Management of Primary and Metastatic Tumors to the Liver

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By Armando Sardi, MD, FACS [2] and Alisher Akbarov, MD [3]

Primary and metastatic liver tumors continue to be a significant health problem in the United States. Hepatic resection or, in selected cases, transplantation are the only curative therapies for patients with resectable tumors.

Introduction

Primary and metastatic tumors to the liver continue to be an important health problem in the United States. Hepatocellular cancer is one of the most common and most malignant tumors occurring in males; in some areas of Asia and Africa, incidence of this cancer continues to increase. Hepatocellular carcinoma varies in incidence from 30 per 100,000 population per year in high-risk regions, such as Asia and Africa, to less than 3 per 100,000 population per year in low-risk regions, such as northern Europe and North America [1]. In 1995, the estimated incidence of primary liver and biliary cancers was 18,500 cases in the United States, with 7,800 estimated deaths from these cancers.

Metastatic neoplasms are much more common and represent the most common malignant tumor of the liver. The relative proportion of primary to secondary neoplasms is estimated to be 1:20. The incidence of primary colorectal cancer, the most common cancer metastasizing to the liver, is estimated to be 138,200, with 55,300 deaths [2]. It is expected that as many as 25% of patients with colorectal cancer will have liver metastases at presentation and 50% will have liver metastases develop metachronously. About 20% of patients, or 27,640, will present with or eventually develop metastatic disease confined to the liver [3].

A common feature in patients with hepatocellular cancer is the presence of cirrhosis. The risk of developing hepatocellular carcinoma is approximately 10% in patients with nutritional cirrhosis (micronodular), 20% in patients with cirrhosis secondary to hepatitis B, 13% in those with hemochromatosis, and 40% in those with alpha-1-antitrypsin deficiency [1].

Although surgical resection is the treatment of choice for hepatocellular carcinoma and, along with transplantation, offers the only chance for cure, resection is not indicated in 70% to 90% of cases. Three conditions preclude liver resection: an unacceptable risk based on the degree of cirrhosis, evidence of extrahepatic disease, and tumor spread within the liver that prevents the attainment of clear surgical margins. Surgical resection in the presence of hepatic cirrhosis is associated with higher intraoperative morbidity and mortality. The presence of compromised liver function, thrombocytopenia, and coagulopathy with increased intraoperative blood loss can lead to postoperative hepatic decompensation and failure. Operative mortality is less than 3% for noncirrhotic patients, as compared with 7% to 25% for cirrhotic patients [1].

Other rare primary tumors also are seen in the liver. Intrahepatic cholangiocarcinomas represent less than 0.5% of liver tumors. These diffuse tumors are rarely detected early enough, and resection usually is not possible. Thus, prognosis is poor.

Surgical resection also is the only potential curative treatment for metastatic cancer to the liver. Without surgery, the median survival of patients with metastatic colorectal cancer confined to the liver is measured in months, with the majority of patients dying within a year (Table 1) [4-11]. Patients with liver metastases from other solid tumors also are candidates for resection. Patients with Wilms' tumor are excellent candidates for resection of hepatic metastases, as are those with a solitary liver metastasis from renal cell carcinoma. Hepatic metastases from other tumors, such as melanoma and gastric, pancreatic, lung, and breast cancer, do not appear to benefit from such efforts.

Liver metastases from endocrine tumors rarely present with localized disease that can be completely resected, but if localized, surgical resection is the treatment of choice. In this group of patients, surgical debulking can be used in those in whom symptoms cannot be controlled by medical treatment and are incapacitating. Patients with endocrine tumors have a long median survival even...
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in the presence of metastatic disease [12].
In this article, we will discuss the present management of patients with primary and metastatic liver tumors, focusing on the currently available imaging techniques and new treatment modalities.

Preoperative Evaluation

The initial diagnosis of a liver tumor can be suggested by symptoms, findings on physical examination, or elevation of a tumor marker, such as carcinoembryonic antigen (CEA) in a patient with a previous history of colorectal cancer, alpha-fetoprotein (AFP) in a patient with hepatocellular carcinoma, or 5-hydroxyindoleacetic acid (5-HIAA) in a patient with a carcinoid tumor. A complete physical examination is mandatory to assess the patient's overall performance status and to look for potential sites of metastases (eg, cervical or inguinal lymph node metastases) that will render the use of any other diagnostic tests unnecessary.

After the diagnosis has been made, a careful preoperative evaluation is crucial to avoid unnecessary surgical explorations that considerably reduce the quality of the short remaining life span of patients with unresectable liver tumors. Only 3% to 30% of patients with hepatocellular carcinoma have disease that can be completely resected [13]. For colorectal cancer, the fraction of patients who may benefit from hepatic resection at some time in the disease process has been estimated to be 5% to 10% [14,15].

Role of Imaging Techniques

Imaging techniques play a major role in the preoperative assessment of patients with hepatic tumors. These imaging techniques help select patients who are candidates for an aggressive surgical approach and help exclude those who present with diffuse liver involvement, unresectable disease because of location (confluence of hepatic veins, hilum of liver with involvement of the main portal vein), and extrahepatic metastases. Although the segmental location is not the sole criterion for determining resectability, such knowledge is useful for planning the type of resection.

Cross-sectional imaging techniques that are used in the selection of candidates for hepatic resection include computed tomography (CT), dynamic CT arterial portography (CTAP), magnetic resonance imaging (MRI), spiral CT (SCT), ultrasound (US), and intraoperative ultrasound (IOUS). All of these technologies have limitations. The surgeon needs to be aware of these drawbacks in order to provide good care. Also, imaging technologies need to be applied in an orderly manner to avoid unnecessary and discouraging surgical explorations, while also keeping cost as low as possible. Lastly, the sensitivity and specificity of the tests used should be high so that patients are not denied potentially curative surgery based on a false result.

The ability to accurately image liver lesions has been limited. In a recent study, among patients considered resectable on the basis of careful preoperative evaluation that included intravenous contrast CT and CTAP, 29% were found to be unresectable at the time of intraoperative staging. Of these, 19.8% had extrahepatic disease and 9.2% had unresectable liver disease. Of the patients with extrahepatic disease, 9.2% had peritoneal implants and 10.6%, periportal lymph node metastases [3].

CT of the abdomen and pelvis has been the imaging modality most frequently used to help define the extent of liver disease. However the sensitivity of the CT scan for detecting liver lesions is rather low, varying from 52% to 85%; in the majority of reports, the sensitivity of this technique is close to 60% (Table 2) [16-27]. The sensitivity of CT for detecting tumor in other areas of the abdomen and pelvis drops significantly, to 27% for the extrhepatic abdomen and 22% for the pelvis. In a study by Sardi et al in which the extent of disease was documented by laparotomy in every instance, the overall sensitivity of abdominal CT was only 41%. In 5 of 15 patients with liver metastases and with true-positive results, the CT scan underestimated the extent of disease [19]. In another study, the sensitivity of abdominal CT was 85%, but the false-positive rate was high (45%) [17]. Problems in differentiating recurrent tumor from postoperative and post-radiation changes on the CT scan may account for the false-positive results seen with this technique. Consequently, CT has a number of disadvantages: It is unable to detect an intra-abdominal recurrence in approximately half of patients. Also, in patients with positive results, it fails to satisfactorily show the extent of disease. Of patients thought to have resectable disease based on CT evidence alone, 25% to 60% were found to have unresectable tumors at laparotomy [3,28,29].

It should be mentioned that routine CT is not indicated for the follow-up of patients after primary resection of colorectal cancer. Rather, CT should be performed after recurrence disease is suggested by symptoms, elevation of a CEA, or findings on physical examination, to try to identify sites of recurrence. This policy is supported by studies in which routine CT was shown to be of little value,
even when scans were done as frequently as three times yearly [17].

**CT Scan of the Chest**—It has been our practice that patients who have resectable liver metastases based on findings on a CT scan of the abdomen and pelvis should undergo a CT scan of the chest (even in the presence of a normal chest x-ray) before any other diagnostic modality is employed, to define the extent of disease within the lung. Schaner et al found that CT defined more pulmonary nodules than either whole lung tomography or chest radiography. Of the 26 nodules seen on CT but not on chest radiograph, 12 (46%) were malignant. However, only 66% of nodules defined by CT were proven to be metastases at reoperation, whereas 78% of those defined by conventional tomography and 90% of those defined by chest radiography were metastatic [30]. Therefore, the finding of a pulmonary nodule should not be assumed to be metastatic disease until histologically confirmed. The finding of metastatic disease in the chest makes additional hepatic imaging unnecessary.

**Dynamic CT arterial portography** is considered an important preoperative imaging modality since it clearly outlines the hepatic and portal veins, helping to define the extent of disease and its relationship to other structures. The appearance of the liver parenchyma is thereby markedly enhanced and the intrahepatic vascular structures are well demonstrated. Hepatic tumors, with their predominant arterial supply, are shown as hypodense perfusion defects on CTAP (Figure 1).

Dynamic CTAP has been considered the procedure of choice in selecting potential candidates for hepatic resection. Until recently, it was considered the most sensitive imaging technique for primary and metastatic hepatic tumors. It has been found superior to both CT and MRI in identifying liver lesions. Dynamic CTAP has been shown to predict resectability in up to 97% of patients but has been associated with false-positive findings in 10% to 42% of cases, indicating that the findings of these investigations should be interpreted with some caution [16,23,26,31,32]. With the use of a higher injection rate of contrast medium and precontrast transcatheter injection of papaverine hydrochloride, which increases portal blood flow, the false-positive rate has decreased [33]. The results of CTAP should be analyzed very carefully, with special attention given to defects that are more likely to be false-positive. If the findings are suggestive of advanced disease, this should be ruled out by percutaneous biopsy. However, clear signs of unresectability of large or central tumors, such as bilateral vein involvement, should not be ignored.

Dynamic CTAP has a high incidence of perfusion defects, which usually appear as peripheral wedge-shaped areas or perfusion defects in segment IV. The coexistence of cirrhosis complicates the interpretation of these results (Figure 2). In a study by Peterson et al, [34] round perfusion defects represented malignancy in only 58% of the lesions. In noncirrhotic patients, 67% of the round perfusion defects were malignant, whereas 52% of these defects were malignant in cirrhotic patients. In contrast, the intermediate-attenuation perfusion defects were consistent with malignancy in only 5% and 7% of noncirrhotic and cirrhotic patients, respectively. Pathologic diagnosis for benign perfusion defects included cirrhotic nodules, cysts, hemangiomas, focal nodular hyperplasia, focal fibrosis, focal fatty changes, nonspecific regenerative changes, and normal liver parenchyma. Only one (2%) peripheral wedge-shaped defect was malignant. All peripheral flat defects were benign. Defects in characteristic locations, adjacent to the intersegmental fissure and anterior to the porta hepatitis, were uniformly benign. In the same study, 14% of patients who underwent CTAP examination had a benign perfusion defect in this location. Fifty-six percent of soft-tissue attenuation defects were malignant [34]. Overall, approximately one-third of the perfusion defects seen on CTAP can be classified as benign or malignant with high probability. All other types, however, are not specific. In view of these data, a biopsy should be considered if a lesion does not have a high probability of being malignant, so as not to exclude patients who will benefit from an aggressive surgical approach. Familiarity with a variety of pseudolesions (nontumorous defects) seen on CTAP is crucial to accurate interpretation. Focal fatty infiltration or, paradoxically, focal sparing may result from variations in perfusion and may show up as focal lesions on CTAP and as hyperperfused areas on arterial-phased enhanced CT or MRI [34].

In conclusion, CTAP is less accurate in the presence of cirrhosis because of portal hypertension (shunting of contrast opacified blood away from the liver, resulting in poor opacification of normal background liver) and the presence of regenerating nodules and fibrosis, which account for many of the perfusion defects seen on CTAP (Figure 2). In addition, CTAP is not sensitive for the detection of metastases located high in the hepatic dome. This phenomenon is well known and is probable due to respiratory movements. Spiral CT seems to eliminate this problem, as will be discussed below.

Some retrospective studies have demonstrated a survival benefit (ie, greater survival in years 2 to 4) in patients who were evaluated with CTAP, as compared with those who underwent liver resection without the use of CTAP. This improved survival was multifactorial but can be attributed, in part, to
better selection secondary to the use of CTAP [35].

**Magnetic Resonance Imaging**—One of the advantages of MRI has been the low incidence of false-positive results. Also, MRI provides better characterization of lesions than do CT and CTAP, but, with a sensitivity of 78%, MRI has not proved to be more sensitive than CT for the detection of hepatic metastases [21,33]. In a prospective study, the sensitivity of CTAP was 94% vs 78% for MRI ($P < .05$) [33].

**Advances in three-dimensional techniques** have improved the preoperative assessment of the resectability of hepatic metastases and have allowed for planning of the surgical approach. In a comparison of two-dimensional and three-dimensional CTAP, 90% of the lesions were detected by either modality. However, two-dimensional CTAP was 78% accurate in determining the segmental location of hepatic metastases, as compared with a 94% accuracy for the three-dimensional technique [36].

Newer MRI techniques have also demonstrated a higher sensitivity. For example, multislice-fast-low-angle shot MRI during arterial portography had a sensitivity of 95%, as compared with 74% for combined spin-echo and multislice FLASH MRI [37]. With new advances in MRI techniques, more studies will be necessary.

**Spiral CT** is the latest advance in rapid scanning techniques and is now available in many institutions. In the spiral scan mode, image acquisition is continuous, as patients are advanced at a constant rate through the CT gantry. This eliminates interscan delay and the gap between scan slices. Because the scan can be completed within a single breath-hold, respiratory misregistration of adjacent scan slices is eliminated. These improvements also contribute to high-quality multidimensional displays, eg, coronal and sagittal views [38].

Spiral CT offers several technical advantages in the evaluation of the liver: data continuity; three-dimensional CT reconstruction of hepatic anatomy, which previously was inadequately imaged owing to respiratory artifacts; and scanning of the liver and hepatic vasculature during peak contrast enhancement in the early phase. These technical advantages may permit improved or comparable diagnostic information to be obtained with the use of lesser amounts of intravenous contrast material. The most significant benefit is improved confidence in the evaluation of smaller lesions [39].

Tumor detection can be further enhanced by using spiral mode CT with arterial portography (SCTAP). With this method, contrast material is injected into a catheter in the superior mesenteric artery and is delivered to the liver via the portal vein. Because both primary and metastatic liver neoplasms are supplied largely by the hepatic artery, lesions usually are detected as hypoattenuating areas, in comparison to the normal contrast medium-enhanced parenchyma [38]. The SCTAP technique results in excellent contrast dynamics, with nearly constant high levels of vascular and liver parenchymal enhancement throughout the scanning interval.

Fujita et al reported on the results of a comparison between conventional CT and SCT in patients with hypervascular hepatocellular carcinoma. Of 7 lesions < 10 mm in diameter, none was seen by either technique. Of 17 lesions 10 to 20 mm in diameter, 4 (24%) were detected by precontrast CT plus conventional contrast-enhanced CT (CECT), whereas 14 (82%) were detected by precontrast CT plus SCTAP. No lesions were detected by CECT alone, whereas 10 lesions were detected by SCTAP alone ($P < .01$) [40].

Murakami et al published even more impressive results on the use of SCT to detect small hypervascular hepatocellular carcinomas. In the detection of hepatocellular carcinomas < 1 cm in diameter, SCTAP (87.3%) was superior to both intravenous MRI and intravenous SCT (63.5% and 54%, respectively; $P < .001$). Intra-arterial SCT was the best modality for detecting hypervascular hepatocellular carcinomas, and there was no significant difference between intravenous MRI and intravenous SCT [41].

Helmberger et al found that SCT offers similar sensitivity to IOUS (96%) in the detection of liver metastases. The sensitivities of conventional CT, SCT, and SCTAP for detecting lesions < 1 cm were 51%, 89%, and 92%, respectively. The three methods had sensitivities of 66%, 94%, and 95%, respectively, for lesions 1 to 2 cm, and sensitivities of 95%, 95%, and 100%, respectively, for lesions > 2 cm. The overall sensitivities of CT, SCT, and SCTAP were 57%, 94%, and 96%, respectively [42]. Thus, SCT represents an important technique for the diagnosis and follow-up of liver metastases.

**Intraoperative ultrasound** is the most sensitive test for the detection of liver tumors, with a reported sensitivity of 98% to 100%. Intraoperative ultrasound establishes the relationship of tumors with critical vascular structures (hepatic or portal veins). It has been reported to have changed management in 15% to 49% of patients with metastatic liver cancer [22,26]. By improving patient selection and permitting resection of clinically occult metastases. IOUS may contribute to improved
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survival by permitting complete resection. At the time of primary resection for colorectal cancer, IOUS identified additional liver disease in 25% to 35% of patients. Among patients with negative findings on preoperative imaging, occult liver disease was found in 3% to 10% of patients at the time of primary resection [24,43-45]. We feel that IOUS should be used routinely in patients undergoing liver resection to ensure that complete resection of all possible tumor is performed. In summary, CT has been demonstrated to have a sensitivity of 56% to 76%; CTAP, 65% to 95%; MRI, 56% to 78%; SCT, 94%; SCTAP, 96%; and IOUS, 80% to 100% (Table 2).

Immunoscintigraphy with Monoclonal Antibodies

Immunoscintigraphy using monoclonal antibodies is still under investigation. The only monoclonal antibody imaging technique approved by the FDA, indium-111 CYT-103 (OncoScint), is more sensitive that CT in detecting lesions outside the liver but is less sensitive than CT in detecting hepatic metastases [46]. The current value of monoclonal antibody technology, which is still in its infancy, lies in its ability to identify patients with extrahepatic disease. OncoScint was able to identify the site of recurrence in 75% of patients with an elevated CEA level and no evidence of disease by any other imaging modality [46]. However, this technique has a high false-positive rate. Thus, before patients are excluded from liver resection, the results should be pathologically confirmed. As the specificity of the monoclonal antibodies increases, this technology will become an important preoperative testing modality. Further studies are needed to better define the role of immunoscintigraphy in patient management.

Treatment Options

Once the location and extent of disease have been defined, the following therapeutic options are available: surgical resection, transplantation, cryoablation, chemoembolization, percutaneous alcohol injection, and hepatic artery infusion chemotherapy. Furthermore, patients who present with recurrences in the liver following resection can also be considered for reoperation.

Surgical Resection

Patients with untreated colorectal metastasis to the liver usually survive a few months; the 5-year survival rate in these patients approaches 0% (Table 1). Our present understanding of liver anatomy has led to marked improvements in the techniques and safety of liver resection (Figure 3). Major hepatic resection can now be performed with low morbidity and mortality. Current data indicate that liver resection is the only available treatment that produces long-term survival with the possibility of cure in patients with primary and metastatic liver tumors. The operative mortality of liver resection is 0% to 11%, with the majority of reports showing a mortality under 5%. The overall 5-year survival rate has ranged from 22% to 60% (Table 3) [47-59]. In 1986, Hughes reported on the results of a multi-institutional study of 859 patients treated with hepatic resection for colorectal metastases. The 5-year actuarial overall survival rate was 33%, and the disease-free survival rate was 21% [52]. Fuhrman et al demonstrated a 5-year actuarial survival rate of 44% in 107 patients who were successfully resected, 31% in patients who met preoperative criteria of resectability, and 0% in patients who had more than four metastases or metastases that were not amenable to a margin-negative resection and were not resected [3]. Minton et al, in a group of 98 consecutive hepatic resections, reported an operative mortality of 0%. Rates of survival at 5 and 8 years were 60% and 50%, respectively [60]. In considering surgical resection, four basic principles apply: (1) extirpation of all tumor; (2) preservation of a functioning liver; (3) preservation of portal and hepatic venous blood flow; and (4) preservation of good biliary drainage. Hence, the clinical presentation; the number, size, and location of the metastases; and the presence of extrahepatic disease, in addition to the presence of compensatory hypertrophy of the remaining lobe and the presence or absence of cirrhosis, are crucial aspects in decision planning. Although some adverse prognostic factors may discourage the use of an aggressive approach in some patients, it has been the philosophy of our group as well as others, that without established extrahepatic disease, patients who can withstand an operation and whose disease can be completely resected should be considered for surgery.

Metastases from Colorectal Cancer--In patients with metastases from colorectal cancer, both the clinical presentation and characteristics of the tumor may be important variables. Some researchers have suggested an association between age and gender and survival [52,56], but this association has not been documented by others [61,62]. There appears to be a relationship between primary tumor stage and survival [11,52,59,63], but real differences do not appear to be significant enough to preclude liver resection in the presence of an advanced primary tumor. Also, tumor grade does not seem to influence prognosis [7,50,58]. It has
been suggested that patients who present with symptoms due to liver metastases do not fare as well as asymptomatic patients [52,63]. Also, patients in whom the disease is discovered incidentally, by a CEA elevation, by findings of a routine imaging modality, or at surgery, do better than patients who present with symptoms [59,64].

Some studies have suggested a better prognosis for patients who have metachronous disease on presentation [58]. Hughes et al demonstrated that patients with a disease-free interval of > 1 year have a 5-year survival rate of 42%, as compared with a rate of 24% for patients in whom the disease-free interval is < 1 year (P < .01) [52]. The available data seem to show that patients with one or two metastases have an equivalent survival and that patients with four or more metastases may have a poorer prognosis. In the study by Hughes et al, 5-year survival rates were 37%, 34%, 9%, and 18%, for patients with one, two, three, or four or more metastases, respectively [65]. The best way to treat these patients is still debatable, but even in the presence of four or more metastases that can be resected, 5-year survival after resection is better than that after no resection [60,65]. Thus, data suggest that it is reasonable to remove four or even more metastases from the liver, as there is a chance of long-term benefit. It has been our practice to resect all metastases, provided that the patient can be rendered disease free.

Some investigators have suggested that large tumors have a worse prognosis than smaller tumors [52], but this concept is not universally accepted [50,58,66,67]. Hence, the size of the lesion should not influence the decision of whether or not to perform a resection, provided that the lesion can be completely resected, with at least 1 cm of clear margin.

In general, the location of the metastatic lesions in the liver has not been correlated with patient survival. Some studies have demonstrated that patients with multiple metastases have a worse prognosis if the disease involves both hepatic lobes [67], but other studies have shown no such survival difference [52,58,65]. The presence of regional lymph node involvement, even when the involved nodes are removed at the time of the liver resection, carries a poor prognosis. In one study, the 5-year actuarial survival rate of patients with regional node involvement was 4%, with only one 5-year survivor [65]. It also has been demonstrated that the presence of satellite lesions close to a larger tumor is a poor prognostic sign. This finding suggests intrahepatic tumor spread. In a study by Rosen et al, 30% of patients with solitary metastases, 18% of patients with multiple scattered lesions, and 11% of patients with satellite lesions survived 5 years (P = .005) [59]. In a study by Scheele et al, the 5-year survival rate was 45% in patients without satellite lesions, as compared with 17% for patients with satellite lesions (P = .0003) [58].

The extent of hepatic involvement has been suggested as a prognostic indicator. According to Eckberg et al [86], survival rates for patients with < 25%, 25% to 50%, and > 50% of liver involvement were 22%, 9%, and 0%, respectively. Hepatocellular cancer remains difficult to treat, and in the past, has had a poor prognosis, with most series reporting a 3- to 6-month median survival after the onset of symptoms [13]. Until further research is able to delineate the specific interactions among environmental factors, hepatic injury, hepatic regeneration, host factors, and molecular mechanisms of malignant transformation that can lead to specific preventive and treatment interventions, the control of hepatocellular carcinoma will continue to rely on modifications of currently available treatment modalities. Even so, the results of newer treatments suggest that some improvements may already have been achieved.

Surgical resection remains the mainstay of treatment. The 3-year survival rate ranges from 20% to 69% and the 5-year survival rate, from 25% to 65% (Table 4) [51,67-77]. Resection has a mortality of 0% to 27%, reflecting the high proportion of cirrhotic patients. Resection has been limited primarily by low resectability rates and recurrent disease.

The most favorable patient subgroups for resection are those with: (1) tumors < 5 cm in diameter, (2) unifocal tumors, (3) well-differentiated tumors, (4) lack of vascular invasion, (5) absence of cirrhosis, and (6) the fibrolamellar variant.13 Despite the presence of adverse prognostic factors, liver resection should be considered in patients who have disease localized to the liver that can be completely excised. It is clear that long-term survival is possible in poor-prognosis subgroups, and decisions regarding surgery should be individualized.

The extent of liver resection depends on the size and location of the tumor. It is known that survival is the same regardless of the extent of resection, provided that at least 1 cm of clear margins is obtained [65]. The relationship of the tumor to vascular structures and bile ducts determines the extent of resection. The options include: wedge, segmental, lobectomy, and trisegmentectomy. The techniques of resection have been well described.
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Hepatic Transplantation

Hepatocellular Carcinoma—For patients with hepatocellular carcinoma and cirrhosis, the low resectability, high recurrence, and perioperative morbidity associated with partial hepatectomy have stimulated interest in total hepatectomy and liver transplantation. The results of liver transplantation are shown in Table 5 [75,78-83]. Rates of 3- and 5-year survival were 21% to 49% and 20% to 45%, respectively.

The incidental finding of hepatocellular carcinoma following transplantation on subsequent pathologic analysis is known to be associated with a more favorable prognosis. Iwatsuki et al reported a 0% recurrence rate after transplantation for incidental hepatocellular carcinoma, and 12 of 13 patients were alive from 4 months to 13 years post-transplantation [84]. Others have described similar results [82,83].

Bismuth et al, in a nonrandomized comparison of transplantation and hepatic resection, showed that the rate of survival without recurrence was better in transplanted than in resected patients (46% vs 27%, respectively; P < .05) [75]. In the case of small uninnodular or binodular tumors (< 3 cm), transplantation had better results than resection. Rates of survival without recurrence were 83% and 18% for the two respective treatments (P < .001). In this study, patients with a high risk of recurrence after transplantation included those with a diffuse form, more than two nodules > 3 cm, or the presence of portal thrombus. Bismuth et al concluded that the best candidates for transplantation were patients with small uninnodular or binodular tumors. Unresectable, large, multinodular or diffuse tumors seemed to represent less favorable indications for transplantation.

In summary, there is a small cohort of patients with stage I, II or III hepatocellular carcinoma and no evidence of systemic disease who are good candidates for liver transplantation. Such patients exhibit 5-year survival rates of 75%, 68%, and 52%, respectively.

Other Indications—Transplantation for intrahepatic cholangiocarcinoma has shown very poor results. Also, liver transplantation is not justified for most types of metastatic cancer. Pichlmayer et al reported on 43 cases of transplantation for metastatic cancer, mostly of colorectal origin, with a 28% survival rate at 1 year and 15% survival at 2 years [85]. With the shortage of liver grafts and improved survival with transplantation in a variety of conditions, clear indications for transplantation need to be well defined.

Repeat Hepatic Resection of Liver Metastases

Following initial hepatic resection for metastatic colorectal cancer, 14% to 42% of patients will have recurrences confined to the liver, while 10% to 47% will have disease in the liver and other sites [50,53,86-88]. Studies have shown that, in carefully selected patients, reoperation for recurrent colorectal cancer confined to the liver can be performed safely. There were only four operative deaths (2.6%) in the collected series presented in Table 6 [50,53,89-98]. The complication rate was between 15% to 58% [90,92,94,98], and the median hospital stay was 10 to 11 days [92,98]. These studies should be evaluated carefully, however, as they were retrospective in nature, usually spanned a period of several years, and involved a small number of very select patients.

We described eight patients who underwent a total of 19 operations for recurrent liver disease. There were no operative deaths. Following the first hepatic intervention, two patients remained alive and free of disease at 43 and 47 months and 56 and 100 months, respectively, after diagnosis [92]. Although no conclusive results can be obtained from this very select group of patients, it is clear that a small number of carefully chosen patients will benefit from repeat hepatic resections.

Cryoablation

Cryosurgery (the in situ destruction of tissue using subzero temperatures) has been used to treat primary and metastatic liver tumors. Cryosurgery with ultrasound monitoring permits the precise destruction of tumors with an additional margin of normal liver. Zhou et al described 60 patients with hepatocellular carcinoma who were treated with cryosurgery. Rates of survival at 3 and 5 years were 20.8% and 11.4%, respectively. In the 21 patients with tumors < 5 cm in diameter, 3- and 5-year survival rates were 50% and 37.5%, respectively. There was no operative mortality in this series [99]. These results compare very favorably with those of surgical resection (Table 4).

Ravikumar et al treated 32 patients with cryosurgery. Of these, 24 patients had metastatic colorectal carcinoma. At a follow-up of 5 to 60 months (median, 24 months), 28% of patients remained disease free, 24% were alive with disease, and 38% had died. Of the patients with colorectal carcinoma, 39% were disease free and 39% were alive with recurrence. No operative deaths occurred, and the median hospital stay was 6 days [100].

Onik et al reported similar results with cryosurgery. After a mean follow-up of 28.8 months, 4 (22%) of 18 patients were in complete remission [101]. In another study, Onik et al treated 56 patients with unresectable hepatic metastases. The disease-free survival rate at a mean follow-up of 21 months
was 27% [102]. Although complications of cryosurgery do occur, they are few, and rapid postoperative recovery is the rule. Complications include hypothermia, coagulopathy, myoglobinuria, renal failure, cracking of the hepatic capsule, and elevation of liver enzymes [99-102].

In summary, cryosurgery is a safe, effective technique for the treatment of unresectable primary and metastatic liver tumors. Patients with poor functional liver reserve, centrally located tumors, tumors close to the inferior vena cava, confluence of hepatic veins, or hepatic hilum can be treated with this technique.

**Chemoembolization**

The disappointing results of current chemotherapeutic regimens have led investigators to attempt novel approaches for treating hepatic tumors, including infusion of chemotherapeutic drugs directly into the hepatic artery or portal vein. Direct hepatic artery infusion permits selective targeting of drugs to tumors while minimizing systemic toxicity. Hepatic artery embolization selectively deprives tumors of blood flow, while the normal liver tissue is supported by portal flow.

Chemoembolization combines hepatic artery embolization with gelatin sponge particles, a concentrated dose of chemotherapeutic drugs, and oil. This approach has several theoretical advantages: (1) embolization renders the tumor ischemic, depriving it of nutrients and oxygen; (2) tumor drug concentrations are 10 to 25 times higher than those achieved by infusion alone; (3) the dwell time of the chemotherapeutic agent is markedly prolonged; and (4) because up to 85% of the drug is retained in the liver, systemic toxicity is minimized even at high doses. Results in specific diseases include a combined series of 800 patients with unresectable hepatoma treated with chemoembolization in the Orient, Europe, and United States. Response rates, as measured by decreases in tumor volume and serum AFP levels, were 60% to 83%. Cumulative probability of survival ranged from 54% to 88% at 1 year, from 33% to 64% at 2 years, and from 18% to 51% at 3 years; the best results were obtained with repeat chemoembolization [103-108]. There are some less favorable reports about chemoembolization, however. The Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire from France conducted a prospective randomized trial comparing Lipiodol chemoembolization and conservative treatment in patients with unresectable hepatocellular carcinoma. Lipiodol chemoembolization reduced tumor growth but often caused acute liver failure and did not significantly improve survival [109]. The significant inhibition of tumor growth seen in the patients receiving chemoembolization may have been offset by worsened liver function, particularly in those with cirrhosis. Three-fifths of the patients treated with chemoembolization had at least one episode of liver decompensation and one patient died. Post-embolization syndrome, characterized by pain, fever, nausea, vomiting and marked but transient liver enzyme elevations, occurs in 80% to 90% of patients. Major complications of hepatic embolization include hepatic insufficiency, hepatic abscess, tumor rupture, cholecystitis, and nontarget embolization to the bowel. The collective incidence of these serious events is 3% to 4% [103-109].

Chemoembolization with doxorubicin emulsified in ethiodized oil and iopamidol is effective in the treatment of hepatic metastases from endocrine tumors. This technique appears to result in less morbidity than particulate embolization alone [110]. Ruszniewski et al reported that chemoembolization results in control of the carcinoid syndrome and regression or stabilization of liver tumors in 80% of patients [111]. More prospective randomized studies with larger number of patients are required to better define the role of chemoembolization. At present, use of this therapy should be restricted to patients with unresectable primary or metastatic malignancies confined to the liver. These include hepatoma, intrahepatic cholangiocarcinoma, and metastases from colorectal cancer, ocular melanoma, islet-cell tumors, carcinoids, and sarcomas.

**Percutaneous Ethanol Injection**

This technique involves the percutaneous injection of absolute (99.5%) alcohol into a hepatic tumor using ultrasound guidance. Levraghi et al used percutaneous ethanol injections (3 to 24 injections) to treat 32 hepatocellular carcinomas < 4.5 cm in 23 patients. At a follow-up of 6 to 27 months, all lesions were smaller by radiographic criteria and had normal histopathologic findings on fine-needle aspiration biopsy. Four patients underwent lobectomy, and complete pathologic responses were seen. At the time of writing of the report, 15 patients were disease free and diffuse hepatocellular carcinoma had developed in 4 patients [112].

Ebara et al reported on the use of percutaneous ethanol therapy in 95 patients with 120 unresectable hepatocellular carcinomas < 3 cm in diameter. All main lesions decreased in size, and 42% of these became undetectable by ultrasonography. Median survival was 4.1 years, with 1-, 2-,
and 5-year actuarial survival rates of 93%, 81%, and 28%, respectively. None of the originally detected tumors recurred, but new lesions developed in 48% of patients [113]. Based on the fact that up to 40% of tumors can be missed by ultrasound (as discussed above), these results are not surprising.

The use of percutaneous ethanol injections in patients with liver metastases has been evaluated recently.114 Of the 55 tumors treated, complete necrosis occurred in 31 cases (56.3%). The median survival of the 40 patients was 21 months, with a 3-year actuarial survival rate of 39%. The median survival of patients with metastases from colorectal origin was 28 months, as compared with 14 months for patients with tumors of other origin. This difference was not statistically significant. At present, percutaneous ethanol injection is an alternative therapy for small unresectable tumors. However, it cannot be recommended for larger tumors because of the technical difficulties associated with injection, as well as poor survival rates.

**Hepatic Artery Infusion Chemotherapy**

Hepatic artery infusion (HAI) chemotherapy has been proposed for the following reasons: (1) regional therapy has the advantage of producing high drugs levels in the liver; (2) hepatic metastases obtain most of their blood supply from the hepatic artery; and (3) there is a high extraction of certain drugs in the liver, allowing for the use of a high chemotherapy dose with less risk of systemic toxicity. Another rationale, especially for patients with metastatic colorectal cancer, is the stepwise pattern of metastatic progression. Removal of hepatic metastases or hepatic infusion of chemotherapeutic drugs may then salvage some patients.

Systemic chemotherapy for liver metastases has been disappointing, with objective response rates of less than 25% in most randomized trials. Continuous HAI of floxuridine (FUDR) via an implantable pump has been used extensively for the last 10 years. Six randomized studies have compared hepatic arterial to systemic chemotherapy (Table 7) [115-120]. All these studies demonstrated a significantly higher response rate with HAI chemotherapy in the treatment of hepatic metastases from colorectal carcinoma. As shown in Table 7, both complete and partial response rates were higher in the groups who received HAI than in those given systemic infusion (42% to 62% vs 0% to 38%).

Because of the early successes with intrahepatic infusion, some of the studies allowed patients from the systemic arm to receive intrahepatic therapy after tumor failure on the systemic therapy; therefore, no meaningful survival comparison can be carried out between the arms of these studies. All of the larger US studies have been crossover studies. These studies demonstrated a survival advantage for patients who received subsequent hepatic arterial treatment, with a mean 1-year survival rate of 69% for the patients who crossed over from systemic therapy to hepatic infusion, as compared with 35% for the group who did not cross over [115-117].

In Europe, two large randomized studies had no crossover; both studies recorded a significant survival advantage for the HAI group [118,121]. In the multicenter French study, the median time to hepatic progression was 15 months in patients given HAI chemotherapy vs 6 months in those given systemic therapy. Median survival was 14 months for the HAI group and 10 months for the systemic group. Rates of survival at 2 years for the two respective groups were 22% and 10% (P < .02). Hepatic toxicity was high in the HAI group, with 35% of patients experiencing sclerosing cholangitis by 1 year and 50% by 2 years [118].

A more recent study from Memorial Sloan-Kettering Cancer Center used a combination of chemotherapy and other agents to achieve increased response rates [122]. Floxuridine and leucovorin given via HAI yielded an objective response rate of 62%, with a 2-year survival rate of 62%. Floxuridine and dexamethasone, a combination studied for the possibility of decreasing hepatic toxicity, also seemed to increase response to 71%. A combination of all three medications (floxuridine, dexamethasone, and leucovorin) led to an even higher response rate of 78% [122]. Further studies are needed to better define the role of HAI and also to determine the combination regimen that will maximize response rates while minimizing toxicity.

**Radioimmunoguided Surgery**

Radioimmunoguided surgery (RIGS) involves injecting the patient with a radiolabeled murine monoclonal antibody. A hand-held gamma-detecting probe (Neoprobe TM system) is then used to assist the surgeon with intraoperative tumor detection. This technique has been used for a variety of tumors, including primary and recurrent colorectal cancer, as well as pancreatic, ovarian, and breast cancer. It helps the surgeon identify tumors that are unrecognized during surgery 25% of the time when inspection or palpation is used alone [19,123-126].

In a multicenter trial in 105 patients with colorectal cancer, occult tumors were identified in 26 patients at 30 sites, which included peri-aortic lymph nodes and tumors in the pelvic, periportal, and
celiac regions. An intraoperative decision to extend resection was made, based on RIGS findings, in 23% of cases; of the 37 patients who were deemed unresectable, decisions in 27% were based conclusively on probe-directed findings [127].

In a review of the records of 86 patients who underwent RIGS procedures with B72.3 at the Ohio State University, patients were divided into three groups: (1) RIGS resectable (N = 40)—ie, those in whom all gross tumor and RIGS-positive tissue were resected; (2) RIGS unresectable (N = 13)—those in whom gross tumor appeared to be resectable, but RIGS tissue was unresectable; and (3) traditional unresectable (N = 33)—those in whom all gross tumor was unresectable. Disease-free survival rates in the three groups were compared at 2, 3, and 4 years following laparotomy. Rates of survival in the RIGS-resectable patients were 74% at 4 years and 60% at 5 years, whereas both the RIGS-unresectable and traditional-unresectable groups had 0% survival at 4 and 5 years. Patients whose tumors seemed to be completely resectable based on traditional findings but were unresectable based on RIGS findings (RIGS unresectable) had survival rates similar to the traditional-unresectable group [127].

Improved survival in the RIGS-resectable group vs the RIGS-unresectable group suggests that RIGS provided important information at the time of laparotomy, helping to select patients who would derive greater benefit from major resection.

In an attempt to improve the clinical utility of the RIGS system, a second-generation anti-TAG-72 monoclonal antibody CC49 was developed. Initial results using the RIGS technique with CC49 in 51 patients have been reviewed [128]. The gamma-detecting probe localized tumor in 18 (86%) of 21 patients with primary colorectal cancer and 29 (97%) of 30 patients with recurrent colorectal cancer, representing a significant improvement in sensitivity compared with B72.3. Based on RIGS information, the operative plan was altered for 12 (50%) of 24 patients with primary tumors and 14 (47%) of 30 patients with recurrent tumors. Information provided by RIGS at the time of laparotomy led to an extension of the operative procedure in many cases but in three patients resulted in the abandonment of planned major liver resection because of the presence of extensive, but clinically occult, extrahepatic disease.

Arnold et al recently evaluated the RIGS system using CC49 in 36 patients undergoing laparotomy for primary colorectal cancer. The RIGS findings resulted in an altered operative procedure in 25% of patients. Nine patients (30%) who were upstaged from stage I or II to stage III disease became eligible for adjuvant chemotherapy based solely on the finding of clinically occult tumor by the RIGS system. These results challenge the value of traditional surgical decision-making in patients undergoing laparotomy for primary colorectal cancer [126].

The clinical significance of micrometastatic lymph node involvement that is clinically occult but detected by RIGS has not yet been determined. Nor do we know much about the incidence of clinically significant lymph node involvement in the periportal, retroperitoneal, and celiac regions. However, a retrospective review of 124 patients who had RIGS procedures with either B72.3 or CC49 revealed 9 patients who developed recurrence in the periportal lymph node regions. These patients all had RIGS-directed biopsies of the periportal lymph nodes at the time of surgery, and histologic evaluation either by frozen section or hematoxylin and eosin staining revealed no evidence of tumor. Based on the frozen-section diagnosis of no tumor at the time of laparotomy, patients did not have complete removal of the RIGS-localized periportal lymph nodes. However, retrospective immunohistochemistry of these paraffin blocks revealed convincing evidence of antibody bound to tumor antigen in 70% of the sampled nodes that were frozen-section-negative, and cytokeratin staining confirmed the presence of tumor in 7 of 9 patients [127].

The main value of RIGS in patients undergoing liver resection is the detection of extrahepatic disease that cannot be identify by routine intraoperative evaluation. Thus, this technique helps identify patients who will be early failures following liver resection. Radioimmunoguided surgery is still investigational. Results of a prospective multicenter trial completed in 1995, but which are not yet available, will help clarify the usefulness of this technique.

**Laparoscopy**

Laparoscopy is now used frequently in the management of several intra-abdominal conditions. In the management of liver malignancies, its use has been limited to obtaining liver biopsies in patients in whom percutaneous biopsy could not be performed and to evaluate the extent of disease in patients with questionable findings on imaging techniques.

We use laparoscopy in patients with potentially resectable lesions in whom a monoclonal antibody imaging technique has demonstrated a potential site of extrahepatic disease (research protocols). In these cases, laparoscopy is performed at the time of planned surgical resection. If extrahepatic disease is confirmed, the liver resection is abandoned.
In such patients, laparoscopy is directed to the site in question. We do not use laparoscopy routinely in view of the fact that these patients frequently have extensive adhesions from previous resection of the primary tumor, making complete exploration with laparoscopy difficult and time consuming. We do perform complete abdominal exploration and lysis of adhesions routinely at the time of laparotomy. Babineau et al have advocated routine laparoscopy before laparotomy for liver resection [129]. Although liver resection with laparoscopy is feasible, it should not be considered routine until appropriate instrumentation is available and randomized studies are performed.

**Conclusions**

It is clear that patients who have disease confined to the liver that can be completely resected will benefit from an aggressive surgical approach. Proper understanding of the different imaging techniques and overall evaluation of the patient will lead to better outcome. Continued research to help identify parameters for better selection of patients is ongoing.

**References:**

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