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Radiofrequency Ablation and Microwave Ablation in Liver Tumors: An Update

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Hepatocellular carcinoma • Liver metastasis • Radiofrequency ablation • Microwave ablation • Efficacy

Abstract

This article provides an overview of radiofrequency ablation (RFA) and microwave ablation (MWA) for treatment of primary liver tumors and hepatic metastasis. Only studies reporting RFA and MWA safety and efficacy on liver were retained. We found 40 clinical studies that satisfied the inclusion criteria. RFA has become an established treatment modality because of its efficacy, reproducibility, low complication rates, and availability. MWA has several advantages over RFA, which may make it more attractive to treat hepatic tumors. According to the literature, the overall survival, local recurrence, complication rates, disease-free survival, and mortality in patients with hepatocellular carcinoma (HCC) treated with RFA vary between 53.2 ± 3.0 months and 66 months, between 59.8% and 63.1%, between 2% and 10.5%, between 22.0 ± 2.6 months and 39 months, and between 0% and 1.2%, respectively. According to the literature, overall survival, local recurrence, complication rates, disease-free survival, and mortality in patients with HCC treated with MWA (compared with RFA) vary between 22 months for focal lesion >3 cm (vs. 21 months) and 50 months for focal lesion ≤3 cm (vs. 27 months), between 5% (vs. 46.6%) and 17.8% (vs. 18.2%), between 2.2% (vs. 0%) and 61.5% (vs. 45.4%), between 14 months (vs. 10.5 months) and 22 months (vs. no data reported), and between 0% (vs. 0%) and 15% (vs. 36%), respectively. According to the literature, the overall survival, local recurrence, complication rates, and mortality in liver metastases patients treated with RFA (vs. MWA) are not statistically different for both the survival times from primary tumor diagnosis and survival times from ablation, between 10% (vs. 6%) and 35.7% (vs. 39.6), between 1.1% (vs. 3.1%) and 24% (vs. 27%), and between 0% (vs. 0%) and 2% (vs. 0.3%). MWA should be considered the technique of choice in selected patients, when the tumor is ≥3 cm in diameter or is close to large vessels, independent of its size. ***The Oncologist*** 2019;24:e990–e1005

Implications for Practice: Although technical features of the radiofrequency ablation (RFA) and microwave ablation (MWA) are similar, the differences arise from the physical phenomenon used to generate heat. RFA has become an established treatment modality because of its efficacy, reproducibility, low complication rates, and availability. MWA has several advantages over RFA, which may make it more attractive than RFA to treat hepatic tumors. The benefits of MWA are an improved convection profile, higher constant intratumoral temperatures, faster ablation times, and the ability to use multiple probes to treat multiple lesions simultaneously. MWA should be considered the technique of choice when the tumor is ≥3 cm in diameter or is close to large vessels, independent of its size.

Introduction

Tumor ablation is a minimally invasive approach that is commonly employed in the treatment of hepatic tumors [1]. Ablation therapy is considered a potential first-line treatment in many patients with small hepatocellular carcinomas [2] or an alternative for people who are not fit for surgical resection or have failed chemotherapy [3]. Moreover, tumor ablation can

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also be useful as an adjuvant therapy or may provide an alternative strategy to surgery or be used in association with resection in case of patients with poor functional liver reserve (FLR) [3]. Most ablation systems comprise a generator and an electrode (needle-like device) that delivers the energy directly to the target area to cause tissue necrosis. Typically, treatments can be performed percutaneously under image guidance by inserting the electrode into the target area and applying energy to induce coagulative necrosis. Ablation may also be performed laparoscopically or via open surgery [4].

Radiofrequency ablation (RFA), microwave ablation (MWA), high-intensity focused ultrasound, and laser therapy are hyperthermic procedures that apply energy to heat the tissue to at least 60°C for maximum efficacy, whereas the cryoablation systems is hypothermic, cooling the tissue to less than −40°C to cause necrosis [4, 5]. The most clinically verified and used ablation modalities are RFA and MWA. Each of these technologies has its own strengths and weaknesses when applied to treatment of tumors in a variety of solid organs [4, 5].

The primary endpoint of ablation therapy is to obtain a complete necrosis (similar to R0 resection) of liver tumors that is linked to create a safety margin of at least 10 mm round the external margin of the lesion. However, the effectiveness of the treatment is linked to numerous features, such as tumor size, location, blood flow, and equipment utilized [5]. RFA is a widely employed procedure to treat both primary and metastatic hepatic tumors [6, 7]. MWA is a new procedure that has similar benefits of the RFA, with several advantages, such as a greater volume of cellular necrosis, procedure time reduction, and higher temperatures delivered to the target lesion, and is less susceptible to variation in the morphology of the treatment zone because of heat-sink effects from adjacent vasculature. However, with larger zones of necrosis, it increases the risk of potential complication owing to collateral injury to adjacent nontarget organs [8, 9]. So, with adequate physician experience and hospital financial resources allowing the opportunity for acquisition of MWA technology, more effective treatment of larger tumors in a timely and efficient manner can be performed [5].

This overview is an independent study and did not require institutional review board approval and registration number.

Search Criterion

Numerous electronic datasets were examined: PubMed (U.S. National Library of Medicine, http://www.ncbi.nlm.nih.gov/pubmed), Scopus (Elsevier, http://www.scopus.com/), Web of Science (Thomson Reuters, http://apps.webofknowledge.com/), and Google Scholar (https://scholar.google.it/). The following search criteria were used: "radiofrequency ablation" AND "Liver" AND "HCC" AND "metastasis," "microwave ablation," AND "Liver" AND "HCC" AND "metastasis," "radiofrequency ablation" AND "Liver" AND "complication," "microwave ablation" AND "Liver" AND "complication," "radiofrequency ablation" AND "Liver" AND "safety" AND "efficacy," "microwave ablation" AND "Liver" AND "safety" AND "efficacy". The research covered the years from January 1990 to June 2017.

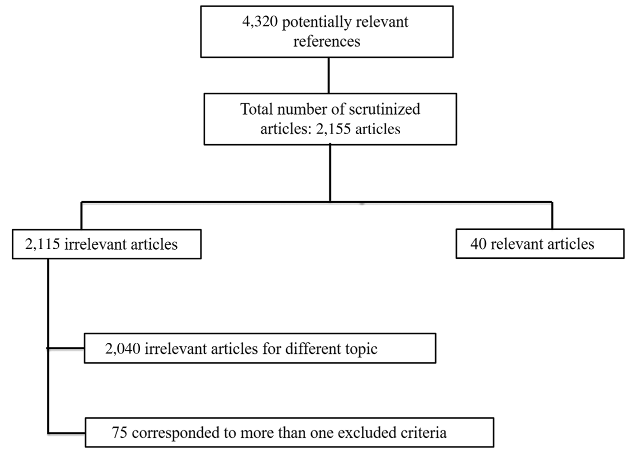

Figure 1. Study flow diagram showing the included and excluded studies in the systematic review.

All titles and abstracts were analyzed, and only the studies reporting RFA and MWA safety and efficacy on liver tumors were retained.

The inclusion criteria were clinical study evaluating RFA safety and efficacy to treat liver metastases, clinical study evaluating RFA safety and efficacy to treat hepatocellular carcinoma (HCC), clinical study evaluating MWA safety and efficacy to treat liver metastases, and clinical study evaluating MWA safety and efficacy to treat HCC. Articles published in the English language from January 1990 to June 2017 were included. Exclusion criteria were unavailability of full text, general overview articles, and congress abstracts.

We identified 4,320 potentially relevant references through electronic searches. After removing 2,180 duplicates, we obtained 2,140 references. We identified 15 references through scanning reference lists of the identified randomized trials that we added to the 2,140 references previously selected (total number of scrutinized articles was 2,155). We then excluded 2,040 clearly irrelevant articles through screening titles and reading abstracts. We retrieved 100 references for further assessment. We excluded 75 references for the reasons listed in the exclusion criteria. A total of 40 clinical trials met the inclusion criteria. The reference flow is summarized in the study flow diagram (Fig. 1).

Background

Although the technical features of RFA and MWA are similar, the differences arise from the physical phenomenon used to generate heat. RFA causes cellular death thanks to thermocoagulation necrosis. MWA is based on dielectric heating. The major distinction between RFA and MWA heating is that during MWA treatment heat is contained in a volume around the applicator antenna, whereas during RFA, it is restricted to areas of high current density [10]. Radiofrequency (RF) heating needs an electrically conductive pathway, which is not necessary during MWA because microwaves can propagate through tissues without conductivity. This means that low-conductivity tissues inhibit or reduce RF current flow, whereas they do not modify microwave propagation [10]. Microwaves also offer upgraded techniques for multiple-applicator ablation. Volume heating means that multiple antennas can be activated uninterruptedly and all together nearby, or in distinct sites. When electromagnetic

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fields are overlapped, heating rises by N^2, where N is the number of fields applied [4, 10]. Presently, RFA needs switching between electrodes when multiple antenna are applied [6–10]. An essential feature when comparing RF and MWA will be the tumor's host organ and site within the organ; in fact, the tissue properties of ablated area and normal tissue are dissimilar and should be evaluated for both RF and MWA [4–10].

Physical Principles

Radiofrequency Ablation

RFA causes cellular death thanks to thermocoagulation necrosis. Heat is produced by ionic excitement and impact relational to strength of applied energy. At present, two types of RFA devices are clinically used. Monopolar (MP) RFA employs a unique antenna, whereas bipolar (BP) RFA uses dual antennas, or two electrodes on the same antenna facing each other. Monopolar RFA is generally used for liver cancer ablation. Recently, BP-RFA findings have shown ablation of a much larger tumor volume in comparison with MP in a single ablation, and BP-RFA is less affected by heat-sink effect compared with MP [10]. According to the size and the shape of the needle's tip, a spherical ablated area is generated in about 10–30 minutes, generally from 2 to 5 cm in diameter [11]. With RFA, the zone of active tissue heating is limited to a few millimeters surrounding the active electrode, with the remainder of the ablation zone being heated via thermal conduction [10, 11]. With an increase in the size of the target area, the efficacy of the treatment is reduced, as the maximum result is obtained for volumes less than 3.5 cm [12, 13]. Moreover, some tissue properties, such as electrical conductivity, thermal conductivity, dielectric permittivity, heat capacity, and blood perfusion rate, have substantial effect on the growth of ablation zones. Additionally, as the ablation progresses, the tissue can become dehydrated and charred, which can increase tissue impedance to electrical current flow [4, 5]. So, RFA is limited by increasing in impedance and an excessive local temperature [12, 13]. Several technical devices exist to avoid this effect, such as monitoring temperature or impedance during procedure or simultaneously instilling saline solution into the tissue surrounding the RF needle [14].

Microwave Ablation

MWA is based on dielectric heating, which occurs when an imperfect dielectric material is exposed to an alternating electromagnetic (EM) field [4, 15]. A microwave (MW) field oscillates rapidly (2,450 MHz = 2.45 billion times a second), rotating polar molecules, primarily water, that oscillate out of phase, so some EM energy is absorbed and changed to heat. During treatment, MWA produces EM waves around an insulated, electrically independent antenna. The majority of the heat is due to the excitement of polar water particles, whereas ionic polarization influences for a much smaller part of the generated heat [16, 17]. The MWA's devices use frequencies ≥900 MHz. The two main frequency categories used are 915 and 2,450 MHz. The category of 2,450 MHz is the one most commonly employed, whereas 915 MHz can produce deeper penetration, thus potentially creating larger ablation zones [18]. MW energy creates a larger zone of active heating (up to 2 cm surrounding the antenna) permitting more uniform necrosis in the target lesion. MWA has some theoretical benefits compared with RFA: the target to be treated can be larger because it produces a larger area of necrosis; the time of treatment is shorter; and MWA is less influenced by the defense of the neighboring tissues due to vaporization and charring, so as the heat-sink effect influences less the efficacy of treatment. Because of the EM nature of microwaves, MWA is not limited by tissue conductance, as the propagation of energy is not dependent on electrical tissues properties, unlike RFA treatment [19].

Heat-Sink Effect

Thermally ablative devices coagulate and cause necrosis tissue with two distinct heating zones: an active heating zone and a passive heating zone. The active heating zone occurs within the tissue nearest to the device where the intensity of energy is high and its absorption by tissue is fast, whereas the passive zone occurs outside the active zone, further from the ablation device where the intensity of energy is lower. Passive zone extension beyond the active zone is determined by local physiology and its inherent ability to circumvent thermally damaging temperatures [20, 21]. Ablating focal lesions adjacent to large vasculature is a particularly difficult task. To fully understand this phenomenon, the heat-sink effect should be thought of from both thermal and electrical perspectives [22]. The thermal effect impacts both current- and field-based technologies. Consider flowing blood through a volume of heated tissue will draw the heat away through convection and temperature differences, countering the ablative effect. Thermal sink is particularly problematic when the passive zone is relied upon to ablate tissue around a vessel. In these cases, the lower energy intensity within the passive zone is not able to achieve thermally toxic temperatures in proximity to the cooling vasculature [22]. With RFA current-based technologies, ablation near large vessels is not recommended, as the combined effect of electrical and thermal sink dramatically increases the risk of incomplete necrosis of malignant cells and local recurrence [23].

MWA field-based technologies, in contrast, have found a niche in achieving coagulation of tissue around large vasculature, as this energy source is not challenged by the energy sink effect [24, 25]. For both RFA and MWA, however, attempting to ablate tissue around a vessel with a passive zone of ablation will continue to be a losing battle in the face of thermal sink. If the passive zone of ablation continues to be relied upon to extend ablation volumes beyond active heating patterns, we risk local recurrence rates remaining high [23–25]. Bhardwaj et al. evaluated MW, RF, and cryoablation histologically and found no perivascular hepatocyte survival with MW ablation but did find perivascular hepatocyte survival within the ablated volume for cryoablation and conspicuous perivascular hepatocyte survival within the RF ablation zones [26].

Discussion

RFA causes cellular death thanks to thermocoagulation necrosis; conversely, MWA is based on dielectric heating, so that MW energy creates a larger zone of active heating permitting more uniform necrosis in the target lesion

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Table 1. Overall survival, local recurrence, complication rates, disease-free survival, and mortality in patients with HCC treated with RFA

Study	OS; 1, 3, 5 yr OS rates, %	Local recurrence, %	Complications rates, %	DFS; 1, 3, 5 yr OS rates, %	Mortality, %
Park et al. [27]	53.2 ± 3.0 mo	63.1	10.5	22.0 ± 2.6 mo	0
Kim et al. [28]	66 mo	59.8	–	39 mo	–
Liu et al. [29]	97, 83, 66	63	–	–	–
Wang et al. [30]	91.6, 73.5, 57.4	57	–	67.1, 46.4, 38.0	–
Gory et al. [31]	–, 62, 37 (for ≤5 cm HCC);–, 66, 39 (for ≤3 cm HCC)	–	2	–	–

Abbreviations: –, not applicable; DFS, disease-free survival; HCC, hepatocellular carcinoma; mo, months; OS, overall survival; yr, year.

compared with RFA. MWA is not limited by tissue conductance, and is less influenced by the defense of the neighboring tissues so as the heat-sink effect influences less the efficacy of treatment unlike RFA treatment.

Regarding patients with HCC, ablative treatment is accepted as the best therapeutic choice for nonsurgical patients with early stage HCC. Patients are required to have either a single tumor smaller than 5 cm or as many as three nodules smaller than 3 cm each and no evidence of vascular invasion or extrahepatic spread. In the scenario of metastatic disease, percutaneous ablation is generally indicated for nonsurgical patients with colorectal cancer metastases isolated to the liver. The number of lesions should not be considered an absolute contraindication to percutaneous ablation if successful treatment of all metastatic deposits can be accomplished. Tumor size is a prognostic feature to predict the outcome of treatment. The target tumor should not exceed 3–4 cm in longest axis to ensure complete ablation with most of the currently available devices [13, 25]. Another important feature that affects the success rate of ablative treatment is the ability to ablate all viable tumor tissue and an adequate tumor-free margin. To achieve rates of local tumor recurrence with these treatment that are comparable to those obtained with hepatic resection, physicians should produce a 360 degree, 1-cm-thick tumor-free margin around each tumor. This cuff will assure that all microscopic invasions around the periphery of a tumor have been eradicated [13]. Thus, the target diameter of an ablation must be ideally 2 cm larger than the diameter of the tumor that undergoes treatment. Otherwise, multiple overlapping ablations can be performed [13, 26].

HCC and RFA

Among all the ablative procedures, RFA is a frontline technique for HCCs smaller than 20 mm (Table 1) [2]. Several studies have evaluated the efficacy of RFA with respect to resection and have established that RFA is a noninvasive and effective ablative treatment [27–31]. Although these studies focused on RFA as a stand-alone therapy contained valuable information regarding treatment safety and response, they lacked sufficient follow-up to define important long-term outcomes such as survival. Only recently have survival data become available on RFA-treated patients with HCC. Large clinical series from Europe, the U.S., and Asia have demonstrated 5-year post-RFA survival rates between 33% and 55%, comparable to those seen in series of hepatic resection [27–31].

According to the literature, the overall survival, local recurrence, complication rates, disease-free survival, and mortality in patients with HCC treated with RFA vary between 53.2 ± 3.0 months and 66 months, between 59.8% and 63.1%, between 2% and 10.5%, between 22.0 ± 2.6 months and 39 months, and 0% and 1.2%, respectively.

Park et al. evaluated the morbidity, mortality, overall survival (OS), and disease-free survival (DFS) rates in patients with HCC patients who underwent RFA and hepatic resection (HR). They found no significant difference between the two study populations. The DFS rates of the HR group were significantly higher than the RFA group. Multivariate analysis identified that recurrence and portal hypertension were associated with OS and that portal hypertension and increased serum α-fetoprotein were factors significantly associated with DFS. They concluded that the patients who underwent RFA had similar OS rates compared with HR, confirming that RFA could be an alternative treatment for patients with HCC smaller than 3.0 cm who are not eligible for surgical resection [27]. Kim et al. evaluated 604 patients (273 underwent liver resection and 331 RFA). The survival rates at 5 and 10 years for HR and RFA groups were 87.6% versus 82.1% and 59.0% versus 61.2%, respectively, with a recurrence-free survival rates at 5 and 10 years of 60.6% versus 39.4% and 37.5% versus 25.1%, respectively. In the propensity score-matched cohort (152 pairs), there were no differences in HCC-specific survival, whereas recurrence-free survival again differed between the treatment groups. This study demonstrated that, although RFA carried a higher risk of treatment-site recurrence than HR, it provided similar overall survival probability in patients with a single small HCC without a raised bilirubin level or portal hypertension [28].

Gavriilidis et al. compared the survival benefits and treatment efficacy of repeat hepatic resection (RHR) and RFA for recurrent HCC. They evaluated five retrospective studies including 639 patients and demonstrated that there were no differences in DFS and OS. Comparison between the two groups demonstrated similar 5-year DFS and 5-year OS. However, RFA had a lower morbidity rate (2%) compared with RHR (17%) [32].

Several comparative trials also have been conducted evaluating RFA against other conventional ablative modalities. The majority of these studies originated in East Asia and compare RFA with the standard chemical ablation techniques. Dong et al. completed a meta-analysis comparing clinical outcomes between HR and ablation therapies (AT) for small HCC. They evaluated 12 studies that involved 1952 patients (HR vs. AT), five studies that involved 701 patients

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(RFA vs. percutaneous ethanol injection [PEI]), and five additional studies (RFA vs. RFA + transcatheter arterial chemoembolization [TACE]) that all addressed the treatment of small HCC. In HR versus AT, the authors found no significant difference in OS rate at 1-year; however, there was a significant rise in the HR group in OS rate at 5 years. They found no significant differences between the two groups in disease-free survival rates at 1 year and 5 years, whereas the HR group showed higher disease-free survival rate at 3 years. In studies of RFA versus PEI, the results showed that RFA procedure was connected with significantly higher 2-year OS rates; however, there were no significant differences in the 1-year OS rate or incidence of complications. In studies of RFA versus RFA + TACE, they found no significant differences in the 1-year or 3-year OS rate; however, the 5-year OS rate was higher in the RFA + TACE group than the RFA group. The results also showed that the incidence of complications after AT was lower than that in the HR population, which might be due to specific features of these therapies. The local recurrence rate was higher after RFA than after HR, which highlights the importance of patient selection, tumor size, vascular abutment, and thorough treatment when using RFA. Dong et al. concluded that RFA is the best single ablation technique. However, RFA plus TACE were better than RFA alone for the treatment of small HCC [33].

Hung et al. evaluated the clinical outcomes of Hepatic resection and ablative procedures in elderly patients with HCC (defined as aged ≥70 years) [34]. They investigated 23 studies that included 12,482 patients. A total of 6,341 patients were subjected to HR, 3,138 to RFA, and 3,003 to TACE. Among the HR group, the elderly had significantly more respiratory comorbidities compared with that younger group, whereas there were no significant differences of cardiovascular comorbidities and diabetes between the two groups. At 1 year, the elderly patients had significantly increased survival rates after HR than the younger patients. However, Hung et al. showed that there were not significant differences of the survival outcomes with HR between elderly and nonelderly patients at 3 years and 5 years. When they evaluated postoperative complications, they showed that the rate were comparable between the elderly and younger patients. Conversely, among the RFA group, the elderly and nonelderly patients showed similar survival outcomes for the first and third year, whereas elderly patients had significantly worse survival rates than nonelderly patients for the fifth year. Among the TACE group, the elderly showed significantly increased survival compared with the nonelderly patients for the first and third year, whereas the researchers showed that, at the fifth year, there were no significant differences in overall survival between all patients [34]. These studies demonstrated that RFA-treated patients showed significantly better recurrence and survival rates than their chemically ablated counterparts. Furthermore, the number of treatment sessions required to induce complete response was significantly less in the RFA treatment group. Although RFA was superior to chemical ablation in terms of inducing responses, limiting recurrence, and prolonging survival, it was associated with a higher complication rate [31–34].

Salhab et al. suggested that RFA should be the first-line treatment in patients with a single small HCC tumor ≤3 cm. However, when the tumors is greater than 3 cm, RFA is characterized by high incomplete ablation and local recurrence rates, [35]. A meta-analysis of 95 studies including 5,224 liver tumors treated by RFA reported a local recurrence rate of 12.4%. Local recurrence was substantially higher following treatment of tumors >3–5 cm (24.1 %) or >5 cm (58.1 %) in diameter [36].

HCC and MWA

With the microwave technology progress and a continuously cooled electrode development, MWA has recently been used more recurrently in treatment of HCC (Fig. 2, Table 2) [4, 10, 19].

According to the literature, overall survival, local recurrence, complication rates, disease-free survival, and mortality in patients with HCC treated with MWA (compared with RFA) vary between 22 months for focal lesion >3 cm (vs. 21 months) and 50 months for focal lesion ≤3 cm (vs. 27 months), between 5% (vs. 46.6%) and 17.8% (vs. 18.2%), between 2.2 % (vs. 0%) and 61.5% (vs. 45.4%), between 14 months (vs. 10.5 months) and 22 months (vs. no data reported), and between 0% (vs. 0%) and 15% (vs. 36%), respectively.

Baker et al. assessed safety and efficacy of MWA in 340 patients with HCC. Median value of lesion size was 3.2 cm (range, 1–6). A total of 89.5% of patients had cirrhosis, 60.7% related to hepatitis C, and 8.2% related to hepatitis B. Slightly over one third (35.9%) were Child-Pugh class B/C cirrhotic. Laparoscopic MWA procedures were performed in 96.8% of the patients. Four patients died within 30 days (1.8%). Clavien-Dindo grade III complications happened in 3.2% of patients. Complete necrosis was recognized in 97.1% of tumors, whereas local recurrence was 8.5% at 10.9 months median follow-up (0–80 months). Local recurrence happened in 34.8% of patients at 10.9 months median follow-up, and metastatic recurrence rate was appreciated in 8.1% of patients. At 1 year, OS was 80.0%, whereas at 2 years OS was 61.5%. The researchers established that MWA could be performed safely, even in patients with advanced disease. The minimally invasive procedure determines low morbidity and mortality with acceptable incomplete necrosis rates and regional recurrence [37].

Swan et al. assessed MWA in the treatment of 54 patients with HCC (73 tumors) with advanced disease. Median value of tumor size was 2.6 cm (range, 0.5–8.5). A total of 92.6% of patients had cirrhosis; among these, 27.8% had a Child-Pugh score of B/C and 59.3% had chronic hepatitis C. A minimally invasive procedure was performed in 94.5%. The authors showed that there were no deaths within 30 days. The 30 days morbidity frequency was 28.9%, with grade III complications in 11.5% of cases. A total of 7.8% of patients reported delayed complications, with a mortality percentage of 5.6% at 90 days. Incomplete necrosis was found in 5.9% of lesions, with a local recurrence percentage of 2.9% at 9 month median follow-up. Local and metastatic recurrence was detected in 27.5% and 11.8% at 9-month median follow-up. Median OS was not reached at 11-month median follow-up. One- and 2-year OS frequencies were 72.3% and 58.8%, respectively. The researchers showed that MWA could be performed safety in HCC lesions [38].

According to Swan et al. [38], previous studies proved that MWA is safe in both percutaneous and open settings

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Figure 2. A 53-year-old man with hepatocellular carcinoma on IV hepatic segment near the gallbladder. In the axial plan **(A)** and **(B)** the multiplanar reconstruction in the coronal plan, multidetector CT scan before microwave ablation (MWA) treatment during arterial phase of contrast study; the lesion shows hyperenhancement. After MWA treatment **(C** and **D)**, the lesion appears without enhancement (arrow). No biliary complications are evident.

Table 2. Overall survival, local recurrence, complication rates, disease-free survival and mortality in patients with hepatocellular carcinoma treated with microwave ablation (vs. radiofrequency ablation)

Study	OS; 1, 3, 5 yr OS rates (vs. RF), %	Local recurrence (vs. RF), %	Complications rates (vs. RF), %	DFS; 1, 3, 5 yr OS rates (vs. RF), %	Mortality (vs. RF), %
Swan et al. [38]	72.8, –,–	2.9	28.9	22 mo	5
Liang et al. [39]	–	–	2.6	–	0.2
Lu et al. [43]	32.5 mo (vs. 27.1 mo)	11.8 (vs. 20.9)	8.2 (vs. 5.7)	15.5 mo (vs. 16.5 mo)	0 (vs. 0)
Simo et al. [45]	–	7.7 (vs. 0)	61.5 (vs. 45.4)	–	15 (vs. 36)
Ohmoto et al. [47]			14.3 (vs. 0)	–	–
1-yr	89 (vs. 100)	13 (vs. 9)			
2-yr	70 (83)	16 (9)			
3-yr	49 (vs. 70)	19 (vs. 9)			
4-yr	39 (vs. 70)	19 (vs. 9)			
Thornton et al. [49]	–	5 (vs. 46.6)	10 (vs. 20)	14 mo (vs. 10.5 mo)	–
Abdelaziz et al. [51]		17.8 (vs. 18.2)	2.2 (vs. 0)	–	–
Focal lesion ≤3 cm	50 mo (vs. 27 mo)			81.20 (vs. 70)	
Focal lesion >3 cm	22 mo (vs. 21 mo)			65.10 (vs. 14)	

Abbreviations: –, not applicable; DFS, disease-free survival; OS, overall survival; RF, radiofrequency.

[39–41]. Liang et al. testified a mortality frequency of 0.2% and a major complication percentage of 2.6% following percutaneous ultrasound-guided MWA in 1,136 patients with 1,928 primary and secondary liver tumors over 13 years [39]. Regional recurrence following MWA may be equivalent or lower than RFA [42–44]. Simo et al. compared safety and efficacy of laparoscopic-assisted (Lap) MWA with Lap-RF. They evaluated 35 patients with HCC. Twenty-seven tumors in 22 patients were subjected to Lap-RFA, whereas 13 patients (15 tumors) received Lap-MWA. Average ablation

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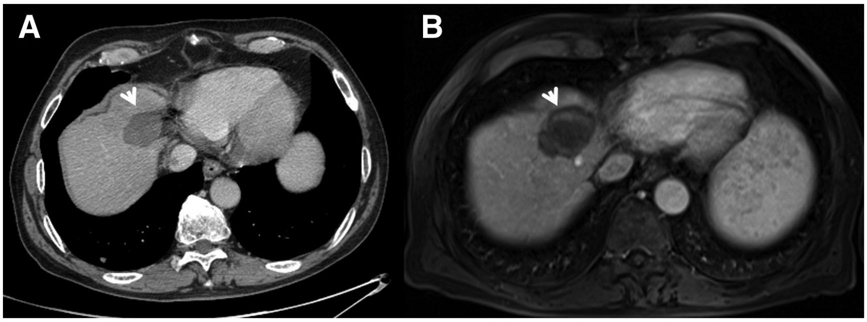

Figure 3. A 62-year-old man with hepatocellular carcinoma on VIII hepatic segment. Post- microwave ablation (MWA) treatment Multidetector CT scan [**(A)** arterial phase of contrast study] and magnetic resonance imaging study [**(B)** volume-interpolated breath-hold examination T1 weigthed fat sat during arterial phase of contrast study]. The lesion shows no contrast enhancement, with hypodense **(A)** and hypointense signal compared with surrounding liver parenchymal (arrow).

volumes were similar for Lap-RFA and Lap-MWA at 23.43 and 28.99 cm. Operative times were 149 ± 35 min for Lap-RFA and 112 ± 40 min for Lap-MWA. Lap-RFA group had a mean follow-up of 19 months: 50% were alive without disease evidence, 9% were alive with disease, 36% died, and 5% were lost to follow-up. The Lap-MWA group had a mean follow-up of 7 months: 54% were alive without disease evidence, 31% were alive with disease, and 15% died. Even if the safety of Lap-MWA is similar to Lap-RFA, this procedure offers shorter operative times and more complete necrosis rate [45].

Lesions located to VIII segment are often the most challenging to treat with laparoscopic or percutaneous method because of cephalad location near the diaphragm (Fig. 3). Because there was a 20% failure rate for lesions of segment VIII, these patients are candidates for repeat ablation [46]. Abe et al. described complete ablation of HCC lesions of segment VIII in 9 of 15 lesions. In their cases, among the six lesions that had incomplete necrosis, two were near the diaphragm. The authors do not recommend MWA treatment for lesions that are in contact with the diaphragm because there was an increase of incomplete ablation risk, diaphragm injury, and pneumothorax [46]. Additionally, the researchers showed that the lesions near to the gallbladder are difficult for complete coagulation to be achieved. Thus, the authors recommend ablation in close proximity to the gallbladder be performed, combining it with laparoscopic cholecystectomy. Conversely, Simo et al. [45] used MWA for two segment IVB lesions that were close to the gallbladder, and they obtained complete necrosis without residual tumor or complications.

Ohmoto et al. assessed the therapeutic efficacy and safety of RFA and percutaneous MWA to treat HCCs smaller than 2 cm in diameter [47]. Thirty-seven HCCs in 34 patients were subjected to RFA and compared with 56 HCCs (49 patients) that underwent to MWA. The procedure was repeated until complete tumor ablation. The efficacy and complications were compared between the two approaches. There were significantly fewer treatment sessions in the RFA group than in the MWA group, but the ablation area was significantly larger in the former group. Regional recurrence rate was significantly lower with RFA than MWA, although the ectopic recurrence percentage showed no significant difference. The cumulative OS was significantly higher for RFA than MWA. The pain and fever incidence was significantly higher for MWA than RFA. Bile duct injury, pleural effusion, and ascites were also significantly more common after MWA [47].

Zanus et al. evaluated the macroscopic and microscopic evidence of complete tumor ablation on explanted liver specimens [48]. A total of 154 patients with HCC were treated with several treatment approaches: percutaneous ablation (73 patients) for 114 nodules (mean size, 35.6 ± 18.3 mm) was performed with 85 sessions; model for end-stage liver disease (MELD) score was 9.3 ± 2.6. Video-assisted laparoscopic ablation was performed in 69 patients with 89 nodules and a mean size of 30.1 ± 15.7 mm. Video-thoracoscopic ablation was successful in three patients with posterior lesions located in an area not otherwise treatable with a noninvasive technique, and open ablation was performed in nine patients combined with other laparotomy resection procedures. Six patients underwent orthotopic liver transplantation (OLT) with cava-preserving technique. Two patients were subjected to MWA downstaging with return to OLT criteria after ablative treatment; four patients were subjected to MWA while awaiting OLT, seeking to reduce the list dropout risk. Independently of the procedure (percutaneously or laparoscopically), the specimens showed resolution of treated nodules by histological findings without peritoneal carcinomatosis and lymph node involvement at the time of OLT. According to Zanus et al. [48], MWA appeared to be a safe procedure to treat unresectable HCC. The technological progress ("mini-choke") permits researchers to obtain a larger diameter of necrosis area more quickly than with RFA [48]. Thornton et al. compared the initial response, local recurrence, and complication rates of RFA versus MWA when combined with neoadjuvant bland transarterial embolization (TAE) or drug-eluting microsphere chemoembolization (TACE) for the treatment of HCC [49]. Thirty-five patients with HCC with Barcelona Clinic Liver Cancer (BCLC) very early and early stage (range, 1.2–4.1 cm) underwent TAE (23), TACE (12), RFA (15), or MWA (20). Complete response rate was 80% (12/15) for RFA + TAE/TACE and 95% (19/20) for MWA + TAE/TACE. Local recurrence rate was 30% (4/12) for RFA + TAE/TACE and 0% (0/19) for MWA + TAE/TACE. Durability of response, defined as local disease control for the duration of the study, demonstrated a significant difference in favor of MWA. There was no statistical difference in complication rates (3% vs. 2%) [49]. In contrast to Thornton et al. [49], Vasnani also compared the efficacy of RFA and MWA in combination with transarterial chemoembolization (DEB-TACE), demonstrating that both RFA and MWA in sequential combination with DEB-TACE are equally efficacious at inducing HCC tumor coagulation [50].

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The authors assessed 42 patients who underwent combined therapy: 11 tumors (2.9 cm; range, 1.8–4.3) treated with DEB-TACE/RFA and 40 tumors (mean, 2.4 cm; range, 1.1–5.4) with DEB-TACE/MWA. The mean TACE sessions in the RFA and MWA groups were 1.3 (range, 1–2) and 1.3 (range, 1–3), respectively. The mean thermal ablations in the RFA and MWA groups were 1.2 (range, 1–2) and 1.3 (range, 1–3), respectively. Tumor necrosis was assessed on explanted livers. For RFA and MWA groups, necrosis was of 88.9% (range, 0%–100%) and of 90.5% (range, 30%–100%), respectively. Complete tumor coagulation percentage for RFA and MWA was of 45% and of 53%, respectively. No difference in tumor necrosis was found between the two groups when tumors <3 cm and >3 cm were considered separately. Among all 51 tumors, mean tumor coagulation of 95.8% was found on the 36 complete response on imaging at liver transplantation (LT). No correlation was reported between tumor coagulation and initial tumor size or time interval to LT. No tumor seeding was demonstrated along the ablation tracts [50]. Abdelaziz et al. demonstrated that TACE-MWA obtained better response rates than TACE-RFA with tumor size of 3–5 cm, with no difference in survival rates [51]. They assessed 22 patients who underwent TACE-RFA and 45 who underwent TACE-MWA. All patients were classified as Child-Pugh class A/B cirrhotics, and no lesion was larger than 5 cm in diameter. TACE was followed within 2 weeks by either RFA or MWA. The TACE-MWA group had a higher complete response rates than TACE-RFA group. This was mainly apparent with lesions size of 3–5 cm. The researchers showed that there were no significant difference of rates of complications between the groups, as well as the recurrence-free survival (RFS) at 1- year, 2-, and 3- years (for the TACE-RFA group, 70%, 42%, and 14%, respectively and for TACE-MWA group, 81.2%, 65.1%, and 15.1%). Overall median survival was 27 months. In relation to the size of focal lesions, they found no statistically significant difference in the survival proportions between the groups [51].

Yi et al. compared RFA or MWA and TACE with RFA or MWA monotherapy in HCC. They enrolled 94 patients with HCC ≤7 cm who were randomly allocated into the combined treatment group (TACE-RFA or TACE-MWA) and control group (RFA alone or MWA alone). The primary objective was OS. The secondary objective was recurrence-free survival, and the tertiary objective was adverse effects. Seventeen patients in the combined group died at the time of the report (median follow-up time was 47.5 ± 11.3 months). Twenty-five patients in the control group died (median follow-up time was 47.0 ± 12.9 months). The researchers showed that the patients in the TACE-RFA or TACE-MWA group had better OS than the RFA or MWA. In fact, the 1-, 3-, and 5-year OS for the TACE-RFA or TACE-MWA group were 93.6%, 68.1%, and 61.7%, respectively, whereas for the RFA or MWA, the rates were 85.1%, 59.6%, and 44.7%, respectively. Also, they showed that the combined group had a better RFS than RFA or MWA. They concluded that RFA or MWA combined with TACE to treat HCC lesions ≤7 cm was superior to RFA or MWA alone [52]. In fact, iodized oil and gelatin sponge particles used in TACE can increase RFA- or MWA-induced coagulation necrosis by going through multiple arterio-portal communications, and effects are improved in terms of shorter ablation time, maximum output, and portal angiography by TACE with iodized oil. Several authors showed that recurrent lesions usually arose in the liver at a segment distant from resection margin or at multiple liver segments [53, 54]. Therefore, TACE, thanks to the possibility of creating an enlarged ablated area, gives better control on microlesions and increases the chance of total necrosis of satellite nodules, reducing the risk of recrrence, and improving patients outcomes [55].

RFA is now the most common and extensively employed ablation therapy. It had several advantages, such as safety, tolerability, efficacy, ease of use, and cost-effectiveness. Several studies showed that RFA, among all ablative procedures, is to be chosen in patients with HCC smaller than 3 cm, because it reported a complete necrosis frequency of 99% of treated lesions [56]. A large number of studies have confirmed the efficacy of RFA in patients with early HCC, suggesting this procedure as feasible therapeutic option in unresectable early stage. Considering the state of the art of the literature, RFA provided 5-year survival rates of 40%–70% and beyond in HCC series [27–36]. However, despite the high rate of necrosis, the recurrence frequency is extremely variable, from 2% to 39% [27–36]. Unlike OS, reported rates of LR after RFA are not univocally ranging [27–36], maybe because of different etiologies of HCC in the published series, different approaches to the problem of insufficient ablative margins, use of combined treatment and, above all, different definition of radiologic tumor recurrence at imaging. Moreover, an insufficient ablation margin after the treatment appear to be an important prognostic factor for LR. The main limits of RFA are associated with poor energy penetration into tissues with high thermal and electric impedance, the intrinsic 100°C upper temperature threshold that causes tissue charring, and the slow tissue heating mechanism leading to tissue sensitivity to convective heat-sink effects induced by blood circulation in proximity to the ablation area. MWA exceeds all these limits. However, higher heating velocity and efficacy are achieved through a somewhat increased technological complexity, and costs compared with RFA [57]. Early MWA systems had some technical limits, such as inadequate power handling to large probe diameter, poor predictability of the radiated field pattern, and uncontrolled back-heating effects. MW devices upgrade allowed treatment of medium and large HCC lesions through a percutaneous or laparoscopic approach. Therefore, hepatic nodules close to gallbladder, bile ducts, or gastrointestinal tract could be safely treated in this way. Laparoscopic MWA can also be a feasible choice for patients unsuitable for HR because of impaired liver function or severe comorbidities [57].

A large number of studies have confirmed the efficacy of RFA in patients with early HCC, suggesting this procedure as feasible therapeutic option in unresectable early stage. Considering the state of the art of the literature, RFA provided 5-year survival rates of 40%–70% and beyond in HCC series.

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The major open question is related to the optimal size range of liver tumors amenable to ablation therapy, which has not

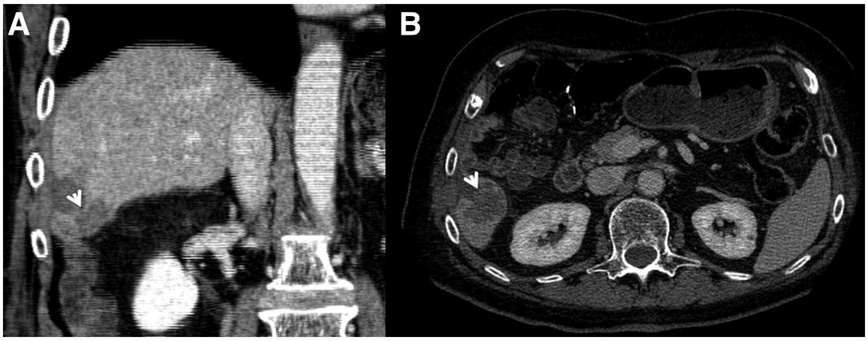

Figure 4. A 48-year-old woman with colorectal liver metastasis on VI hepatic segment treated with radiofrequency ablation. In **(A)** (Multiplanar reconstruction in coronal plane) and **(B)** (Multidetector CT in axial plane during portal phase of contrast study), incomplete ablation with residual disease (arrow) that shows less hypodense feature compared with ablated zone.

been clearly defined and is closely related to anatomic factors, such as proximity to major vessels that influence the ability to deposit sufficient thermal dose to coagulate tissue. Likewise, the number of tumors in a single patient that can undergo ablation is difficult to specify because the size of each tumor will also play a role in effectiveness. Although there is no established threshold of tumor diameter or tumor number that is associated with ablation treatment success or failure, our current understanding of hepatic tumor ablation indicates that HCCs 5 cm or less in diameter have a higher probability of having complete ablation compared with those greater than 5 cm in diameter. Indeed, this size stratification has been taken further to show superior results with tumors smaller than 3 cm, intermediate but acceptable results for those measuring 3–5 cm, and fairly dismal results for tumors larger than 5 cm [26].

Metastases and Ablative Techniques

The increase of knowledge in oncology and the necessity to manage patients with metastatic disease within a multidisciplinary team has improved the clinical outcome [58]. In fact, today the median OS frequency for patients with metastatic colorectal cancer is 30 months, more than double that of 20 years ago; the features involved are a closer patient follow-up to obtain an earlier detection of metastatic disease, efficacy increase of systemic therapies based on patient selection, and an increase in the number of patients undergoing complete surgical resection of metastases [59]. Additionally, the spread of ablative techniques [60] and of chemotherapeutic targeted therapies [61, 62] can be selectively applied with the aim to make the patient eligible for resection. Although surgical resection is still the gold standard for the management of metastatic liver cancer, most patients are not eligible for this procedure because of anatomic limitations, insufficient functional liver reserve, multifocal nature of the disease, extrahepatic metastases, or medical comorbidities [63]. Consequently, several ablative or interstitial therapies have been developed for the treatment of unresectable liver metastases.

Metastases and RFA

RFA has become a recognized therapy because of its efficacy, safety, and availability [58]. However, major limits are high local recurrence frequencies (Fig. 4), mainly for lesions larger than 3 cm [64, 65], and a potential incomplete ablation of lesion near large vessels (>3 mm in diameter). In this setting, multiple overlapping probe placements are required to achieve larger ablation zones, which makes the procedure more consuming and less safe for the patient [65]. Therefore, technological progresses resulted in the development of new ablative techniques such as the MW (Table 3).

Metastases and MWA

MWA energy is not limited by charring and tissue desiccation, whereas the size and shape of the ablation zone may be more consistent and less dependent on the heat-sink effect (Fig. 5) [8–10]. MWA zone can be up to 6 cm surrounding the MW antenna, allowing for a large cell destruction volume within the targeted area [66–68]. Size and geometry of the ablated area are further features from which depend local recurrence after ablative treatment. Studies on the ablated area size after MWA versus RFA are contradictory, as little is known about the ablated zone geometry [69, 70]. Several authors demonstrated that larger necrosis area can be obtained with multiple or clustered MW antennas [71–73]. In fact, using simultaneous multiple-probe MWA, it is possible to obtain more uniform necrosis area with a better performance near blood vessels that might decrease recurrence rates after treatment. However, the use of multiple-probe MWA could cause an increased "comet effect" and unwanted collateral damage to neighboring structures [74]. Conversely for tumors with dimeter <2.0 cm, one or two deployments of the RF monopolar multiple array needle electrode are sufficient to produce complete tumor necrosis. However, with increasing tumor size, there is an increase in the number of RF needle electrode deployments and in the time to produce complete coagulative necrosis. Generally, RFA is a safe, well-tolerated, effective treatment for unresectable hepatic malignancies with a dimeter <6.0 cm [75]. Velez et al. assessed the safety and efficacy of ablative therapies in preclinical study on F344 rats (150 g, $n = 96$) with subcutaneous R3230 breast adenocarcinoma tumors, testing the device effect and heating parameters on local tissue reactions and distant tumor growth [76]. They evaluated RFA (70°C for 5 minutes), rapid higher-power MWA (20 W for 15 seconds), slower lower-power MWA (5 W for 2 minutes), or a sham procedure (needle placement without energy). The rats were sacrificed at 6 hours and up to 7 days. Distant tumor growth frequencies were determined to 7 days after

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Table 3. Overall survival, local recurrence, complication rates, disease-free survival, and mortality in liver metastases patients treated with RFA or MWA

Study	OS 1, 3, 5 yr OS rates, RFA (vs. MWA)	Local recurrence, RFA (vs. MWA)	Complications rates, RFA (vs. MWA)	DFS 1, 3, 5 yr OS rates, RFA (vs. MWA)	Mortality, RFA (vs. MWA)
Scaife et al. [60]	–	10	22	–	2
van Duijnhoven et al. [64]	27.8 mo	35.7	–	15 mo	–
van Tilborg et al. [77]	not statistically different for both the survival times from primary tumor diagnosis and survival times from ablation	3 mo, 9.3 and 12 mo, 21.9 (vs. 25.0 and 39.6)	3.2 (vs. 57.1)	–	0 (vs. 0)
Correa-Gallego et al. [79]	no difference (55 mo [IQR 25-NR] vs. NR [IQR 25-NR] for RFA and MWA, respectively, *p* = .5)	20 (vs. 6)	24 (vs. 27)	–	–
Liu et al. [81]	84.9, 48.8, 36.3	20.3 (vs. 8.6)	1.1; no difference	–	0 (vs. 0)
Ding et al. [87]	–	–	3.5 (vs. 3.1)	–	0.31 (vs. 0.36)

Abbreviations: –, not applicable; DFS, disease-free survival; MWA, microwave ablation; mo, months; NR, not appropriate; OS, overall survival; RFA, radiofrequency ablation; yr, year.

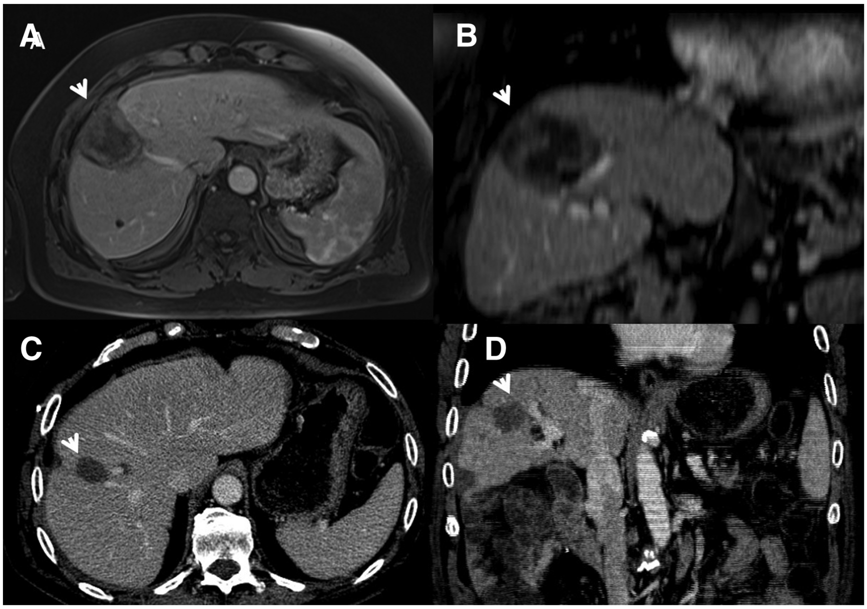

Figure 5. A 51-year-old man with colorectal liver metastasis. Magnetic resonance imaging [**(A)** VIBE T1-W FS during portal phase of contrast study and **(B)** Multiplanar reconstruction in coronal plane] and multidetector CT [**(C)** portal phase of contrast study on axial plane and **(D)** MPR in coronal plane] studies show lesion without enhancement, with regular enhancement of portal branch near to the treated area. The time between the MDCT examination and MR scan is 7–10 days.

treatment. They assessed liver heat shock protein (HSP) 70 levels (at 72 hours) and macrophages (CD68 at 7 days), tumor proliferative indexes (Ki-67 and CD34 at 7 days), and serum and tissue levels of interleukin 6 (IL-6) at 6 hours, hepatocyte growth factor (HGF) at 72 hours, and vascular endothelial growth factor (VEGF) at 72 hours. At 7 days, they showed that 5-W MWA and RFA amplified distant tumor size than to 20-W MWA and the sham procedure RFA and 5-W MWA improved postablation tumor growth proportions compared with the 20-W MWA and sham arms. Tumor proliferation (Ki-67 percentage) was increased for 5-W MWA (82% $\pm$ 5) and RFA (79% $\pm$ 5), followed by 20-W MWA (65% $\pm$ 2), compared with sham (49% $\pm$ 5). Also, distant tumor microvascular density was greater for 5-W MWA and RFA. Furthermore, 5-MWA and RFA resulted in increased HSP 70 expression and macrophages in the peri-ablational rim. Last, IL-6, HGF, and VEGF elevations were seen in 5-W MWA and RFA compared with 20-W MWA and sham. They concluded that although MWA can cause peri-ablation inflammation and increased distant tumor growth similar to RFA in an animal tumor model, higher-power, faster heating protocols might theoretically reduce undesired effects [76].

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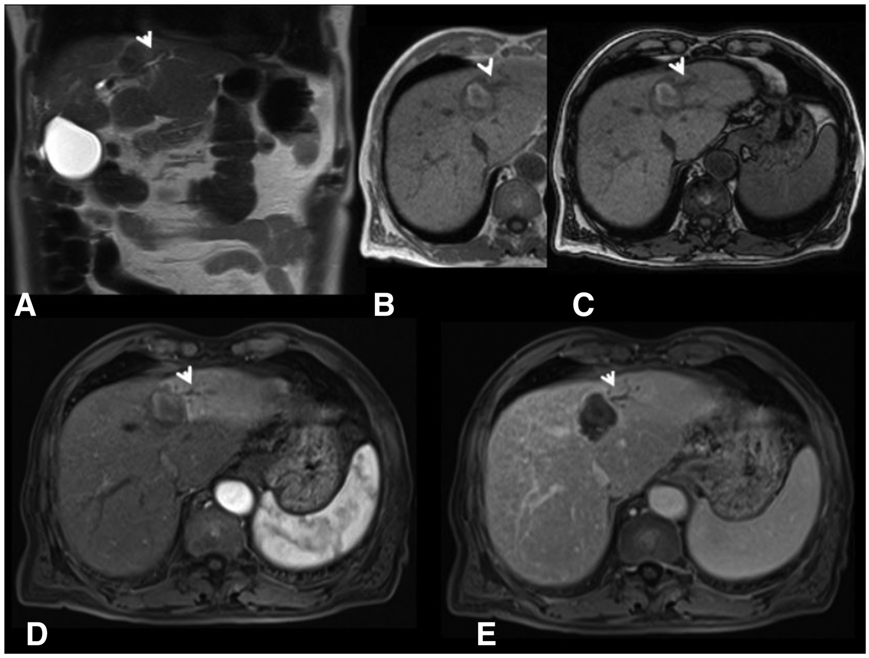

Figure 6. A 72-year-old woman with peribiliary colorectal liver metastasis treated with microwave ablation. Magnetic resonance imaging [**(A)** half-Fourier acquired single-shot turbo spineEcho T2 weighted coronal plane; **(B)** T1-W in of phase in axial plane; **(C)** T1-W out of phase in axial plane; **(D)** volume-interpolated breath-hold examination T1 weigthed fat sat during arterial phase of contrast study; **(E)** VIBE T1-W FS during portal phase of contrast study] study shows the lesion with hypointense signal on T2-W, hypointense signal on T1-W (**B** and **C**), without contrast enhancement (**D** and **E**) and with biliary injury (dilation of a biliary branch; arrows).

A paper by van Tilborg et al. reported RFA and MWA safety and efficacy in the treatment of unresectable colorectal liver metastases (CRLMs) near large vessels and/or major bile ducts. It is known that heat could cause acute or chronic damage to major bile ducts. Although MWA in several preclinical and clinical studies has been suggested to be more effective than RFA for perivascular nodules [20, 21, 23–25], the authors showed that for perivascular CRLM, RFA and MWA are both safe options that effective treatments. MWA is currently supported as superior to RFA for perivascular lesions, whereas RFA represent a safer option for peribiliary CRLM because of the less aggressive heat production and superior ablation zone predictability (Fig. 6). The authors evaluated 243 patients with 774 unresectable CRLM. One hundred and twenty-two patients had at least one perivascular or peribiliary lesion (*n* = 199). Primary efficacy rate of RFA was superior to MWA after 3 and 12 months of follow-up; however, after multivariate analysis, this difference was nonsignificant at 12 months and disappeared after repeat ablations [77]. Complications were classified according to the conventional criteria for adverse events (CTCAE version 4.0) and divided into three categories: (a) electrode or antenna placement, (b) thermal injury, and (c) secondary to the general procedure [78]. More CTCAE grade III complications happened after MWA versus RFA (18.8 vs. 7.9 %). Thermal ablation near to major bile ducts appears effective, although major complications can occur. Similar efficacy and lower complication rates were demonstrated for RFA in lesions that are located in the vicinity of the main bile ducts [77].

Contrary to van Tilborg et al. [77], Correa-Gallego et al. [79] demonstrated that MWA is more effective than RFA, with a decrease in local recurrence rate. They treated 351 tumors (222 RFA and 129 MWA). Twenty-five percent of patients showed post-treatment complications. The researchers showed that the morbidity rates were similar between the MWA and RFA group (27% vs. 24 %, respectively). Regional recurrence was seen in 19% of cases. MWA group had lower recurrence rates compared with RFA group, whereas follow-up time was significantly shorter for MWA group (18 months) than RFA group (31 months). There was no difference between groups in median values of OS [79].

In a recent systematic review (75 studies enrolled; years range between 1994 and 2010), the authors evaluated clinical outcomes and local recurrence rates postablative therapies in colorectal liver metastases. They showed that RFA had regional recurrence rates (between 10% and 31%) lower than cryotherapy (12%–39%). MWA showed the lowest regional recurrence percentages (5%–13%). These publications cover a long time period, during which the criteria to define resectable a hepatic lesion have changed dramatically, thus making a comparison between these cohort studies intrinsically flawed [80].

Liu et al. assessed the RFA and MWA efficacy and safety not only in colorectal metastases [81]. One hundred and thirty-two liver metastases in 89 patients (size, 0.8–5.0 cm) were treated with MWA or RFA. Local tumor control, complications, and long-term survival were analyzed. MWA resulted in less local recurrence than RFA. Complete necrosis was relived in 117 of 132 (88.6%) nodules. Local recurrence was relived in 17 of 117 (14.5%) nodules. A

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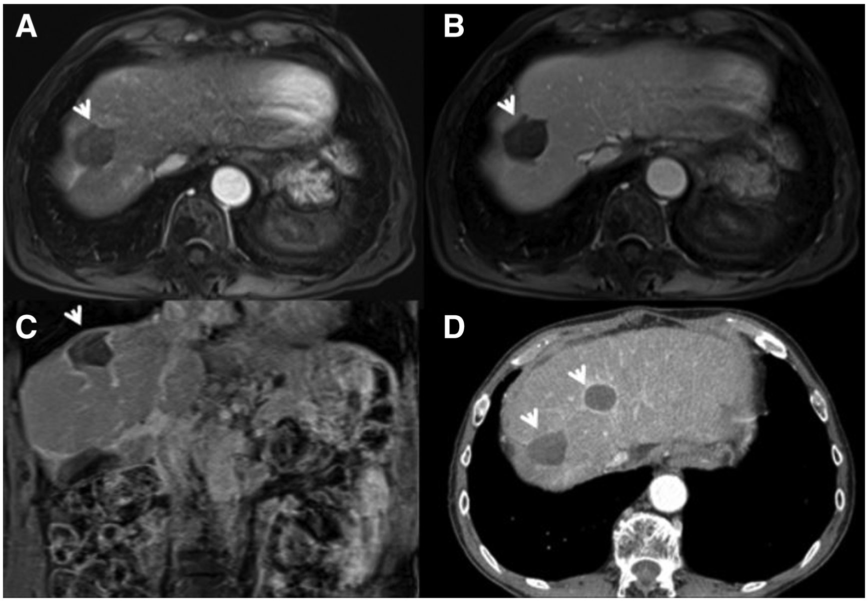

Figure 7. A 72-year-old man with microwave ablated colorectal liver metastasis (CRLM) on VIII-VII hepatic segment. Magnetic resonance imaging [**(A)** volume-interpolated breath-hold examination T1 weigthed fat sat during arterial phase of contrast study in axial plane; **(B)** volume-interpolated breath-hold examination T1 weigthed fat sat during portal phase of contrast study in axial plane; **(C)** volume-interpolated breath-hold examination T1 weigthed fat sat during portal phase of contrast study in coronal plane] study shows no residual disease and no diaphragm injury and pneumothorax. In **(D)** Multidetector CT scan during portal phase of contrast study follow-up at 1 years post a new microwave ablation treatment for another CRLM: no residual disease and no diaphragm injury and pneumothorax.

significant trend toward a lower local recurrence rate with MWA was observed. Multivariate analysis indicated that the number of cycles of chemotherapy was the significant prognostic factor for overall recurrence, whereas disease-free interval was the significant prognostic factor for distant recurrence. Ablation modality showed potential prognostic significance for regional recurrence. Major complications occurred in 1.1% of patients. The 1-, 2-, 3-, and 5-year OS were 84.9%, 59.6%, 48.8%, and 36.3%, respectively [81]. The efficacy and limits of RFA for liver metastases have widely been reported. Because of the physical limits in energy penetration, the RFA efficacy in local tumor control decreases increasing lesion size, so the site close to large vessels can influence the effectiveness as previously reported. As is reported for HCC, in the treatment of metastases, MWA causes larger ablation areas than RFA and appears to be less influenced by heat-sink effect. Several studies showed that outcomes of RFA and MWA in patients with up to six metastases (with dimeter <6 cm) are comparable, with 3-year OS of 28%–46% and 46%–51%, respectively, and 5-year OS of 25%–46% and 17%–32%, respectively [82, 83].

According to the literature, the overall survival, local recurrence, complication rates, and mortality in patients with liver metastases treated with RFA (vs. MWA) are not statistically different for both the survival times from primary tumor diagnosis and survival times from ablation, between 10% (vs. 6%) and 35.7% (vs. 39.6), between 1.1% (vs. 3.1%) and 24% (vs. 27%), and between 0% (vs. 0%) and 2% (vs. 0.3%).

To date, in most centers of interventional oncology or interventional radiology, the procedure choice depends on the physician's experience or technical availability. However, these techniques have specific advantages and limitations that can make each of them more appropriate than the other one to treat patients with different characteristics. RFA is the longer recognized ablative technique, and its efficacy has been largely proven; subcapsular or high-risk location of the tumors is considered a relative contraindication to RFA, so, as lesions from >2 to 2.5 cm, need multiple overlapping ablations to obtain a complete necrosis. This is also the case if tumors close to large blood vessels can be incompletely treated because of the heat-sink effect. MWA can cause necrosis in a larger target area; has deeper penetration of energy, with better propagation across the poorly conductive tissue; and shows less sensitivity to heat-sink effect than RFA. In contrast, MW energy is more difficult to distribute than RF energy [11]. Consequently, MWA appears less feasible than RFA in the treatment of high-risk located and subcapsular nodules. Also, the cost of the procedure could be considerate during the work up of the patient. In fact, the cost of MW antennas in the U.S. is about $3,000, whereas the RFA probes are much less; conversely, in Europe the costs are similar, with a difference of about 500 Euros. Some authors suggest that the reference centers for thermal ablation should be equipped with all available procedures so as to be able to use the best and the most suitable one for each type of tumor [84]. Recently, according to advantages and limits of the different ablative techniques, and to the number, size, and location of the liver lesions and cost-saving considerations, an algorithm has been proposed [85]. On the basis of this algorithm, a single nodule <2 cm in size could be treated using all the thermal procedures, but RFA and laser thermal ablation

Table 4. Mayor complication rates, minor complication rates and mortality in liver tumor treated with RFA or MWA

Study	Technique	Mayor complication rates, %	Minor complication rates, %	Mortality, %
Park et al. [27]	RFA	10.5	–	0
Gory et al. [31]	RFA	2	–	–
Swan et al. [38]	MWA	28.9	–	5
Liang et al. [39]	MWA	2.6	–	0.2
Lu et al. [43]	MWA/RFA	8.2/5.7	–	0/0
Simo et al. [45]	MWA/RFA	61.5/45.4	–	15/36
Ohmoto et al. [47]	MWA/RFA	14.3/ 0	–	–
Thornton et al. [49]	MWA/RFA	10/20	–	–
Abdelaziz et al. [51]	MWA/RFA	2.2/0	–	–
Scaife et al. [60]	RFA	22		2
Simon et al. [73]	MWA	No direct post-treatment complications were noted	–	5 related to hepatic resection
van Tilborg et al. [77]	RFA/MWA	3.2 /57.1		0/0
Gillams et al. [82]	RFA	4	6	–
Ding et al. [87]	RFA/MWA	3.5/3.1		0.31/0.36
Liang et al. [89]	MWA	2.6	100	0.2
Livraghi et al. [90]	MWA	2.9	7.3	0

Abbreviations: –, not applicable; MWA, microwave ablation; RFA, radiofrequency ablation.

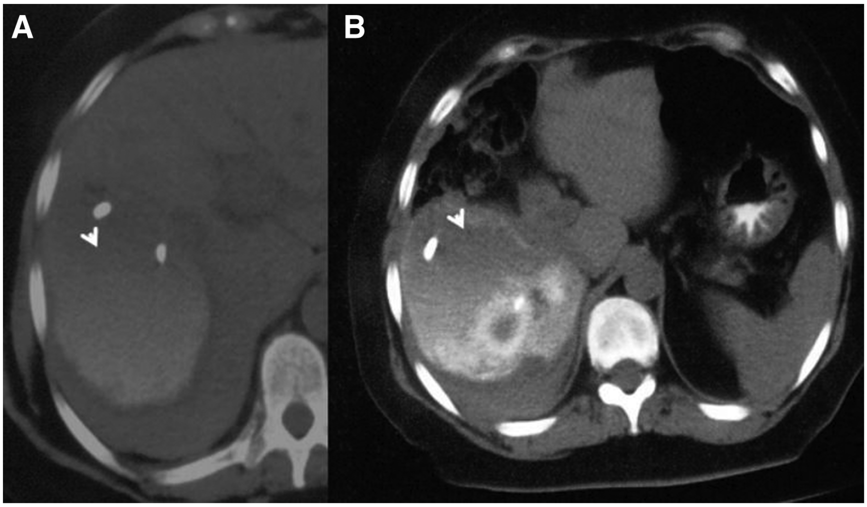

Figure 8. Multidetector CT scan without contrast medium during emergency setting **(A** and **B)** for hemoperitoneum post-radiofrequency ablation treatment. The bleeding is hyperdense (arrow).

(LTA) are cheaper than MWA and should be preferred. Conversely, MWA should be preferred in case of tumor size ≥3 cm in diameter (Fig. 7) or in case of large vessels close to lesion independently by its size. LTA should be preferred in case of multiple small and variably sized lesions. This algorithm reflects the personal experience and opinion of the authors [84].

Complications

Goldberg et al. defined a major complication as an event that leads to substantial morbidity and disability, increasing the level of care or resulting in hospital admission or substantially lengthened hospital stay. Events different from this scenario are minor complications [86]. To date, RFA and MWA do not show statistically significant difference in mortality or major or minor complications rates (Table 4) [87]. Specifically, MWA is a safe technique for the treatment of unresectable liver tumors with a mortality that ranges from 0% to 0.36% [88–91]. RFA and MWA have the same rate of major complications [88–91]. To reduce major complications incidence (Fig. 8), the patient selection and percutaneous or surgical approach choice are essential; high-risk patients for infections, coagulation disorders, and previous abdominal surgery should be evaluated to establish the right cost-benefit rate of the ablation method. Gastrointestinal perforation or thermal biliary injury should be avoided using

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thermocouples to check the temperature and allow timely procedure interruption. Moreover, physicians learning curve and MW antenna technology progress have considerably reduced complications from thermal damage [91].

RFA and MWA do not show statistically significant difference in mortality or major or minor complications rates (Table 4). Specifically, MWA is a safe technique for the treatment of unresectable liver tumors with a mortality that ranges from 0% to 0.36%. RFA and MWA has the same rate of major complications. To reduce major complications incidence (Fig. 8), the patient selection and percutaneous or surgical approach choice are essential; high-risk patients for infections, coagulation disorders, and previous abdominal surgery should be evaluated to establish the right cost-benefit rate of the ablation method.

Conclusion

Surgical resection is the gold standard for treatment of primary or metastatic liver cancer. However, most patients are not candidates for hepatic resection because of anatomic limitations, multifocal nature of the disease, insufficient functional liver reserve, extrahepatic metastases, or comorbidities. The most commonly used thermal ablation modalities are RFA and MWA. RFA has become a recognized treatment approach because of its efficacy, reproducibility, low complication rates, and availability. According to the literature, the overall survival, local recurrence, complication rates, disease-free survival, and mortality in patients with HCC treated with RFA vary between 53.2 ± 3.0 months and 66 months, between 59.8% and 63.1%, between 2% and 10.5%, between 22.0 ± 2.6 months and 39 months, and 0% and 1.2%, respectively. However, despite the high rate of necrosis, the recurrence frequency is extremely variable. Unlike OS, reported rates of LR after RFA are not univocal ranging. The benefits of MWA are an improved convection profile, higher constant intratumoral temperatures, faster ablation times, and the ability to use multiple probes to treat multiple lesions simultaneously. MWA target area size and shape may be more consistent and less dependent on the heat-sink effect from vascular structures in proximity of the lesion. RFA has been available used in the time and is the more established thermal technique, but lesions with a diameter >2–2.5 cm need multiple overlapping ablations, and subcapsular or high-risk location of tumors is considered a relative contraindication to RFA. MWA should be preferred when tumor size is ≥3 cm in diameter or in case of lesion near to large vessels independently of size, Moreover, MWA can reach larger ablation volumes without heat-sink effect. According to the literature, overall survival, local recurrence, complication rates, disease-free survival, and mortality in patients with HCC treated with MWA (compared with RFA) vary between 22 months for focal lesion >3 cm (vs. 21 months) and 50 months for focal lesion ≤3 cm (vs. 27 months), between 5% (vs. 46.6%) and 17.8% (vs. 18.2%), between 2.2 % (vs. 0%) and 61.5% (vs. 45.4%), between 14 months (vs. 10.5 months) and 22 months (vs. no data reported), and between 0% (vs. 0%) and 15% (vs. 36%), respectively.

According to the literature, the overall survival, local recurrence, complication rates, and mortality in patients with liver metastases treated with RFA (vs. MWA) are not statistically different for either the survival times from primary tumor diagnosis or survival times from ablation, between 10% (vs. 6%) and 35.7% (vs. 39.6), between 1.1% (vs. 3.1%) and 24% (vs. 27%), and between 0% (vs. 0%) and 2% (vs. 0.3%).

Therefore, the thermal ablation approach should depend on patient characteristics. Reference centers for thermal ablation should be equipped with all available techniques to be able to use the best and the most suitable approach tailored to each patient.

Regarding metastases, both RFA and MWA are safe options for effective treatment. MWA is currently supported as superior to RFA for perivascular lesions, whereas RFA represents a safer option for peribiliary CRLM because of the less aggressive heat production and superior ablation zone predictability.

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Disclosures

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