

Thermal ablation of liver tumors

Review Article

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Summary

The liver is a common site of malignant disease, either primary liver cancer or metastatic disease. Resection remains the best treatment available, however for many patients resection is not an option. Newer techniques have evolved to allow for liver tumor destruction with acceptable rates of morbidity and mortality, and with promising short-term results.

I. Introduction

The American Cancer Society, (2004) estimates over 18,000 cases of primary liver cancer will be diagnosed United States in 2004, of which over one-half are hepatocellular carcinoma. Hepatocellular carcinoma (HCC) is one of the most prevalent solid cancers worldwide, especially in East Asia and South Africa, with over one million new cases annually (Qin and Tang, 2002). The liver also is a common site of metastasis, particularly from colorectal cancer (Weiss et al, 1986). Surgical resection is remains the treatment of choice for patients with hepatic malignancies, with contemporary series demonstrating 5-year survival rates of 25% to 40% for both colorectal malignancies (Sugihara et al, 1993; Rees et al, 1997; Fong et al, 1999) and HCC (Vauthey et al, 1995; Hanazaki et al, 2000; Poon et al, 2000; Ercolani et al, 2003). However, the majority of patients with liver tumors are not candidates for resection due to tumor size, location, multifocality, inadequate liver reserve, and other health problems (Nagorney et al, 1989).

The treatment options for patients with unresectable hepatic tumors include systemic chemotherapy, chemoembolization, and locally ablative techniques (including ethanol ablation, cryoablation, and radiofrequency, laser or microwave ablation). Results for systemic chemotherapy have been abysmal for HCC, with short median survivals and low response rates (Friedman, 1983; Lin et al, 1997; Patt et al, 2003). Additionally, the presence of cirrhosis often limits the cytotoxic agents

available for treatment. Recently, progress in systemic chemotherapy for metastatic colorectal cancer has resulted in increased response rates and modest increases in median survival, but still there are few long-term survivors (Conti et al, 1996; Bajetta et al, 2004; Cunningham et al, 2004). For HCC or other hypervascular tumors, embolization or chemoembolization may provide hepatic disease control for patients that are neither resectable nor appropriate for transplantation (Llovet et al, 2002; Lo et al, 2002; O'Suilleabhain et al, 2003).

There are several ablative therapies available for treatment of unresectable hepatic tumors. Percutaneous ethanol injection (PEI) can be effective for small HCC tumors, but usually requires multiple treatments (Lencioni et al, 1997). PEI has been shown to be an effective alternative to resection, but is most beneficial in patients with adequate hepatic function and small, well-circumscribed tumors (Mazzanti et al, 2004). PEI has limited effects on colorectal metastases and non-vascular tumors. PEI may be combined with other cytotoxic agents to enhance tumor cell kill (Kurokohchi et al, 2004). Cryoablation has been used for a number of malignant liver tumors, however may be associated with a complication rate that is higher than some other ablative techniques (Sohn et al, 2003). The "heat sink" effect may limit the efficacy of cryoablation of tumor located near large hepatic blood vessels. The complication rate and the local recurrence rate have made cryoablation less

attractive than other ablative therapies (Adam et al, 2002; Kerkar et al, 2004).

Currently, the most widely used hepatic ablative strategies are the thermal ablative techniques of radiofrequency ablation (RFA), laser-induced thermotherapy (LITT), and microwave ablation (MA). These techniques share a common method for inducing tumor killing: they heat the tumor resulting in coagulative necrosis. Thermal ablative techniques result in permanent cellular damage and death by achieving temperatures above 50° to 60°C (McGahan et al, 1992; Patterson et al, 1998). These three techniques appear promising for the future treatment of liver malignancies because they may be used in a minimally invasive setting, are relatively inexpensive, versatile, and have acceptably low rates of morbidity and mortality.

II. Radiofrequency ablation

RFA was first mentioned as a treatment for hepatic malignancies in 1990 by McGahan and Rossi. Since then, the popularity of RFA as a viable treatment for unresectable HCC and hepatic metastases has increased exponentially, mainly due to the technique's versatility and effectiveness. RFA can be employed in a number of ways: through traditional open surgery, laparoscopically, or percutaneously under guidance of ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). RFA needle electrode probes release high-frequency (460 kHz) alternating current into the target tissue. The ions in the tissue are frictionally heated as they attempt to change direction with the alternating current. After frictional heating rises above 50° to 60°C, the tissue surrounding the probe forms an area of necrosis as the cells die.

RFA systems include an electrical generator, grounding pads, and needle electrodes (ranging from 14-gauge to 19-gauge). Three companies currently market commercially available RFA devices in the United States: Rita Medical Systems of Mountain View, CA (Mountain View, CA), Radiotherapeutics (Mountain View, CA) and Radionics (Burlington, MA) (McGhana, 2001; Wong et al, 2001). It is presently unclear whether any system is superior to another in terms of ablation size, reproducibility, or local tumor control (de Baere et al, 2001).

Grounding pads are placed on the patient's thighs prior to an RFA procedure. The needle electrode is advanced into the liver tumor either by an open, laparoscopic, or percutaneous approach, and ultrasound-guidance is used to position the electrode accurately. The RFA generator will heat the tissue and maintain the desired temperature by changing the power output over time. Once the ablation is complete, the electrode is generally removed slowly while the track is cauterized to prevent tumor seeding and minimize bleeding. Multiple overlapping ablations may be required for larger tumors. A successfully ablated lesion should have a region of complete necrosis encompassing the entire tumor and 1 cm of the surrounding normal hepatic parenchyma.

The cooling effect of large vessels in close proximity to the electrode creates a heat sink, which limits the size of the ablation zone and can cause irregularly shaped

ablations. Inflow occlusion during the ablation may help to mitigate this problem, and can result in larger areas of ablation, as well as aid in ablating tumors abutting large blood vessels. Occlusion of the hepatic inflow by the Pringle maneuver has been shown in several studies to increase the size and regularity of ablations and possibly to enhance tumor kill (Chinn et al, 2001; Chang et al, 2002; Yamasaki et al, 2002).

In addition to its utility in the initial placement of the electrode, ultrasonography can be used to monitor the progression of the ablation during the procedure. Ablated areas become hyperechoic due to gas bubbles generated by the heated tissue. Gas bubbles generated by an ablation may interfere with accurate ultrasonography of tissues deep to the electrode, which can hinder repositioning of the electrode for overlapping ablation zones when treating larger tumors. Ablating the deepest portions of the tumor first and re-deploying the electrode serially as it is withdrawn may obviate this phenomenon. Imaging-related difficulties may be more pronounced with the percutaneous approach, as transcutaneous ultrasound may not be as accurate as intra-operative ultrasonography.

Percutaneous RFA is the least invasive mode of delivery, and can be performed in an outpatient setting, making it an acceptable alternative for many patients. Laparoscopic RFA has the advantages of providing more accurate cancer staging using laparoscopy and laparoscopic ultrasound and minimizing the probability of injury to nearby organs, while still being minimally invasive. The advantages of an open approach to RFA include excellent cancer staging, accessibility to all sections of the liver, ease of intra-operative ultrasound examination, inflow occlusion (Pringle maneuver), minimal risk to peripheral organs, and the ability to perform a resection in conjunction with the ablation. The main disadvantage is its invasiveness, which leads to recovery time, and length of hospital stay (Machi et al, 2001).

Whether RFA should be performed percutaneously, laparoscopically, or via an open approach should be individualized for each patient. Percutaneous RFA is well suited for patients who have a limited number of small tumors and who are not good candidates for more invasive procedures due to co-morbid conditions. Cirrhotic patients with a small hepatocellular carcinomas and patients with one or two intrahepatic recurrences following hepatectomy are good examples of patients who might be best served by the percutaneous approach. Laparoscopic RFA is a good option for patients with a small number of tumors for which percutaneous RFA would not be safe, such as peripherally situated tumors near adjacent organs such as the stomach or colon. Patients may recover more quickly from a laparoscopic RFA as opposed to an open RFA, yet substantial surgical judgment must be used in selecting patients for which the laparoscopic approach is best. Open surgical RFA is preferable for patients with large tumors, multiple tumors, and tumors near large blood vessels (because of heat sink effect). Hepatic inflow occlusion diminishes the heat sink effect from large intrahepatic vessels, and is easier with open surgery as opposed to laparoscopic surgery. Additionally, the open approach

allows extremely accurate intra-operative ultrasound to be done, which facilitates ablation of large tumors near blood vessels (**Figure 1**). Peripherally situated tumors may be safely ablated by packing the adjacent organs away from the liver, thus providing a layer of protection difficult to achieve with the other approaches.

Multiple studies about RFA of hepatic malignancies have been published since 1990; however, many of these studies are not well controlled in respect to patient selection, type of cancer, stage of disease, and treatment approach. The high variability of patients in each study make definitive conclusions difficult, but the results do point strongly toward RFA being an effective tool against hepatic malignancies. One concern for all of the ablative techniques has been local failure. An analysis of several of the larger RFA trials shows local recurrence per ablated tumor to range from 1.8% to 26.6% and overall recurrence (outside the ablation zone) to range from 18% to 73.3% (Curley et al, 1999, 2000; Rossi et al, 2000; Bowles et al, 2001; Wong et al, 2001; Kuvshinoff and Ota, 2002; Jiang et al, 2002; Kosari et al, 2002; Bleicher et al, 2003; Komorizono et al, 2003) (**Table 1**). In a large trial conducted at the M. D. Anderson Cancer Center, Abdalla

and colleagues (Abdalla et al, 2004) compared recurrence and survival between patients with colorectal cancer metastases treated with resection, resection and RFA, RFA alone, or chemotherapy alone (including some patients treated with hepatic infusional therapy). Overall and liver-only recurrences were more common following RFA compared to resection. Indeed, the liver-only failure rate was a full four-fold higher for ablated patients as opposed to resected patients (Abdalla et al, 2004). While this increased recurrence rate likely reflects the higher risk among unresectable patients because of a greater number of tumors and other factors, it supports the generally accepted notion that patients with resectable tumors should undergo resection, rather than ablation, whenever possible (Machi et al, 2001).

Tumor size has been shown to be an important factor affecting the rate of local recurrence following RFA (Wood et al, 2000; Machi et al, 2001; Chan et al, 2002; Kosari et al, 2002; Kuvshinoff and Ota, 2002; Bleicher et al, 2003). Machi et al, (2001), Kuvshinoff and Ota, (2002) and Kosari et al, (2002) all noted significantly higher risk for local recurrence for tumors ≥ 4 cm in greatest diameter. Interestingly, Machi (2001) also associated higher local recurrence rates with metastatic tumors than with primary hepatomas. Some studies have also shown that the approach chosen for delivery of RFA (open, laparoscopic, or percutaneous) may impact local recurrence. Kuvshinoff and Ota, (2002) and Scaife and Curley, (2003) showed lower rates of local recurrence for open and laparoscopic RFA versus a percutaneous approach. The increased access to the liver and use of intra-operative ultrasound are likely the main reasons for lower local recurrence rates for operative RFA.

The complication rate associated with RFA is quite acceptable, ranging from 2.4% to 27% in several trials (Curley et al, 1999, 2000; Bowles et al, 2001; Wong et al, 2001; Jiang et al, 2002; Iannitti et al, 2002; Kosari et al, 2002; Kuvshinoff and Ota, 2002; Bleicher et al, 2003; Komorizono et al, 2003), (**Table 1**). In a large review by Scaife and Curley, (2003) reported an overall mortality rate of 0.5%, a major complication rate of 2%, and a minor complication rate of 6% by combining over 1300 patients from 18 different studies. The complications following RFA include wound infections, intra-abdominal abscess, renal failure, hepatic abscess, biliary injury, pleural effusion, fever, pain, and minor hemorrhage. RFA-associated morbidity, mortality, and local recurrence are low enough to justify its use for unresectable liver tumors.

In non-randomized studies, the available evidence suggests that RFA extends survival. As with other hepatic directed therapies, recurrence either in unablated areas of the liver or in other organs is common, even in the absence of local recurrence (Curley et al, 1999, 2000; Wood et al, 2000; Kosari et al, 2002). Kosari et al, (2002) reported distant failure in 51% of the patients following RFA and local failure in only 1.8% of the hepatic malignancies ablated, but new hepatic or systemic disease still developed in 27.6% of patients at a median follow-up of 15 months. These high figures for distant failure suggest that RFA may best improve long-term survival when

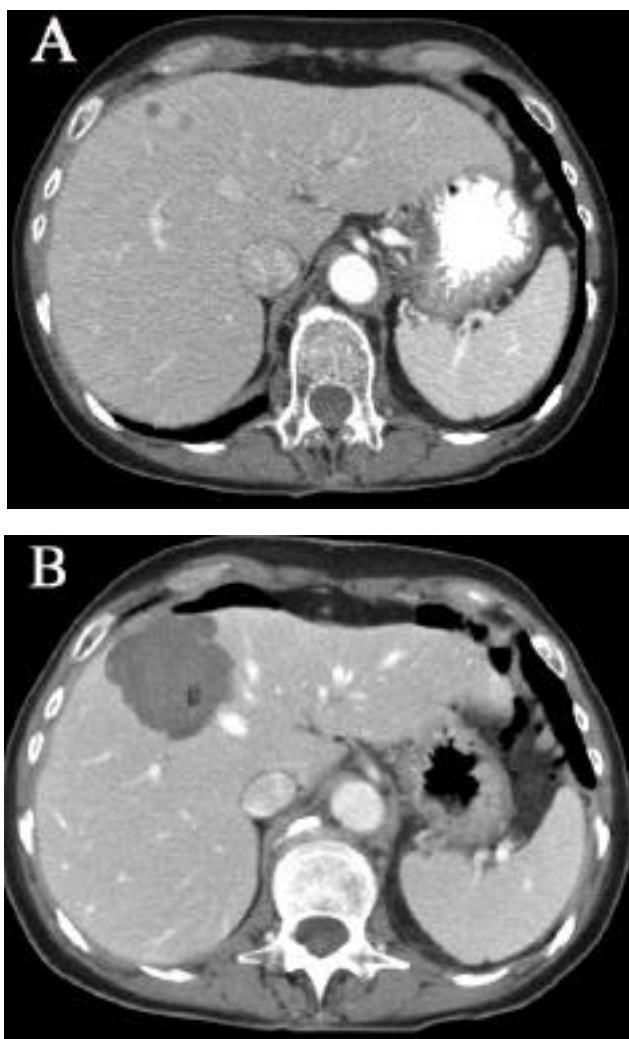


Figure 1. (A) CT demonstrating 2 hepatic metastases from an obstructing right colon adenocarcinoma. (B) Post-RFA CT demonstrating complete ablation of metastatic disease.

Table 1. Results for RFA of unresectable liver tumors

Author, year	N	Tumor type	Median	Recurrence Rate		Morbidity
			F/U	per tumor	per patient	
Curley et al, 2000	110	HCC 100%	19	3.6%	45.5%	12.7%
Rossi et al, 2000	62	HCC 100%	12	18%	30%	12.9%
Wong et al, 2001	40	HCC 5% Mets 95%	NR	10%	27.5%	20%
Bowles et al, 2001	76	HCC 32.9% Mets 67.1%	15	9%	60%	17%
Kuvshinoff and Ota, 2002	45	HCC 24.4% Mets 75.6%	12	26.6%	73.3%	22%
Jiang et al, 2002	36	HCC 58.3% Mets 41.7%	10	16.7%	NR	11.1%
Kosari et al, 2002	45	HCC 11% Mets 89%	19.5	7.7%	73%	27%
Bleicher et al, 2003	153	HCC 13.7% Mets 86.3%	11	20.9%	NR	11.7%
Komorizono et al, 2003	56	HCC 100%	16	26%	18%	21.4%

N, number of patients; F/U, follow-up in months; HCC, hepatocellular carcinoma; Mets, metastases (including colorectal); NR, not reported.

combined with other systemic and intra-hepatic treatments. Some studies have now reported overall survival statistics after RFA with moderate follow-up time. Solbiati et al, (2001) reported overall survival to be 93%, 62%, and 41% at one, two, and three years, respectively. Iannitti et al, (2002) reported overall survival for patients with colorectal metastases treated with RFA to be 87%, 77%, and 50% at one, two, and three years, respectively. They also reported 92%, 75%, and 60% overall survival rates at one, two, and three years, respectively for patients with HCC treated with RFA (Iannitti et al, 2002). When compared to liver resection, however, RFA clearly benefits patients less, with four-year survival of 22% as compared to 65% for resection (Abdalla et al, 2004). Survival for unresectable patients with colorectal cancer metastases is better following RFA than with nonsurgical treatments (Abdalla et al, 2004).

III. Laser-induced thermotherapy

Laser-induced thermotherapy (LITT) is another non-resectional therapy that has been used to treat liver malignancies. LITT, like other thermal ablative techniques, kills tumors by raising the temperature above 55° to 60° C. LITT uses photons from a low-intensity laser, which are absorbed by natural molecular chromophores in all human cells and converted into heat (Izzo, 2003). Diode lasers (wavelength 800-980 nm) or N-YAG lasers (wavelength 1064 nm) operating at low energy generate zones of ablation during LITT (Germer et al, 1998; Muralidharan and Christophi, 2001). Similar to RFA, LITT can be combined with blood flow occlusion and multiple overlapping laser applications to increase the volume of ablation (Heisterkamp et al, 1997; Stureson et al, 1997). Placing multiple laser fibers into the target tissue may create overlapping zones of ablation (Ivarsson et al, 1998). LITT has the same indications as RFA: unresectable primary and secondary liver tumors, and like

RFA, can be performed by percutaneous, laparoscopic, or open surgical approaches.

LITT application kits used for percutaneous procedures include a cannulation needle with a tetragonally sharpened tip, a guide wire, and a sheath system. The catheter aids in easy removal of the laser fibers and prevents direct contact between the fibers and the treated tissue. The applicator has magnetic markers on it that allow the use of MR-guidance for precise placement. The laser is transmitted via an optical fiber cable that is placed in the desired treatment area by advancing it through the applicator system (Vogl et al, 2001).

One of the main advantages of LITT is its compatibility with MR-guidance. It does not interfere with MR-imaging like RFA and microwave ablation. Ultrasound or CT may be used for tumor targeting and placement of the laser fibers, followed by MR imaging of the ablation. Alternatively, intraoperative MRI can provide precise targeting and ablation in a single unit. MR imaging provides increased lesion visibility, three-dimensional laser navigation, and allows monitoring of temperature changes and tissue coagulation (Vogl et al, 1995; Dick et al 2003a, b). Real-time temperature monitoring is a notable advantage because it allows the clinician to assure temperatures are high enough in the tumor for a successful ablation and low enough in surrounding tissue to minimize collateral damage. However, present limitations of MRI thermal mapping have precluded this technique from widespread acceptance.

There have been even fewer large-scale studies of LITT than of RFA (Heisterkamp et al, 1999). In one large European study, Mack et al, (2001) treated liver tumors with LITT and demonstrated impressive local control rates, survival data, and low morbidity. They used MR-guided LITT and reported results for 1981 lesions in 705 patients, including 97.9% local tumor control at 6 months, 93% one-year survival, 74% two-year survival, 50% three-

year survival, 30% five-year survival, and only a 7.5% rate of complications. In a study of 74 patients with single tumors ≤ 4 cm or one to three tumors ≤ 3 cm in greatest dimension, Pacella et al, (2001) reported a 6% local recurrence rate and overall survival rates of 99%, 95%, 68%, and 15% at one, two, three, and five years, respectively. An analysis of the complications associated with the LITT in 899 patients with 2520 lesions concluded that the procedure had an acceptably low morbidity (Vogl et al, 2002). It remains to be seen whether other centers can duplicate these intriguing results; however, the results of these authors are encouraging and warrant further study.

IV. Microwave ablation

Microwave ablation developed out of technology first used for hemostasis and coagulation during hepatic resection (Tabuse and Katsumi, 1981; Tabuse et al, 1986). It has since been adapted and used to treat small HCC tumors in the liver and has been most extensively studied in Japan for the treatment of patients with cirrhotic HCC lesions. Microwaves create dielectric heat in tissue and cells by stimulating tissue water molecules, which leads to frictional heating and necrosis in a similar manner to RFA and LITT (Izzo, 2003). MA can be applied percutaneously, laparoscopically, or as an open surgical procedure. Indications for MA include unresectable hepatic malignancies and patients not suited for major hepatectomy. The needle electrode is advanced directly into the tumor under ultrasound guidance and microwave emission commences. As with the other thermal ablative techniques, multiple overlapping zones of ablation are created to ablate larger tumors. Newer antenna designs, including looping coils may allow for more precise geometric ablation zones to be created with shorter treatment times (Wright et al, 2003; Shock et al, 2004). Our initial experience in a cohort of 20 patients with a multiple antennae MA system (Vivant Medical, Mountain View, CA) has been very favorable; this system allows ablation of multiple tumors at the same time, large (5 to 7 cm) ablation zones, complete tumor ablation, rapid ablation times (5 to 10 minutes maximum), and does not require grounding pads that can potentially result in skin burns such as in RFA systems (Martin et al, unpublished data).

There are few studies on MA with data on local recurrence and complications following treatment, and most of the studies that have been published have reported small numbers of patients. One study involving 19 patients with 31 tumors (mean tumor size 2.1 cm), reported 9.7% local recurrence per tumor (Sato et al, 1996). Microwave ablation has been shown to be a valid treatment option in cirrhotic patients with HCC. Local failure rates are similar to those seen with the other thermal ablative techniques (Xu et al, 2004). In a large study by Dong et al, (Dong et al, 2003) 234 patients with 339 HCC tumors were treated percutaneously with MA. Survival rates of 92% were seen at one year, and long-term survival at five years of 56.7% was reported (Dong et al, 2003). The majority (88.5%) of the patients were Child's class B cirrhotics. There were no perioperative deaths and very few minor complications,

indicating this is a safe technique, even in patients with severe comorbid conditions (Dong et al, 2003).

V. Conclusion

The past several years have seen rapid advances in the treatment of patients with liver tumors. Thermal ablative techniques have become a valid treatment option for patients with unresectable liver tumors and for patients whose underlying disease state or physical condition will not permit a hepatectomy. Resection remains the treatment of choice for liver malignancies; however, most patients have tumors that are not resectable. RFA, LITT, and MA appear to be safe, effective treatments for such patients. The available evidence from non-randomized studies suggests that, given the limited efficacy of systemic therapy, the ability to completely ablate liver tumors extends survival. The range of thermal ablation approaches also permits minimally invasive treatment of recurrence in the liver following resection or ablation. Further study is necessary to demonstrate conclusively the survival benefit of thermal ablation, to aid in patient selection for various approaches, and to determine the most effective ablation systems and techniques. With improvements in the technology, it also remains to be determined whether thermal ablation can replace resection in selected patients.

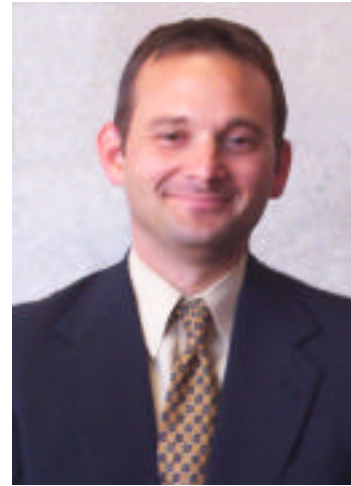
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