# Chapter 9
# Thermal Ablation for Treating Malignant Tumors to the Liver

**Andreas H. Mahnken and Thierry de Baère**

## 9.1 Introduction

Most thermal ablation techniques were initially established for treating inoperable hepatocellular carcinomas (HCC). In the face of the technical success, ease of use, and relatively low complication rates, the indications for local ablation were rapidly extended and are now established for treating a wide range of primary and secondary liver malignancies. Moreover, its use has been described in virtually all major organs. Several thermal ablation techniques are currently in clinical use, including radiofrequency (RF) ablation, microwave ablation (MWA), and cryoablation.

A.H. Mahnken (✉)
Department of Diagnostic and Interventional Radiology, University Hospital Marburg, Philipps University of Marburg, Marburg, Germany
e-mail: mahnken@med.uni-marburg.de

T. de Baère
Department of Interventional Radiology, Institute Gustave Roussy, Villejuif, France



E. Van Cutsem et al. (eds.), *Locoregional Tumor Therapy*,
https://doi.org/10.1007/978-3-319-69947-9_9

Nowadays new promising nonthermal ablation techniques such as irreversible electroporation are under investigation, but due to the lack of clinical data still have to be considered experimental. Most clinical data deals with radiofrequency (RF) ablation. Therefore this chapter will focus on RF ablation.

## 9.2 Ablation Techniques

### *9.2.1 Radiofrequency Ablation*

RF ablation requires a closed-loop circuit created with an RF generator, an active tip electrode inside the target lesion, neutral electrodes placed on the patients' skin, or less commonly another electrode inside the target lesion (multipolar ablation). High-frequency alternating currents (360–480 KHz) applied via the electrodes cause heat to form due to ionic agitation within the target tissue. The resultant ionic agitation creates frictional heat which spreads via conduction, leading to cell death from coagulative necrosis. In order to achieve reliable tumor destruction, the target needs to be treated with >60 °C. Temperatures higher than 100 °C can cause gas formation (vaporization) and carbonization. These effects are known to reduce ablation effectiveness. Effectiveness can be improved by various probe designs (e.g., internal cooling, umbrella, etc.), use of multiple probes, current modulation, and energy output of the generator.

### *9.2.2 Microwave Ablation*

For MWA a high-frequency oscillating electromagnetic field (915 MHz or 2.45 GHz) is delivered to the target lesion via an active antenna. This high-frequency oscillating electromagnetic field induces rapid realignment of water molecules in the target lesion. This results in friction and subsequent tissue heating. Tissues with a high concentration of water are particularly susceptible to microwave heating. The antenna design and active length is limited due to physical dependencies between frequency and active tip length. Microwave ablation is known to create higher temperatures and bigger lesions in less time than RF ablation. Like in RF ablation, MWA creates coagulative necrosis. The use of multiple probes, different cooling systems, and higher energy output can enhance lesion size.

### *9.2.3 Cryoablation*

Cryoablation utilizes the Joule–Thomson effect. It works by passing high-pressure argon gas through a thin probe. Rapid expansion of the gas in an expansion chamber at the tip of the probe results in cooling of the metal of the probe down to −180 °C and less. As the probe cools, surrounding tissues are also cooled, creating a visible iceball. For thawing helium gas is then forced through the probe causing warming of the probe and of the adjacent tissues. A different technique using fluid nitrogen for creating an iceball is much less effective and outdated. The cooling and subsequent thawing of the probe results in cell death caused by several processes. Firstly, cooling results in intracellular ice crystal formation, leading to cell membrane damage and cell death. Secondly, larger ice crystals form during slow thawing, resulting in a shearing effect triggering a different mechanism of cell death. Thirdly, ice crystal formations in small blood vessels cause ischemia. The lethal isotherm for cryoablation is somewhere between −40 and −20 °C, well inside the visible iceball, which marks the 0 °C isotherm. The use of multiple probes with different active lengths allows to individually tailor the size of the iceball.

## 9.3 Outcomes

### *9.3.1 HCC*

RF ablation is an established competitor for surgery in the treatment of small HCC, and it is accepted for bridging the time to liver transplantation. Guidelines recommend the use of RF ablation for treating up to 3 HCC foci measuring up to 3 cm in case of contraindication to surgery [1]. RF ablation has been proven to be superior to percutaneous ethanol injection therapy [2]. The most important predictor of long-term survival is an initially complete ablation with an adequate safety margin [3]. There is some conflicting data from randomized controlled trials comparing RF ablation to surgery in small HCC [4–6]. The overall survival rates after RF ablation are quite similar to those of surgery [5, 6], but the disease-free survival is longer after resection. With overall survival being the most relevant parameter in HCC, RF ablation appears to be more or less equal to surgery in HCC tumors within the Milan criteria.

As stated above, the comparative data on RF ablation versus resection is conflicting. A current meta-analysis comparing RF ablation and resection for HCC within the Milan criteria including 877 patients concluded that resection appears to be superior to RF ablation [7]. However, this meta-analysis was based on only six studies, while other studies which should have qualified for this analysis were not included. In contrast, a recent systematic review on the same topic identified eight studies, including two prospective trials, fulfilling the same inclusion criteria [8]. In this systematic review, there were no differences in 1-, 3-, and 5-year overall survival in patients inside the Milan criteria [9–16], while some studies with patients outside the Milan criteria showed surgery to be superior to RF ablation alone [17, 18]. Thus, RF ablation is likely to provide similar results to surgery in patients inside the Milan criteria if performed in expert hands (Table 9.1).

**Table 9.1** Summary of comparative studies on thermal ablation vs. resection in HCC

| | | | | Overall survival | | | |
|---|---|---|---|---|---|---|---|
| Author | Method | Patients (*n*) | Tumor size (cm) | 1 year (%) | 3 years (%) | 5 years (%) | *p* |
| Vivarelli (2004) [18] | Surgery | 79 | n.a. | 83 | 65 | n.a. | 0.002 |
| | RFA | 79 | n.a. | 78 | 33 | n.a. | |
| Hong (2005) [9] | Surgery | 93 | 2.5 ± 0.8 | 97.9 | 83.9 | n.a. | 0.240 |
| | RFA | 55 | 2.4 ± 0.6 | 100 | 72.7 | n.a. | |
| Montorsi (2005) [35] | Surgery | 40 | n.a. | 84 | 73 | n.a. | 0.139 |
| | RFA | 58 | n.a. | 85 | 61 | n.a. | |
| Cho (2005) [16] | Surgery | 61 | 3.4 ± 1 | 98.3 | 77.4 | n.a. | 0.77 |
| | RFA | 99 | 3.1 ± 0.8 | 95.8 | 80.0 | n.a. | |
| Ogihara (2005) [36] | Surgery | 47 | 7.4 ± 5.2 | 75 | 65 | 31 | n.s. |
| | RFA | 40 | 4.6 ± 2.9 | 78 | 58 | 39 | |
| Lü (2006) [5] | Surgery | 54 | n.a. | 91.3 | 86.4 | n.a. | 0.808 |
| | RFA | 51 | n.a. | 93.5 | 87.1 | n.a. | |
| Chen (2006)[a] [6] | Surgery | 90 | n.a. | 93.3 | 73.4 | n.a. | n.s. |
| | RFA | 90 | n.a. | 94.4 | 68.6 | n.a. | |
| Lupo (2007) [10] | Surgery | 42 | 4 (3–5) | 91 | 57 | 43 | 0.824 |
| | RFA | 60 | 3.65 (3–5) | 96 | 53 | 32 | |
| Takahashi (2007) [13] | Surgery | 53 | 2.5 (1–5) | n.a. | n.a. | 70.4 | 0.561 |
| | RFA | 171 | 2.1 (0.7–4.8) | n.a. | n.a. | 76.8 | |
| Guglielmi (2008) [17] | Surgery | 91 | n.a. | 84 | 64 | 48 | 0.01 |
| | RFA | 109 | n.a. | 83 | 42 | 20 | |
| Abu-Hilal (2008) [37] | Surgery | 34 | 3.8 (1.3–5.0) | 91 | n.a. | 56 | 0.302 |
| | RFA | 34 | 3 (2–5) | 83 | n.a. | 57 | |
| Hiraoka (2008) [15] | Surgery | 59 | 2.27 ± 0.55 | 98.1 | 91.4 | 59.4 | n.s. |
| | RFA | 105 | 1.98 ± 0.52 | 95.1 | 87.8 | 59.3 | |
| Huang (2010)[a] [4] | Surgery | 115 | n.a. | 98.3 | 92.2 | 75.5 | 0.001 |
| | RFA | 115 | n.a. | 87 | 69.6 | 54.8 | |
| Kobayashi (2009) [14] | Surgery | 199 | 2 (0.9–3.0) | 96.9 | 90.3 | 79 | n.s. |
| | RFA | 209 | 1.8 (0.8–3.0) | 99 | 87.4 | 74.8 | |
| Ueno (2009) [11] | Surgery | 123 | 2.7 ± 0.1 | 99 | 92 | 80 | 0.06 |
| | RFA | 155 | 2.0 ± 0.1 | 98 | 92 | 63 | |

(continued)

**Table 9.1** (continued)

| Author | Method | Patients (*n*) | Tumor size (cm) | Overall survival 1 year (%) | 3 years (%) | 5 years (%) | *p* |
|---|---|---|---|---|---|---|---|
| Santambrogio (2009)[a] [12] | Surgery | 78 | 2.87 ± 1.21 | 93 | 85 | 54 | 0.163 |
| | RFA | 74 | 2.66 ± 1.06 | 88 | 66 | 41 | |
| Nanashima (2010) [38] | Surgery | 144 | n.a. | n.a. | 77 | 57 | n.a. |
| | RFA | 56 | n.a. | n.a. | 59 | 51 | |
| Nishikawa (2011) [39] | Surgery | 69 | 2.68 ± 0.49 | 100 | 81.4 | 75.6 | 0.259 |
| | RFA | 162 | 1.99 ± 0.62 | 95.4 | 79.6 | 63.1 | |
| Hung (2011) [40] | Surgery | 229 | 2.88 ± 1.06 | 97.3 | 88.2 | 79.3 | 0.009 |
| | RFA | 190 | 2.37 ± 0.92 | 96.6 | 77.3 | 67.4 | |
| Wang (2012) [41] | Surgery | 52 | Very early stage | 98 | 98 | 91.5 | 0.298 |
| | RFA | 91 | | 96.7 | 89.3 | 72 | |
| Wang (2012) [41] | Surgery | 208 | Early stage | 96.1 | 87.8 | 77.2 | 0.088 |
| | RFA | 254 | | 91.6 | 73.5 | 57.4 | |
| Feng (2012)[a] [42] | Surgery | 84 | 2.6 ± 0.8 | 96 | 87.6 | 74.8 | 0.342 |
| | RFA | 84 | 2.4 ± 0.6 | 93.1 | 83.1 | 67.2 | |
| Peng (2012) [43] | Surgery | 74 | 1.1 ± 0.5 | 90.5 | 70.9 | 62.1 | 0.048 |
| | RFA | 71 | 1.2 ± 0.6 | 98.5 | 87.7 | 71.9 | |
| Zhang (2016) [44] | Surgery | 122 | 2.7 ± 0.4 | 98.4 | 93.6 | 55.2 | 0.153 |
| | MWA | 68 | 2.7 ± 0.3 | 97.1 | 87.7 | 51.0 | |
| Zhang (2016) [45] | Surgery | 73 | Small | 95.2 | 71.4 | 38.1 | n.s. |
| | MWA | | | 96.7 | 53.3 | 43.3 | |

*n.a.* not available, *n.s.* not significant
[a]Prospective study

In HCC the combination of RF ablation and transarterial chemoembolization (TACE) is particularly useful. There are three randomized controlled trials indicating the combination of RF ablation and TACE to be superior to RF ablation alone, although only one of these trials found a significant advantage in overall survival for the combination of RF ablation plus TACE. These findings are supported by two retrospective studies comparing RF ablation plus TACE with RF ablation alone.

The same is true for recurrent HCC. In a prospective randomized trial, the sequential combination of RF ablation plus TACE was shown to result in a significantly longer overall survival, when compared to RF ablation alone in recurrent HCC [19, 20]. So far there is only limited data on the combination of TACE plus RF ablation in comparison to resection. Most of these studies indicated that the survival after a combination of embolization and RF ablation is not different from surgery, even in patients outside the Milan criteria [21–23]; the only prospective study, however, favored surgery over locoregional treatments (Table 9.2).

**Table 9.2** Summary of comparative studies on RF ablation in combination with embolization vs. resection in HCC

| | | | | Overall survival | | | |
|---|---|---|---|---|---|---|---|
| Author | Method | Patients ($n$) | Tumor size (cm) | 1 year (%) | 3 years (%) | 5 years (%) | $p$ |
| Maluccio (2005) [23] | Surgery | 40 | 4.6 (1.8–7) | 97 | 77 | 56 | 0.200 |
| | RFA and TACE | 33 | 4 (1.7–7) | 81 | 70 | 58 | |
| Yamakado (2008) [22] | Surgery | 62 | 2.7 ± 1.1 | 97 | 93 | 81 | 0.870 |
| | RFA and TACE | 104 | 2.5 ± 0.8 | 98 | 94 | 75 | |
| Kagawa (2010) [46] | Surgery | 55 | 2.8 (1–5) | 92.5 | 82.7 | 76.9 | 0.788 |
| | RFA and TACE | 62 | 2.4 (0.8–5) | 100 | 94.8 | 64.6 | |
| Tashiro (2011) [47] | Surgery | 199 | 2.1 ± 0.63 | 95.6 | 90.9 | 76 | 0.11 |
| | RFA and TACE | 87 (69 TACE) | 1.8 ± 0.52 | 97.6 | 81.4 | 71 | |
| Liu (2016) [50][a] | Surgery | 100 | 3 (0.6–5) | 97.0 | 83.7 | 61.9 | 0.007 |
| | RFA and TACE | 100 | 2.8 (0.6–5) | 96.0 | 67.2 | 45.7 | |
| Bholee (2017) [52] | Surgery | 782 | 3 ± 1.1 | 94.6 | 75.1 | 55.3 | 0.488 |
| | RFA and TACE | 74 | 2.9 ± 1.1 | 91.2 | 64.4 | 47.7 | |

[a]Prospective study

While RF ablation was the dominant ablative technique for treating small HCC, there is now a growing body of evidence on the use of MWA in HCC (Table 9.1). The data is promising, but there still is no relevant prospective randomized trial comparing MWA and surgery. Several studies compared RF ablation and MWA. While there is no statistically significant difference between both techniques, there is a trend toward better outcomes after MWA [24]. Data on cryoablation of liver tumors is scarce, and the only meta-analysis on HCC indicates RF ablation to be superior to cryoablation, particularly in terms of safety [25].

### *9.3.2 Metastatic Liver Disease*

Resection offers the best long-term survival in colorectal liver metastases with 5-year overall survival rates of about 50% [26]. In contrast even the most recent chemotherapeutic regimen only provides a median survival of up to 22 months [27]. With only 25% of liver metastases being resectable, thermal ablation was evaluated for treating secondary liver disease. While there is only very limited data of mostly poor quality on microwave ablation, cryoablation, and laser-induced thermal therapy, there is a huge body of data on RF ablation for treating liver metastases. Two prospective studies on RF ablation in colorectal liver metastases resulted in a median survival of 24 (percutaneous approach) and 39 months (open and percutaneous approach), respectively [28, 29]. However, there were marked differences in patient selection limiting comparability of results. In general, RF ablation results in higher local recurrence rates when compared with surgery, while survival data varies (Table 9.3). A recent meta-analysis indicated a better survival for patients undergoing resection when compared to RF ablation, but the

**Table 9.3** Summary of studies on RF ablation in colorectal liver metastases

| Author | Method | Patients (*n*) | Tumor size (cm) | Overall survival 2 years (%) | 3 years (%) | 5 years (%) | *p* | Median survival |
|---|---|---|---|---|---|---|---|---|
| Oshowo (2003) [48] | Surgery | 20 | 4 (2–7) | n.a. | 55.4 | n.a. | n.s. | 41 |
| | RFA | 25 | 3 (1–10) | n.a. | 52.6 | n.a. | | 37 |
| Abdalla (2004) [49] | Surgery | 190 | n.a. | n.a. | 73 | 58 | 0.0001 | n.a. |
| | Surgery + RFA | 101 | n.a. | n.a. | 43 | n.a. | | n.a. |
| | RFA | 57 | 2.5 | n.a. | 37 | n.a. | | n.a. |
| Aloia (2006) [51] | Surgery | 150 | 3 (1–7) | n.a. | 79 | 71 | 0.001 | n.a. |
| | RFA | 30 | | n.a. | 57 | 27 | | n.a. |
| Park (2008) [53] | Surgery | 59 | 3.1 (0.5–8) | n.a. | n.a. | 48 | 0.0002 | 56 |
| | RFA | 30 | 2 (0.6–4) | n.a. | n.a. | 19 | | 36 |
| White (2007) [20] | Surgery | 30 | 2.7 (1–5) | 100 | 82 | 65 | n.a. | 80 |
| | RFA | 22 | 2.4 (1–5) | 100 | 28 | 0 | | 31 |
| Berber (2008) [54] | Surgery | 90 | 3.8 ± 0.2 | n.a. | n.a. | 40 | 0.35 | n.a. |
| | RFA | 68 | 3.7 ± 0.2 | n.a. | n.a. | 30 | | n.a. |
| Lee (2008) [55] | Surgery | 116 | 3.29 (0.5–18) | n.a. | n.a. | 65.7 | 0.227 | 44.7 |
| | RFA | 37 | 2.25 (0.8–5.0) | n.a. | n.a. | 48.5 | | 40 |
| Hur (2009) [56] | Surgery | 42 | 2.8 (0.6–8) | n.a. | 70 | 60 | 0.026 | 60 |
| | RFA | 25 | 2.5 (0.8–3.6) | n.a. | 50.1 | 25.5 | | 41 |
| Reuter (2009) [57] | Surgery | 192 | n.a. | n.a. | n.a. | 23 | n.s. | n.a. |
| | RFA | 66 | n.a. | n.a. | n.a. | 21 | | n.a. |
| McKay (2009) [58] | Surgery | 58 | 4.1 (1–14.5) | n.a. | n.a. | 43 | 0.021 | 45.6 |
| | RFA | 43 | 3 (1–7.5) | n.a. | n.a. | 23 | | 27.6 |
| Otto (2010)[a] [59] | Surgery | 28 | 5 (1–14) | n.a. | 67 | 51* | 0.721 | n.a. |
| | RFA | 82 | 3 (1–5) | n.a. | 60 | 48* | | n.a. |
| Schiffman (2010) [60] | Surgery | 94 | 5.6 | 92* | 81* | 65* | 0.005 | n.a. |
| | RFA | 46 | 3.9 | 81* | 64* | 42* | | n.a. |

(continued)

**Table 9.3** (continued)

| Author | Method | Patients (*n*) | Tumor size (cm) | Overall survival 2 years (%) | 3 years (%) | 5 years (%) | *p* | Median survival |
|---|---|---|---|---|---|---|---|---|
| Lee (2012) [61] | Surgery | 25 | 4 | n.a. | n.a. | n.a. | 0.017 | 41 |
| | RFA | 28 | 2.05 | n.a. | n.a. | n.a. | | 24 |
| Ko (2014) [62] | Surgery | 12 | 3.59 | n.a. | n.a. | 66.7 | 0.29 | n.a. |
| | RFA | 17 | 2.02 | n.a. | n.a. | 37.8 | | n.a. |
| Lee (2015) [63] | Surgery | 102 | 1.7 | | 73.9 | 55.2 | 0.194 | n.a. |
| | RFA | 51 | 1.8 | | 62.4 | 48.2 | | n.a. |

*n.a.* not available, *n.s.* not significant
[a]Prospective study

data needs to be interpreted carefully as the raw data was only of limited quality [30]. In addition, the lower complication rate for RF ablation has to be acknowledged. For RF ablation major complication rates are about 4.5% with a mortality of 0.15%. Local recurrence rates of 9–33% have been reported.

While there are no prospective randomized controlled trials comparing RF ablation with surgery, there is a single prospective randomized controlled trial comparing chemotherapy alone with chemotherapy plus RF ablation [31]. This study suffered several shortcomings in the study design and patient accrual. While the primary end point was met with a 30-month overall survival rate of 61.7% for combined treatment, overall survival of systemic treatment alone was much better than expected (57.6% at 30 months). Median overall survival in the combination arm was better (45.3 months) than with chemotherapy alone (40.5 months), but failed to reach significance ($P = 0.22$). Progression-free survival, however, was significantly better in the combination arm (16.8 vs. 9.9 months; $p = 0.025$). Long-term analysis may reveal if this translates in a better overall survival.

Unlike in the treatment of HCC, there are only few case series on the combination of embolization and local ablation in liver metastases. Most patients in these reports were poor candidates for ablation, and the combination treatment was thought to improve outcome [33]. The most recent case series on the combination of TACE and ablation in colorectal liver metastases indicates this approach to be safe and worthwhile considering a 3-year survival rate of 50% in patients deemed unresectable [32].

There is a variety of case series on thermal ablation in liver metastases from a broad variety of different tumor entities. These studies, however, are of limited value as the natural course of the different tumor entities varies significantly. Nevertheless, the available data indicates the potential benefit achievable by interventional treatment in patients, who are otherwise considered unfit for surgery (Table 9.4). For MWA and cryoablation, there are only case series including a variety of primary tumors; therefore, this data is very difficult to interpret, as tumor biology varies.

Liver metastases from neuroendocrine tumors (NET) are a separate topic. In these patients cytoreductive liver surgery is well established in symptomatic patients in order to improve the quality of life [34]. This goal can also be achieved by local ablation as a less invasive approach. Consequently encouraging results have been reported from local ablation with a median survival after ablation ranging from 29 to 72 months and relief from symptoms in more than 90% of patients (Table 9.4).

## 9.4 Study Results

**Table 9.4** Summary of studies on RF ablation in liver metastases other than colorectal cancer

| Author | Patients/ lesions [*n*] | Entity | Lesion size [cm] | Overall survival 1 year (%) | 3 years (%) | 5 years (%) | Median survival (months) |
|---|---|---|---|---|---|---|---|
| Livraghi (2001) [64] | 24/64 | Breast | 1.9 [1–6.6] | n.a. | n.a. | n.a. | n.a. |
| Lawes (2006) [65] | 19/46 | Breast | 3 [1.4–7.3] | n.a. | n.a. | n.a. | n.a. |
| Sofocleous (2007) [66] | 12/14 | Breast | n.a. | n.a. | 70 | 30 | 60 |
| Gunabushanam (2007) [67] | 14/16 | Breast | 1.9 [1.1–4] | 64 | n.a. | n.a. | n.r. |
| Jakobs (2009) [68] | 43/111 | Breast | 2.1 [0.5–8.5] | 95 | 68 | 48 | 58.6 |
| Meloni (2009) [69] | 52/87 | Breast | 2.5 [0.7–5] | 68 | 43 | 27 | 29.9 |
| Gillams (2005) [70] | 25/189 | NET | 3.5 [1–9] | 92 | 80 | 72 | 29 |
| Mazzaglia (2007) [71] | 63/384 | NET | 2.3 [0.5–10] | 91 | n.a. | 48 | 47 |
| Akyildiz (2010) [72] | 89/547 | NET | 3.6 [1–10] | n.a. | n.a. | 57 | 72 |
| Yamakado (2005) [73] | 7/16 | Gastric | 2.4 [2–3] | 86 | n.a. | n.a. | 16.5 |
| Kim (2010) [74] | 20/29 | Gastric | 5.1 ± 2.2 | 66.8 | 40.1 | 16.1 | 30.7 |
| Mylona (2009) [75] | 22/36 | CUP | 2.7 [1.1–4.8] | n.a. | n.a. | n.a. | 10.9 |
| Gervais (2006) [76] | 6/6 | Ovarian | 2.7 [1.5–5.3] | 83 | n.a. | n.a. | n.r. |

Of note, there were no prospective studies available
*n.a.* not available, *n.r.* not reached, *NET* neuroendocrine tumor, *CUP* cancer of unknown primacy

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