Minimally Invasive Approaches in Management of Hepatic Tumors

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ABSTRACT

Traditionally, the only curative option for patients with liver tumors has been hepatic resection. Unfortunately, only 10%-20% of patients with liver tumors can undergo surgical resection due to limited hepatic reserve, high surgical risk, or unfavorable tumor location. Ablation of liver tumors is currently the main alternative to formal liver resection. Tumor cell death is achieved through a number of technologies, which may be separated into three categories: chemical (percutaneous ethanol injection), cold-based (cryotherapy), and heat-based (radiofrequency and microwave ablation or laser hyperthermia). Although long-term data are limited, ablation may be curative in some patients with a three- and five-year survival rate approaching that of resection. The main factors to success include proper patient selection, excellent diagnostic and procedural imaging, and careful post-procedure management and follow up. Long-term success following tumor ablation will be most dependent on the underlying tumor biology and the ability to achieve a negative margin. Future directions in ablation will include the use of adjunctive agents such as chemotherapeutics, further advances in energy delivery, improved imaging and lesion targeting, and continued refinements of current technology and technique.
INTRODUCTION

In 2002, approximately 150,000 new cases of colorectal cancer are estimated to have been diagnosed in the United States alone, with 57,000 deaths. Among men 40 to 79 years old, colorectal cancer is the second leading cause of cancer death. The majority of these deaths are due, at least in part, to liver metastases. Additionally, 16,600 new cases of primary liver tumors will have been discovered in 2002 in the United States, with more than 14,000 deaths. Worldwide, the number of patients with primary hepatocellular carcinoma (HCC) is even greater. An estimated 437,000 new cases were reported in 1990, with the highest incidences occurring in Asia and Middle Africa. The incidence of primary liver cancer appears to be increasing, perhaps due to a rise in the number of persons living with hepatitis.

Traditionally, the only curative option for patients with liver tumors has been hepatic resection, with five-year survival rates between 25% and 60%, compared to a 0% five-year survival rate without resection. Unfortunately, only 10%-20% of patients with liver tumors have disease amenable to surgical resection due to limited hepatic reserve, high surgical risk, or unfavorable tumor location. In recent years, much attention has been directed toward alternative techniques for local control of liver tumors, because chemotherapy has not been successful in treating either primary or secondary liver tumors.

Ablation of liver tumors is currently the main alternative to formal liver resection. The goal of liver tumor ablation, regardless of technique, is to kill the entire treated tumor along with a margin of surrounding tumor. Tumor cell death is achieved through a number of technologies, which may be separated into three categories: chemical [percutaneous ethanol injection (PEI)], cold-based (cryotherapy), and heat-based [radiofrequency (RF) ablation, microwave coagulation therapy, and laser hyperthermia]. Studies of hepatic tumor ablation have focused primarily on tumor response and recurrence as end points; however, more data are becoming available regarding five-year survival rates following tumor ablation.

ABLATION TECHNIQUES: PEI

In general, PEI has been useful in treatment of HCC, but not metastatic colorectal adenocarcinoma. Sterile absolute ethyl alcohol is injected throughout the tumor with a small needle (18-22 gauge) under ultrasound or computed tomography (CT) guidance. The total volume of ethanol required to ablate a tumor can be calculated by determining the volume of the tumor and adding an additional amount of ethanol to account for an ablative margin ($4/3 \pi [r+0.5]^3$). In general, the amount of ethanol injected in one session is limited to 20 mL due to the risk of hypotension at higher volumes. However, some authors have injected large volumes of ethanol in a single session under general anesthesia. Serious complications with ethanol injections are rare. Complications include fever (10%-15% of patients), chemical cholangitis, pleural effusion, portal thrombosis, tumor seeding or implantation, and abscess. Ethanol tends to concentrate within the tumor, because hepatocellular tumors usually are surrounded by a pseudo-capsule of cirrhotic liver. Cell death is due to cellular dehydration and protein denaturation, as well as small-vessel thrombosis. Relative contraindications to PEI include coagulopathy, thrombocytopenia, and tumor location on the surface of the liver or near major hilar structures. An alternative to ethanol injection is acetic acid injection.
injection, which may be more effective in causing tissue necrosis. 21

For HCC, complete tumor response rates range from 40%-80%, 22,24 Tumor response appears to be better in smaller tumors, with excellent results in tumors less than 2 cm. 24 A recent Japanese survey compared resection and PEI in more than 12,000 patients with HCC. Resection demonstrated better survival rates among patients with tumors larger than 2 cm and for those with good liver function and tumors less than 2 cm. 25 Unfortunately, results of PEI for metastatic tumors are much lower, ranging from 0% to 58% response rates, probably because the soft normal liver surrounding metastases does not represent a barrier to the spread of ethanol. Therefore, injections of ethanol into the hard tumor diffuse rapidly into the surrounding liver. Despite the low cost and safety of this procedure, PEI appears currently to have been supplanted in most centers by other ablation modalities, primarily due to the requirement for multiple treatments and availability of newer treatment options.

ABLATION TECHNIQUES: CRYOTHERAPY

Use of cold in the treatment of malignancies was first noted in the 1800s, but was first used widely in the 1960s. Initial attempts at hepatic cryoablation resulted in uncontrolled freezing and high complication rates. Refinements in intraoperative ultrasound lead to a revival of the technique in the 1980s. Cryotherapy causes tumor cell death through rapid freezing of extracellular water, with resultant cellular dehydration and cell membrane rupture. 12 There also may be immune- or cytokine-mediated effects of cryotherapy that have not been elucidated fully.

Cryotherapy has a number of advantages over other ablation techniques. First, multiple probes may be placed simultaneously, which allows treatment of large or multiple lesions and reduces procedure time. Second, the area of frozen tissue (“iceball”) is highly echogenic, which allows careful monitoring of the freezing process by intraoperative ultrasound. A close correlation exists between estimates of lesion size by ultrasound and of actual lesion size by pathologic analysis. Third, cryoablation performs relatively well near large blood vessels (in comparison to heat-based ablation modalities), which causes hepatic tissue necrosis and leaves vessel walls unharmed. However, like all thermal ablation modalities, cryoablation is least effective when performed in the immediate vicinity of large blood vessels.

Cryotherapy is performed routinely during open laparotomy, but may be performed by minilaparotomy, laparoscopically, or even percutaneously. One or more needle cryo-probes are inserted into the target lesion, usually guided by intraoperative ultrasound. Large tumors that require multiple overlapping lesions generally are treated from back to front, because of acoustic shadowing. The cryoprobes may be cooled by either liquid nitrogen or argon gas. In the latter case, tissue cooling is due to the Joule-Thompson principle, with rapid cooling due to expansion of gas in the cryoprobe. Currently, two cryotherapy systems are available in the United States (Endocare, Inc., Irvine, California, and Galil Medical, Woburn, Massachusetts).

Cryotherapy results in excellent local control of hepatic tumors. Reported local recurrence ranges from 10% to 15%. Complications of cryosurgery include: bleeding, injury to adjacent structures, biloma, abscesses, and the “cryoshock” phenomenon of disseminated intravascular coagulation, acute respiratory distress syndrome, and acute renal.

Figure 2. Computed tomography (CT) appearance of A) hepatic tumor; B) two cryotherapy lesions immediately post-treatment; C) four months following treatment.
failure. Cryoshock is believed to be mediated by cytokine release, and appears to be associated with large-volume hepatic cryoablation. Whereas several review articles cite high morbidity rates with cryotherapy, this has not been borne out in the literature. Siefert and Morris surveyed 72 centers that performed hepatic cryosurgery, collected data on 2173 patients, and reported a mortality rate of only 2% and morbidity rate of 7%. Cryoshock was reported in 21 patients, which caused 6 deaths.

We perform open cryoablation routinely in treatment of colorectal metastases, either alone or in combination with resection. Our preference is cryoablation rather than RF ablation in the intraoperative setting, due to the ease of monitoring by ultrasound and ability to place multiple probes simultaneously. This approach allows for safe treatment of large and multiple tumors. In a series of 38 patients, local recurrence was reported in 12%. Two deaths occurred early in our experience, both due to uncontrolled hemorrhage in large-volume lesions in cirrhotic livers. These deaths would likely have been prevented by more careful patient selection. The six complications included bleeding (3), acute renal failure (1), transient liver insufficiency (1), and pneumonia (1). In an overlapping series of 23 patients who underwent cryoablation or cryoablation in combination with resection, our five-year actuarial survival rate was 37%. Careful patient selection, preoperative treatment planning, and intraoperative monitoring are crucial in prevention of complications and deaths.

Figure 3. Commercially available radiofrequency (RF) ablation devices. A) Starburst XL, RITA Medical Systems (umbrella-type electrode; inset: Starburst XLI saline perfusion electrode); B) LaVeen Needle Electrode, Radiotherapeutics Corp.; C) Radionics Cool-Tip™, Tyco Healthcare (internally cooled straight probe; inset: three-probe cluster); D) HiTT RF Ablation System, Berchtold GmBH (straight saline perfusion electrode; inset: close up of perfusion ports). Some images courtesy of manufacturer.

**ABLACTION TECHNIQUES: RF ABLATION**

RF ablation is currently the ablation modality used most commonly. Tissue is coagulated by application of high-frequency alternating current through a monopolar needle electrode placed into the liver. Rapid vibration of ions leads to frictional heat in an area within 1 mm-2 mm of the electrode. The majority of tissue is heated by passive thermal conduction away from this small area of active heating. The amount of heating can be estimated mathematically by the Bioheat equation, and is affected by current density, thermal and electrical tissue properties, and heat loss due to perfusion. RF ablation is, therefore, subject to the “heat sink” effect of relative protection of tissue abutting large (>3 mm) vessels. Heating also is
limited by a rise in impedance due to tissue boiling and char formation as temperatures rise over 100°C. A bare RF electrode is capable of generating a 1.6-cm lesion in perfused tissue.

A number of enhancements to RF ablation delivery systems have increased the size and uniformity of ablation lesions (Fig. 3). A deployable “umbrella” array increases the effective surface area of the electrode, which allows ablations up to a claimed 5 cm or more in diameter (Starburst XL, RITA Medical Systems, Mountain View, California, USA and LaVeen Electrode, Radiotherapeutics Corp., Sunnyvale, California, USA). To generate these large lesions, power delivery must be regulated by either a temperature or impedance-based feedback circuit to prevent tissue boiling and charring. Alternatively, charring may be prevented through internal saline cooling of a straight-needle electrode, which allows greater current delivery. Lesions generated with this system are on the order of 3 cm in diameter using a single electrode, and may be up to 5 cm using a clustered triple electrode (Cool-Tip’, Radionics, Inc., Burlington, Massachusetts, USA).

Lesion size may also be increased by perfusing the surrounding liver with saline or other electrolyte solutions to increase electrical and thermal conductivity and cool adjacent tissue, which prevents charring. Two commercially available perfusion-mediated RF ablation systems have been introduced recently in the United States (the HiTT System from Berchtold GmBH, Tuttingen, Germany, and the Starburst XLI from RITA Medical Systems Inc., Mountain View, California, USA), claiming up to a 7-cm ablation diameter. It remains to be seen, however, if ablation lesions made by these systems will be irregular due to uneven distribution of saline in tissue. In addition, systems that rely on infusion of solutions may be difficult to control, and may cause inadvertent damage to adjacent tissues. In an alternative approach to increasing thermal lesion size and effectiveness, RF ablation may be enhanced through concomitant intravenous administration of chemotherapeutic agents such as liposomal doxorubicin.

Currently available RF ablation systems are limited to a single active electrode due to electrical interference between two electrodes at similar electric potentials (Faraday shielding). This limitation may be overcome by a switching device that alternates current between two or more electrodes. The ability to perform RF ablation with multiple probes should allow for increased lesion size, better control of the ablation zone, and reduced time of application.

Intraoperative use of RF ablation is limited by relatively poor visualization of the developing ablation lesion by intraoperative ultrasound compared to cryotherapy. In our practice, RF ablation is reserved for percutaneous use in patients unable to undergo operative resection or cryoablation due to poor hepatic reserve or those being ablated for palliation of symptoms. Our early experience was with an expandable umbrella array. Placement of these deployable probes has a steep learning curve, and close attention to surrounding structures is critical. Additionally, in porcine studies, we have shown that lesions created with multiple-prong electrodes may be less uniform, due either to tissue cooling by local blood vessels or irregularities in deployment of the prongs due to mechanical effects. Currently, we use a saline-cooled straight electrode. Placement of this electrode is straightforward and lesions appear to be more uniform (Fig. 4). In our experience, actual lesion diameter is somewhat smaller than manufacturer’s claims for all RF ablation systems.

Results following RF ablation vary widely. Local recurrence rates in large recent series have been as low as 2%/15 and as high as 39%, but appear to cluster between 15% and 20%. Most local recurrences appear within the first year following treatment. Complications following RF ablation include abscess, biloma/biliary leak, bleeding, skin burns, injury to adjacent organs, and liver failure. Complication rates in large series are approximately 5%-15%, with a 0%-5% mortality rate. In a recent large European series of 117 patients with 179 colorectal metastases, local recurrence was high but the median disease-free survival was 36 months, and three-year survival rate was 46%. Many of the patients with a local recurrence or new hepatic lesions were managed with repeat hepatic ablation.

It appears the variability in local recurrence rates may be due to patient selection criteria and approach. In general, open or laparoscopic series have shown lower recurrence rates than reported in studies of percutaneous ablation. These data may be due to patient and disease-factors (patients who undergo percutaneous ablation may be more ill, have more advanced disease, or be anatomically unsuitable for resection), or better lesion targeting by intraoperative ultrasound compared to trans-abdominal ultrasound or CT imaging. Also, the open approach may allow identification of additional lesions that require either ablation or resection. In one recent series of 179 patients believed to have resectable dis-
ease by preoperative CT imaging, 34 were reported to have unresectable disease at the time of open exploration.66 An additional 80 patients had more lesions discovered at surgery than detected by CT imaging. In total, intraoperative findings changed the course of action in 96 of the 179 patients. Similarly, Wood and colleagues reported that intraoperative ultrasound detected additional disease in 25 of 66 patients.62

To date, relatively few studies have compared RF ablation and cryotherapy. In a non-randomized study, Bilchick and colleagues reported that RF ablation and cryotherapy had comparable local recurrence rates for tumors less than 3 cm, with less blood loss, reduced thrombocytopenia, and shorter hospital stays with RF ablation.67 However, for tumors greater than 3 cm, the local recurrence rate was 38% for RF ablation and only 17% for cryotherapy. Large tumors also required four times the operative time for RF ablation compared to cryotherapy (60 minutes vs. 15 minutes). In contrast, Pearson and colleagues reported, in a non-randomized comparison, that RF ablation was significantly better than cryotherapy in both local recurrence rates (2% vs. 14%) and complication rates (3% vs. 41%).68

The relatively higher complication rate of cryotherapy may be due to increased production of inflammatory cytokines. In an in vivo rat model, Chapman and colleagues demonstrated increased NF-κappaβ activation in lung alveoli and elevated tumor necrosis factor-α levels in serum from animals treated with hepatic cryoablation, but not hepatic RF ablation.69 On electron microscopy, cryoablation caused bursting of hepatocyte plasma membranes and leakage of intact organelles into the space of Disse, whereas RF ablation destroyed intracellular organelles but left intact plasma membranes. In theory, any heat-based ablation modality should have a similar effect on cellular architecture and cytokine release. Heat-based ablation modalities, other than RF ablation, also should have lower complication rates than cryotherapy, although this has not yet been studied.

Ablation Techniques: Microwave Ablation

Although not available commercially in the United States, microwave ablation has a number of theoretical advantages over RF ablation. In microwave ablation, a thin antenna is inserted into the tumor, much like a RF probe (Fig. 5). The surrounding tissue is then heated by application of microwave energy. Microwave ablation does not appear to be limited by tissue heating and charring; therefore, temperatures may be driven to a much higher extreme than that in RF ablation. Also, most tissue heating is due directly to microwave application, whereas RF ablation is primarily an indirect process. The zone of active RF ablation heating is only 1 mm-2 mm, with the remainder of heating being due to passive thermal conduction. However, microwaves have a much broader penetration into the surrounding tissue, with a zone of active heating that extends 1 cm-2 cm from the antenna. As in RF ablation, heating can be estimated mathematically using the Bioheat equation.

Whereas published data on microwave ablation are rather limited, results to date are promising. Lu and colleagues performed microwave ablation on 107 hepatocellular tumors in 50 patients, with a 5% local recurrence rate and three-year overall survival rate of 73%.70 Shibata and colleagues randomized 30 patients with hepatic metastases from colorectal cancer to either resection or microwave ablation, with median survival times being not significantly different between the two groups (25 months for ablation vs. 27 months for surgery).16

We have extensive experience with microwave ablation in an animal model and have noted that it reproducibly creates uniform zones of coagulation necrosis, hyperechoic by intraoperative ultrasound and hypo-attenuated by postoperative CT imaging (Fig. 6). Lesion sizes are comparable to RF ablation, but ablation times are relatively short. Ease of application is similar to the cooled-tip RF ablation device and easier than the expandable-array RF ablation systems, because the microwave antenna is straight. Although several theoretical advantages of microwave ablation exist, the best clinical advantage is the ability to use multiple probes simultaneously. Microwave lesions created using three simultaneously active probes were six times larger than those created by a single probe, and three times larger than those made by three separate insertions of a single antenna (Fig. 7).71 Simultaneous activation of multiple probes also improved performance near blood vessels, even preferentially treating peri-vascular tissue often left untreated by RF ablation or cryoablation. We are currently performing a Phase I clinical study of microwave ablation in treatment of hepatic metastases from colorectal cancer.

Alternative to Ablation: Minimally Invasive H epatic Resection

A number of recent series have explored the possibility of laparoscopic
hepatic resection. Technically, this may be performed with or without hand-assistance, requires facility with laparoscopic ultrasonography, and is best suited to small lesions of the left lobe (Fig. 8). In a retrospective survey of 11 European centers, 37 patients underwent laparoscopic liver resection. Approximately one-third were for HCC, and the rest for metastatic colorectal cancer. Approximately 90% were in the left lobe or anterior segments of the right lobe, with a 14% rate of conversion to open hepatectomy, 22% complication rate, and 30% of patients had a surgical margin less than 1 cm. In a prospective analysis of 34 patients who underwent laparoscopic-assisted and conventional hepatectomy, the laparoscopic procedures were significantly more time consuming, but patients were, on average, discharged four days earlier.

CONCLUSIONS

The ‘gold standard’ treatment for hepatic tumors remains surgical resec-

Figure 6. A) Placement of microwave antenna; B) ultrasound appearance of microwave lesion in an in vivo porcine model.

Figure 7. Microwave lesions generated by A) one antenna; B) three antennas; C) five antennas. Note extension of the three-probe lesion out along the local blood vessel.
tion. However, a large number of patients are not amenable to resection alone, and tumor ablation increases the number of patients amenable to potentially curative therapy. Ablation is curative in some patients, with a three- and five-year survival rate approaching that of resection. The main factors to success include proper patient selection, excellent diagnostic and procedural imaging, and careful post-procedure management and follow up. Long-term success following tumor ablation will be most dependent on the underlying tumor biology and ability to achieve a negative margin. The choice of ablation technique is dependent on the skills of the practitioner, and will likely change as new technologies are developed and refined. The proper approach (percutaneous vs. open, cryotherapy vs. RF ablation vs. microwave) continues to be debated. Currently, it appears clear that most patients will benefit from open exploration with intraoperative ultrasound guidance. Future directions in ablation will include the use of adjunctive agents such as chemotherapeutics, further advances in energy delivery through the use of new devices and energy sources (ie, microwave), improved imaging and lesion targeting, and continued refinements of current technology and technique.

REFERENCES


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