Technology Brief:

Treatments for Unresectable Liver Cancer

Background AND Patient Populations

Liver cancer, most commonly hepatocellular carcinoma, affects more than 600,000 people worldwide. While it is most common in Africa and Asia, prevalence is increasing in the United States (approximately 20,000 cases diagnosed per year), Europe and Japan. Most of this increase is attributed to the rising rate of Hepatitis C infection (HCV).[i] Unresectable disease is disease that which cannot be treated by a hepatectomy (partial removal of the liver), either because the disease has spread beyond the liver or because there is portal vein or other blood supply involvement or because the liver is too affected. Two year survival without a transplant in unresectable disease is less than 5%.

Overview of the technology

Aside from transplant, there are several treatment options for unresectable liver cancer. These include ablative technologies, intra-arterial approaches, systemic therapy and portal vein embolization. These therapies may also be applied in cases of liver metastases of other primary cancers, which are not covered here.

Ablation technologies: Ablation for hepatocellular carcinoma may be done using radiofrequency, lasers, cold (cryoablation), microwave or ethanol.

- RF ablation produces thermal injury through the use of alternating electric current in the radio-frequency range (460-500 kHz). Subsequent ionic agitation in the surrounding tissue causes frictional heat, which spreads outward from the electrode via conduction.
- Percutaneous microwave ablation was first used as an adjunct to liver biopsy in 1986, but it has since been used for hepatic tumor ablation. As with RF ablation, microwave ablation involves placement of a needle electrode directly into the target tumor, typically under US guidance. Each ablation also produces a hyperechoic region around the needle, similar to that observed with RF ablation. Unlike RF ablation, however, no retractable prongs are used, and the resulting ablation tends to be much more elliptical. For this reason, the expected diameter of ablation is less than with RF ablation and measures slightly greater than 2 cm. Therefore, more sessions may be needed to treat larger tumors. However, the treatment sessions may be shorter than for RF ablation because an ablation is produced in 60 sec with microwave therapy. Despite the differences, the indications, contraindications, and patient selection criteria for microwave ablation are similar to those presented for RF ablation.
- Laser ablation has been shown to be effective in inducing complete necrosis in HCC and hepatic metastases. As would be expected, long-term success is related to tumor size, with patients treated for smaller tumors faring better. Survival rates for patients with hepatic metastases vary

in the literature, but 5-year survival rates of 26% and median survival rates of 27 to 39 months have been reported. Reported complications from laser ablation are not unique to this technique, having also been reported for the other forms of ablation discussed here.

- Cryoablation in the liver is less well studied than RF ablation but may have some advantages. While part of the success of RF ablation may be due to trapping the heat of the tumor, it may limit effectiveness for satellite lesions, not affected by the heat. There are some concerns that cryoablation is associated with more beeding as there is no cauterization effect. In additional, approximately 1% of patients may experience "cryoshock" Hinshaw and Lee conclude that cryoablation should be considered, despite the possibility of complications, especially in those cases where a large and/or precise ablation zone is needed.
- Ethanol Injection is an ablation technique that destroys the liver tumor using alcohol rather than heat. Ethanol injection is used much less frequently and usually only applies to hepatocellular cancers that are small (<2 to 3 cm) and cannot be treated using another technique.

Currently, three RF devices are commercially marketed in the United States. Two of these devices (RITA Medical Systems Inc., Mountain View, CA, and Radiotherapeutics, Mountain View, CA) consist of a needle with a movable hub that deploys a variable number of curved electrodes into the adjacent tissue in a radial manner. The configurations of the multiple electrodes are designed to produce large spherical thermal injuries. The third device (Radionics, Burlington, MA) consists of a straight, internally cooled needle electrode. The internal cooling is designed to prevent charring of the adjacent tissues and thus a larger thermal injury. This latter device may be used alone or in a triangular three-needle configuration. The three-needle configuration has been reported to enhance the size of the thermal injury to as much as 5 cm. The major factor limiting the size of the thermal injury produced by all three devices is hepatic perfusion. Normal blood flow through the liver produces perfusion-mediated tissue cooling. One method to overcome this limitation involves temporarily occluding flow in the hepatic artery and portal vein (Pringle maneuver), thus limiting the amount of heat carried away by the blood flow through the liver.

The FDA has approved the use of the Evident Microwave Ablation System, for nonresectable liver tumors, offering an option for patients who are not candidates for surgical resection and making possible percutaneous, laparoscopic, or open surgical soft-tissue ablation.

Information from the manufacturer, Covidien, notes that the Evident system allows ablations to be achieved in approximately 10 minutes, which is about 60% faster than with other ablation products, meaning that less time is spent in the operating or radiology rooms for both patients and medical professionals as well as less time under anesthesia for patients.

Embolization and Intra-arterial technologies

- Intra-arterial therapies for unresectable hepatocellular carcinoma consist of a group of treatments where therapeutic and/or embolic agents are intra-arterially directed to target tumors. These therapies selectively and locally deliver intra-arterially therapeutic agents to the tumor, which receives its blood supply largely via the hepatic artery. Embolization may be performed without (TAE) or with (TACE) chemotherapeutic agents. A review of these

technologies appears here:
http://www.springerlink.com/content/4j714805qrm4uk66/fulltext.html

- Additional approaches include drug eluting beads and Yttrium-90 bead therapy. Yttrium-90 microsphere radioembolization is an FDA approved, non-surgical procedure used to treat inoperable liver cancer. With yttrium-90 microsphere radioembolization, a catheter inserted through a tiny incision in the groin and threaded through the arteries until it reaches the hepatic artery. Once the catheter is properly placed in the hepatic artery, millions of tiny beads, or microspheres, which contain the radioactive element yttrium-90, are released into the blood stream. These microspheres lodge into the smaller blood vessels that feed the tumor. In addition to preventing blood flow to the tumor, the microspheres emit radiation that helps destroy the cancerous cells.

Current Evidence

The National Comprehensive Cancer Network hepatocellular carcinoma guidelines state that microwave ablation, cryotherapy, RFA, and percutaneous ethanol injection may be used in the treatment of unresectable nonmetastatic hepatocellular carcinoma, for patients with nonmetastatic hepatocellular carcinoma who do not agree to surgery, and to treat hepatocellular carcinoma which is local but inoperable (e.g., due to poor performance status or presence of comorbidity). NCCN guidelines make no distinction with respect to these different ablative methods. NCCN guidelines state that ablative therapy of colorectal cancer metastases to the liver using RFA or cryosurgery at the time of colon resection can also be considered when all measurable metastatic disease can be treated.

In a review on the use of RFA for the treatment of primary and metastatic liver tumors, Garrean et al[ii] concluded that although RFA has been readily adopted into treatment paradigms, more rigorous trials are needed to solidify its place in the armamentarium of therapeutic strategies for hepatic malignancy.

In a systematic review on the current role of RFA in the management of hepatocellular carcinoma, Lau and Lai concluded that the evidence in the medical literature showed RFA was more effective than other local ablative therapies, and supported its use in the treatment of unresectable small hepatocellular carcinoma, recurrent small hepatocellular carcinoma, and as bridging therapy before liver transplantation, and as a primary treatment in competition with partial hepatectomy for resectable small hepatocellular carcinoma.[iii]

In a meta-analysis of randomized controlled trials, Llovet et al found that chemoembolization improves survival in a subset of patients with unresectable HCC and that chemoembolization may be considered the standard treatment for them.[iv]

A recent review drew the following conclusions: “Chemoembolization improves survival and offers improved tumor response compared to systemic treatment. More studies are needed to standardize chemoembolization preparations and techniques. RFA provides better results than PEI but has not been

compared with cryoablation. Radioembolization appears to be as effective as chemoembolization, but the preprocedure evaluation and costs may limit its use." [v]

Costs

Most institutions are able to provide these technologies, although some investment is necessary. Because the techniques are primarily applicable to non-resectable tumors, costs are likely to increase as compared to palliative care, but the therapies are like to be cost effective.

Cost-effectiveness

There have been no comparative studies of cost-effectiveness of these therapies, but there are two somewhat older studies that both suggest RF is a cost-effective approach for non-resectable tumors, but not cost-effective compared to resection in resectable liver tumors.[vi] Many of the therapies are relatively new and efficacy data are still being gathered. In general, reviews even of efficacy are of limited value given the variation in therapies as they are currently being used.

Coverage

Many of these technologies are frequently covered, though there is some variation.

- Aetna considers chemoembolization (CE) and intra-hepatic microspheres medically necessary
- Anthem considers selective internal radiation therapy (SIRT medically necessary as palliative treatment.
- CIGNA covers percutaneous ethanol injection (PEI), cryoablation, and radiofrequency ablation (RFA) as medically necessary for the treatment of unresectable primary liver cancer and unresectable liver metastases.
- Health Net, Inc. considers percutaneous ethanol injection (PEI) for unresectable primary, localized hepatocellular liver cancer medically necessary if
    - Tumors are < 5cm in diameter; and
    - Tumor is encapsulated, with well defined margins, and not located near the surface of the liver.

Summary

There appears to be a clinical role for new technology in the treatment of unresectable liver cancer. However, these treatments have not been well evaluated, nor compared to each other. It is unclear which therapies will provide the best outcome for which tumors and more research is needed to determine this.

[i] El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States.***N Engl J Med***. 1999;340:745-750. Thomas MB, Abbruzzese JL. Opportunities for targeted therapies in hepatocellular carcinoma.***J Clin Oncol***. 2005;23:8093-8108

[ii] Garrean S, Hering J, Saied A, et al. Radiofrequency ablation of primary and metastatic liver tumors: A critical review of the literature. Am J Surg. 2008;195(4):508-520

[iii] The Current Role of Radiofrequency Ablation in the Management of Hepatocellular Carcinoma: A Systematic Review. Wan Yee Lau, MD, FRCS, FACS, FRACS (Hon); Eric C. H. Lai, MB, ChB, MRCSEd, FRACS. Annals of Surgery. 2009;249(1):20-25

[iv] Llovet JM, Real MI, Montana X. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. May 18 2002;359(9319):1734-9

[v] Davis, CR. nterventional radiological treatment of hepatocellular carcinoma. Cancer Control. 2010 Apr;17(1):87-99

[vi] Gazelle et al 2004, Shetty et al 2001

National Institute for Health and Clinical Excellence (NICE). Microwave ablation of hepatocellular carcinoma. Interventional Procedure Guidance 214. London, UK: NICE; March 2007)