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ORIGINAL ARTICLE

# Impact of target area selection in $^{125}$Iodine seed brachytherapy on locoregional recurrence in patients with non-small cell lung cancer

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**Keywords**
$^{125}$Iodine radioactive seed; non-small cell lung cancer; radioactive seed brachytherapy; target area selection; treatment plan system (TPS).

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## Abstract

**Background:** Computed tomography (CT)-guided percutaneous implantation of $^{125}$Iodine radioactive seeds requires the precise arrangement of seeds by tumor shape. We tested whether selecting target areas, including subclinical areas around tumors, can influence locoregional recurrence in patients with non-small cell lung cancer (NSCLC).

**Method:** We divided 82 patients with NSCLC into two groups. Target areas in group 1 ($n$ = 40) were defined along tumor margins based on lung-window CT. Target areas in group 2 ($n$ = 42) were extended by 0.5 cm in all dimensions outside tumor margins. Preoperative plans for both groups were based on a treatment plan system, which guided $^{125}$I seed implantation. Six months later, patients underwent chest CT to evaluate treatment efficacy (per Response Evaluation Criteria in Solid Tumors version 1). We compared locoregional recurrences between the groups after a year of follow-up. We then used the treatment plan system to extend target areas for group 1 patients by 0.5 cm (defined as group 3 data) and compared these hypothetical group 3 planned seeds with the actual seed numbers used in group 1 patients.

**Results:** All patients successfully underwent implantation; none died during the follow-up period. Recurrence was significantly lower in group 2 than in group 1 ($P < 0.05$). Group 1 patients and group 3 data significantly differed in seed numbers ($P < 0.01$).

**Conclusion:** Our results imply that extending the implantation area for $^{125}$I seeds can decrease recurrence risk by eradicating cancerous lymph-duct blockades within the extended areas.

## Introduction

Radioactive seed brachytherapy (RSB) is an effective treatment approach for some inoperable solid tumors.[1,2] It is effectively radiotherapy with precision.[3] Implantation of radioactive seeds should allow the target area to reach prescribed dose (PD). The challenge with RSB is to ensure that edges of the target area reach PD, while normal tissues surrounding the target area receive minimum damage.[4] This requires careful planning of seed arrangements according to the shape of the tumor.[5] We hypothesized that target area selection influences the locoregional recurrence rate in patients with non-small-cell lung cancer (NSCLC). Our results suggest that by also targeting the subclinical area surrounding the tumor body, RSB can eradicate cancerous lymph-duct blockades within the extended area and decrease the risk of recurrence.[6,7]

## Methods

### Patients

We selected 82 patients with peripheral primary NSCLC who were admitted to our hospital between June 2011 and June 2014 for RSB. Subjects were mostly elderly patients

  

**Table 1** Patients' clinicopathological factors

| Factors | | Group 1 | Group 2 |
|---|---|---|---|
| Patient number | | 40 | 42 |
| Gender | Male | 29 | 32 |
| | Female | 11 | 10 |
| Age | | 55.9 ± 10.9 | 59.6 ± 13.1 |
| Pathology | Squamous carcinoma | 25 | 29 |
| | Adenocarcinoma | 15 | 13 |
| TNM | IIIa | 18 | 17 |
| | IIIb | 16 | 22 |
| | IV | 4 | 3 |
| Nidus diameter (cm) | | 2.6 ± 0.5 | 2.8 ± 0.7 |

TNM, tumor node metastasis.

with late-stage NSCLC (tumor node metastasis stage IIIb or IV), or had other co-morbidities that made them ineligible for pulmonary lobectomies. Target areas for RSB were determined based on lung-window computed tomography (CT). All patients were randomly divided into two groups (Table 1). In group 1 ($n$ = 40), RSB target areas were defined by tumor edges. In group 2 ($n$ = 42), RSB target areas were extended by 0.5 cm outside the tumor margins. Radioactive seeds of $^{125}$Iodine ($^{125}$I) were then implanted to the target areas.

## Inclusion criteria

We included patients: (i) whose diagnoses were confirmed via biopsy or cytopathology studies; (ii) with preoperative Karnofsky Performance Scale >60 (which predicts survival time >6 months); (iii) with no active systemic, pulmonary, or pericardial infections; (iv) who had not received any other treatment for NSCLC prior to seed implantation (including chemotherapy, radiotherapy, or surgery); and (v) who did not receive any other treatment to target cancer after seed implantation, until disease progression.

## Equipment used

Radioactive seeds were $^{125}$I with a half-life of 60.2 days. The radioactivity of these seeds is 0.8 mCi ($2.59 \times 10^7$Bq), the energy of gamma-ray radiation from the seed is 27–35 keV, and tissue penetration from the seed is around 1.7 cm in depth. The PD was 120 Gy.

The seeds and implantation equipment were obtained from Seeds Biological Pharmacy Ltd. (Tianjin, China) and the calibrator was obtained from the Image Processing Center of BeiHang University (Beijing,China). Single-use implantation needles were manufactured and disinfected in Shanghai. Other equipment used included the treatment plan system (TPS) developed by Prowess Inc. (Concord, CA, USA) and a GE 64-slice spiral CT scanner (GE Healthcare, Chicago, IL, USA).

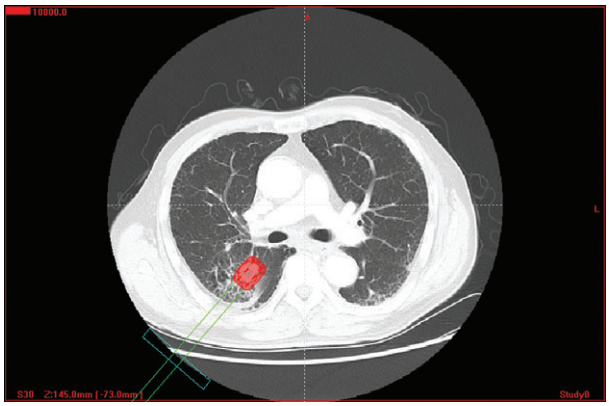

**Figure 1** In group 1, target areas were selected within tumor margins.

## Determining target areas

Patients in both groups underwent preoperative chest CT. Group 1 target areas were selected at the margins of the tumor (Fig 1), and group 2 at 0.5 cm outside the tumor margin, extended in all dimensions (Fig 2). Group 3 did not include actual patients, but was the data derived from extending the target areas of group 1 patients by 0.5 cm (as in group 2 patients) after the first procedures (Fig 3).

## Implantation and postoperative evaluation

Prescribed dosage, seed radioactivity, and other relevant information were entered into the TPS, which provided instructions such as the number of required seeds and

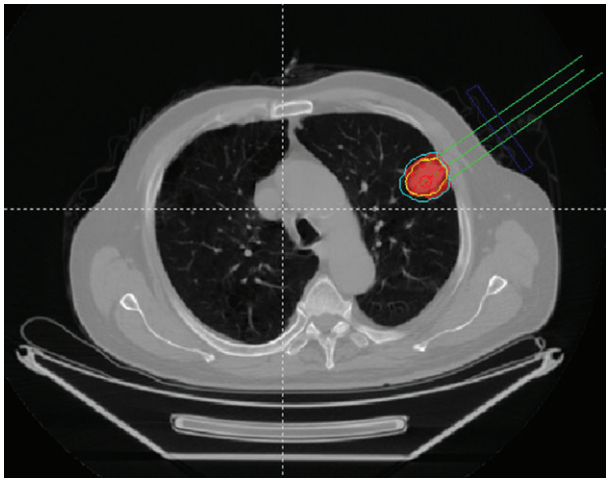

**Figure 2** In group 2, target areas were set to include tissue 0.5 cm outside the tumor margins, extended in all dimensions.

 

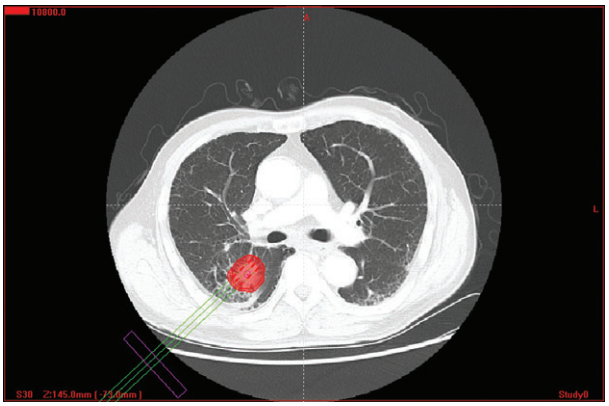

**Figure 3** Group 3 was based on data from patients in group 1. Target areas for group 3 were set to include tissue 0.5 cm outside the target areas for group 1.

implantation channels. Implantation procedures were guided by CT scan and were performed strictly according to the TPS output. Patients underwent post-procedure CT and the results were entered into TPS to evaluate the quality of the procedure (Figs 4,5). Group 3 used only the recalculated target areas for treatment plans (Fig 6). Data were compared and statistically analyzed between groups 1 and 2, and 1 and 3.

## Evaluation standard and follow-up

All patients received CT scans every three months after implantation to check for locoregional recurrence, and were followed up for one year. They underwent six-month post-procedural chest CTs to evaluate treatment efficacy according to Response Evaluation Criteria in Solid Tumors version 1.1.[8] Complete response (CR) was defined by the

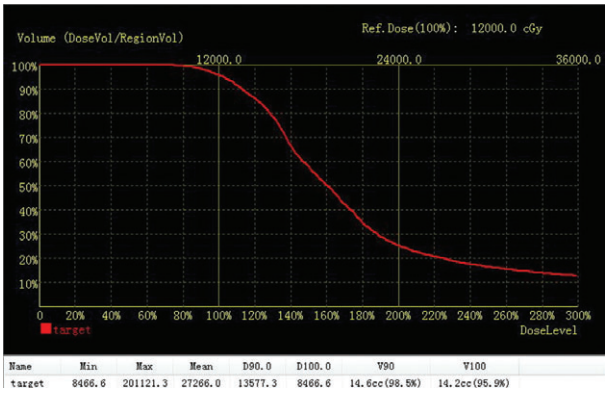


**Figure 4** Dose volume histogram of group 1 to evaluate the quality of the procedure. Prescribed dose (PD) = 120 Gy, radioactivity = 0.80 mCi, maximum dose = 2011.22 Gy, minimum dose = 84.67 Gy, average dose = 272.66 Gy, $D_{90}$ = 135.77 Gy, $D_{90}$ > PD, $V_{100}$ = 95.9%, seed number = 17.

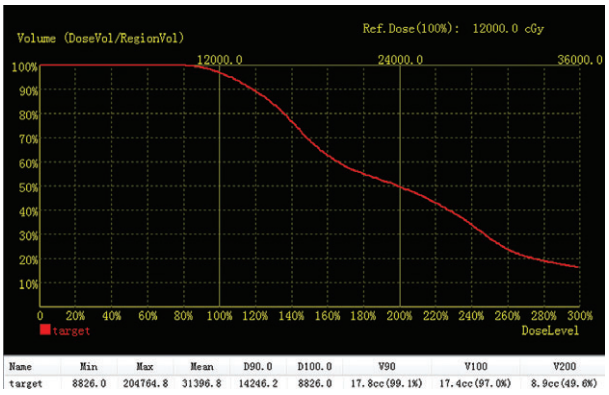


**Figure 5** Dose volume histogram of group 2 to evaluate the quality of the procedure. Prescribed dose (PD) = 120 Gy, radioactivity = 0.80 mCi, maximum dose = 2047.65 Gy, minimum dose = 88.26 Gy, average dose = 313.97 Gy, $D_{90}$ = 142.46 Gy, $D_{90}$ > PD, $V_{100}$ = 97.0%, seed number = 20.

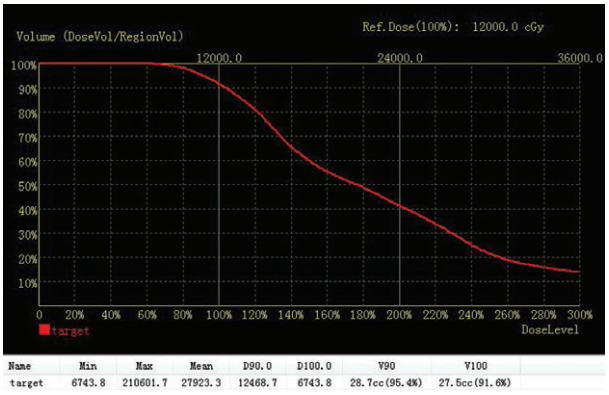


**Figure 6** Dose volume histogram of group 3, according to the preoperative treatment plan system; no implantation. Prescribed dose (PD) = 120 Gy, radioactivity = 0.80 mCi, maximum dose = 2106.02 Gy, minimum dose = 67.44 Gy, average dose = 279.23 Gy, $D_{90}$ = 124.69 Gy ($D_{90}$ > PD). $V_{100}$ = 91.6%, seed number = 25.

disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have decreased in the short axis to <10 mm. Partial response (PR) was defined by at least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. Progressive disease (PD) denoted at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum in the study (including the base line sum if that was the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (note, the appearance of one or more new lesions is also considered progression). Stable disease (SD) referred to insufficient reduction to qualify for PR or insufficient increase to qualify for PD, taking as reference the smallest sum diameters in the study.

  

**Table 2** Dosimetric parameters after implantation and efficacy analysis

| Parameters | | Group 1 | Group 2 | Group3† |
|---|---|---|---|---|
| Number of seeds | | 18.6 ± 7.3 | 20.2 ± 8.9 | 25.3 ± 6.1 |
| Dosimetric parameters | Prescribed dose (Gy)‡ | 120.0 | 120.0 | 120.0 |
| | $D_{90}$ (Gy) | 135.14 ± 9.26 | 143.95 ± 12.31 | 151.72 ± 11.04 |
| | $D_{100}$ (Gy) | 90.36 ± 15.83 | 95.12 ± 18.54 | 100.22 ± 14.39 |
| | $V_{100}$ | (93.16 ± 5.29)% | (97.58 ± 3.24)% | (93.95 ± 4.23)% |
| Locoregional recurrence§ | | 6(15%) | 2(4.8%) | |
| Efficacy analysis | CR | 8(20%) | 10(23.8%) | |
| | PR | 27(67.5%) | 26(61.9%) | |
| | SD | 3(7.5%) | 5(11.9%) | |
| | PD | 2(5%) | 1(2.4%) | |
| Effective rate¶ | CR + PR | 87.5% | 85.7% | |

†Group 3 data were not implemented, but were based on changing the treatment plan and dose volume histogram for group 1 to include tissue 0.5 cm outside the tumor margin (i.e. as the treatment areas for group 2 patients were calculated). ‡Gy is a radiation dosimetry indicator that shows per-unit mass of the affected object absorbed by the ionizing radiation, (1Gy = 1 J/kg). §Rates of locoregional recurrence between group 1 and 2 significantly differ ($t$ = 2.44; $P$ < 0.05). ¶Groups 1 and 2 did not significantly differ in their effective rates ($P$ > 0.05).
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

### Statistical analysis

SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Chi-squared and paired $t$ tests were performed. $P$ < 0.05 was considered significant.

## Results

All 82 patients underwent successful implantation procedures, with no serious complications (such as major blood vessel or main airway injuries). However, routine postoperative CT showed that 20 patients (24.4%) had pneumothorax, for which nine patients underwent tube thoracostomy and 11 underwent thoracocentesis. Fifteen patients (18.3%) had intrapulmonary hemorrhage –four with hemoptysis but without progressive hemothorax. After management, hemoptysis symptoms resolved and chest CT taken a month later showed blood reabsorption.

### Comparisons between groups 1 and 2.

Treatment efficacy for both groups was assessed from each patient's six-month post-procedural chest CT (Table 2).

Median treatment values for group 1 ($n$ = 40) were: number of seeds 18.6 ± 7.3, $D_{90}$ 135.14 ± 9.26 Gy; and $V_{100}$ 93.16 ± 5.29%. Outcomes included CR 20.0% (8/40), PR 67.5% (27/40), SD 7.5% (3/40), PD 5.0% (2/40), and effective rate 87.5% (Fig 7). Six group 1 patients developed locoregional recurrences.

Median treatment values in group 2 ($n$ = 42) were: seed numbers 20.2 ± 8.9, $D_{90}$ 143.95 ± 12.31 Gy, and $V_{100}$ 97.58 ± 3.24%. Outcomes were CR 23.8% (10/42), PR 61.9% (26/42), SD 11.9% (5/42), PD 2.4% (1/42), and effective rate 85.7% (Fig 8). Only two patients from group 2 had locoregional recurrences.

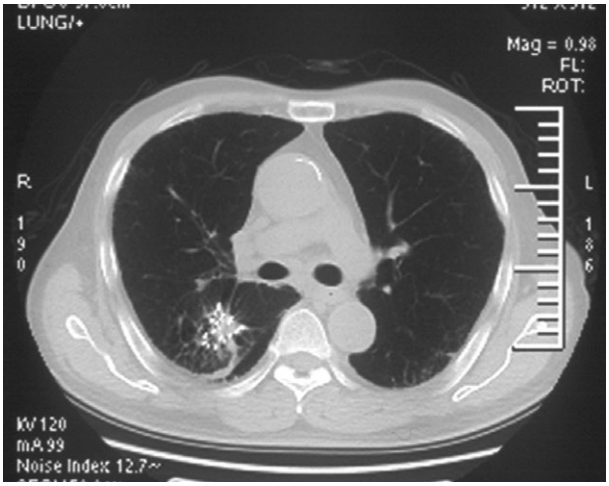


**Figure 7** Chest computed tomography scan of a patient in group 1, six months after his procedure, shows a more than 50% decrease in the diameters of the target lesions (partial response).

Although the effective rate did not significantly differ between the groups ($P$ > 0.05) group 1 had a significantly higher rate of locoregional recurrence than group 2 ($t$ = 2.44, P < 0.05).

### Comparison between groups 1 and 3

Median data for group 3 (which was not utilized, but was based on calculating an extended target area according to TPS and dose volume histogram) were: seed number 25.3 ± 6.1, $D_{90}$ 151.72 ± 11.04 Gy ($D_{90}$ > PD), and $V_{100}$ 93.95 ± 4.23%. The number of radioactive seeds planned for group 3 and actually used in group 1 significantly differed (paired $t$ test; $t$ = 4.269; $P$ < 0.01).

 

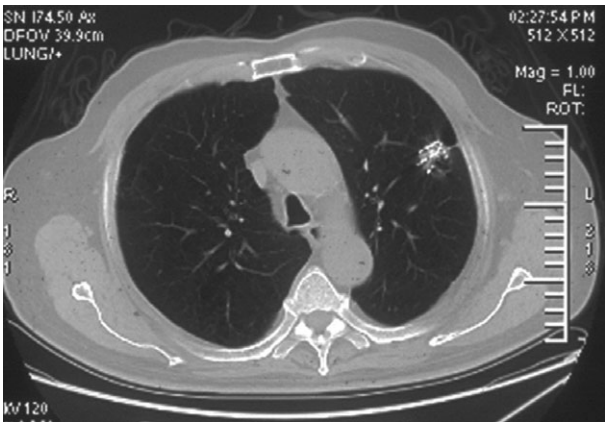


**Figure 8** Chest computed tomography scan of a patient in group 2, six months after his procedure, shows the target lesion has disappeared (complete response).

## Discussion

Non-small cell lung cancer is a highly malignant cancer. Peripheral primary NSCLC usually has non-specific symptoms and is typically detected during patients' regular health check-ups.

Using a three-dimensional directional technique, $^{125}$I radioactive seeds are planted into the tumor with CT guidance. These seeds are intended to be highly destructive to tumor tissues but not damaging to surrounding normal tissues. These seeds should limit the recurrence rate while protecting the normal tissue function.[9]

The American Brachytherapy Society guidelines suggest that all patients who receive radioactive seeds should have a preoperative plan in place to predict the distribution of the radiation dosage, and show dosage distribution around the tissue edges to ensure suitable seed arrangement and better likely outcomes.[5–7,10] Therefore, selection of target areas to reduce the risk of locoregional recurrence has become a major topic in clinical studies.

In this study, all patients had target areas within D100, which decreased to ≤40% at D200. This suggested that seeds were evenly distributed and that prescribed dosages were reached. Group 1, for whom target areas were set at tumor edges, had a higher locoregional recurrence rate than group 2, for whom target areas were extended to 0.5 cm outside the tumor ($P < 0.05$). When planning hypothetical seed arrangements for group 3, we found that the group 3 plans called for more radioactive seeds than were used in group 1 ($P < 0.01$). From this evidence, we concluded that extending the target area by 0.5 cm could reduce the recurrence rate. Because of resolution limitations, we were not able to observe local tumor infiltration via lung-window or mediastinal-window CT scans. Some micro-tumor blockade and small infiltrates can occur outside obvious tumor margins. Therefore, if we only include the tumor margins seen by the naked eye in target areas, we will inevitably miss small lesions, which will not receive effective dosages of radiation, and thus can create recurrences.

On the other hand, extending the target area by 0.5 cm can also lead to radiation damage. However, as tumor masses in peripheral NSCLC tend to be located away from the mediastinum, airways, heart, major vessels, or other major organs, the extra radiation damage is limited. In addition, TPS also helps to reduce radiation damage. TPS can predict dosage distribution, ensure effective coverage of the target area, and provide precise locations for input needles, so that surrounding tissues receive minimal damage. Finally, TPS can also evaluate radioactive dosage after the procedure.[11,12]

In conclusion, implantation plans before RSB procedures are essential as the careful selection of target areas significantly affects treatment outcome. Our findings indicate that extending the target area by 0.5 cm outside the tumor margin can reduce the risk of locoregional recurrence. However, CT-guided radioactive $^{125}$I seed implantation in malignant lung cancer is a relatively new therapeutic approach in China and insufficient evidence is available to guide our practice. For this treatment to reach its full potential, further clinical studies are needed to ensure its reliability and effectiveness.

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## Disclosure

No authors report any conflict of interest.

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