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RFA for Liver Tumors: Does It Really Work?

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Key Words. Radiofrequency ablation • Liver tumors • Hepatocellular carcinoma • Liver metastases

Abstract

The use of radiofrequency ablation (RFA) is increasing in the treatment of both primary and metastatic hepatic tumors. However, the role of RFA has yet to be clearly defined in patients who are still considered amenable to surgical intervention. Future prospective studies are needed to define whether RFA can be used as an alternative to surgery in certain patient populations. In the interim, radiofrequency ablation technology will continue to advance and serve as both a palliative and potentially curative intervention for individuals with hepatic tumors. The Oncologist 2006;11:801–808

Introduction

The use of radiofrequency ablation (RFA) to treat both primary and metastatic hepatic disease continues to expand. Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and is the fifth most common type of cancer in the U.S., accounting for nearly one million deaths annually worldwide [1, 2]. The incidence of HCC is on the rise in the U.S. and is expected to continue to do so largely as a result of the increasing dissemination of the hepatitis B and C viruses [3, 4]. The vast majority of hepatic tumors are metastatic in origin. Colorectal cancer metastases comprise the majority of such tumors that are considered surgically resectable. In this paper, we briefly explain RFA and discuss its use in HCC and metastatic disease to the liver.

RFA

RFA of tumors was first described in the early 1990s, but the concept of heat to treat tumors dates back to Egyptian and early Greek times [5]. Since its modern inception, huge technical advances have been made in the field of RFA. The methods of approach (percutaneous, laparoscopic, or open), instruments used, and clinical applications all continue to evolve.
RFA-associated complications were an open versus percutaneous group. In that study, the only two predictive factors of not statistically different between the open and percutaneous treatment groups were seen in 2.4% of patients and were late complications, those occurring more than 30 days after RFA, were seen in 7.1% of patients. Patients who underwent open RFA had a significantly higher early complication rate (8.6%) than those who underwent percutaneous RFA (4.4%); however, overall RFA-related mortality was quite low, at 0.5%. Interestingly, late complications, those occurring more than 30 days after RFA, were seen in 2.4% of patients and were not statistically different between the open and percutaneous group. In that study, the only two predictive factors of RFA-associated complications were an open versus percutaneous approach and the presence of cirrhosis.

Interestingly, late complications, those occurring more than 30 days after RFA, were seen in 2.4% of patients and were not statistically different between the open and percutaneous group. In that study, the only two predictive factors of RFA-associated complications were an open versus percutaneous approach and the presence of cirrhosis. The current treatment of HCC depends on several factors, including the size of the lesion, number of lesions, presence of metastatic disease, and remaining liver function. Perhaps the single most important factor to influence the management of HCC is whether it develops in a cirrhotic patient with underlying hepatitis B or C. Noncirrhotic patients are known to have far better outcomes and are best treated by surgical resection if possible, whereas liver transplantation remains the gold standard in eligible patients who have underlying cirrhosis. The following provides a discussion of the role of RFA in the treatment of HCC and its use as an adjunct to surgery in certain patients.

RFA and Hepatocellular Carcinoma

Liver transplantation has been used with curative intent for HCC, but its use is limited by organ availability. The Milan criteria were developed to determine which patients would be best suited for transplant. Transplant candidates have one lesion <5 cm or three or fewer lesions with the largest being not >3 cm. Transplantation provides the advantage of both eradicating the tumor as well as removing the diseased, cirrhotic liver in which new tumors could arise if left in vivo. A patient can wait several months to more than a year on the transplant list before a suitable donor becomes available, resulting in high dropout rates as a result of primary tumor growth or the development of synchronous or metastatic lesions that remove patients from transplant eligibility.

The efficacy of RFA in wait-listed transplant candidates has been studied. Johnson et al. [23] reported on eight pretransplant patients treated solely by RFA and matched to a similar group by age, sex, Child-Turcotte-Pugh class, and Model for End-Stage Liver Disease (MELD) score who did not undergo treatment prior to transplant. Patients pretreated with RFA were able to remain on the transplant list for longer periods of time than their matched counterparts, thus...
increasing their probability of receiving a new liver. However, that paper failed to define the etiology of the patients’ cirrhosis or look at long-term outcomes after transplantation to see if the delay in transplant yielded similar rates of survival. Additionally, upon removal of the native liver, histological analysis revealed a high rate of local recurrence in the previously ablated tumor bed, indicating incomplete disease eradication. In a more recent study by Sotiropoulos et al. [25], patients with explanted livers that demonstrated complete histologic tumor necrosis after RFA had excellent short-term, disease-free survival rates, supporting the need for complete ablation of the lesion. Nodule size appeared to be the most important factor that correlated with degree of necrosis in a recent retrospective study by Pompili et al. [26], with lesions <3 cm demonstrating a higher rate of complete destruction than larger nodules. In that review, 30 HCC nodules were treated with RFA, yielding a nearly 50% rate of complete necrosis. Fifty-two patients in a study by Lu et al. [13] underwent RFA, with 41 of those patients going on to orthotopic liver transplant (OLT). None of the transplanted patients developed recurrent HCC after a mean of 14.9 months, and overall 1- and 3-year survival rates were excellent at 85% and 76%, respectively. In one of the largest prospective studies recently published, 50 cirrhotic patients with HCC were treated with RFA prior to undergoing OLT. The actuarial 1- and 3-year survival rates were 95% and 83%, respectively, with only two patients dying of recurrent disease [27]. Finally, 15 patients at the University of Michigan were successfully bridged to transplant with RFA out of an original group of 23, with a 3-year actuarial post-transplantation survival rate of 85%. However, two of the transplanted patients developed disease recurrence [28]. These survival rates are superior to those of non-RFA-treated patients transplanted for HCC, who can expect 1- and 3-year survival probabilities of 82% and 66%, respectively [29].

The use of RFA as a bridge to transplant has proven to be an effective strategy. Control of tumor size and the theoretical prevention of metastatic disease formation allow patients to remain on the list for longer periods, increasing their likelihood of obtaining a donor organ. Dropout rates without RFA have been shown to be as high as 40%; however, the use of RFA has decreased to as low as 20%. RFA remains limited in its ability to provide complete necrosis of large tumors and should not be expected to do so in patients who are near the upper limits of transplant candidacy because of size criteria.

**Resection Versus RFA**

Surgical resection is the gold standard of treatment for HCC in noncirrhotic and cirrhotic patients who can tolerate hepatic resection. Noncirrhotic patients with HCC can usually undergo resection. However, patients with underlying cirrhosis are rarely candidates for resection and often face a dismal prognosis. As a result, prospective studies comparing patients who are surgical candidates and underwent RFA with those who underwent resection are fairly limited (Table 1). In a study by Vivarelli et al. [30], 158 cirrhotic patients with HCC, 123 of whom had underlying hepatitis B or C, were divided into a surgical group and an RFA group. All of the patients included in the RFA group had no contraindications to undergoing surgical resection. The 1-year survival rates in the surgery and RFA groups were similar at 83% and 78%, respectively. However, survival at 3 years showed a dramatic difference at 65% and 33%, respectively. Disease-free survival was also significantly longer for those patients who had undergone resection. The major flaw of that study is that patients who underwent RFA were more likely to have multiple nodules and a higher Child-Pugh class than their surgical counterparts. It is possible that the RFA patients in the study had livers more prone to de novo tumor formation as a result of their underlying liver disease, making them more prone to recurrence.

A more recently published study details 161 patients with solitary HCC lesions <5 cm who were randomized to either surgical resection or percutaneous ablative therapy [31]. These patients were all surgical candidates and had well-preserved hepatic function (Child-Pugh class A) and no previous treatment for HCC. In that study, no significant difference was noted in overall or disease-free survival at all intervals up to 4 years between the two groups. In addition, when patients were separated by tumor size, no difference was noted between the groups whose lesions were <3 cm and those whose tumors were between 3.1 cm and 5 cm. That study clearly provides support for the use of RFA in small lesions (<5 cm) regardless of whether or not they are amenable to surgical resection. One disadvantage to the study is that it fails to differentiate underlying virology in the patient population used, which makes it difficult to ascertain the likelihood of recurrent or de novo disease, as is often seen in patients with hepatitis B and C. Additionally, almost one third of the RFA-treated patients required multiple treatments, consisting of repeat RFA, percutaneous ethanol injection, or transarterial chemoembolization because of incomplete tumor necrosis on postprocedure computed tomography (CT) scan.

Another well-matched group of patients with a single HCC lesion <4 cm and well-preserved hepatic function provided some more evidence that RFA may provide equivalent survival outcomes to surgical resection. In both the surgical and RFA group, >90% of the patients had underlying hepatitis B and/or C. Patients were enrolled in the RFA branch of the study based on their refusal of surgery and other minor
criteria. Local recurrence rates were higher in the RFA group, but a statistically significant difference was not seen in the overall survival rate or remote recurrence rate [32]. Another study compared 58 patients who underwent laparoscopic RFA (LRFA) with 40 patients who underwent segmental resection [33]. Inclusion criteria used were a single nodule <5 cm, Child class A or B and no previous treatment for HCC. The baseline characteristics of the patient populations were closely matched, and remarkably, actuarial survival rates at 4 years were not statistically different. However, intrahepatic recurrence rates were statistically higher after LRFA, mainly because of local recurrence, and those patients were treated by repeat ablation. The similar overall survival rates seen with RFA in both of these studies may be a result of repeat ablation after local recurrence. Additionally, the use of intraoperative ultrasound (IUS) in the latter study provides better detection of smaller lesions that would not otherwise be visualized by radiologic imaging such as CT scan. The inability to use IUS highlights one of the disadvantages of using a percutaneous approach to RFA rather than laparoscopy or an open technique.

The role of RFA in surgical candidates in HCC is still too controversial and not well enough established to recommend as an equivalent form of treatment to surgery. Although it seems that the most successful predictor of outcome is the underlying state of the liver, RFA may one day play a role in individuals with small nodules that could undergo resection. However, larger tumors that are still resectable are unquestionably best managed by surgery over RFA. More work needs to be done to further delineate the role of RFA as an alternative to resection.

The Use of RFA in Nonsurgical Candidates

The reported rate of resectable HCC is low and ranges from 9%–27% [34]. It is limited by the proximity of the tumor to major vascular and biliary structures that would preclude negative resection margins, but more importantly by the degree of underlying liver disease and the ability of the patient to tolerate hepatectomy [35]. The use of RFA has emerged as an alternative in patients who are not operative candidates and has grown rapidly. Small tumors are generally best suited for RFA and provide the best results. However, larger lesions have also been ablated with mixed success, occasionally even providing overall long-term survival in some patients with HCC.

Small lesions are generally considered those that are <3–3.5 cm in diameter. These lesions can often be treated with a single probe insertion into the center of the tumor bed, especially if an expandable probe is used. Like surgical resection, a 0.5- to 1-cm margin from the tumor edge is considered optimal [36]. Overall survival rates were reported to be as high as 89% and 62% at 1 and 3 years, respectively, in a group of patients undergoing RFA for lesions <3.5 cm [37] (Table 2). Unfortunately, a disease-free survival rate of 24% at 3 years is less encouraging, with local recurrence playing a large role in disease relapse. This can be partially explained as a result of the field defect created in a setting of chronic inflammation produced in cirrhotic patients with chronic hepatitis B or C infection. In addition to tumor size, poor pathologic differentiation and tumor stage are two other risk factors for early tumor recurrence after percutaneous RFA of single small lesions [36]. However, most patients who recur locally are able to undergo repeat RFA.

In a series by Lencioni et al. [38], a group of 187 patients with a single lesion <5 cm or three lesions <3 cm who were not surgical candidates underwent RFA. The end point of that study was overall survival, with 1- and 3-year survival rates of 97% and 71%, respectively. Local tumor progression was seen in only 10 patients, but the development of new intrahepatic lesions occurred in almost half of the patients at 3 years. In a more recent study, 56 cirrhotic patients of largely viral etiology were treated with RFA for unresectable HCC lesions <5 cm in diameter. An overall recurrence rate of 41% at a mean follow-up of 32 months was noted in this group, with the vast majority multifocal in nature despite documentation of complete necrosis in 96.8% of patients initially after ablation [39]. This can be attributed to the field defect, or multicentricity known to

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Table 1. Surgical resection versus radiofrequency ablation (RFA) in patients with resectable hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of destruction</th>
<th>No. of patients</th>
<th>1-yr survival</th>
<th>3-yr survival</th>
<th>4-yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vivarelli et al. [30]</td>
<td>Surgery</td>
<td>79</td>
<td>83%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RFA</td>
<td>79</td>
<td>78%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Chen et al. [31]</td>
<td>Surgery</td>
<td>90</td>
<td>93.3%</td>
<td>73.4%</td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td>RFA</td>
<td>71</td>
<td>95.8%</td>
<td>71.4%</td>
<td>67.9%</td>
</tr>
<tr>
<td>Hong et al. [32]</td>
<td>Surgery</td>
<td>93</td>
<td>97.9%</td>
<td>83.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RFA</td>
<td>55</td>
<td>100%</td>
<td>72.7%</td>
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</tr>
<tr>
<td>Montorsi et al. [33]</td>
<td>Surgery</td>
<td>40</td>
<td>84%</td>
<td>73%</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td>RFA</td>
<td>58</td>
<td>85%</td>
<td>61%</td>
<td>45%</td>
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</table>
occur with HCC in an underlying cirrhotic liver, but failure of complete ablation of the primary tumor with intrahepatic metastases cannot be excluded.

Larger lesions are known to be more difficult to treat using RFA. Tumors >3 cm often require repositioning of the electrode or multiple treatment sessions in order to obtain clear margins. However, even using a more aggressive approach, the efficacy of RFA has been proven to be limited by tumor size [36]. Lesions measuring >5 cm have at best only a 50% chance of being completely ablated [40]. Therefore, most authors do not recommend the use of RFA for tumors >5–6 cm because of the technical limitations of the current equipment used and their inability to provide complete coagulative necrosis [7].

Despite the size limitations of RFA, its use in unresectable HCC is significant. Those who are not transplant candidates or are unable to undergo resection face a dismal prognosis, and RFA provides a chance for survival, especially for patients with smaller lesions. However, the use of RFA should be discouraged in patients with large lesions or those who have evidence of metastatic disease, because these groups have such a poor outcome that RFA is unlikely to provide any tangible benefit.

Surgery in Combination with RFA
Patients with multifocal disease may be treated by a combined approach using both surgical resection and RFA. The bulk of the tumor burden is initially resected, and RFA is then performed on any remaining unresectable lesions. However, there are few data to support this approach, especially in the setting of HCC. Most agree that if HCC has progressed this extensively, the patient is unlikely to be cured even by aggressive combined modalities of this nature. Additionally, although well tolerated intraoperatively, RFA combined with hepatic resection does place the patient at a higher risk for postoperative liver failure and death [41]. This is especially true in the cirrhotic patient with poor reserve prior to intervention. Therefore, the role of RFA in conjunction with surgery must be used judiciously and mandates further review before it can be recommended in the treatment of HCC.

Metastatic Colorectal Cancer
The liver is the most common site of distant metastases in colorectal cancer (CRC) [42]. Initially considered to be a terminal diagnosis, resection of these lesions has provided significantly better outcomes for many of these patients. Unfortunately, the majority of those diagnosed with stage IV disease are not candidates for resection. In this group, alternative options, such as RFA alone or in conjunction with other therapeutic modalities, are being explored to further improve survival.

Resection Versus RFA
As in primary liver tumors, the gold standard of treatment for CRC metastases to the liver is surgical resection. For those who undergo resection of isolated liver metastases, the traditional 5-year survival rate is approximately 30%–40% [42–45] but has recently been shown to be as high as 58% [46]. Prospective studies that compare RFA with surgery in operative candidates are extremely limited. One study from Italy did compare a group of 88 patients who were candidates for resection but instead underwent percutaneous RFA. In that series, surgical candidates with no more than three metastatic lesions, each not >4 cm, were treated with RFA. Complete tumor necrosis was initially documented radiologically in 60% of patients, and 26% were disease free at a median follow-up of 26 months [47]. The disadvantage to that study is that the patients enrolled had small lesions, which are known to be more amenable to RFA. Although RFA may one day play a role in the treatment of small metastatic lesions, surgical intervention is still considered the optimal treatment for metastatic CRC.

The Use of RFA in Unresectable Metastases
As many as 90% of patients with metastatic CRC are not candidates for surgical treatment [48]. Criteria for unresectable metastases include bilobar disease that cannot be completely excised, proximity to major vasculature structures precluding margin-negative resection, and comorbid conditions that preclude surgery [49]. For these untreated patients, survival is <5%–10% at 5 years [43]. This emphasizes the need for alternative forms of disease management.

RFA has emerged as a viable option for many patients who are not surgical candidates. Overall survival rates of patients treated with RFA for CRC metastases are in the range of 85%–100% at 1 year to 33%–52% at 3 years [8, 48, 50]. Local recurrence remains an issue in RFA-treated patients and is in the range of 3%–39% [49–51]. This is

<table>
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<tr>
<th>Study</th>
<th>No. of patients</th>
<th>1-yr survival</th>
<th>3-yr survival</th>
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<tbody>
<tr>
<td>Buscarini et al. [37]</td>
<td>88</td>
<td>89%</td>
<td>62%</td>
<td>33%</td>
</tr>
<tr>
<td>Lencioni et al. [38]</td>
<td>187</td>
<td>97%</td>
<td>71%</td>
<td>41%</td>
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laboratory results in a limited disease-free survival duration. Predictors of survival in 135 consecutive patients treated with RFA for CRC metastatic to the liver were analyzed over a 5-year period [52]. The patient population included those who were not surgical candidates—almost one third had extrhepatic disease and many had several lesions, with a mean number of 3.2 tumors ablated per patient. Additionally, 80% of the patients had received varying forms of chemotherapy prior to referral for RFA and 14% had undergone liver resection. The median survival time for all comers was 28.9 months after RFA, compared with a recent series that demonstrated a median survival time of 14.9 months with modern chemotherapeutics alone [53]. The size of the largest lesion ablated was significantly associated with survival, with patients whose largest tumor was <3 cm in diameter having a median survival time of 38 months, versus 34 months for those with tumors in the range of 3–5 cm and only 21 months for patients with tumors >5 cm. Interestingly, no significant survival advantage was seen in patients who underwent pretreatment chemotherapy or documented extrhepatic disease.

In a study by Oshowo et al. [48], RFA was used to treat patients with unresectable, solitaire CRC metastases, and these were compared with a group of patients who were surgical candidates. The overall 3-year survival rate was not statistically different between the two groups, at 52.6% and 55.4% for the RFA and surgical groups, respectively. However, the two patient populations differed in that the RFA group contained some patients with known, stable extrhepatic disease, which was not seen in the surgical group. This fact highlights the efficacy of RFA despite more extensive disease in the RFA group.

Although RFA-treated patients may experience recurrence of their metastatic disease, options are limited in patients who are not surgical candidates, and every effort should be made to treat with curative intent when feasible. With the addition of new chemotherapeutic regimens, RFA may play an increasing role in combination with chemotherapy. Considering the low morbidity and mortality of RFA, the results achieved thus far provide support that RFA may provide a potential extension of life when compared with the outcomes of untreated patients.

The role of chemotherapy in metastatic CRC is well established and currently provides the only accepted method of palliation and treatment. As new chemotherapeutic agents are developed, survival of patients with metastatic CRC continues to improve. For patients who are unable to be cured by surgery, a combination of RFA and regional chemotherapy has recently been introduced with encouraging results [54]. The addition of RFA for patients treated with transarterial chemoembolization has recently been shown to improve overall survival in patients with unresectable CRC metastases to the liver [55]. Many additional studies are needed to further evaluate this approach in patients who are not surgical candidates, but it is likely that RFA will play a role in conjunction with chemotherapy, especially as new agents are developed and RFA technology continues to advance.

Surgery plus RFA
In a large study comparing hepatic resection, RFA, and combined resection/RFA for metastatic CRC, hepatic resection alone was determined to be the treatment of choice. Patients who underwent only surgical resection fared far better than the RFA-treated groups, with an overall survival rate of 73% at 3 years. Additionally, no benefit was seen in those who underwent surgery and RFA versus those who underwent RFA only. Despite a higher rate of tumor recurrence in the RFA only group, the overall survival rate at 3 years was not statistically different, at 43% and 37% for the combined resection/RFA and RFA only groups, respectively [46].

Large trials evaluating the combination of RFA and resection are limited, and it is therefore difficult to make definitive conclusions regarding its efficacy and safety. As larger portions of hepatic parenchyma are resected or ablated, the risk for liver failure increases, making it difficult to support the use of a combined approach without achieving a survival benefit. At this time, there are no data to support combining RFA with surgical resection, and those that choose to undergo this approach should be enrolled in prospective studies in order to define its value in the treatment of metastatic disease.

Other Metastatic Tumors
The goal of surgical resection and RFA in most cases of both primary and metastatic liver disease is curative. However, neuroendocrine tumors represent a unique group of slowly growing, often highly symptomatic tumors that are unlikely to be cured by resection. Many of these patients undergo debulking procedures not for curative intent but rather for palliation of symptoms. In patients who are unlikely to be cured by surgery or are unable to tolerate an invasive form of treatment, RFA has been shown to improve symptoms and decrease circulating hormone levels in metastatic neuroendocrine tumors [5]. This can be done with a relatively low risk for major complications and mortality rate (<1%), especially when compared with laparotomy [56]. The efficacy of RFA in this scenario is well documented and it should be considered as a therapeutic modality in symptomatic patients unable to tolerate laparotomy.
CONCLUSION
The technology behind RFA and its many uses has progressed dramatically in the past 15 years. There are now well-documented roles for its use in a variety of circumstances. Although surgery is still the recommended treatment modality in patients with both primary and metastatic hepatic tumors, the majority of these patients are not surgical candidates. In nonoperative patients, RFA will likely play a significant role in the future, with a potential curative intent. In the interim, randomized, prospective studies are needed to fully evaluate what part RFA will play in the treatment of these patients.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
The authors indicate no potential conflicts of interest.

REFERENCES


