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Clinical Observation of Immunotherapy Combined with CT-Guided Stereotactic Ablation Brachytherapy for Early-Stage Unresectable Non-Small Cell Lung Cancer

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Abstract

Background: To observe the safety and efficacy of immunotherapy combined with CT-guided stereotactic ablation brachytherapy(I-SABT) in early-stage unresectable non-small cell lung cancer (NSCLC). **Methods:** Collect early-stage unresectable non-small cell lung cancer patients who received I-SART in our hospital from January 2019 to December 2023. Evaluated the safety and efficacy of treatment, and analyzed their prognostic factors. **Results:** A total of 23 patients with early-stage non-small cell lung cancer (T1-3N0M0 stage Ia-IIb) were included, including 17 cases of squamous cell carcinoma and 6 cases of adenocarcinoma (all driver genes tested negative); There were 14 smokers and 9 non-smokers, all patients were deemed ineligible for surgery or declined standard radiotherapy or chemoradiotherapy. The median follow-up time was 36.5 months (range: 17.2 - 77.5). The median event free survival (mEFS) was 49.2 months, and DCR at 1, 3, and 4 years were 100.0% (23/23), 91.3% (21/23), and 82.6% (19/23), respectively. Procedure-related adverse events were predominantly Grade I-II: pneumothorax (10/23, 43.5%), hemorrhage (3/23, 13.0%), and pain (1/23, 4.3%). Pneumothorax incidence was significantly associated with patient positioning and number of needle passes. Lateral decubitus positioning resulted in a higher pneumothorax rate (83.3%, 5/6) compared to supine/prone positioning (29.4%, 5/17; P = 0.022). >9 needle passes

led to a higher pneumothorax rate (66.7%, 8/12) versus ≤9 passes (18.2%, 2/11; P = 0.019). Immune-related adverse events were limited to Grade I-II: fatigue (6/23, 26.1%), hypothyroidism (2/23, 8.6%), and immune-mediated pneumonitis (3/23, 13.0%). Univariate analysis showed that ECOG 0 - 1, smoking, left lung disease, GTV D90 ≥ 140 Gy and PD-L1 expression ≥ 1% had better mEFS ($p < 0.05$); Multivariate analysis showed that GTV D90 and PD-L1 expression were independent prognostic factors for EFS ($p < 0.05$). **Conclusions:** I-SABT can improve the survival benefits of patients with early-stage unresectable non-small cell lung cancer, and demonstrates a favorable safety profile. GTV D90 ≥ 140 Gy and PD-L1 expression ≥ 1% were associated with improved clinical outcomes. Patients receiving I-SABT exhibited superior prognosis compared to conventional therapies.

Keywords

Stereotactic Ablation Brachytherapy, Immunotherapy, Radioactive Seed Implantation, Early-Stage Non-Small Cell Lung Cancer

1. Introduction

Lung cancer is the malignant tumor with the highest incidence rate and mortality in the world, which more than 80% is non-small cell lung cancer (NSCLC), early-stage lung cancer accounts for approximately 20% - 30% [1]. Surgery and stereotactic radiotherapy are the main treatment methods for early-stage non-small cell lung cancer (NSCLC). For unresectable early-stage NSCLC, stereotactic ablation radiotherapy (SABR) is considered the best choice [2]. However, some patients cannot undergo surgery and external radiotherapy for various reasons, resulting in poor prognosis and a 5-year survival rate of less than 10% [3]. With the development of clinical research, stereotactic ablation brachytherapy (SABT) has been widely used in local treatment of tumors [4]. SABT involves implanting radioactive I-125 particles into tumors and using continuous gamma ray irradiation generated by the particles to kill tumor cells [5]. It has the characteristics of high dose and low segmentation and has been widely used in the treatment of various solid tumors [6]-[9]. A retrospective study showed that SABT treatment has significant survival benefits and good safety for patients with early-stage unresectable non-small cell lung cancer [10]. In addition, with the continuous development of immunotherapy, PACIFIC studies have shown that immune consolidation therapy after synchronous radiotherapy and chemotherapy can reduce local recurrence and improve survival in stage III NSCLC [11]. However, the efficacy of immunotherapy in stage I-II NSCLC is still unclear. A phase II clinical randomized controlled trial of SABR combined with immunotherapy (I-SABR) in early-stage NSCLC patients led by MD Anderson Cancer Center showed that compared with using SABR alone, I-SABR significantly improved the 4-year event free survival rate of patients with early-stage untreated or pulmonary parenchymal recurrent

lymph node negative NSCLC, and the toxicity was tolerable [12]. Some patients with early-stage NSCLC decline surgical treatment due to advanced age or refuse radiotherapy (including stereotactic body radiotherapy) owing to factors such as large tumor size, extensive pulmonary fibrosis, interstitial lung disease, excessive respiratory motion, or ultracentral tumor location. However, immunotherapy combined with CT-guided SABT (I-SABT) is rarely used for the treatment of early-stage tumors, and there are limited data on its efficacy in these cases. This study analyzed data from early-stage NSCLC patients receiving I-SABT to further clarify the clinical efficacy and safety, and provide evidence for real-world clinical practice.

2. Method

2.1. Study Subjects

Select early-stage NSCLC patients admitted to our oncology department from January 2019 to December 2023. Inclusion criteria: (1) Pathological diagnosis of NSCLC (squamous cell carcinoma or adenocarcinoma, excluding other types of NSCLC) at the first visit, with negative driver genes; (2) According to the UICC TNM 8th edition classification criteria, the stage was T1-3N0M0 (Ia IIb stage) (systematic evaluation methods include CT/MRI and/or PET-CT); (3) Not suitable for surgery or stereotactic radiotherapy, decided by a multidisciplinary consultation of experienced thoracic surgeons and oncologists for lung cancer; (4) I-SABT and immunotherapy were used as initial treatments; (5) Gross Tumor Volume(GTV) D90 (dose covering 90% of GTV) was ≥ 120 Gy during post-treatment evaluation. A total of 23 patients met these criteria and were included in this study. Perform I-SABT treatment after obtaining informed consent from the patient and their family members.

2.2. Methods

This study protocol was registered with the China Clinical Trial Registration Center (identifier: ChiCTR1800019571, Reg Date: 2018/11/18) and approved by the Medical Ethics Committee of Yueyang Central Hospital (identifier: 20181201). I-SABT was conducted by six oncologists (Jie Weng with 20 years of experience, Fang Wen with 15 years of experience Xiang Yao with 6 years of experience, Jia Xiao with 10 years of experience, Wangti Xie with 12 years of experience, and Yu Wu with 10 years of experience, all had the latest professional certificates). According to the Declaration of Helsinki (revised in 2013), all patients voluntarily participated in this clinical trial. A total of 23 patients met these criteria and were included in this study. Instruments and devices: (1) CT: HiSpeed (GE Healthcare). (2) I-125 seeds: Model 6711(Atomic High Tech Co.), half-life 59.4 days, dose rate constant 0.97 cGy/(h·U). (3) Implantation Device: Mick applicator (Mick Radio-Nuclear Instruments). (4) Treatment Planning System (TPS): KLSIRPS-3D (Beijing University of Aeronautics and Astronautics & Tianyi Technology Co, Ltd.) The source data for the planning system comes from official, supplementary, and

reported sources, as well as updates, of the American Association of Medical Physicists (AAPM) [13] [14]. Preoperative plan: An enhanced CT scan with a slice thickness of 5 mm will be performed within one week prior to implantation. The imaging data will be transmitted to the treatment planning system for preoperative evaluation and planning design. The treatment plan design includes outlining GTV and organs at risks (OARs); determining prescription dosage and particle radioactivity; determining the direction, distribution, and insertion depth of the puncture needle; determining the number of seeds; And simulating the spatial distribution of seeds. The prescription dose is set to ≥ 120 Gy based on experience. Particle implantation: Particle implantation was performed under 1% lidocaine infiltration anesthesia. Under CT guidance, insert a disposable particle implant needle into the target lesion. The needle tip was positioned 0.5cm away from the distal edge of the tumor. The space between each row of needles and each particle were 0.5 - 1.0 cm. After implantation, CT scan should be performed to ensure that the particle distribution conforms to the treatment plan. Radioactive seed implantation should be increased to avoid dose cold spots. Postoperative management and dose validation: All patients received anti-infective and hemostatic treatment after radioactive seed implantation, and underwent chest CT scan 24 hours after surgery to rule out complications such as pneumothorax and bleeding. Immunotherapy: 2 - 4 weeks after radioactive seed implantation; if there are no obvious contraindications for immunotherapy, (200mg/cycle for Sintilimab and 200 mg/cycle for Pembrolizumab monoclonal antibody, 1 cycle/3 weeks, lasting for 2 years) will be administered. If grade III-IV adverse events occur, the medication will be discontinued (**Figure 1**). The decision to reuse immunotherapy requires comprehensive evaluation by two senior clinical physicians in the oncology department.

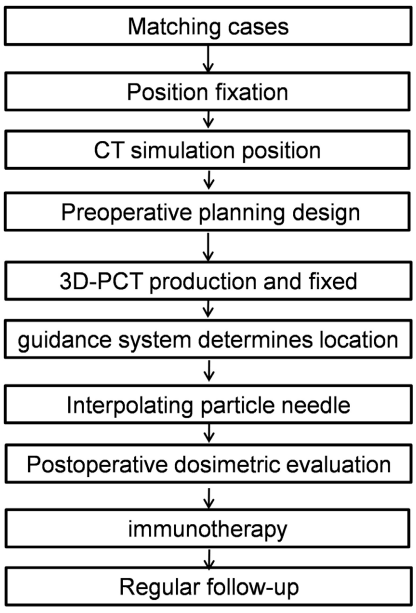

Figure 1. Flowchart of radioactive particle implantation and immunotherapy procedure.

2.3. Observation Indicators

The main outcome measure of this study is median event-free survival (mEFS), while the secondary outcome measures are disease control rate (DCR)and adverse events (AEs). The efficacy evaluation refers to RECIST version 1.1, which includes complete response (CR), partial response (PR), disease stability (SD), and disease progression (PD); DCR = (CR + PR + SD)/total number of cases × 100%, review head MRI, neck chest abdominal CT, and bone scan every 2 months for efficacy evaluation. Adverse reactions refer to the evaluation criteria for adverse reactions specified by the National Cancer Institute (NCI) in CTCAE version 5.0 [15]. Our department is one of the national clinical drug trial bases, and patient data is collected based on our registration and follow-up system. All patients were followed up by returning to the hospital for follow-up or phone calls. The evaluation factors that affect prognosis include gender, ECOG, stage, pathological type, smoking, lesion location, PD-L1 expression and GTV D90 (dose received by 90% GTV). Our department is one of the national clinical drug trial bases, and patient data is collected based on our registration and follow-up system. All patients were followed up by returning to the hospital for follow-up or phone calls.

2.4. Statistical Analysis

All data were analyzed using SPSS 25.0, with measurement data expressed as median (range) or mean ± standard deviation, count data expressed as absolute value and/or percentage, and inter-group rate comparison used chi-square test. Kaplan Meier method was used to calculate mEFS and DCR, Log rank test was used for univariate analysis, Cox regression analysis was used for multivariate analysis, and $P \leq 0.05$ was statistically significant.

3. Results

3.1. Efficacy Analysis

The patient characteristics are listed in Table 1. Median follow-up was 36.5 months (ranger: 17.2 - 77.5), with a median event-free survival (mEFS) of 49.2 months. The DCR for 1 year, 3 years, 4 years was 100.0%, 91.3% (21/23), 82.6% (19/23), respectively. Within 4 years, a total of 4 patients experienced treatment failure, including 1 case (4.3%) of local recurrence and 3 cases (13.0%) of distant metastasis.

Table 1. Patient characteristics.

Patient characteristics		n = 23
Sex	Man	16
	Female	7
Age	Median age (range)	51 (40 - 68)
ECOG	0 - 1	17
	2	6

Continued

Smoking (Y/N)	Y	14
	N	9
Lesion location	Right upper lung	10
	Right middle lung	3
	Right lower lung	2
	Left upper lung	5
	Left lower lung	3
Pathological type	Squamous cell carcinoma	17
	adenocarcinoma	6
Stage	T1NOMO	3
	T2NOMO	18
	*T3NOMO	2
PD-L1 expression (TPS)	<1%	7
	1% - 49%	12
	≥50%	4

Note: *T3, tumor size>5 cm and ≤ 7 cm.

3.2. Analysis of Factors Affecting the Results

Univariate analysis showed that factors significantly associated with better EFS included ECOG 0 - 1, smoking, left lobe lesions, GTV D90 ≥ 140 Gy, and PD-L1 expression ≥ 1% (all $P < 0.05$) (Table 2). If the dose was further subdivided, the 4-year EFS rates for patients with GTV D90 of 120 - 140 Gy, 140 - 160 Gy, >160 Gy was 75.6%, 80.5%, 95.8%, respectively ($P = 0.004$). Multivariate analysis showed that PD-L1 expression and GTV D90 were independent factors of EFS ($P < 0.05$) (Table 3).

3.3. Adverse Events Analysis

Procedure-related adverse events included pneumothorax, subcutaneous emphysema, hemothorax, hemoptysis, and seed displacement. Immune-related adverse events included fatigue, dermatitis, hypothyroidism/hyperthyroidism, and immune-mediated organ injury. In this study, procedure-related adverse events were predominantly Grade I-II: pneumothorax (10/23, 43.5%), hemorrhage (3/23, 13.0%), and pain (1/23, 4.3%). Pneumothorax incidence was significantly associated with patient positioning and the number of needles passes. Lateral decubitus positioning resulted in a higher pneumothorax rate (83.3%, 5/6) compared to supine/prone positioning (29.4%, 5/17; $P = 0.022$). >9 needle passes led to a higher pneumothorax rate (66.7%, 8/12) versus ≤9 passes (18.2%, 2/11; $P = 0.019$). Immune-related adverse events were limited to Grade I-II: fatigue (6/23, 26.1%), hypothyroidism (2/23, 8.6%), and immune-mediated pneumonitis (3/23, 13.0%). All events resolved with supportive care. No cases of radiation pneumonitis, dermatological reactions, esophagitis, myelitis, or other toxicities were observed.

Table 2. Univariate analysis of factors associated with EFS.

Factors	n	EFS (months)	p
Sex			0.409
Man	16	49.6	
Female	7	54.8	
ECOG			0.009
0 - 1	17	63.2	
2	6		
Smoking			0.006
Yes	14	46.9	
No	9	41.8	
T Stage			0.113
T1	3	39.4	
T2 - 3	20	52.9	
Lesion location			0.028
Left lung	8	59.6	
Right lung	15	46.7	
Pathological type			0.276
Squamous cell carcinoma	17	53.1	
adenocarcinoma	6	45.8	
GTV D90			0.007
<140 Gy	6	38.9	
≥140 Gy	17	55.5	
PD-L1 expression			0.004
<1%	7	39.4	
≥1%	16	56.3	

Table 3. Multivariate analysis of factors associated with EFS.

Factors	HR	95% CI	P
PD-L1 expression (≥1% vs <1%)	0.127	0.0340 - 0.471	0.002
GTV D90 (≥140 Gy vs <140 Gy)	0.199	0.060 - 0.653	0.008

4. Discussion

Surgery and radical external radiotherapy are the standard treatment options for T1-3N0M0 (Ia IIb) NSCLC [2]. At present, even without surgery or external radiation therapy, few clinical doctors choose SABT as a treatment method for early-stage NSCLC patients. Ji *et al.* [10] conducted a retrospective analysis of 99 early-stage NSCLC patients treated with SABT in 8 medical centers. The results showed that SABT had similar efficacy to SABR in the treatment of inoperable early-stage

NSCLC, and had lower radiation toxicity. SABT treatment has advantages such as high dose rate within the tumor, low dose rate in surrounding tissues, uniform dose distribution, simple operation process, one-time operation, and short hospitalization time. In addition, immunotherapy has been widely used in the treatment of various solid tumors, with good efficacy and controllable adverse reactions [11] [16]-[24]. The efficacy of immunotherapy in stage I-II NSCLC is not yet clear. Chang J Y *et al.* [12] included 141 patients with early-stage NSCLC and compared the efficacy of I-SABR and SABR, I-SABR significantly improved the 4-year EFS of untreated or pulmonary parenchymal recurrent lymph node negative NSCLC patients, and the toxicity was tolerable. Currently, the Chinese CSCO guidelines recommend SABR combined with immunotherapy for T1-3N0M0 (Ia IIb) NSCLC patients in Class II [25]. However, in practical clinical practice, there are still some early-stage NSCLC patients who cannot accept surgery or external radiation therapy, refuse external radiation therapy and chemotherapy, and accept I-SABT treatment. This study is a single arm study conducted by our tumor center, and we hope that the efficacy and toxicity data obtained from this study can help clinical doctors understand and evaluate the safety and efficacy of SABT treatment for early-stage NSCLC.

In this study, the DCR at 3 and 4 years were 91.3% and 82.6%, respectively. Ji *et al.* [10] reported 3- and 5-year DCRs of 77.5% and 75.7% with SABT in T1-3N0M0 NSCLC. Our higher DCR (91.3% at 3 years) likely reflects immunotherapy synergy, consistent with SABR outcomes (3-year DCR ≥ 90%) [26]-[28]. It can be considered that the DCR of I-SABT may be comparable to that of SABR. In this study, the prescription dose was controlled between 120 Gy and 180 Gy, and GTV D90 was an independent predictor of EFS. For patients with GTV D90 ≥ 140 Gy, the 4-year EFS over reached 82.6%, and no grade 3 or above toxic reactions occurred. ECOG score, smoking, lesion location, GTV D90, and PD-L1 expression were factors that affected survival. However, in multivariate analysis, only GTV D90 and PD-L1 expression were independent factors affecting survival, indicating that dose may play a more important role in survival than T stage. In the future, relevant dosimetric studies should be conducted to further clarify the optimal tumor control dose. In addition, in our study, smoking patients had better survival. Wang GZ *et al.* [29] showed that smoking can induce PD-L1 expression on lung epithelial cells in vitro and in vivo through aromatic hydrocarbon receptor-mediated cigarette smoke and carcinogenic benzo [a] pyrene, thereby enhancing the therapeutic effect of PD-L1 inhibitors. In our study, the mEFS was 49.2 months, and distant metastasis remained the main cause of failure (13.0%), which was similar to SABR. Chang JY *et al.* [12] founded that the occurrence of grade III or above AEs in early-stage NSCLC patients treated with I-SARB was fatigue, with an incidence rate of 15.2%, while no grade III or above AEs were observed in this study, which might be related to the small sample size.

Unlike external radiation therapy, SABT is an invasive surgery. In this study, 3D-printing non coplanar template (3D-PNCT) technology, CT guidance tech-

nology, and intraoperative navigation technology were used to achieve millimeter level treatment accuracy, but puncture related adverse reactions still occurred. Xie *et al.* [30] included 60 patients with pulmonary nodules who underwent puncture biopsy. They were randomly divided into two groups: 3D-printing coplanar template (3D-PCT) combined with CT guidance (n = 30) and CT guidance (n = 30). The most common puncture complication was pneumothorax, with incidence rates of 20% and 33.3%, respectively. The most common complication in this study was pneumothorax, with an incidence rate of 52.2%, which was related to the position and number of injections during treatment. The proportion of pneumothorax occurring in the lateral position was higher than that in previous studies [10], indicating that it is possible to avoid lateral positioning and reduce the number of injections. No grade III or above puncture related adverse reactions were observed. In this study, immune related adverse reactions were commonly fatigue, with an incidence rate of 26.1%. After symptomatic treatment, the condition improved and no radiation pneumonitis occurred. Overall, according to the data from this study, the efficacy and safety of I-SABT treatment were considered acceptable.

5. Conclusion

I-SABT achieves comparable oncologic outcomes to SABR and lower radiotoxicity in inoperable early-stage NSCLC, with reduced radiation-induced toxicity. Despite its unique advantages, I-SABT is not recommended as a superior treatment option to SABR due to invasive nature of procedure and high incidence of pneumothorax. If surgery or external radiation therapy cannot be used and standard radiotherapy and chemotherapy are refused, it can be considered as one of the treatment options after multidisciplinary consultation evaluation and informed consent. Especially for patients with prescription dose greater than 140 Gy and PD-L1 expression ≥ 1% may bring better results. With the more standardized application of radioactive seed implantation in clinical practice, if we can further improve surgical quality and reduce the incidence of complications, I-SABT is expected to become a competitive treatment method.

Abbreviations

SABT, stereotactic ablation brachytherapy; I-SABT, immunotherapy and stereotactic ablation brachytherapy; SABR, stereotactic ablation radiotherapy; I-SABR, immunotherapy and stereotactic ablation radiotherapy; NSCLC, non-small cell lung cancer; EFS, event free survival; DCR, disease control rate; AEs, adverse events; CR, complete response; PR, partial response; SD, disease stability; PD, disease progression.

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Author's Contribution

In 2019, our hospital established lung cancer MDT with the following members. Xie Wangti is responsible for designing research plans, implementing research, and writing papers; Yu Wu, Xiaoshan Cheng, Jianbing Hu, Jie Weng, Fang Wen, Jia Xiao, Rong Dang, Xiang Yao, Xianggan Huang, Yuan Liu and Dunqian Liu are responsible for collecting clinical data, proposing research ideas, providing technical guidance, imaging guidance, pathologic diagnosis and revising papers; Xiang Yao, Jia Xiao and Rong Dang are responsible for literature search and data analysis.

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Availability of Data and Materials

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

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee of Yueyang Central Hospital (20181218) on 2018/12/18.

Conflicts of Interest

This study was independently conducted by the undersigned author in accordance with the following statement of contribution, and no undue position or financial interest was accepted as a result of conducting the study, thereby re-evaluating the independence of the study sex and scientificity are guaranteed.

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