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# CT-guided iodine-125 brachytherapy as salvage therapy for recurrent mediastinal lymph node metastasis

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## Abstract

**Background:** The treatment of recurrent mediastinal lymph node metastasis (MLNMs) is challenging. We conducted this study to evaluate the effectiveness and safety of computed tomography (CT)-guided percutaneous iodine-125 brachytherapy for MLNMs.

**Methods:** We retrospectively analyzed 33 patients with recurrent MLNMs treated with CT-guided interstitial implantation of iodine-125 seeds. Regular contrast-enhanced CT was conducted to evaluate the tumor response. Follow-up survival, quality of life, and adverse events were analyzed.

**Results:** The number of implanted seeds was 16–85 (median, 40). The matched peripheral dose was 110–160 Gy. The patients were followed up for 5–24 months (median, 14 months). At the last follow-up or death, complete response to therapy was achieved in 11 patients (33.3%) and partial response in 18 patients (54.5%). The median survival time of this cohort was 15.2 months (95% confidence interval [CI], 9.9–20.5 months); the estimated one- and two-year survival rates were 68.6% and 31.1%, respectively. The Karnofsky performance score increased significantly after the procedure ($p = 0.007$). Pneumothorax with pulmonary compression of 30% to 40% occurred in five (15.2%) patients and was cured after drainage. No severe complications occurred.

**Conclusions:** CT-guided iodine-125 brachytherapy provided a safe and effective choice for recurrent mediastinal lymph node metastasis with significant local therapeutic effects and minor complications, especially for patients who were not eligible for surgical resection and had failed to benefit from systemic therapy.

KEYWORDS
brachytherapy, iodine-125, lymph node metastasis, salvage therapy

## INTRODUCTION

Thoracic cancer and other malignancies often lead to mediastinal lymph node metastasis (MLNMs).[1,2] Approximately 25%–35% of patients with early lung cancer who underwent surgical resection presented with MLNMs.[3] Recurrence is considered the major prognostic factor for patients with esophageal cancer, non-small cell lung cancer (NSCLC), and thyroid cancer.[2,4,5] Moreover, recurrent MLNMs are more likely to compress the proximal critical structures and cause severe symptoms such as pain, dysphagia, dyspnea, and superior vena cava syndrome.[6] Longer survival may be predicted after effective treatment of lymph node recurrence.[7] The treatment of MLNMs is challenging, given their specific location and the modality of previous multiple therapies, such as surgery, chemotherapy, and radiation.[2,8] Currently, there is no standard treatment approach for recurrent MLNMs. Surgical salvage can be infeasible due to the unstable physical condition of the patient, or the involvement of proximal critical organs.[9] Chemoradiotherapy is recommended by the National Comprehensive Cancer Network (NCCN) for recurrent MLNMs, but the efficacy is not promising.[10,11] Iodine-125 brachytherapy has been considered a standard therapy for prostate carcinoma and is also used to treat various tumors with adequate efficacy.[12–14] However, there are few reports regarding iodine-125 brachytherapy for recurrent MLNMs, and the clinical value of this therapy needs to be further evaluated. Therefore, we conducted this study to evaluate the effectiveness and safety of iodine-125 brachytherapy for the treatment of recurrent MLNMs to provide an alternative therapy for these difficult cases.

## METHODS

### Patients

This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Institutional Ethics Committee of our hospital. Written informed consent forms were provided and signed by the patients or their authorized trustees. A total of 62 patients were diagnosed with recurrent MLNMs between March 2017 and September 2019 in our hospital. Of the 62 patients, 15 patients declined iodine-125 brachytherapy. Seven patients were excluded because the primary tumor was considered uncontrollable ($n = 3$), or the patient had severe cardiac dysfunction ($n = 2$), uncontrolled coagulation dysfunction ($n = 1$), or a poor Karnofsky performance score ($n = 1$). Seven patients were lost to follow-up. A total of 33 patients were included in the final data analysis. All 33 patients (14 men and 19 women; mean age, 64 years; range, 43–81 years) had primary tumors of the following origins: lung cancer ($n = 18$), esophageal cancer ($n = 9$), hepatocellular carcinoma ($n = 4$), and gastric cancer ($n = 2$). All patients had surgical treatment to remove the primary tumor combined with systemic therapy (in 24 patients) or with radiotherapy plus systemic therapy (in nine patients). Symptoms reported included coughing in 16 patients, shortness of breath in 14 patients, pain in 11 patients, and hoarseness in five patients. Additionally, six patients presented with superior vena cava syndrome.

The initial diagnosis of MLNMs was made using contrast-enhanced computed tomography (CECT). The description of MLNMs was based on the international lymph node map of lung cancer developed by International Association for the Study of Lung Cancer (IASLC).[15] A total of 30 patients underwent CT-guided needle biopsy to obtain histological evidence of metastasis before undergoing iodine-125 brachytherapy. The other three patients refused biopsy and received iodine-125 brachytherapy based on diagnostic imaging and clinical features. The mean size of the MLNMs was 3.8 ± 1.5 cm (range, 1.4–7.4 cm) with the largest diameter. Baseline clinical characteristics of the 33 patients are shown in Table 1.

**TABLE 1** Baseline characteristics of the patients and mediastinal lymph node metastasis (MLNMs)

| Variables | Datum |
|---|---|
| Patients | 33 |
| Age (years) | |
| Mean | 53.6 ± 12.4 |
| Range | 33–75 |
| Sex | |
| Male | 14 (42.4%) |
| Female | 19 (57.6%) |
| Site of MLNMs | |
| Upper mediastinal | 13 (39.4%) |
| Paraaortic | 5 (15.2%) |
| Lower mediastinal | 11 (33.3%) |
| N1 | 4 (12.1%) |
| Original tumor | |
| Lung cancer | 18 (54.5%) |
| Esophageal cancer | 9 (27.3%) |
| Hepatocelluar carcinoma | 4 (12.1%) |
| Gastric cancer | 2 (6.1%) |
| Prior treatments | |
| Surgery | 33(100%) |
| System therapy | 33(100%) |
| Radiotherapy | 9(27.3%) |
| Tumor size (cm) | |
| Mean | 3.8 ± 1.5 |
| Range | 1.4–7.4 |
| Symptoms | |
| Cough | 16 (48.5%) |
| Shortness of breath | 14 (42.4%) |
| Pain | 11 (33.3%) |
| Superior vena cava syndrome | 6 (18.2%) |
| Hoarseness | 5 (15.2%) |

Inclusion criteria for this study included patients: (i) with solitary mediastinal lymph node metastasis with a short-axis diameter larger than 1.0 cm, (ii) no other evidence of recurrence, except the MLNMs, (iii) who were not eligible for surgery after a multidisciplinary comprehensive evaluation, and (iv) with MLNMs that were proven to have no response to systemic therapy (including chemotherapy, immunotherapy, or molecular targeted therapy) or radiation therapy.

Exclusion criteria for this study included patients with: (i) malignant tumors involving other systems or other sites (excluding MLNMs), (ii) an expected survival time ≤ 3 months, (iii) a Karnofsky Performance Score (KPS) < 60, (iv) severe dysfunction of the liver, kidney, or coagulation system, and (v) severe cardiovascular and/or cerebrovascular disease.

### Iodine-125 seeds

The iodine-125 seeds (Chinese Jaco Pharmaceuticals Co., Ltd.) used in this study were cylindrical and 4.5 mm long with a diameter of 0.8 mm. The seed activity was 0.6 mCi and had a half-life of 59.6 days. The tissue half-value layer was 1.7 cm. The seeds continued to decay and release low-dose γ-rays (5% of 35 keV) to target the tumor. About 93%–97% of the energy of the seed was delivered into the tumor after 8–10 months.

## Preoperative planning

Contrast-enhanced CT (General Electric Medical System) was performed of the area of interest less than seven days before seed implantation. A treatment planning system (TPS) (Beijing University of Aeronautics and Astronautics) was used to develop a treatment plan. A specialized medical physicist and radiologist delineated the planning target volume (PTV) of target MLNMs together in every slice. PTV was obtained by applying 5 mm of expansion to the gross target volume (GTV). The matched peripheral dose (MPD) was prescribed as 110–160 Gy. For the nine patients who had prior radiotherapy, such factors as time interval since previous radiotherapy and previous dose to the adjacent risk organs were considered in the TPS plan. If the interval was less than three months, previous dose and iodine-125 brachytherapy dose were converted to biologically effective doses (BEDs). For external radiotherapy, BED was calculated according to the formula: $BED = Nd[1 + d/(\alpha/\beta)]$; for iodine-125 brachytherapy, BED was calculated according to the formula: $BED = D[1 + R_0/(\mu + \lambda)\ (\alpha/\beta)]$. In these formulas, N is number of fractions, d is dose/ fraction (Gy), D is total dose, $R_0$ is initial dose rate, μ is cell repair constant, λ is radionuclide decay constant; assuming α/β value of 10 for acute toxicities, and assuming α/β value of 3.0 for late toxicities. The TPS plan was made based on the summation of BEDs. Dose constraints of normal tissue were based on the Radiation Therapy Oncology Group (RTOG) 0236 and 0813 guidelines. The information including the dose-volume histogram (DVH), number of seeds implanted, and isodose curves was acquired from the TPS. The entry position and approach of the applicator were determined based on the location of the MLNMs in order to avoid injury to the surrounding vital tissue.

## Procedure

The procedures were performed under intravenous anesthesia with dexmedetomidine combined with local anesthesia using lidocaine. The appropriate position of the patient was fixed based on the preoperative plan using a vacuum cushion. The entry site of the applicator was marked according to the plan. Then, 18-gauge coaxial needles (Hakko Co., Ltd.) were punctured into the target, and the tips were inserted into the distal edge of the lesion under CT guidance. Iodine-125 seeds were implanted into the tumor with a clip implant applicator (Chinese Jaco Pharmaceuticals Co., Ltd.) in compliance with the TPS plan. Repeat CT scans were performed immediately after the implantation to verify the placement and dose distribution and ensure that no complications occurred. Supplementary seeds were implanted into the cold area where the dose was measured as inadequate. All iodine-125 brachytherapy was carried out by the interventional radiologists who had more than 10 years of experience. After implantation, the patients were clothed with a radiation protection pad (containing 0.25 mmPb) and transferred to a ward separate from other wards. These patients were required to be more than 75 cm away from the vulnerable population, including pregnant women and children for six months after being discharged.[16]

## Follow-up and study endpoints

Follow-up CECT was conducted at one month after the procedure, three months after the procedure, and then every three months thereafter. The primary endpoint of this study was the objective response rate (ORR). The secondary endpoints included the clinical benefit response (CBR), overall survival (OS), and incidence of adverse events. The objective response rate (ORR) was defined as the proportion of patients achieving complete response (CR) and partial response (PR). The therapeutic effectiveness of iodine-125 brachytherapy was assessed based on the Response Evaluation Criteria in Solid Tumors Version 1.1.[17] The CBR was evaluated according to the KPS score, with a positive CBR indicating an improvement in the patient's functional impairment.[18] Overall survival (OS) was defined as the time between the date of iodine-125 brachytherapy and the last follow-up or death. Adverse reactions were assessed according to the new classification of the Society of Interventional Radiology.[19]

## Statistical analysis

The data analysis was performed using SPSS (version 24; SPSS). Continuous variables were expressed as the mean ± SD. Comparisons of KPS before and after the procedure were performed using the Mann–Whitney U test. Survival analysis was assessed by Kaplan–Meier methods. A *p*-value $<0.05$ was considered to be of statistical significance.

# RESULTS

## Iodine-125 implantation and dosimetry description

A total of 30 patients underwent one brachytherapy session followed by a postoperative dose evaluation. The other three patients received supplemental seed implantation to meet the TPS criteria. A median number of 40 (range 16–85) iodine-125 seeds were implanted with a median MPD of 130 Gy (range 110–160 Gy) and median dose 90 (D90, minimum absorbed dose at 90% target volume) of 146 Gy (range, 118.7–155.3 Gy).

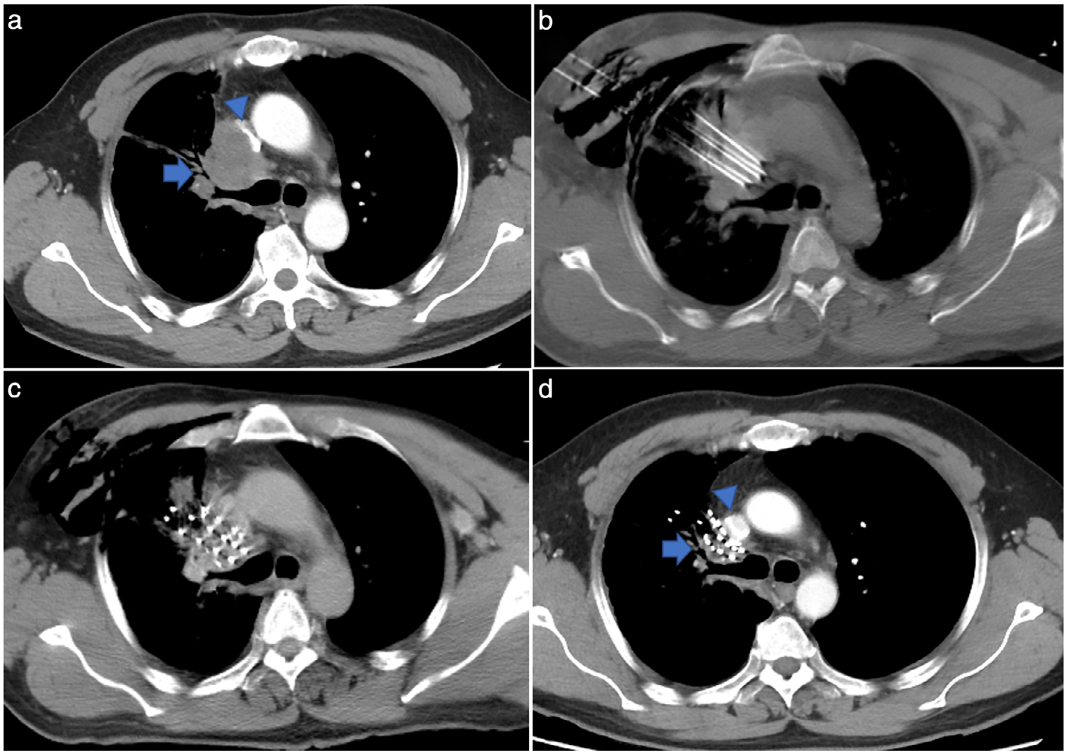


**FIGURE 1** Case 1. (a) Contrast enhanced computed tomography (CT) showed mediastinal metastatic lymph node recurrence from lung cancer after surgery and systemic therapy. The superior vena cava (triangle) and right bronchus (arrow) were compressed. (b) Multiple 18 gauge needles were inserted into the tumor accurately under CT guidance. (c) Iodine-125 seeds were implanted into the tumor with satisfactory distribution. (d) A CT scan six months after brachytherapy showed that the tumor had disappeared and the compressed superior vena cava (triangle) and right bronchus (arrow) were relieved

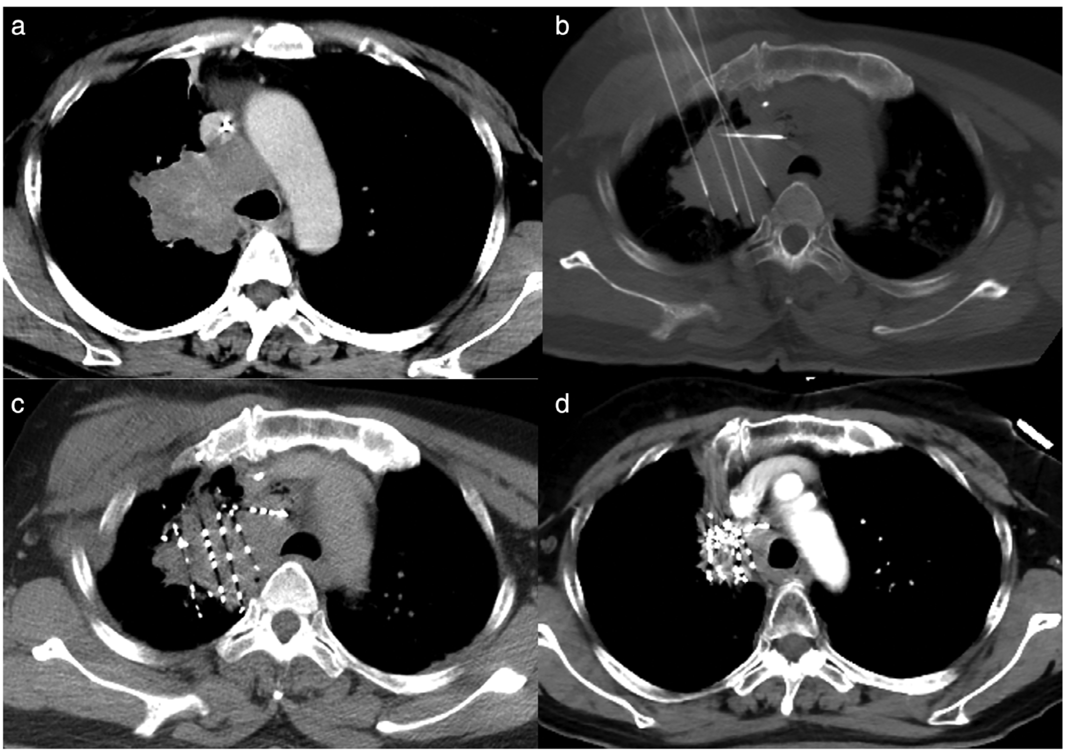


**FIGURE 2** Case 2. (a) CT image showed recurrence of mediastinal metastatic lymph nodes. (b) Multiple 18 gauge needles were inserted into the lesion. (c) Iodine-125 seeds were implanted into tumors via the 18 gauge needles. (d) Follow-up CT scan six months later showed that the metastatic lymph nodes had disappeared and the iodine-125 seeds were gathered together

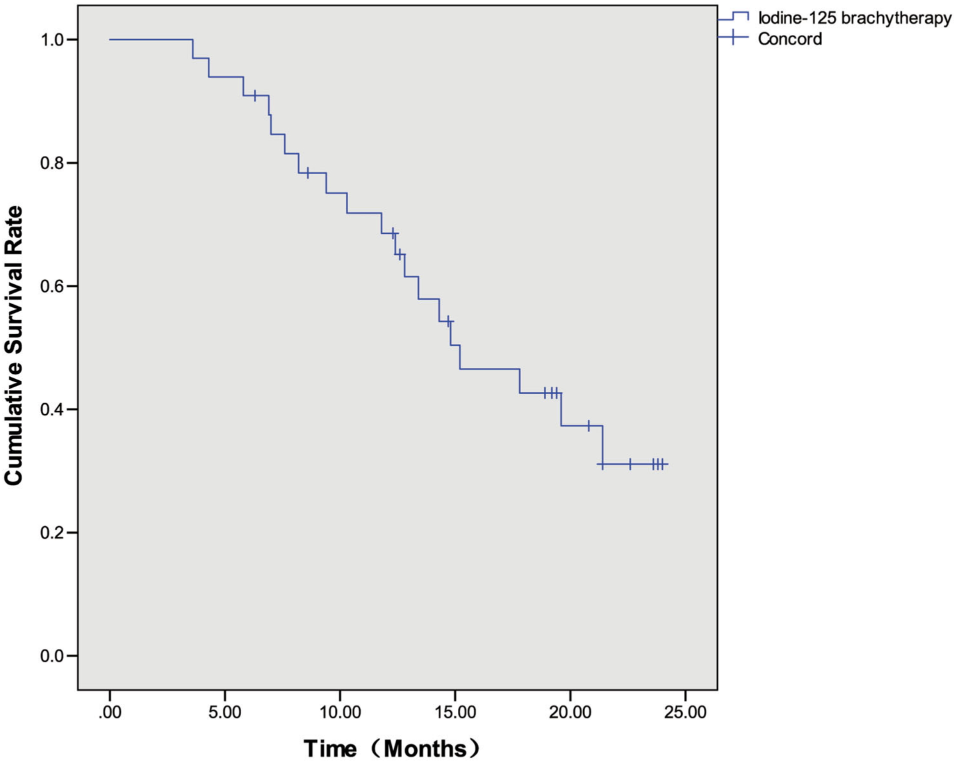


**FIGURE 3** Kaplan–Meier overall survival of iodine-125 seeds brachytherapy for recurrent mediastinal lymph node metastasis. The median survival time was 15.2 months (95% CI: 9.9–20.5 months); the estimated one-year and two-year survival rates were 68.6% and 31.1%, respectively

**TABLE 2** Change of Karnofsky physical score

| | Karnofsky physical score | | | | | |
|---|---|---|---|---|---|---|
| | 100 | 90 | 80 | 70 | 60 | *p*-value |
| Before | 0 (0/33) | 6 (2/33) | 21 (7/33) | 45 (15/33) | 27 (9/33) | 0.007* |
| After | 0 (0/33) | 21 (7/33) | 42 (14/33) | 21 (7/33) | 15 (5/33) | |

Note: Data are presented as % (cases).
*Mann–Whitney U test.

## Tumor response and overall survival

The patients were followed for 5–24 months (median, 14 months). At the last follow-up or death, complete response was achieved in 11 patients (33.3%) (Figures 1 and 2) and partial response in 18 patients (54.5%). The ORR in this group was 87.8%. A total of 19 patients died during follow-up, with a median time from brachytherapy to death of 11.8 months (3.6–21.4 months). The main cause of death was multiple metastases. The median survival time of this cohort was 15.2 months (95% CI: 9.9–20.5 months); the estimated one- and two-year survival rates were 68.6% and 31.1%, respectively (Figure 3).

## Clinical benefit response

Patients obtained a varying degree of alleviation of symptoms in cough (75%, 12/16), shortness of breath (71.4%, 11/14), pain (63.6%, 7/11), those relating to superior vena cava syndrome (66.7%, 4/6), and hoarseness (40%, 2/5). The KPS increased significantly after iodine-125 brachytherapy, which indicated that the patients had a positive CBR ($P = 0.007$) (Table 2).

**TABLE 3** Adverse events related to iodine-125 brachytherapy for mediastinal lymph node metastasis (MLNMs)

| Complications | No. of complications |
|---|---|
| Mild adverse events | |
| Pneumothorax | 11 (33.3%) |
| Hemoptysis | 12 (36.4%) |
| Local hematoma | 4 (12.1%) |
| Seeds displacement | 2 (6.1%) |
| Moderate adverse events | |
| Pneumothorax | 5 (15.2%) |
| Severe adverse events | 0 |
| Disabling adverse events | 0 |
| Deaths | 0 |

## Adverse events

Mild and moderate pneumothorax occurred in 16 (48.5%) patients. A total of 11 (33.3%) of the 16 patients had mild pneumothorax and did not need therapy. The other five (15.2%) patients with mild cases were cured after drainage. Mild hemoptysis occurred in 12 (36.4%) patients but had resolved two days after the procedure without intervention. Mild local hematoma in the lung related to needle puncture occurred in four (12.1%) patients. Two (6.1%) patients presented with seed displacement. No radiation pneumonitis or esophagitis was observed. No severe complications such as significant hemorrhaging occurred. The aforementioned adverse events related to iodine-125 brachytherapy are summarized in Table 3.

# DISCUSSION

Mediastinal lymph nodes are common sites of metastases for malignant tumors.[3] A total of 79 % of lung cancer cases are diagnosed after regional lymph nodes or distal organ involvement.[20] MLNMs are the major form of locoregional recurrence and are independent predictors of overall survival.[7,21] The standard therapy for recurrent MLNMs recommended by NCCN guidelines is concurrent chemoradiation and systemic therapy.[22] However, for patients in which chemoradiotherapy and systemic therapy were unsuccessful or could not be tolerated, no clear effective treatment option has existed, other than supportive treatment. In the present prospective study, CT-guided iodine-125 brachytherapy achieved encouraging results in regards to both efficacy and safety for this patient group.

Iodine-125 brachytherapy was first utilized for head and neck tumors in 2002 and is mainly used to treat prostate cancer in the West.[23] Evidence of clinical value of this therapy has emerged rapidly in the treatment of lung cancer, pancreatic cancer, liver tumors, and other solid tumors.[13,14,24] A significant advantage of iodine-125 brachytherapy compared with external radiotherapy is the higher dose delivered to the tumor, which is associated with a better local control rate. It is considered to be an ablative dose if the biological effective dose is more than 100 Gy.[25] In this study, MPD of 130 Gy and median D90 of 146 Gy were achieved with iodine-125 brachytherapy for MLNMs. An encouraging local control rate was found with an ORR of 87.8% in these 33 patients, which was better than that reported using conventional radiotherapy.[26] Moreover, our results appeared to be in line with those of previous studies. Lin et al. treated 13 patients with recurrent MLNMs using iodine-125 brachytherapy, and the ORR was 100% (CR 85.7%, PR 14.3%).[27] Gao et al.[28] and Liu et al.[29] also showed promising therapeutic effects for the treatment of MLNMs using this therapy. Wang et al. found that iodine-125 implantation provides a better local control rate and quality compared with second-line chemotherapy for NSCLC after failure of first-line chemotherapy.[30] We believe that brachytherapy may be an alternative therapeutic modality that would provide a remarkable improvement for MLNMs, especially for patients who are ineligible for surgery or continued to progress after system therapy or radiation therapy.

A total of 22 of these 33 patients died during follow-up in this study, although the ORR was high. The main cause of death was multiple metastases. The reason for this could be that iodine-125 brachytherapy was a local treatment modality, but was not systemically treating other malignancies. Concomitant or sequential effective systemic therapy should be applied to improve overall survival. Potentially synergistic effects of iodine-125 brachytherapy and other therapies is possible. Li et al. found that the combination of iodine-125 and lobaplatin could be a better therapy for hepatocellular carcinoma.[31] A meta-analysis including 1 188 cases showed that the combination of iodine-125 brachytherapy and chemotherapy significantly improved the OS and clinical efficacy for advanced NSCLC with no difference in complications.[32] Sui et al. reported encouraging results using iodine-125 brachytherapy and anti-PD-1 antibodies for lung cancer.[33]

The key to success of iodine-125 brachytherapy for MLNMs was the accurate placement of the needles and seeds according to the preoperative plan. The complex mediastinal anatomy, especially the vital organs, such as the aorta, pulmonary artery and vein, and esophagus, must be taken into account when planning the puncture path and performing the procedure.

Unintended injury of these vital structures could lead to serious complications such as a massive hemorrhage. We performed iodine-125 seed implantation under CT guidance, which helped display the tumor volume, the surrounding vital organs, the needles, and the distribution of iodine-125 seeds clearly, allowing accurate insertion or adjustment of needles, proper implantation of the seeds, and reduction of the risk of injury to important organs. For MLNMs adjacent to the esophagus, the stomach tube was intubated to distinguish the tumor from normal tissue. Tissue deformation and tumor distortion during needle insertion and retraction should be concerned to prevent misplaced seeds.[34]

Pneumothorax and hemoptysis are common adverse events in transpulmonary puncture procedures. Haramati et al. performed CT-guided needle biopsy through the lung in 79 cases and pneumothorax occurred in 36 (46%) cases.[35] The complication rate of pneumothorax in this study was 48.5% (16/33). However, 68.8% (11/16) of the pneumothorax was mild and the fluid absorbed by itself. Hemoptysis and local hematoma were attributed to lung injury, which occurred with numerous punctures through the lungs. No radiation injury complications such as radiation pneumonia and/or esophagitis were found in any of the included patients, which was consistent with the results reported by Gao et al.[28] We encountered no massive bleeding or other severe complications during the procedure and follow-up, indicating the adequate safety of this procedure.

Common symptoms for patients with MLNMs include cough, shortness of breath, pain, superior vena cava syndrome, and hoarseness. These symptoms can seriously affect the patient's quality of life. It has been reported that these symptoms may be improved with palliative radiotherapy.[36] In our study, more than half of the patients acquired positive CBR and continuous alleviation of symptoms during follow-up, which indicated that iodine-125 brachytherapy offered substantial control of MLNMs. This finding is consistent with the results reported by Wang et al. who also used iodine-125 seed implantation for lymph node metastasis.[37]

This study had several limitations. First, the number of patients included was relatively small. A study of a larger cohort should be conducted in the future to confirm our findings. Finally, this study is a single-arm study with a lack of parallel controls, and only external historical data can be compared to evaluate the safety and efficacy of this method. It is difficult to obtain historical research data that is completely consistent with the current study design, resulting in a bias in evaluating the results.

In conclusion, CT-guided iodine-125 brachytherapy provided a safe and effective choice for recurrent MLNMs with significant local therapeutic effect and minor complications. This therapy may especially benefit patients who are not eligible for surgical resection and/or fail to benefit from systemic therapy.

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## CONFLICT OF INTEREST

No authors report any conflict of interest.

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## REFERENCES

1. Mahon TG, Libshitz HI. Mediastinal metastases of infradiaphragmatic malignancies. Eur J Radiol. 1992;15:130–4.
2. Casali C, Stefani A, Natali P, Rossi G, Morandi U. Prognostic factors in surgically resected N2 non-small cell lung cancer: the importance of patterns of mediastinal lymph nodes metastases. Eur J Cardiothorac Surg. 2005;28:33–8.
3. Sakao Y, Miyamoto H, Yamazaki A, Ou S, Shiomi K, Sonobe S, et al. The spread of metastatic lymph nodes to the mediastinum from left upper lobe cancer: results of superior mediastinal nodal dissection through a median sternotomy. Eur J Cardiothorac Surg. 2006; 30:543–7.
4. Mariette C, Balon JM, Piessen G, Fabre S, Van Seuningen I, Triboulet JP. Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease. Cancer. 2003;97:1616–23.
5. Moritani S. Impact of superior mediastinal metastasis on the prognosis of papillary thyroid carcinoma. Endocr J. 2016;63:349–57.
6. Noble J, Ellis PM, Mackay JA, Evans WK. Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: a systematic review and practice guideline. J Thorac Oncol. 2006; 1:1042–58.
7. Nakagawa S, Kanda T, Kosugi S, Ohashi M, Suzuki T, Hatakeyama K. Recurrence pattern of squamous cell carcinoma of the thoracic esophagus after extended radical esophagectomy with three-field lymphadenectomy. J Am Coll Surg. 2004;198:205–11.
8. Li H, Pan Y, Wang R, Li Y, Sun Y, Chen H. Response to crizotinib observed in metastatic mediastinum lymph node from a non-small cell lung cancer patient harboring EZR-ROS1 fusion. J Cancer Res Clin Oncol. 2015;141:185–7.
9. Salah S, Tanvetyanon T, Abbasi S. Metastatectomy for extra-cranial extra-adrenal non-small cell lung cancer solitary metastases: systematic review and analysis of reported cases. Lung Cancer. 2012;75:9–14.
10. Tieu BH, Sanborn RE, Thomas CR Jr. Neoadjuvant therapy for resectable non-small cell lung cancer with mediastinal lymph node involvement. Thorac Surg Clin. 2008;18:403–15.
11. Sonobe M, Yamada T, Sato M, Menju T, Aoyama A, Sato T, et al. Identification of subsets of patients with favorable prognosis after recurrence in completely resected non-small cell lung cancer. Ann Surg Oncol. 2014;21:2546–54.
12. Yorozu A, Kuroiwa N, Takahashi A, Toya K, Saito S, Nishiyama T, et al. Permanent prostate brachytherapy with or without supplemental external beam radiotherapy as practiced in Japan: outcomes of 1300 patients. Brachytherapy. 2015;14:111–7.
13. Song Z, Ye J, Wang Y, Li Y, Wang W. Computed tomography-guided iodine-125 brachytherapy for unresectable hepatocellular carcinoma. J Cancer Res Ther. 2019;15:1553–60.
14. Wang W, Li P, Wang Y, Liu B, Li Y. Percutaneous stenting and chemotherapy for unresectable pancreatic cancer: comparison of irradiation stents vs conventional metal stents. Pancreatology. 2019;19:957–62.
15. Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol. 2009; 4:568–77.
16. Zhuo SQ, Chen L, Zhang FJ, Zhao M, Zhang L, Liu J, et al. Environmental radiation dose monitor after 125I radioactive seed implantation. Ai Zheng. 2007;26:666–8.
17. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.
18. Hwang SS, Scott CB, Chang VT, Cogswell J, Srinivas S, Kasimis B. Prediction of survival for advanced cancer patients by recursive partitioning analysis: role of Karnofsky performance status, quality of life, and symptom distress. Cancer Invest. 2004;22:678–87.
19. Khalilzadeh O, Baerlocher MO, Shyn PB, Connolly BL, Devan AM, Morris CS, et al. Proposal of a new adverse event classification by the Society of Interventional Radiology Standards of practice committee. J Vasc Interv Radiol. 2017;28:1432–7.e1433.
20. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al. SEER cancer statistics review, 1975-2016. Bethesda, MD: National Cancer Institute; 2019. https://seer.cancer.gov/csr/1975_2016/.
21. Yang MZ, Hou X, Liang RB, Lai RC, Yang J, Li S, et al. The incidence and distribution of mediastinal lymph node metastasis and its impact on survival in patients with non-small-cell lung cancers 3 cm or less: data from 2292 cases. Eur J Cardiothorac Surg. 2019;56:159–66.
22. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Non-small cell lung cancer, Version 8.2020. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

23. Jeremic B, Shibamoto Y, Milicic B, Milisavljevic S, Nikolic N, Dagovic A, et al. External beam radiation therapy alone for loco-regional recurrence of non-small-cell lung cancer after complete resection. Lung Cancer. 1999;23:135–42.
24. Chen C, Wang W, Yu Z, Tian S, Li Y, Wang Y. Combination of computed tomography-guided iodine-125 brachytherapy and bronchial arterial chemoembolization for locally advanced stage III non-small cell lung cancer after failure of concurrent chemoradiotherapy. Lung Cancer. 2020;146:290–6.
25. Chang JY, Cox JD. Improving radiation conformality in the treatment of non-small cell lung cancer. Semin Radiat Oncol. 2010;20:171–7.
26. Kelsey CR, Clough RW, Marks LB. Local recurrence following initial resection of NSCLC: salvage is possible with radiation therapy. Cancer J. 2006;12:283–8.
27. 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;82:2061–6.
28. Gao F, Li C, Gu Y, Huang J, Wu P. CT-guided 125I brachytherapy for mediastinal metastatic lymph nodes recurrence from esophageal carcinoma: effectiveness and safety in 16 patients. Eur J Radiol. 2013;82:e70–5.
29. Liu B, Li Y, Wang Y, Wang W, Wang L, Hertzanu Y, et al. (125) iodine brachytherapy via a trans-superior vena cava approach in patients with metastases in middle mediastinal lymph nodes: a novel approach. Asia Pac J Clin Oncol. 2017;13:219–25.
30. Wang H, Lu J, Zheng XT, Zha JH, Jing WD, Wang Y, et al. Oligorecurrence non-small cell lung cancer after failure of first-line chemotherapy: computed tomography-guided (125)I seed implantation vs. second-line chemotherapy. Front Oncol. 2020;10:470.
31. Li D, Wang WJ, Wang YZ, Wang YB, Li YL. Lobaplatin promotes (125)I-induced apoptosis and inhibition of proliferation in hepatocellular carcinoma by upregulating PERK-eIF2α-ATF4-CHOP pathway. Cell Death Dis. 2019;10:744.
32. Zhang W, Li J, Li R, Zhang Y, Han M, Ma W. Efficacy and safety of iodine-125 radioactive seeds brachytherapy for advanced non-small cell lung cancer-a meta-analysis. Brachytherapy. 2018;17:439–48.
33. Sui A, Song H, Yu H, Zhang H, Hu Q, Lei Y, et al. Clinical application of iodine-125 seed brachytherapy combined with anti-PD-1 antibodies in the treatment of lung cancer. Clin Ther. 2020;42:1612–6.
34. Roberson PL, Narayana V, McShan DL, Winfield RJ, McLaughlin PW. Source placement error for permanent implant of the prostate. Med Phys. 1997;24:251–7.
35. Haramati LB, Austin JH. Complications after CT-guided needle biopsy through aerated versus nonaerated lung. Radiology. 1991; 181:778.
36. Gressen EL, Werner-Wasik M, Cohn J, Topham A, Curran WJ Jr. Thoracic reirradiation for symptomatic relief after prior radiotherapeutic management for lung cancer. Am J Clin Oncol. 2000;23: 160–3.
37. Wang Z, Lu J, Gong J, Zhang L, Xu Y, Song S, et al. CT-guided radioactive $^{125}$I seed implantation therapy of symptomatic retroperitoneal lymph node metastases. Cardiovasc Intervent Radiol. 2014;37:125–31.


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