ORIGINAL ARTICLE

Salvage treatment of NSCLC recurrence after first-line chemotherapy failure: Iodine-125 seed brachytherapy or microwave ablation?

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Abstract

Background: Salvage treatments for recurrent NSCLC after first-line chemotherapy remain challenging. This study was conducted to evaluate the clinical value of microwave ablation (MWA) and iodine-125 brachytherapy, including overall survival (OS), disease free survival (DFS), local control, hospital stay, and health economics.

Methods: The data of 51 and 32 patients who were treated with MWA and brachytherapy was retrospectively analyzed. The number of lesions was limited up to two, with a diameter <4 cm and patients diagnosed with unilateral lung disease. Peripheral tumors were treated with MWA, while lesions close to the hilum were treated with brachytherapy. Contrast-enhanced CT, blood cell count, coagulation function, liver & kidney function and tumor markers were performed for two years, with complications calculated. OS, DFS, local control rate, toxicity, hospital stay and expense were recorded.

Results: The one and two-year OS rates were 96.08% and 92.16% versus 96.88% and 90.62% in the MWA and brachytherapy groups, respectively. The one and two-year DFS rates were 92.16% and 76.47% versus 93.75% and 78.13%, respectively. No significant differences were observed in log-rank analysis between the groups. Local control rates at six and 12 months were 100% and 96.08% versus 100% and 96.88%, while incidences of pleural effusion were 3.92% and 3.13%, respectively ($P < 0.05$). Medical cost was 3356.73 ± 206.87 and 6714.28 ± 35.43 U.S. dollars ($P = 0.014$).

Conclusion: MWA and brachytherapy are effective and safe options for the treatment of NSCLC recurrence after first-line chemotherapy. Which modality should be considered is dependent upon tumor location, tumor size and experience of specialists.

Introduction

As one of the leading malignancies worldwide, lung cancer causes many deaths both in men and women.[1] In 2012, there were 226 150 cases of lung and bronchus cancer and 160 340 related deaths estimated in the United States.[2] Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer cases.[3] Surgery is considered as standard therapy for patients with stage I or II NSCLC. For patients with recurrence after surgical resection or other radical treatments, third-generation chemotherapeutic agents including vinorelbine, gemcitabine, paclitaxel, and docetaxel, combined with platinum is recommended.[4] External beam radiation therapy (EBRT) may improve local control, but also demonstrate toxicity to lung tissue,

surrounding organs and blood vessels. Some advanced modalities, such as altered fractionation schedules, Tomotherapy system radiation therapy and stereotactic body radiation therapy (SBRT), increase local radiation doses but cannot achieve a radical curve for large tumors. Many studies have also confirmed the value of the combination of chemotherapy and EBRT.[5] However, overlying adverse reactions reduce patient compliance and decrease life quality, which eventually limit the application of such combined treatment.

Nowadays, several local treatments have been observed to be effective for recurrences of NSCLC after first-line chemotherapy failure, including radiofrequency ablation (RFA), microwave ablation (MWA) and iodine-125 seed brachytherapy. Compared with RFA, MWA demonstrated faster ablation times, larger ablation zones, and higher intratumoral temperatures in ex and in vivo animal models,[6,7] as well as human patients,[8] which brings broad indications. Iodine-125 seed brachytherapy has been demonstrated to be a feasible and effective treatment for lung tumors, with a good local control rate and improved disease-free survival (DFS).[9–11] To the best of our knowledge, there has been no research which has compared MWA and iodine-125 seed brachytherapy as a salvage treatment for local recurrence of NSCLC after failure of first-line chemotherapy. The purpose of this study was to evaluate the clinical value of these two modalities, including overall survival (OS), disease free survival (DFS), local control, hospital stay and health economics.

Methods

A total of 83 consecutive patients with NSCLC recurrence after first-line chemotherapy (Gemcitabine + Cisplatin, Paclitaxel + Cisplatin) administered four to six times, confirmed by enhanced CT/PET-CT and pathology, and treated with CT-guided percutaneous MWA (MWA group) and iodine-125 brachytherapy (Brachytherapy group) in our center from January 2013 to March 2016, were retrospectively analyzed. A total of 51 cases with peripheral tumors underwent percutaneous MWA and 32 with tumors located near the hilum underwent iodine-125 seed brachytherapy. The hospital ethics committee approved this study, and all patients provided their written informed consent.

Baseline characteristics including gender, age and pathology subtypes were comparable between both groups (Table 1). Multidisciplinary consultation among the Departments of Interventional Medicine, Thoracic Surgery, Respiratory, Oncology, Radiation, Chemotherapy were conducted before the procedures commenced. Contrast-enhanced CT with a slice thickness of 5 mm was carried

Table 1 Baseline characteristics of the MWA and brachytherapy groups

Characteristics	MWA group (%)	Brachytherapy group (%)	*P*-value
No. of patients	51	32	
Gender			
Female	26 (52.13)	17 (52.94)	>0.05
Male	25 (47.87)	15 (47.06)	>0.05
Age (years old)			
<50	10 (19.61)	5 (15.62)	>0.05
50–70	27 (52.94)	18 (56.25)	>0.05
>70	14 (27.45)	9 (28.13)	>0.05
Location			
Peripheral	51 (100%)	2 (6.25%)	-
Near hilum	0	30 (93.75%)	-
Pathology			
SCC	24 (47.06)	15 (46.87)	>0.05
Adenocarcinoma	19 (37.25)	13 (40.63)	>0.05
Large cell lung cancer	8 (15.69)	4 (12.5)	>0.05
Pathology diagnosis			
Percutaneous biology	32 (62.75)	20 (62.5)	>0.05
Bronchoscopy	2 (3.92)	1 (3.13)	>0.05
Sputum cytology	17 (33.33)	11 (35.48)	>0.05

SCC, squamous cell carcinoma.

out within one week before MWA or brachytherapy, to provide basic imaging features of tumors. Laboratory examinations including blood cell count, coagulation function, liver and kidney function, tumor markers and lung function were necessary.

Inclusion criteria was as follows: (i) Local recurrence of NSCLC after first-line chemotherapy demonstrated by enhanced CT or PET-CT, without lymph node involvement or distant metastasis; (ii) number of lesions <2, with unilateral lung disease; (iii) diameter of largest lesion <4 cm; (iv) patients were not considered to be candidates for or refused surgery, external beam radiotherapy (EBRT) or second-line chemotherapy; (v) predicted life span >six months; (vi) Karnofsky score >70.

Exclusion criteria was as follows: (i) More than three lesions, or located in bilateral lungs; (ii) lesions with a diameter >4 cm; (iii) massive hemoptysis; (iv) pulmonary or thoracic wall infection; (v) severe cardiac insufficiency (New York Heart Association class III–IV) or advanced lung disease (determined by consultation with respiratory disease specialists), liver disease (Child-Pugh class C), or kidney disease (grade 3 chronic kidney disease); (vi) severe coagulopathy (prothrombin time > 17 seconds or platelet count $\leq 60 \times 10^9$/L); (vii) patients with implantable cardiac devices or the presence of surgical clips.[12]

Treatment planning system (TPS) plans were essential before brachytherapy. Gross target volume (GTV) was delineated according to the image of the lung window (with

Figure 1 Adenocarcinoma in the right lung of a 64-year-old male.

Figure 2 A MWA applicator was inserted into the lesion under CT guidance.

width of 1000 HU, level of −650 HU),[13] while organs at risk (OARS) according to the mediastinal window. Planning target volume (PTV) should cover GTV and one more centimeter beyond the margin. Activity of iodine-125 seed was recommended as 0.6–0.8 mci, and prescription dose 120–160 Gy. Magnetic resonance imaging (MRI)[14] or PET-CT[15] were applied to delineate the target volume when atelectasis was present.

After diet fasting for six hours, both procedures were performed under intravenous anesthesia with dexmedetomidine. Whether patients were placed in a supine or prone position depended upon the tumor location indicated by the previous CT scan.

MWA procedure

Contrast-enhanced or plain CT scan was repeated to confirm the number, size and location of tumor (Fig 1). Puncture site, depth and angle were chosen to avoid ribs, large vessels, pulmonary fissures and pulmonary bulla. One or two MWA applicators (ECO, Nanjing, China) of appropriate length (15 or 18 cm) and diameter (1.6 or 2.0 mm) were then inserted into the lesion under CT-guidance by 2–3 steps. The shortest puncture pathway was strongly recommended to reduce complications in principle. An ablation was performed after confirming that the ablation applicator was correctly positioned using multiplanar CT imaging (Fig 2). Ablation power and time were determined according to the size the size, geometry and location of lesion. A single session was usually adequate to achieve complete ablation for the lesions selected in this study[16] which was demonstrated by a ground-glass opacity (GGO) appearing in the CT image with a peripheral margin expanding 5 mm or more beyond the preprocedure tumor borders. Ablation of the puncture path of the applicator was obligatory to reduce the possibility of tumor se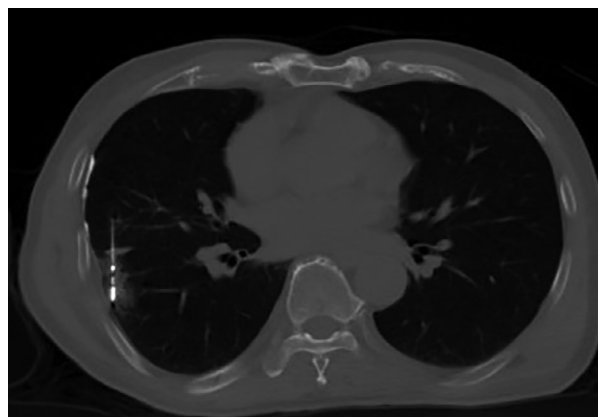eding. Whole-lung CT scan was repeated at the end of the procedure to identify any complications and assess technical success (Fig 3).

Patients' vital signs including blood pressure, heart rate, oxygen saturation and temperature were carefully monitored during the procedure. Chest X-ray or CT scan was performed 24 to 48 hours following the procedure to check for complications such as asymptomatic pneumothorax or pleural effusion. No chemotherapy or radiotherapy was performed after the procedure.

Iodine-125 seed brachytherapy

Contrast-enhanced CT or plain CT was initially repeated to identify the tumor size, location and mark the operation field (Fig 4a). An appropriate intercostal space was selected as the puncture plane, and the puncture site, angle and depth were then determined. Auxiliary technologies such as bone drilling[17] or artificial pneumothorax[18] were applied in cases where the bone acted as a barrier for puncture. The distance among puncture needles was usually 1–1.5 cm or

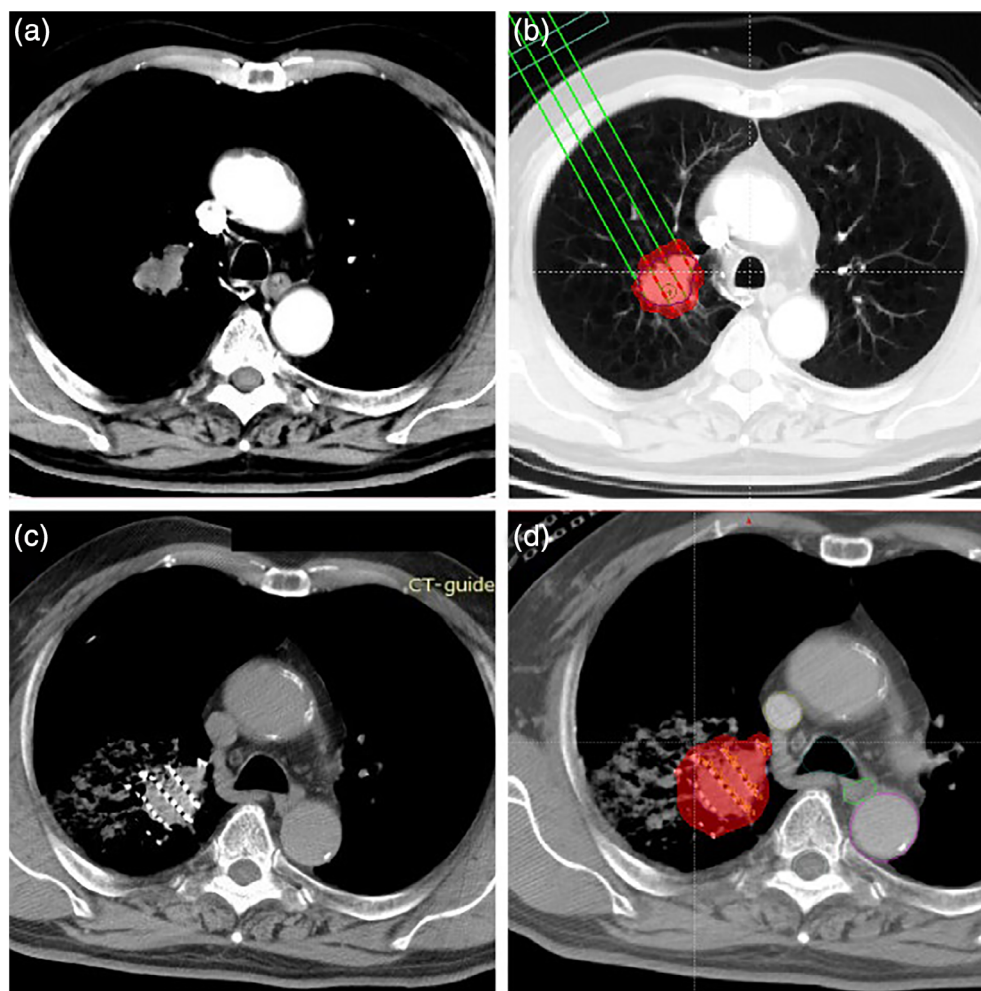**Figure 3** Complete ablation confirmed after MWA.

Figure 4 (**a**) Squamous cell carcinoma in the right lung of a 68-year-old male. (**b**) The TPS plan before brachytherapy. (**c**) Seed implanted according to the TPS plan and dose optimization. (**d**) Dose verification after brachytherapy.

according to the TPS plan (Fig 4b). The puncture of needles could be accomplished at once or as a fractional procedure. After all the needle tips had reached the distal margin of the tumor, the needle was retraced with equal distance or according to the TPS plan, and iodine-125 seeds implanted. A CT scan was repeated several times during the procedure in order to ensure all the seeds were implanted. The TPS plan was revised during the procedure if necessary. After the procedure, plain CT scan covering the whole lung was recommended to check the distribution and number of iodine-125 seeds in every plane (Fig 4c). If there was a "cold area", more seeds were implanted in order to match the dose requirement of the TPS plan. Any complications including pneumothorax or hemorrhage were checked,[19] and percutaneous drainage recommended if necessary. Data of the CT scan after the procedure was imported into

the TPS, and the dose was verified to confirm whether it met the dose requirement of the preoperative plan (Fig 4d).

The operative field was covered by a lead pad with lead equivalent of 0.025 mm. ECG monitoring and oxygen inhalation were necessary until the patients' condition was stable. Chest X-ray or CT scan was repeated 24–48 hours after the procedure to check if there was a pneumothorax, hemothorax or seed drag.[19]

Follow-up

Contrast-enhanced CT and laboratory examinations including blood cell count, coagulation function, liver & kidney function and tumor markers, were performed monthly for the first three months after the procedure. Complications such as perioperative mortality, pneumothorax, pleural

effusion, infection, respiratory failure, coronary/cerebral vascular events or postoperative bleeding requiring intervention, were calculated.

After that, contrast-enhanced chest CT scans and tumor markers were analyzed every three months to detect any local recurrence or new pulmonary lesions for two years. Cerebral CT, ECT, and abdominal ultrasound were performed to define distant metastasis after six, 12, 18 and 24 months after the procedure in all patients. If available, PET-CT provided a more accurate assessment after the procedure.[14]

Efficacy assessment after MWA was carried out according to the report by Ye *et al.*[16] Response evaluation criteria in solid tumors (RECIST) Version 1.1[20] and Chinese expert consensus for permanent iodine-125 seed implantation of lung tumors[11] were applied to assess responses after brachytherapy. OS, DFS, local control rate, toxicity, hospital stay and expense were recorded.

Adverse reactions and complications should be evaluated according to Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)[21] from the U.S. Department of Health and Human Services NIH, National Cancer Institute, and radioactivity response evaluation criteria RTOG/EORTC1987 from U.S. Radiation Therapy Oncology Group (RTOG).

Statistical analysis

IBM SPSS Statistics 24.0 was applied to analyze the data. Categorical variables were presented as number and percentage. Continuous data were presented as means ± standard deviations. Paired *t*-tests were used to compare local control rate, hospital stay and expense. Survival curves were constructed with the Kaplan-Meier method and compared using the log-rank test. A *P*-value less than 0.05 was considered statistically significant.

Results

All procedures were performed successfully with no perioperative mortality. Slight pneumothorax occurred in six cases (11.76%) in MWA group and four (12.5%) in the brachytherapy group ($P < 0.05$). The incidences of pleural effusion in MWA group and brachytherapy group were 3.92% (2/51) and 3.13% (1/32), respectively ($P < 0.05$). No patients complained of suffocation or dyspnea. No tumor seeding, coronary/cerebral vascular events and bleeding requiring intervention were observed in both groups (Fig. 5). (No PRO-CTCAE Grade 3–5 adverse event or RTOG grade 1–4 radiation toxicity was observed.
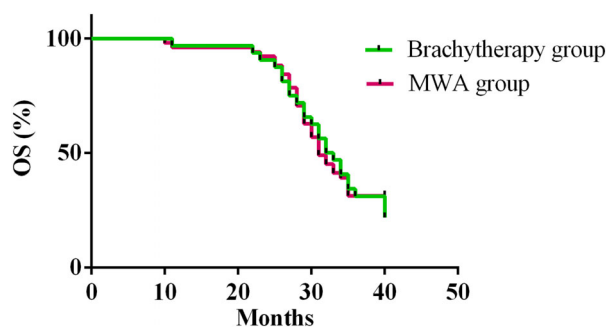

Figure 5 Overall survival (OS) of the MWA group and brachytherapy groups

Local efficacy of MWA and brachytherapy

Contrast-enhanced CT revealed complete ablation one month after MWA. Meanwhile, in the brachytherapy group, continuous tumor shrinking in all cases was demonstrated at one, two and three months. Complete relief (CR) was observed in 10 patients (40.63%) six months after the procedure, and 32 patients (100%) eight months after the procedure. Elevated tumor markers followed a similar trend after the procedures in both groups. Local control rates in six and 12 months were 100%, 96.08% and 100%, 96.88% in MWA and brachytherapy groups, respectively.

Survival

Median survival in the MWA and brachytherapy groups were 30.57 ± 0.74 (10–36) months and 31.63 ± 0.59 (11–36), respectively. The one- and two-year OS were estimated as 96.08%, 92.16% and 96.88%, 90.62% in the MWA and brachytherapy groups, retrospectively (Fig 5). The one- and two-year-DFS were 92.16%, 76.47% and 93.75%, 78.13% (Fig. 6). Log-rank analysis of two sets of data was not significantly different ($P = 0.153$).
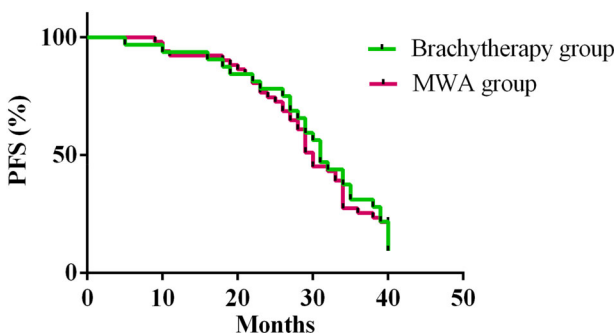

Figure 6 Disease-free survival (DFS) of the MWA group and brachytherapy groups

Health economics

Hospital stay in the MWA and brachytherapy groups were 6.23 ± 0.65 days and 8.67 ± 1.24 days ($P = 0.027$). Medical cost was 3356.73 ± 206.87 and 6714.28 ± 35.43 U.S. dollars ($P = 0.014$). The differences were all significant.

Discussion

Many studies have indicated that MWA is an effective, feasible, and minimally invasive treatment for early stage of NSCLC.[22–24] Brachytherapy has demonstrated good local control for salvage therapy of recurrent lung malignancies after failure of chemotherapy or radiotherapy.[9–11] Theoretically, both procedures are capable of destroying small recurrences of NSCLC with a diameter <4 cm. However, there have been few studies which have compared the clinical outcomes, complications and health economics of the two modalities.

For recurrence of NSCLC after the failure of first-line chemotherapy, the main objective is elimination of local lesions. In our study, tumor elimination was achieved in a shorter time in the MWA group due to the special physical properties of MWA, which contributed to an earlier CR and shorter hospital stay compared to the brachytherapy group. Our research confirmed this since CR was demonstrated in all cases one month after MWA and six or eight months after brachytherapy.

In general, MWA is not recommended for tumors located near the hilum since a heat sink effect may decrease the local control rate[25] and thermal destruction could increase the risk of bronchial fistula and hemorrhage.[26] The study by Zhang *et al.* demonstrated that brachytherapy, despite many punctures, does not add the possibility of hemorrhage,[27] which has also been demonstrated by our study without hemorrhage requiring intervention. Nevertheless, in our study, since the baseline characteristics of tumors were different in both groups, the value of comparison of complications was limited. Importantly, all procedures should be performed by experienced doctors.

Observation of 4–6 days after brachytherapy is recommended in case there is delayed bleeding. For peripheral tumors, treatment with MWA was preferable due to the shorter procedural time and fewer punctures. With regard to brachytherapy, patients were also recommended to stay in hospital for 2–4 days in case pneumothorax or hemorrhage occurred.

Iodine-125 seed is the most common interstitial isotope in China. For one or two lesions with a diameter of 4 cm, dozens of iodine-125 seeds should be implanted into the tumor. In addition to the cost of puncture needles, brachytherapy is usually more expensive than MWA, which commonly consumes one or two applicators. According to our study, the medical cost in MWA and brachytherapy groups was 3356.73 ± 206.87 and 6714.28 ± 35.43 U.S. dollars with a *P*-value of 0.014, indicating economical advantages of MWA over brachytherapy in the salvage treatment of NSCLC.

In conclusion, this study confirmed that MWA and brachytherapy are both effective and safe options for the salvage treatment of NSCLC recurrence after first-line chemotherapy failure, demonstrating similar clinical values with good local control and low incidences of adverse effects or complications. MWA is considered a better option for patients with peripheral tumors, while iodine-125 seed brachytherapy is preferable if the lesions are close to the hilum. Which modality should be considered depends upon the tumor, its size and experience of specialists.

Acknowledgments

Disclosure

The authors report no conflict of interests.

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