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# LIVER UPDATE

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Center for Liver Diseases  
Inova Fairfax Hospital  
3289 Woodburn Road, Suite 375  
Annandale, VA 22003-6800  
Third Tuesday of every month, 7:30 p.m.

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.

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*Medical Editor*

*Director, Center for Liver Diseases*  
Zobair M. Younossi, MD, MPH  
**703-208-6650**

*Managing Editor*

Denise Tatu  
**703-321-2912**

## Modalities for the Treatment of Hepatic Malignancies

James Piper, MD

*Surgical Director, Liver Transplant Program  
Inova Fairfax Hospital*

### METASTATIC DISEASE

The most common hepatic malignancy in the United States remains metastatic lesions from some distant site, with adenocarcinoma being the most common cell type. Historically, the only metastatic adenocarcinoma to the liver that has shown significant benefit from surgical resection is that of colon primaries. Although recent data may suggest some minimal benefit for surgical or ablative therapy for lesions of breast, stomach, esophageal and pancreatic primaries, these are usually not considered to exhibit a significant survival advantage after treatment.

Over 150,000 new cases of colon cancer are diagnosed each year. Fifty percent of these patients will develop metastatic disease at some point, with the liver being the most common site of spread. Patients with metastatic disease have a median survival of less than two years without treatment and the five-year survival rate is two percent. Only one-third of patients show any significant response to chemotherapy and therefore other treatment options should always be considered.

### PRIMARY LIVER TUMORS

Hepatocellular carcinoma, although rare in the United States, is the most common liver tumor worldwide. These tumors are often multiple, with each tumor usually representing a new primary rather than a metastatic lesion. There is a strong correlation between cirrhosis and development of hepatocellular carcinoma, with 90 percent of patients having underlying cirrhosis. Certain disease processes such as hemochromatosis, hepatitis C and hepatitis B further enhance the likelihood of developing a primary hepatic malignancy.

Without treatment, the median survival for patients with primary hepatic malignancies is usually less than a year. Complete surgical resection have yielded long-term disease free survival rates as high as 40 percent, however underlying cirrhosis often limits the ability to surgically resected all identifiable tumor. Even with a potentially curable resection, these patients still have cirrhosis and underlying liver disease. This underlying liver disease can result in progression to end-stage disease and 60 percent of these patients will eventually develop a new primary malignancy. If we are to offer significant benefit for these patients, we need to address not only the primary hepatic malignancy but also the cirrhosis and underlying liver disease through the consideration for liver transplantation.

### TREATABLE PATIENTS

We need to remember that the survival and palliation after incomplete resection is no different than laparotomy alone. We are therefore obligated to ensure that a complete surgical resection can be completed prior to subjecting the patient to any surgical procedure. Evidence of spread outside the liver, even if resectable, will eliminate the ability to potentially cure a patient. The one exception to this rule may be metastatic colon cancer to both the lung and liver, which may benefit from a complete surgical resection.

Hughes published the first article addressing metastatic colon carcinoma to the liver in 1988. He showed that any extrahepatic disease, even if resectable, was a contraindication to proceeding with surgery. This means that anyone who has positive hepatic lymph nodes is considered to have extrahepatic disease and therefore would not be a candidate for resection. Hughes also demonstrated that the number of lesions was important, with four or more lesions eliminating any benefit from surgical resection. Over the last 26 years, the majority of his findings have stood the test of time, but several modifications have been made. Most authors now agree that patients with up to five hepatic metastases can benefit from surgical resection. As

see *MALIGNANCIES*, page 2 ►

► *MALIGNANCIES, from page 1*

stated, there may also be a benefit of resecting hepatic metastases from colon primaries.

The factors that influence recurrence after resection for primary hepatic malignancies are different than those of metastatic lesions. Vascular invasion, whether microscopic or macroscopic, results in a poor prognosis following any treatment modality. Both Nagao and Chen have shown that tumor size influences outcome following treatment, with lesions greater than 5 cm having a significantly worse outcome. Pichlmayer showed that multifocal tumors result in poorer outcomes and patients with more than three lesions, any greater than 3 cm, have a worse prognosis.

### PREOPERATIVE STAGING

There continues to be a debate concerning the best imaging modality to stage a patient prior to proceeding with surgical resection. CT scans, ultrasound, MRI scans and now PET scans have all been shown to be useful in the preoperative evaluation of patients with primary and metastatic cancers to the liver. No single imaging technique has repeatedly been shown to be superior to any of the other techniques. PET scans have shown improved sensitivity in the identification of hepatic malignancies, but specificity data has not conclusively shown its accuracy is better than either CAT scans or MRI scans. The latest techniques that are being used are the fusion of PET scans with either CAT

scans or MRI scans. These computer-fused studies give the benefit of being able to not only look at structural abnormalities but also metabolic changes as well. This fusion gives a better opportunity to determine if there are any structural abnormalities at the site of metabolic changes, which will hopefully improve accuracy in deciding which patient could best benefit from surgical intervention.

Intraoperative ultrasound has been shown to consistently visualize lesions that are 4 mm in size, much smaller than any of the above imaging procedures can routinely identify. The reason for the improved visualization is that ultrasound probes with higher frequencies give better resolution but have very poor penetration.

Interoperative imaging of the liver no longer requires the penetration of skin and muscle, so high-frequency probes with improved resolution can be used. Intraoperative ultrasound also allows for the biopsy of any suspicious lesion, thereby further improving sensitivity, specificity and accuracy. This technique is readily available in most large hospitals throughout the United States and should be considered a useful tool to confirm the preoperative staging or to restage a patient before proceeding with large hepatic resections. Interoperative ultrasound can be done using either laparoscopic or open techniques.

### TREATMENT MODALITIES

Surgical resection remains the gold standard for the treatment of both primary and metastatic lesions. We

must again stress that patient survival and palliation after incomplete resection is no different than laparotomy alone. We therefore need to ensure that complete resection can be accomplished prior to proceeding with hepatic resections.

### PRIMARY LESIONS

Complete surgical resection of a primary hepatic malignancy can yield 40 percent long-term, disease-free survival. The most important prognostic indicators of long-term survival is the severity of the underlying liver disease, the size and number of lesions, the presence of vascular invasion and any evidence of distant disease. Even with favorable tumors and retained hepatic synthetic function, there is a 60 percent chance of developing new hepatic primaries in the future. For this reason, liver transplantation has emerged as a treatment option that can not only address the removal of the hepatic malignancy but also the resolution of the underlying cirrhosis and sometimes the disease process.

We must remember that immunosuppression therapy promotes the rapid growth of any residual tumor after transplantation. Metastatic tumors are never considered transplant candidates because of the rapid spread of tumor following immunosuppression.

Primary hepatic malignancies however, have shown promise following transplantation, despite the need for immunosuppressive medication. Analysis of the data has suggested that certain risk factors increased recurrence rates after transplantation. Patients with single lesions less than five cm, or up to three lesions all less than three cm, have excellent outcomes following transplantation. Any evidence of extrahepatic disease or vascular invasion precludes the ability to proceed with transplantation because of rapid recurrence after immunosuppression.

## *Current Clinical Trial Protocols*

- A Number of Fully-Funded, Novel Treatment Protocols for Hepatitis C, All Genotypes, Previously Untreated
- The Use of Growth Factors for the Management of Pegylated Interferon-Ribavirin Related Cytopenia in Patients with Chronic Hepatitis C
- Clinical Research for Patients with Non-Alcoholic Fatty Liver Disease
- Clinical Research for Patients with Hepatitis B

## Presentations at National and International Meetings

- K Schluach, F Gorreta, T Born, H Elariny, L Del Giacco, K Ziegler, A Van Meter, J Ong, V Chandhoke, R Collantes, Z Goodman, Z Younossi. Hepatic Gene Expression and Serum Protein Profile of Patients with Metabolic Syndrome. Association for Study of Liver Disease. Boston, MA. October 2004.
- Z Younossi, J Chan, K Schlauch, R Collantes, J Assmann, C Santini, J Ong, J Martin, L McAllister, SY Chang. Gene Expression Profiles of Patients with Chronic Hepatitis C Developing Treatment-Related Anemia. Association for Study of Liver Disease. Boston, MA. October 2004.
- Z Younossi, J Ong, H Elariny, F Gorreta, L Del Giacco, K Ziegler, T Born, K Schlauch, A Van Meter, R Collantes, A Baranova, G Grant, Z Goodman, V Chandhoke. Hepatic Gene Expression and Serum Protein Profile of Patients with Obesity-Related Non-Alcoholic Steatohepatitis (NASH). North American Association for the Study of Obesity's Annual Scientific Meeting. Las Vegas, NV. November 2004.
- J Ong, H Elariny, A Younoszai, R Collantes, Z Goodman, V Chandhoke, Z Younossi. Non-Alcoholic Steatohepatitis in Morbidly Obese Patients. North American Association for the Study of Obesity's Annual Scientific Meeting. Las Vegas, NV. November 2004.
- GH Wang, A Mehrotra, J Ong, Z Younossi, Z Goodman. P62 as a Reliable Marker for Mallory Bodies in Non-Alcoholic Steatohepatitis (NASH). United States and Canadian Academy of Pathology Annual Meeting, 2004.

For patients who meet these criteria, transplantation is now considered the best treatment option, resulting in a significant improvement of both short and long-term survivals. These patients require transplantation early in the course of their disease, before their lesions fall outside the parameters acceptable to proceed with transplant, therefore they are afforded a significant advantage on the transplant waiting list.

### METASTATIC LESIONS

The gold standard for the treatment of five or fewer metastatic lesions, confined to the liver, remains surgical resection. Unfortunately, up to 40 percent of patients are identified to have additional disease at the time of exploration, using intra operative ultrasound, and 20 percent are found not to be resectable for a cure. If a curative resection is performed, then 25 to 30 percent of patients will achieve five-year disease-free survivals, usually considered a cure. Recent papers have suggested that favorable lesions, solitary lesions with more than one year between the colon resection and the identification of hepatic metastases, may show a greater than 40 percent five-year disease-free survival.

Recurrence of hepatic metastases after surgical resection can be re-resected if they again are confined to the liver and are five or fewer in number. With re-resection, five-year disease-free survival improves to 40 percent. This improved outcome is because the majority of tumors that recur will also have extrahepatic disease. Those recurrent metastases confined to the liver have proven themselves to be malignancies of low aggressiveness, suggested by the lack of extrahepatic spread, explaining the improved outcomes following re-resection when compared to primary resection.

### ABLATIVE PROCEDURES

If similar outcomes to surgical resection could be achieved without the need for a major surgical procedure, then this would result in a superior treatment modality. The most promising modality remains radiofrequency ablation (RFA). Unfortunately, not all lesions are amenable to radiofrequency ablation. Lesions greater than five cm, lesions adjacent to the biliary system or vascular structures and lesions adjacent to other abdominal organs may not be amenable to curative procedures. Combined approaches using laparoscopic and open techniques are routinely performed to ablate lesions abutting other intra-

abdominal structures. Though the initial data is promising, long-term follow-up has not yet achieved similar outcomes to that seen with surgical resection, especially for larger lesions.

Chemoembolization combines two modalities, intra-arterial chemotherapy and embolization of hepatic tumors. Chemotherapy, along with an agent to occlude the vascular structures - initially Gelfoam powder and more recently oil-based substances - are injected into the tumor from a transarterial route. This has resulted in response rates as high as 70 percent in primary hepatic malignancies, but rarely produce curative results. It usually is reserved for palliation and is not suggested for potentially curable lesions.

### CONCLUSIONS

Any patient with a primary or metastatic hepatic malignancy has numerous options available that can produce long-term cures. It is important that these patients be referred to a center that can offer evaluation by a multidisciplinary team who can help determine the best possible treatment modality. Once a treatment plan has been developed, experienced physicians who have successfully performed hundreds of these procedures will yield the best possible chance of cure.