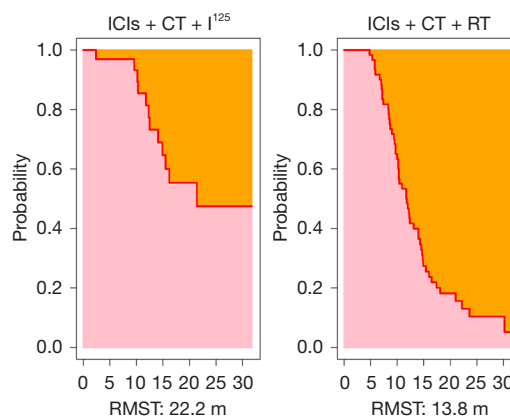


**Figure 2** Comparison of RMST in observation and control groups (at 5.3 months). ICIs, immune checkpoint inhibitors; RT, radiotherapy; CT, chemotherapy; I<sup>125</sup>, iodine-125; RMST, restricted mean survival time.

18.257–26.101) months for the observation group and 13.8 (95% CI: 11.912–15.718) months for the control group, indicating significantly better PFS in the observation group ( $P < 0.001$ ), as depicted in *Figures 2, 3*.

### Adverse events

Pneumothorax and hemorrhage were the major complications associated with I<sup>125</sup> seed implantation in



**Figure 3** Comparison of RMST in observation and control groups (at 31.7 months). ICIs, immune checkpoint inhibitors; RT, radiotherapy; CT, chemotherapy; I<sup>125</sup>, iodine-125; RMST, restricted mean survival time.

the observation group. Of these, 14 patients experienced pneumothorax and had a closed chest drain placed; 13 (39.4%) experienced grade 1–2 adverse events (complete lung reexpansion and removal of drain before discharging from the hospital); and one (3.0%) experienced grade 3 adverse events (discharged with a drain). All of the patients experienced hemorrhage; 32 (97.0%) experienced grade 1–2 adverse events (bleeding up to 50 mL in four cases and less than 20 mL in the remaining cases), and 1 (3.0%) experienced grade 3 adverse events (hemopneumothorax with 100 mL of bleeding). Radiation pneumonitis, radiation esophagitis, and other radiation-related adverse events were observed in the control group. Of these, 17 cases (27.4%) were grade 1–2 adverse events and 16 cases (25.8%) were grade 3 adverse events (receiving hormonal or other treatments). The control group saw a greater prevalence of grade 3 adverse events (Chi-squared test  $P = 0.02$ ).

Furthermore, six patients in the observation group (18.2%) suffered immunotherapy-related diseases (such as immune-associated pneumonia), whereas five patients in the control group (8.1%) had immunotherapy-related diseases, all of which were in grade 1–2. In the two groups, there were 16 (48.5%) and 29 (46.8%) occurrences of myelosuppression, all of which were grade 1–2. Nine (14.5%) extra adverse events, all grade 1–2, happened in the control group while none in the observation group (*Table 2*).

### Analysis of subgroups

Subgroup analyses were conducted on seven parameters:



**Table 2** Adverse event statistics of the observation and control groups

Adverse event	Grade	Observation group (n=33)	Control group (n=62)
Pneumothorax	1–2	13 (39.4)	–
	3	1 (3.0)	–
Hemorrhage	1–2	32 (97.0)	–
	3	1 (3.0)	–
Radiation pneumonitis/ esophagitis, etc.	1–2	–	17 (27.4)
	3	–	16 (25.8)
Immune-associated pneumonia (other diseases)	1–2	6 (18.2)	5 (8.1)
	3	–	0
Myelosuppression	1–2	16 (48.5)	29 (46.8)
	3	0	0
Others	1–2	0	9 (14.5)
	3	0	0

Data are presented as n (%).

tumor size (T-stage), lymph node metastasis (N-stage), distant metastasis (M-stage), pathological type, smoking index, underlying pulmonary disease, and the use of anti-angiogenesis therapy. Analysis of subgroups with distant metastasis, squamous carcinoma, smoking index over 400 pack-years, and those not receiving anti-angiogenesis therapy, compared to their respective controls, identified I<sup>125</sup> seed implantation as an independent prognostic factor for improved PFS. This suggests that I<sup>125</sup> seed implantation may have a better therapeutic outcome for the aforementioned groups (Figure 4).

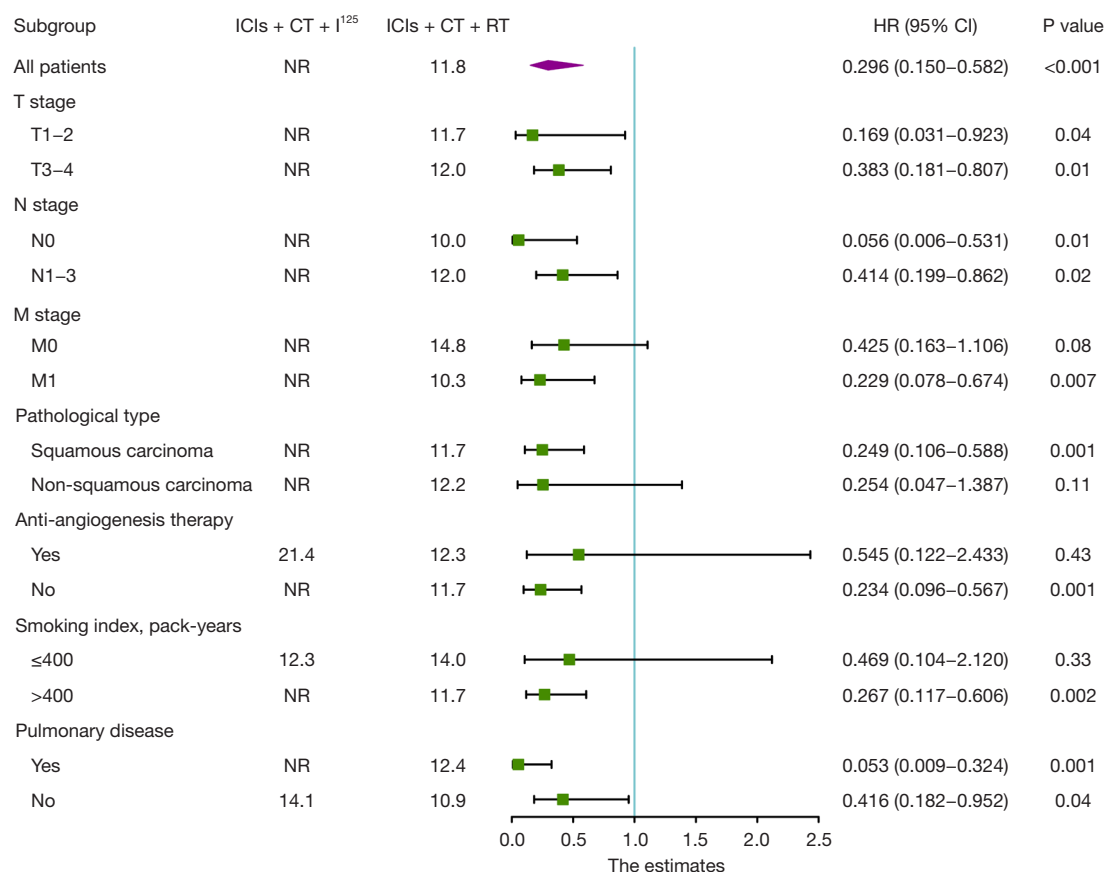
In the observation group, 23 patients were treated solely with I<sup>125</sup> seed implantation. Of these, 16 received seed implantation during the maintenance phase (after 4–6 cycles of CT plus immunotherapy), and seven during the initial phase (before starting CT plus immunotherapy), with respective median PFS of not reached and 15.5 (95% CI: 11.373–19.627) months. Although survival curves suggested a trend towards improved outcomes for maintenance phase implantation, statistical significance was not achieved (log-rank test  $P=0.17$ ; Cox model  $P=0.18$ , HR =0.387), as shown in Figure 5. Notably, patients with maintenance phase implantation exhibited higher 1- and 2-year PFS rates compared to those with initial phase implantation.

## Discussion

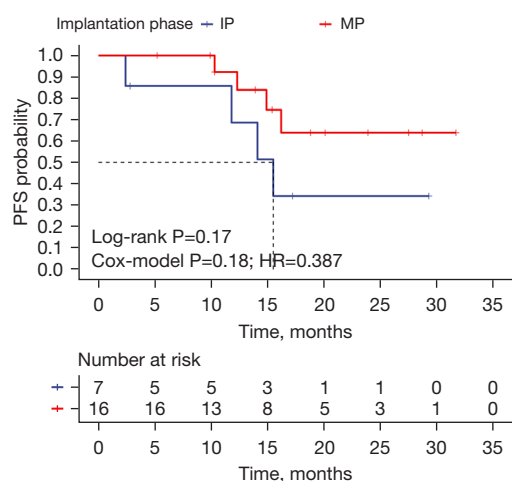
For patients with driver gene-negative NSCLC, traditional platinum-based CT and RT show limited effectiveness. The advent of ICIs targeting programmed death 1 (PD-1) and PD-L1 marks a significant advancement, offering substantial survival benefits. Research, including the PACIFIC and NCT02621398 studies, demonstrates that ICIs, followed by concurrent radio-CT, notably enhance survival in stage III unresectable NSCLC (4,5). Prof. Chang *et al.*'s study (7) further suggests that extending such treatment to early-stage (I and II) unresectable lung cancer with RT plus immunotherapy (I-SABR) considerably improves 4-year event-free survival rates compared to RT alone.

To the best of our knowledge, this research represents the first cohort study exploring the effectiveness and safety of ICIs combined with CT and I<sup>125</sup> seed implantation regimens. In our study, the median PFS in the observation group and control group were not reached and 11.8 months, respectively. As the assumption of proportional hazards was not met, we employed the RMST and the area under the Kaplan-Meier curve as alternative analytical approaches. The survival curves of both groups intersected at 5.3 months, a phenomenon potentially attributable to the limited sample size. This small cohort may have introduced variability into the OS analysis, with the outcomes significantly influenced by individual data points. At this time, the RMST for the observation group was 5.2 (95% CI: 5.043–5.382) months, compared to 5.3 months for the control group (95% CI: 5.276–5.308), a difference that was not statistically significant ( $P=0.36$ ). Notably, at the 31.7-month minimum follow-up, the RMSTs diverged significantly between groups. The observation group demonstrated a RMST of 22.2 (95% CI: 18.257–26.101) months, markedly outperforming the control group's 13.8 (95% CI: 11.912–15.718) months. This superior performance was also reflected in the PFS rates, with the observation group achieving 1- and 2-year PFS rates of 77.3% versus 46.7%, and 46.0% versus 10.4%, respectively. By the follow-up cut-off point, a significant discrepancy in the rate of endpoint events (disease progression) was observed: 52 cases (83.9%) within the control group had progressed, in stark contrast to 13 cases (39.4%) in the observation group. This suggests that the advantages seen in the observation group could become even more pronounced over time.

Radiation pneumonitis predominantly occurs within 2



**Figure 4** Subgroup analysis of PFS in the two groups (NR refers to that the median PFS does not attained). ICIs, immune checkpoint inhibitors; RT, radiotherapy; CT, chemotherapy; I<sup>125</sup>, iodine-125; PFS, progression-free survival; NR, not reached; HR, hazard ratio; CI, confidence interval.



**Figure 5** Comparison of the efficacy of seed implantation at different phases. PFS, progression-free survival; IP, initial phase; MP, maintenance phase.

to 6 months following radiation therapy (8). Key clinical risk factors that heighten the risk for this condition include advanced age, male gender, the location of the tumor, compromised lung function, and the presence of other health conditions (16–19). Moreover, employing ICIs in combination further escalates this risk (20–22). Various studies indicate that 15–40% of patients undergoing chest radiation therapy develop radiation pneumonitis, with an additional 10–20% experiencing severe forms of the illness. Alarmingly, the mortality rate among these patients can reach up to 50% (23). In our study, we observed a notably high incidence rate of radiation pneumonitis/esophagitis in the control group, reaching 53.2% (33 cases), attributed largely to the augmented risk introduced by the use of ICIs. Of these cases, 16 were classified as grade 3 adverse events, necessitating intervention with hormone therapy or alternative treatments. Additionally, it is well-documented

that patients with existing pulmonary conditions, especially those with interstitial lung disease (ILD) or chronic obstructive pulmonary disease (COPD), are at an increased risk of developing radiation pneumonitis (24-28). In our control group, there were 22 cases of underlying pulmonary diseases (19 of COPD/emphysema, one of ILD, one of secondary tuberculosis, and one of pneumoconiosis), leading to 13 instances of radiation pneumonitis as a result of the therapy. Research by Shi *et al.* (29) suggests that patients with NSCLC and normal lung function generally manage the side effects of radiation therapy well. However, those patients with COPD experience a significant reduction in lung function after therapy. Despite these challenges, radiation therapy remains a critical prognostic factor for NSCLC patients with severe pulmonary impairment (30), underscoring the need for tailored treatment strategies for this patient population.

Based on our research, external beam radiation therapy presents a lower safety profile compared to  $I^{125}$  seed implantation. Advances in the TPS for radioactive seed therapy have led to more precise delineation of the target area and three-dimensional (3D) metrology planning. These improvements ensure the tumor receives an adequate dose while minimizing exposure to nearby critical organs and tissues. Pneumothorax and hemorrhage emerged as the predominant complications after  $I^{125}$  seed implantation. In our observation group of 33 patients, 14 (42.4%) experienced pneumothorax and received closed chest drainage treatment. Of these, 13 patients had their drainage tubes removed before discharge, while one patient was discharged with the tube still in place, which was removed after one week. Post-treatment, all patients exhibited full lung re-expansion without any permanent consequences. Bleeding occurred in every patient during the implantation process, with one instance of 100 mL, four instances of 50 mL, and the rest limited to 20 mL. These hemorrhages were effectively managed through symptomatic treatments and medications that facilitated absorption, leading to complete resolution.

For patients receiving combined regimens of RT and ICIs, RT and immunotherapy are typically performed sequentially in order to avoid the superimposed risk of radiation pneumonitis and immune-associated pneumonitis. Local seed implantation not only gets around this restriction but also amplifies the synergistic effect of RT and immunotherapy. After implantation in the body, the  $I^{125}$  particles will produce circular or cylindrical localized radiation, and this sustained killing effect on tumor cells can be maintained for several months (31). In the meantime,

the radioactive seeds keep improving the tumor's immune milieu, which makes it easier for ICIs to have a therapeutic impact. Additionally, our findings demonstrated that while the incidence of immune-related pneumonitis was slightly higher (18.2%) in the group receiving  $I^{125}$  seed implantation, all of the adverse events were grade 1–2 and did not differ statistically ( $P=0.26$ ) from the group receiving conventional RT (8.1%). There was no discernible increase in the risk of immune-related pneumonia from  $I^{125}$  seed implantation while radiation pneumonitis was avoided.

Besides, our study also indicated that timing  $I^{125}$  seed implantation at mid-treatment (maintenance phase after CT combined with immunotherapy) appeared to have a better outcome compared to the initial phase of treatment, with PFS not reached and 15.5 months, respectively. In terms of the trend in the survival curves and the comparison of the PFS rates at 1 and 2 years, the maintenance phase implantation examples outperformed the treatment-initial phase, even though the difference was not statistically significant (log-rank test  $P=0.17$ ; cox-model  $P=0.18$ , HR =0.387). Chemotherapeutic drugs can exert anti-tumor effects early in the course of treatment and gradually display a trend of drug resistance over time. In contrast to ICIs, which typically detect anti-tumor efficacy 2–4 months after treatment due to delayed response (31), and  $I^{125}$  seeds, which have a half-life of 59.43 days and are effective *in vivo* for up to 4 months. Implantation of seeds in the middle of treatment provides a longer period of radio-immuno-coordination compared to the beginning of treatment. Additionally, since this region of the patient responds better to immunotherapy, the implant's maintenance phase is more effective, because patients will select second-line therapies to skip the maintenance period if they do not react to conventional treatment. Thus, it is crucial to forecast and screen the population undergoing immunotherapy using PD-L1, tumor mutation burden (TMB), and other indications. Implanting seeds during the maintenance phase is advised for patients who respond effectively to immunotherapy. Initial use of combination therapies (such as  $I^{125}$  seeds implantation) can help patients with poor immune responses not only limit the spread of the tumor but also potentially enhance the tumor's immunological environment, improving treatment outcomes. To have the optimum treatment outcome, this patient group might require more than two seeds implantations (the initial phase of therapy + treatment maintenance stage).

The following are the limitations of our study: due to the retrospective nature of the study and its single-center



design, bias in sample selection may have occurred; results may have fluctuated more due to smaller sample sizes and the impact of individual samples; I<sup>125</sup> seed implantation required patients to have a better lung condition or general condition than RT, and even though there was no significant difference in the incidence of pulmonary diseases between the observation and control groups, there may still be some potential difference; TMB and PD-L1 expression are linked to the effectiveness of immunotherapy; however, most study participants were not tested for those expressions due to financial or other reasons, and the therapeutic effects of various ICIs and chemotherapeutic agents may differ. Based on preliminary research findings, we are currently establishing a higher-quality prospective cohort study to reduce bias and further enhance the reliability of the results.

## Conclusions

I<sup>125</sup> seed implantation combined with CT and ICIs improves short-term survival and causes fewer side effects in patients with driver gene-negative NSCLC who are not eligible for surgery, compared to RT combined with CT and immunotherapy. It is especially advised for those with significant radiation pneumonia risk factors to receive I<sup>125</sup> seed implantation.

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## Footnote

**Reporting Checklist:** The authors have completed the STROBE reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-24-1403/rc>

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[com/article/view/10.21037/jtd-24-1403/coif](https://jtd.amegroups.com/article/view/10.21037/jtd-24-1403/coif)). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Affiliated Hospital of Army Medical University (No. KY2024028). Medical records obtained in previous clinical treatment were collected and analyzed retrospectively, individual consent for this study was waived.

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