

RESEARCH PROTOCOLS

The following is a list of the research protocols at the Center for Liver Diseases at Inova Fairfax Hospital:

- Triple regimen of Pegylated Interferon Alfa 2b, Ribavirin and Amantadine for treatment of chronic hepatitis C.
- Growth factors for treatment of cytopenia in patients with hepatitis C on Ribavirin/PEG-IFN.
- The use of Interferon Gamma-1b as an anti-fibrotic agent in hepatitis C.
- Pegylated interferon Alpha 2a with or without Thymosin Alpha 1 for chronic hepatitis C.
- Pegylated interferon Alpha 2b maintenance protocol for prevention of complication of HCV-related cirrhosis.
- Lamivudine with or with out monoclonal HBV antibody for chronic hepatitis B.
- Epidemiology for hepatitis B in the United States.
- Epidemiology of Hepatocellular carcinoma in the United States.
- Epidemiology of Non-Alcoholic Fatty Liver Disease.
- Efficacy trials in Non-Alcoholic Fatty Liver Disease

For patient screening or additional information, please call the Center for Liver Diseases at **703-698-3182**, or fax **703-698-3481**.

Publications and Presentations

PUBLICATIONS

- S Saadeh, Z Younossi, E Remer, T Granlich, J Ong, M Hurley, K Mullen, J Cooper and M Sheridan. "The Utility of Radiological Imaging in Nonalcoholic Fatty Liver Disease" *Gastroenterology* 2002.
- BK MulHall, JP Ong, and ZM Younossi. Nonalcoholic Fatty Liver Disease. *Journal of Gastroenterology* 2002.

PRESENTATIONS

- Natural History of NASH; Clinical Symposium, Digestive Disease Week, San Francisco, CA
- The Spectrum of Nonalcoholic Fatty Liver Diseases (NAFL); Clinical Research Single Topic Conference on Nonalcoholic Steatohepatitis (NASH); American Association for the Study of Liver Diseases, Atlanta, GA.
- Nonalcoholic Fatty Liver Disease (NAFL) Abstract Presentations; The Liver Meeting. American Association for the Study of Liver Diseases, Boston, MA.

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diagnosing intrahepatic malignancies. A recent European study showed that 99 percent of lesions were identified when intraoperative verification was used to substantiate the findings. Eleven percent of the patients received additional information that was not seen on either a CAT scan or an MRI scan. Unfortunately 7 percent of the patients were falsely over- staged and 8 percent were under-staged, based on the results of the PET scans.

Intraoperative ultrasound is currently the best imaging technique for detection of small tumors. This modality can consistently find lesions of four mm in diameter and can aid in the biopsy of suspected tumors. Initially, laparotomy was required for this procedure, but with the use of new ultrasound probes, laparoscopic ultrasound can now be performed. Laparoscopic ultrasound gives all the benefits of intraoperative ultrasound, but it is less invasive.

Unpublished data suggests that 15 percent of the patients who undergo laparoscopic ultrasound will have additional lesions identified at exploration. The lesions that are identified tend to share a common feature, in that they tend to be small, superficial lesions over the dome of the right lobe and rarely preclude surgical resection. Despite a probable learning curve with this technique, laparoscopic ultrasound allows the identification of most patients who will be unresectable before open laparotomy is performed. ■

American Liver Foundation Corner

Hepatitis C Support Groups

Inova Fairfax Hospital and the ALF sponsor Hepatitis C Support Groups in the Washington, DC area. The group will meet at the hospital in conference rooms D, E and F on the following dates:

Nov. 19, 2002

Hepatitis C: A Year in Review

Zobair M. Younossi, MD, MPH

Medical Director

Center for Liver Diseases, Inova Fairfax Hospital

Dec. 17, 2002

Open Forum/Discussion

Inova Health System is a not-for-profit health care system based in Northern Virginia that consists of hospitals and other health services including emergency and urgent care centers, home care, nursing homes, mental health and blood donor services, and wellness classes. Governed by a voluntary board of community members, Inova's mission is to provide quality care and improve the health of the diverse communities we serve.

www.inova.org

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Liver Update

A publication of the Center for Liver Diseases and the Inova Transplant Center

New Modalities for the Treatment and Diagnosis of Hepatic Malignancies

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Hepatocellular carcinoma, although rare within United States, is the most common liver tumor worldwide. These tumors are often multiple, with each tumor usually representing a new primary cancer, rather than a metastatic lesion.

There is a strong correlation between cirrhosis and development of hepatocellular carcinomas, with over 90 percent of patients with hepatocellular carcinoma having underlying cirrhosis. The cirrhosis not only predisposes the patient to develop new primary malignancies, but it can also limit the ability to perform surgical resection. Without treatment, the median survival in the United States is only three to six months, but after complete surgical resection, survival rates as high as 25 to 39 percent have been reported.

If surgical resection can be undertaken, the operative mortality rises from one percent in non-cirrhotic patients to as high as 10 percent when cirrhosis is present. Unfortunately, studies have shown that because of the underlying cirrhosis, 60 percent of the patients who undergo curative resection will develop new primary malignancies in the future. Autopsy studies have shown that greater than 90 percent of the patients with primary liver cancers die with disease confined to the liver. It is this population who would most benefit from the elimination of the tumor, and the cirrhosis that cause new primary tumors, from their liver.

Metastatic lesions, especially from colorectal primaries, remain the most common hepatic malignancy in the United States. There are approximately 150,000 new cases of colorectal carcinoma in United States each year and over 50 percent of these will develop metastatic disease. Sixty to 70 percent of the people who develop metastatic disease will have the liver as one site of metastasis. Historically, a complete surgical resection will yield a 25-30 percent long-term, disease-free survival, however it is important to understand that not all patients can benefit from surgical resection. Hughes showed in the 1980's that patients with disease outside the liver, even if resectable, do not receive any benefit in either quantity or quality of life from surgical resection. Recent studies however show that solitary lung metastasis may not preclude surgical resection of the liver if both lung and liver lesions can be completely removed.

The number of lesions also appears to be important in predicting benefit from resection. Hughes showed that patients with more than three lesions within the liver obtain no

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benefit from surgical resection, but recent studies suggest that up to five lesions can be resected with similar long-term, disease-free survivals. Disease-free intervals of greater than one year appear to have a beneficial effect on patient survival. New data suggests that patients with a single lesion and greater than one year, disease-free interval may have a 60 percent chance of long-term, disease-free survival.

SURGICAL RESECTION

Surgical resection remains the gold standard for the treatment of both primary and metastatic liver tumors. It is important to remember that survival and palliation after incomplete resection for any liver tumor is no different than laparotomy alone. It is therefore important to insure that patients who undergo surgical exploration have no evidence of extra hepatic disease, as determined by preoperative imaging studies and intra-operative ultrasound. As mentioned above, recent studies suggest that solitary lung metastasis may be an exception to the no extrahepatic disease rule. Complete resection of both lung and liver lesions may produce good results.

Using new surgical techniques, many of the tumors previously felt to be unresectable can now be removed with minimal risk to the patient. We are now able to safely remove up to 80 percent of the liver and still have excellent outcomes. Perioperative mortality rates, even for extensive resections, should be less than one percent in skilled hands, with fewer than 20 percent of the patients requiring any blood replacement and hospital stays of less than one week. Studies have shown that patients who have already undergone a surgical resection, or other form of ablation procedure, and developed a hepatic recurrence can achieve a 40 percent long-term, disease-free survival with a complete surgical resection of the

recurrent liver metastases. This assumes that they still meet the criteria mentioned above, namely no extrahepatic disease with five or fewer lesions within the liver.

Resectability remains a controversial subject, as the decision truly resides in the eyes of the beholder. Because no other ablative modality can approach the results seen with complete surgical resection, this should be considered the treatment of choice. Aggressive surgical resections of lesions previously felt to be “non-resectable” should be considered a good option as long as the surgeon has a record to show that their results are good with low perioperative mortality.

LIVER TRANSPLANTATION

Liver transplantation for primary hepatic malignancies, but not metastatic disease, is theoretically attractive; however the actuarial survivals have ranged from six to 50 percent, with mortality from the transplant, unrelated to the tumor, as high as 15 percent. The problem is that immunosuppressive therapy promotes rapid growth of any residual tumor after transplantation, resulting in cancer recurrence rates as high as 60 percent for primary tumors and 100 percent for metastatic disease. Analysis of the data has suggested that certain factors increased recurrence rates after transplantation for primary liver tumors. Patients with a single large tumor greater than five cm in diameter or with more than three smaller tumors any greater than three cm in diameter (stage III tumors) have high recurrence rates following transplantation.

Vascular invasion, whether identified microscopically or on preoperative imaging studies, also has a poor prognosis. Any extra hepatic disease suggests that complete excision of tumor cannot be performed and will virtually guarantee an early postoperative recurrence. Some

tumors, such as fibrolamellar variant, are non-aggressive and have a good prognosis after transplantation.

Several centers have published successful series using transplant, combined with adjuvant chemotherapy, for the treatment of large hepatocellular carcinomas. To identify the exact role of transplantation in the treatment of this disease, multiple U.S. trials have been developed. Most studies require patients have a primary hepatocellular carcinoma with no evidence of vascular invasion and no extra hepatic disease. Following transplantation, six months of Adriamycin based chemotherapy has been advocated. Olthoff, Busuttil et al, showed a 46 percent disease-free survival at three years, compared to only a 5.8 percent survival in matched controls. Although it is too early to determine the exact role of transplantation in this disease, no other treatment modality can offer similar long-term survivals in unresectable patients.

Because of these promising results, UNOS has allowed patients with hepatocellular carcinoma confined to the liver and who have stage I or II disease to have a higher priority for transplantation. People with stage I disease (a single lesion of less than 2cm) will be listed with a score that should allow transplantation within six months. Patients with stage II disease (a single lesion less than 5cm, or 2 to 3 lesions all less than 3cm) will be listed at a score that should allow transplantation in less than three months. If transplantation does not occur in the expected time frame, these patients receive additional points to further expedite transplantation. Because patients with stage III disease have not been shown to consistently benefit from transplantation, these patients are given no additional points, but can still receive a transplant if their underlying liver disease warrants the procedure.

ABLATIVE PROCEDURES

Patients who have stage III hepatocellular carcinoma or metastatic adenocarcinoma to the liver are not candidates for transplantation. As discussed previously, surgical resection remains the gold standard in the treatment of such diseases, but some patients find the morbidity associated with surgical resection to be a disincentive towards treatment. For this reason, multiple, less invasive procedures have been developed to try and offer outcomes equivalent to surgical resection without the morbidity and hospital stay seen with surgical resection. We must never lose sight that a procedure needs to have equivalent outcomes to be effective and being less invasive is not a benefit if the long-term results cannot show equivalent survival advantage.

All of the percutaneous procedures have one major disadvantage when compared to open procedures. Despite the advances that have been made in diagnostic imaging, recent studies have shown that intraoperative ultrasonography can identify previously undetected lesions in as many as 40 percent of patients. Studies have shown that intraoperative ultrasound can consistently find lesions four mm in diameter, which is well below the detection threshold of traditional imaging techniques. As we stated previously, incomplete surgical resection or ablation offers no advantage in either quality or quantity of life when compared to no procedure.

TRANS-ARTERIAL CHEMOEMBOLIZATION

Hepatic malignancies derive their blood supply solely from the arterial circulation. For this reason, many authors have believed that intra-arterial chemotherapy would offer improved outcomes as compared to systemic chemotherapy. Unfortunately, no study to date has

shown the anticipated improvement in outcomes. Ligation of arteries supplying the tumor should likewise cause tumor necrosis; however, because of parasitised blood supply to the tumor, any decrease in size is only transient. Chemoembolization combines both of these modalities by injecting thrombogenic agents along with chemotherapy, usually Adriamycin based therapy, into the tumor. This essentially starves the tumor of its blood supply while leaving large amounts of chemotherapy within the tumor. Early studies have shown that 29 percent of treated patients can achieve a decrease in the size of the tumor, and an additional 55 percent have shown stagnation of growth in the tumor. Despite these impressive numbers, the only prospective randomized trial to date has failed to show any improvement in either quantity or quality of life. Despite this study, chemoembolization remains an important modality for the palliative treatment in patients with non-resectable tumors, or to decrease the tumor burden prior to transplantation.

PERCUTANEOUS ETHANOL INJECTION

Based on the fact that alcohol is fatal to all living cells, in 1983 Sugiura began injecting alcohol into primary hepatocellular carcinomas. The results of this modality of treatment have been mixed, but good results are only seen with small primary tumors less than three cm in diameter. The best study comes from Livraghi et al, which is a retrospective review of five previous studies. There were 207 patients with primary liver tumors in this study, with a mean follow-up of two years. Only 7 percent of the tumors showed local recurrence after treatment, but, as expected, 64 percent of patients developed new primary tumors elsewhere in the liver. Most importantly, the stage of the underlying cirrhosis was the most important factor in predicting outcome. Seventy percent of Child's A patients were alive at three years after

treatment, while there were no survivors in a population of Child C patients. The study also confirmed the fact that tumors greater than three cm in diameter had higher local recurrence rates, and worse long-term outcomes, when compared to smaller tumors. Unfortunately no studies have ever shown a benefit when treating metastatic disease to the liver using percutaneous alcohol injection.

PERCUTANEOUS ACETIC ACID INJECTION

Recently the Japanese, instead of alcohol, used acetic acid to treat primary liver tumors as this has been shown to break down the fibrous membranes within the tumor allowing diffusion throughout the tumor. Early results (unpublished communication) have been promising in tumors up to five cm in diameter. A new trial with larger tumors is currently underway comparing acetic acid alone with acetic acid injections one week following chemoembolization. Results of this study are not yet available. Based on the preliminary Japanese data, the FDA has issued a five center IND (investigational new drug) in the U.S. for both primary and metastatic liver tumors and Inova Fairfax Hospital will be one of these centers.

With early results showing a 90 percent sterilization rate for primary liver tumors less than five cm in diameter and little destruction of the surrounding liver tissue, this modality could dramatically change the way we treat primary liver tumors in patients with underlying cirrhosis. We should be able to offer this modality to our patients sometime in 2002.

CRYOSURGICAL ABLATION

Any cell cooled to less than -50(C in an uncontrolled fashion will be fatally injured. Initially, the micro-vascular circulation and the extra cellular fluid are frozen, which results in a solute gradient that causes dehydration of the cells. Finally, there is freezing of

the internal cellular fluid, resulting in the plasma membrane and organelles rupturing. There are also indirect mechanisms of cell destruction, including tissue anoxia, edema, inflammation and potential immunologic effects. These indirect mechanisms result in increased tissue destruction over the several days following freezing.

Cryosurgery has been shown by both Ravikumar and Steele to be an effective means of treating metastatic colorectal carcinomas to the liver, producing results similar to surgical resection for lesions less than five cm in greatest diameter. Unfortunately the size and cost of the cryosurgical unit, combined with the fact that it could only be safely used with open laparotomies, made it a modality that was not well suited to the current health care needs.

RADIOFREQUENCY ABLATION

Radiofrequency ablation destroys tissue by the use of heat instead of cold. The major obstacle which initially limited its use was the fact that char quickly develops on the probe inserted into tissue, dramatically decreasing the ability to transmit heat throughout the tumor. Two separate techniques were developed to overcome this insulating effect of the char.

Water cooled probes were developed to prevent the high temperatures at the tip of the probes which was the ultimate cause of the char, thus allowing a greater distribution of heat throughout the tumor. Unfortunately the size requirements of these water cooled probes limited its use in the destruction of intrahepatic malignancies. These water cooled probes however, are now currently available to assist in the parenchymal dissection for liver resections.

The other technique to prevent char formation consisted of a gradual increase in the current being directed to the probes, preventing the

immediate high temperatures that were responsible for char formation. Even with this advancement however, a large enough area of destruction could not be created to make this clinically useful. A multi-pronged probe was then developed, much like an umbrella without the cloth, which would distribute this energy over a much larger area. Initially probes were created that could create a five cm area of destruction, and more recently, a seven cm area of destruction.

One of the major benefits of this technique is that it can be done either percutaneously or during open surgery. The cost of the machine is much less than the cryosurgery machines and is within the reach of most hospitals, which has resulted in a rapid proliferation of this technique. There is little question that the tissue within the burn is completely destroyed, but the results reported thus far have given rise to some concern. MD Anderson Cancer Center reported that they could only achieve good results when the procedure was performed using an open technique. This was because they found it difficult to accurately place a spherical tumor inside a spherical burn when restricted by the two dimensional imaging techniques in a percutaneous approach. When this was done in an open fashion, intraoperative ultrasound allowed the continuous monitoring of both the probe placement and the burn in three dimensions, ensuring complete tumor destruction.

Livraghi et al, in an Italian study, reported that they could achieve good results performing the procedure percutaneously, but were limited to a three cm tumor size restriction. Both of these studies were done using the five cm probe, so with the seven cm probe larger lesions may be able to be treated with radiofrequency ablation, but with more destruction of surrounding tissue.

A recent review article in September 2002 by Seidenfeld shows there is

currently not a sufficient amount of evidence to allow for comparison of radiofrequency ablation to either surgical resection or other ablative procedures. The main limitation remains the short duration of follow-up reported in the currently published literature, usually less than 12 months. Even though follow-up is short, tumor recurrence rates at the site of the ablation remain low in lesions less than three to five cm in diameter. This finding allows for cautious optimism that radiofrequency ablation may prove to be a viable option in the destruction of liver tumors.

DIAGNOSTIC IMAGING

CT scans have historically only detected between 40 and 65 percent of hepatic lesions. Small lesions, less than one cm in diameter, can only be identified between 10 and 15 percent of the time. Triphasic spiral CT scans can now offer the ability to identify 91 percent of lesions within the liver and can even identify 84 percent of lesions less than one cm. Unfortunately, the improved sensitivity came with a substantial increase in the number of false positive tests. This resulted in a specificity of only 35 percent, with an overall accuracy rate of only 74 percent.

MRI scans are becoming increasingly accurate in their ability to identify intrahepatic malignancies. Two different contrast agents are currently available to assist in the diagnosis, gadolinium and ferumoxide. Recent studies have shown sensitivity rates of greater than 80 percent, with a specificity of 94 percent for gadolinium enhanced MRI scans when compared to the 62 percent sensitivity and 94 percent specificity for ferumoxide enhanced scans.

PET scans have been available for over a decade, but because of their high cost and limited availability little data exists to help predict its role in

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