Microwave ablation of colorectal liver metastases adjacent to the cardiophrenic angle: Parallel versus non-parallel placement of the antenna relative to the diaphragm

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ABSTRACT

Purpose: Microwave ablation (MWA) is difficult to perform in colorectal liver metastases (CRLMs) adjacent to the cardiophrenic angle. Therefore, a modified approach involving antenna array placement parallel to the diaphragm was initially attempted. Its safety and efficacy were compared with those involving non-parallel placement.

Methods: Sixty-three patients with CRLMs adjacent to the cardiophrenic angle (lesions within 10 mm of the diaphragm) who underwent MWA were included in the study. All patients were further classified into parallel and non-parallel groups according to the method of antenna placement. The distance between the lesion and diaphragmatic surface before MWA, complications, and local tumor progression (LTP) at the last imaging follow-up were recorded. LTPs in the two groups were compared using the log-rank test. Prognostic factors for LTP were assessed using the Cox proportional hazards regression model.

Results: Thirty and 33 lesions were ablated using parallel and non-parallel antenna placement, respectively. During the mean follow-up duration of 19.7 ± 8.2 months, the LTP rate in the parallel and non-parallel placement groups were 3.3% (1/30) and 24.2% (8/33), respectively. The log-rank test showed that parallel antenna placement was associated with delayed LTP (p = 0.018). Multivariate Cox regression analysis showed that parallel antenna placement was an independent predictor of delayed LTP after adjusting for possible risk factors, including age, sex, tumor size, and KRAS mutation (hazard ratio, 0.1; 95% confidence interval, 0.00, 0.80; p = 0.034).

Conclusion: The placement of the antenna parallel to the diaphragm is an alternative and effective method for MWA of CRLMs near the cardiophrenic angle and can contribute to the reduction of the LTP rate.

1. Introduction

Colorectal cancer is the third most common cancer globally, with 25–30% of patients presenting with or developing colorectal liver metastases (CRLMs) over the disease course.1 Surgery is the first-line treatment for CRLMs; however, approximately 75% of patients are not eligible for resection at the time of diagnosis due to the extent of disease or medical condition.2,3 For unresectable CRLMs, thermal ablation modalities, including radiofrequency ablation and microwave ablation (MWA), have shown favorable outcomes when combined with standard chemotherapy.4–6 Currently, thermal ablation is an established treatment for CRLMs; it is parenchyma-sparing and allows reinterventions.

In clinical practice, CRLMs adjacent to the cardiophrenic angle are common and difficult to treat with thermal ablation techniques. Previous studies have shown that thermal ablation of liver lesions adjacent to the diaphragm is related to rare diaphragmatic hernias, increased local tumor progression (LTP) rate, and post-procedural pain.7,8 Several measures have been proposed to prevent these unfavorable results, including artificial ascites,9 one-lung ventilation,10 and intra-abdominal carbon dioxide insufflation.11 To date, none of these solutions have focused on antenna placement. As an essential component of pre-ablation planning, antenna placement is vital for treatment safety and efficacy. In most cases, the microwave antenna is placed from the bottom to the top, with the tip pointing to the diaphragmatic surface. This common approach is often associated with risks. It has a risk of puncture or thermal injury to the diaphragm due to the relatively large contact area of the liver and diaphragmatic surfaces. However, the conservative antenna placement depth or ablation

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parameter setting may contribute to insufficient ablation of the index tumor, which increases the incidence of LTP. From a technical perspective, we considered that the placement of the antenna parallel to the diaphragm, which changes the orientation of the antenna tip, may reduce these risks. Hence, in our center, this approach was also applied to ablate the peripheral CRLMs.

To preliminary explore the feasibility of this modified technique, we conducted this study to compare its effectiveness and safety with those of the non-parallel placement approach.

2. Methods and materials

2.1. Patients

This retrospective study was approved by the local institutional ethics committee. Written informed consent was obtained from each patient before the procedure. A total of 746 patients with CRLMs underwent ultrasound-guided MWA at our hospital between January 2015 and December 2019. Of these, 63 patients had CRLMs adjacent to the diaphragm. The eligibility criteria were as follows: (a) 5 or fewer liver lesions with a maximum tumor diameter of \( \leq 3 \) cm, (b) absence of...
malignancies other than colorectal cancer, and (c) absence of uncontrolled extrahepatic metastasis. The exclusion criteria were as follows: (a) location of the lesion not adjacent to the diaphragm, (b) evidence of direct invasion of the diaphragm or vasculature, and (c) follow-up duration <12 months (Fig. 1). In this study, CRLMs near the diaphragm were located <10 mm from the diaphragm on pretreatment contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (CMRI). The images were reviewed by blinded radiologists. The distance from the closest lesion to the diaphragm was measured in both the sagittal and coronal planes. The minimal diameter was used as the criterion for identifying lesions near the diaphragm.

2.2. Patient grouping

All patients were classified into parallel and non-parallel groups according to the method of antenna placement. In the non-parallel group, the microwave antenna was placed in the foot–head direction with the antenna tip pointing at the diaphragmatic surface (Fig. 2A–C). With this approach, the long axis of the antenna was not parallel to the surface of the diaphragm, and patients with CRLMs ablated using this method were allocated to the non-parallel group. In the parallel group, the microwave antenna was placed in the head–foot direction and parallel to the diaphragm (Fig. 2H–J).

2.3. MWA procedures

Before MWA, hydrodissection was performed to alleviate pain and prevent thermal injury to the diaphragm during ablation before antenna placement. To perform hydrodissection, a 22-G needle with a length of 7 cm was inserted into the site between the liver surface and adjacent diaphragm. Subsequently, a 30–50 mL mixture of 2% lidocaine and saline (9:1) was injected for space separation.

Ablation was performed under local anesthesia with lidocaine supplemented by intramuscular injection of pethidine for intraoperative analgesia. Before MWA, all patients received intramuscular injection of 50 mg of Demerol (Chaohui; Shanghai Pharmaceuticals, Shanghai, China). All MWA procedures were performed by a specialized interventional physician with more than 20 years of experience. All ablations were conducted under real-time ultrasonography (LOGIQ E9; GE Healthcare, Milwaukee, WI, USA) using a 2450-MHz MWA system (KY-2000; Canyou Medical Instruments, Nanjing, China), which consists of a microwave generator and 16-G internally cooled antenna with a 5-mm active tip and 10-cm shaft. For lesions with a diameter <2.0 cm, one antenna was inserted. For lesions with a diameter ≥2.0 cm, two needles were inserted at a distance of 1.0–1.5 cm. The energy output was adjusted between 45 and 60 W at 5–10 min for each session. The needle track was ablated at the end of the procedure to prevent bleeding and tumor seeding. Contrast-enhanced ultrasonography (CEUS) was performed immediately after MWA. On CEUS, complete ablation was characterized by the complete overlap of the non-enhancement ablation zone and target tumor. Additional MWA was performed if CEUS suggested incomplete ablation.

2.4. Data measurement and follow-up

The clinical and laboratory data of the patients before and after MWA were collected by reviewing the electronic medical records. CEUS was performed 1, 2, and 3 months after MWA. In the follow-up, CEUS, CECT (Aquilion One, Toshiba Medical System, Tokyo, Japan), or CEMRI (Optima MR360, GE Healthcare, Milwaukee, WI, USA) was performed every 3 months during the first year and every 6 months thereafter.

The primary outcomes were technical success and LTP, assessed according to the standardization of terminology and reporting criteria for image-guided tumor ablation. Technical success was defined as a complete covering of the tumor by the ablation zone on CEUS, CECT, or CEMRI after tumor treatment according to the protocol. LTP was defined as the appearance of a hyper-enhanced nodule with washout located at the marginal area of the ablated zone after the tumor had been documented as having been completely ablated. For lesions with LTP, further ablation was conducted. In patients with LTP who were not eligible for ablation, systemic chemotherapy was administered whenever possible.

The secondary outcome was the presence of complications, which were reported using the most recent version of the Society of Interventional Radiology (SIR) classification standard table. Major complications were defined as events that lead to substantial morbidity and disability, which resulted in an increase in the level of care, hospital admission, or substantial prolongation of hospital stay (SIR classifications C–E). All other complications were considered minor. Regional pain after MWA was recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 of the National Cancer Institute.

2.5. Statistical analysis

Data are presented as mean ± standard deviation for continuous variables and percentages for categorical variables according to the antenna placement method. Continuous variables were compared using the Kruskal–Wallis test, and categorical variables were compared using the

### Table 1

| Patient and tumor characteristics | Non-parallel placement (n = 33) | Parallel placement (n = 30) | P value |
|----------------------------------|-------------------------------|---------------------------|--------|
| Age (years)                      | 55.4 ± 10.2                  | 59.8 ± 10.6               | 0.096  |
| Sex                              |                               |                           | 0.840  |
| Female                           | 7 (21.2%)                     | 7 (23.3%)                 |        |
| Male                             | 26 (78.8%)                    | 23 (76.7%)                |        |
| Tumor size (mm)                  | 15.9 ± 6.9                    | 14.4 ± 5.3                | 0.359  |
| Aspect ratio                      | 1.1 ± 0.1                     | 1.2 ± 0.1                 | 0.282  |
| Synchronous metastases           | 31 (93.9%)                    | 29 (96.7%)                | 0.612  |
| Liver metastases resection pre-MWA |                               |                           | 0.722  |
| Chemotherapy pre-MWA             | 23 (69.7%)                    | 18 (60.0%)                | 0.420  |
| T stage of primary cancer        |                               |                           | 0.976  |
| pT2                              | 1 (3.0%)                      | 1 (3.3%)                  |        |
| pT3                              | 25 (75.8%)                    | 22 (73.3%)                |        |
| pT4                              | 7 (21.2%)                     | 7 (23.3%)                 |        |
| N stage of primary cancer        |                               |                           | 0.860  |
| pN0                              | 9 (27.3%)                     | 10 (33.3%)                |        |
| pN1                              | 15 (45.5%)                    | 12 (40.0%)                |        |
| pN2                              | 9 (27.3%)                     | 8 (26.7%)                 |        |
| Extrahepatic metastases          | 11 (33.3%)                    | 6 (20.0%)                 | 0.234  |
| Degree of differentiation         |                               |                           | 0.255  |
| well differentiation             | 5 (15.2%)                     | 9 (30.0%)                 |        |
| medium differentiation           | 27 (81.8%)                    | 19 (63.3%)                |        |
| poor differentiation             | 1 (3.0%)                      | 2 (6.7%)                  |        |
| KRAS mutation                    | 11 (33.3%)                    | 9 (30.0%)                 | 0.777  |
| Distance from lesion to diaphragm|                               |                           |        |
| >5 mm                            | 3 (9.1%)                      | 1 (3.3%)                  | 0.349  |
| ≤5 mm                            | 30 (90.9%)                    | 29 (96.7%)                |        |
| Ablation time (minutes)          | 8.8 ± 1.6                     | 8.8 ± 2.0                 | 0.979  |
| Ablation power (W)               | 6 (18.2%)                     | 7 (23.3%)                 | 0.614  |
| 40                               | 27 (81.8%)                    | 23 (76.7%)                |        |
| 50                               | 25.5 ± 5.5                    | 25.2 ± 6.4                | 0.829  |
| Number of inserted antenna       | 25 (75.8%)                    | 27 (90.0%)                | 0.137  |
| 1                                | 8 (24.2%)                     | 3 (10.0%)                 |        |
| 2                                | 17.7 ± 9.3                    | 19.0 ± 9.5                | 0.558  |
chi-squared test. The LTP rates were plotted using the Kaplan–Meier method and compared using the log-rank test. The prognostic factors for LTP were assessed using the Cox proportional hazards regression model. Data were analyzed using the R (The R Foundation; http://www.r-project.org; version 3.1.2 2014-10-31) and Empower (R) (www.empowerstats.com; X&Y Solutions Inc.) statistical packages.

3. Results

3.1. Baseline characteristics of patients

A total of 63 patients with 63 CRLMs adjacent to the diaphragm were included in the study. The mean age was 57.5 ± 10.5 years (range, 30–85 years). The mean follow-up duration was 19.7 ± 8.2 months. The mean lesion size was 15.2 ± 6.1 mm. The mean aspect ratio in the longitudinal plane was 1.1 ± 0.1. The mean distance from the lesion to the diaphragm was 1.9 ± 2.4 mm. The baseline characteristics of the parallel and non-parallel groups were well balanced (Table 1).

3.2. Local tumor progression

Fig. 2 shows a representative case before and after MWA for each group. The rate of technical success was 100% (63/63) for CRLMs treated with MWA. During the follow-up, 8 of 33 (24.2%) lesions in the non-parallel group had LTP within 2–14 months, while 1 of 30 (3.3%) lesions in the parallel group had LTP within 4 months (P = 0.018, Fig. 3). The details of the patients with LTP in the two groups are shown in Table 2. Multivariate Cox regression analysis was conducted in all patients. The results showed that parallel antenna placement was independently associated with LTP (hazards ratio [HR], 0.100; 95% confidence interval [CI], 0.000–0.800; p = 0.034) after adjusting for possible risk factors, including age, sex, tumor size, and KRAS mutation (Table 3).

3.3. Complications

There were no major complications related to the ablation of subphrenic lesions. No arrhythmias occurred during or after MWA. No diaphragmatic injury occurred in any patient. Minor complications developed in one patient with a subphrenic lesion in the non-parallel group. In this patient, there was a small remnant of left pleural effusion 3 days after MWA, and no drainage was observed. Pain was the most common side effect of MWA. Fourteen (42.4%) patients in the non-parallel group and 13 (43.3%) patients in the parallel group complained of local pain with CTCAE grades 1–2 after MWA.

4. Discussion

Thermal ablative techniques, as alternative local treatments to surgical resection recommended by the National Comprehensive Cancer Network guidelines and European Society for Medical Oncology consensus guidelines, are intended to eradicate all visible lesions. However, lesions adjacent to the cardiophrenic angle, which make it difficult to achieve a balance between efficacy and safety, are often difficult to ablate. In our previous study, which included 411 CRLMs, the location adjacent to the diaphragm was identified as a risk factor for LTP, which was associated with three times higher risk than other locations. To ensure sufficient ablation margins, ablating lesions adjacent to the cardiophrenic angle requires extensive planning and guidance of antenna placement and appropriate preset of ablation parameters. To ensure safe ablation of these lesions, operator caution often contributes to under-treatment, which may account for the higher incidence of insufficient ablation and LTP than those with lesions in other segments.

In this study, ablation using a parallel approach resulted in a significantly lower LTP rate than that using the non-parallel approach (3.3% vs. 24.2%); the parallel approach can reduce the LTP rate of subphrenic lesions. Theoretically, with the long axis of the antenna parallel to the diaphragmatic surface, the subphrenic part of the targeted lesion may be covered by the short axis of the ablation zone, which enlarges regularly with time. With the microwave antenna, it is simpler to predetermine the ablation area using the side direction than that around the antenna tip. Hence, this approach may provide assurance of sufficient ablation of lesions near the cardiophrenic angle to a great extent. To ensure the feasibility of parallel antenna placement, it is important to fully understand the related anatomy. The part located near the cardiophrenic angle is the bare area of the liver, which is a triangular non-peritoneal area. For lesions in this special anatomical location, the following factors need to be considered for ablation therapy. First, hydrodissection should be performed by injecting diluted lidocaine to distend the space between the liver and diaphragmatic plane before antenna placement, which enhances visibility. Second, for lesions with a long axis that is

![Graph showing Local tumor progression of the parallel and non-parallel placement groups.](Image)
not parallel to the diaphragmatic surface, the deepest part of the ablation zone should be monitored carefully in case of injury to other structures. The current sample size facilitated the identification of the presence of a difference in the LTP rate. Second, selection bias was inherent in this retrospective cohort study. When using ultrasound to guide the ablation procedure, the feasibility of antenna placement should be assessed after considering the visibility of the target lesion and safety of the path, which may be influenced by abdominal scars, xiphoid costal angle, and so on. Further prospective studies with larger samples are warranted, and we hope that our initial results will provide practical foundations for these studies.

In conclusion, our results show that the placement of the antenna parallel to the diaphragm is an alternative and effective method for MWA of CRLMs near the cardiophrenic angle and can reduce the LTP rate.

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Declaration of competing interest

We declare that we have no conflict of interest.

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