Patient Selection for Surgical Management of Primary and Metastatic Liver Cancers: Current Perspectives

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ABSTRACT

The surgical management of liver malignancies remains a mainstay in the treatment of such patients, and has benefited from dramatic advancements over the last two decades. Improvements in surgical technique, better understanding of hepatic anatomy, and improvement in anesthesiological supportive care has resulted in a decline in perioperative morbidity and operative mortality. Proper patient selection for surgical and nonsurgical treatment currently employs a multidisciplinary approach in our institution. This review will focus on the surgical treatment options for both primary and secondary liver cancers.

KEYWORDS: Liver cancer, surgery, ablative therapy

Objectives: Upon completion of this article, the reader should (1) better understand the role of surgical management of patients with primary and secondary liver tumors, (2) become familiar with the indications for operative interventions in patients with liver malignancy, and (3) review results from the recent literature regarding outcomes of surgical interventions.

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The surgical management of liver malignancies has benefited from dramatic advancements over the last two decades. Improvements in surgical technique, better understanding of hepatic anatomy, and improvement in anesthesiological supportive care has resulted in a decline in perioperative morbidity and operative mortality.¹ Thus, surgical management has been offered to a growing number of the estimated 250,000 patients afflicted with primary or secondary hepatic malignancies within the United States.² Proper patient selection for surgical and nonsurgical treatment currently employs a multi-

disciplinary approach in our institution. This review will focus on the surgical treatment options for both primary and secondary liver cancers.

SURGICAL ANATOMY

A thorough understanding of the hepatic segmental anatomy allows for safe and effective resection. Prior to the modern era of hepatic resection, when the true anatomy of the liver was first being understood, liver surgery was a risky and often Herculean task because of

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the major hemorrhage that often occurred. The conceptual understanding of the hepatic anatomy started in 1654 with Glisson's description of the liver capsule, followed with Cantlie's 1897 division of the liver into functional halves, and then Couinaud's 1954 definition of the liver segments. The anatomic division of the liver into right and left halves is based on Cantlie's line, which is an imaginary line that extends from the gallbladder fossa to the left of the vena cava. This is the anatomic course of the middle vein. Each half of the liver is then divided into four other segments based on the venous drainage, portal venous inflow and arterial inflow, for a total of eight segments. The better appreciation for the nuances of liver anatomy has resulted in increased anatomically based resections with improved perioperative outcomes.

SURGICAL PRINCIPLES

When designing an appropriate operation, regardless of whether the tumor is a primary or metastasis, the objective is to safely remove all malignant disease while achieving negative margins, all without compromising liver function. It must be kept in mind that to avoid the risk of postoperative liver insufficiency, at least 25% of the liver volume must remain in a patient with normal liver function and more than 40% must be preserved for those patients with liver dysfunction.³ Almost complete regeneration in the healthy liver should occur in the first 10 postoperative days.⁴ The liver's functional capacity must be assessed prior to committing to an operation. Many of the patients with hepatocellular carcinoma (HCC) will have underlying cirrhosis, and those with colorectal metastasis may have had chemotherapy that may cause steatosis, either of which will have negative effects on the liver's ability to regenerate. Investigating hepatic function is standard in the preoperative evaluation. There are two tests that can be widely used to accomplish this: indocyanine green clearance and the Child-Turcotte-Pugh classification.

Preoperatively determined inadequate liver remnant volume has recently been addressed with portal vein embolization (PVE). PVE is a method of inducing hypertrophy of the segments of the liver that are to remain after resection by diverting portal blood flow containing hepatic-associated regenerative factors away from the segment of liver to be resected.^{5,6} This thereby increases the safety of the procedure by increasing the preoperative functional residual liver volume. One month following PVE, repeat hepatic imaging is performed with volumetric assessment. An estimated 25 to 30% hypertrophy of the liver remnant is anticipated.⁷ Preoperative PVE has been shown in a recent randomized controlled study to reduce postoperative morbidity rates in those patients with chronic liver disease.⁸ Unfortunately, PVE has not been shown to have any effect on long-term survival in patients with HCC.⁹⁻¹¹ One

retrospective analysis showed no difference in survival between patients undergoing prehepatectomy PVE and no PVE followed by hepatectomy.¹¹

At the time of surgery a thorough abdominal exploration is performed with biopsy of any suspicious intrahepatic or extrahepatic nodules.^{12,13} Prior to committing to a resection, the peritoneal cavity, pelvis, retroperitoneum, and porta hepatis must be thoroughly explored to assess for extension of disease outside of the liver and to ensure that a complete and safe resection is possible. Some surgeons advocate laparoscopic exploration prior to resection to assess for extrahepatic disease. Given the improvement in preoperative hepatic imaging and the utilization of positron emission tomography (PET), we utilize laparoscopy selectively for patients at higher risk for harboring radiologically undetectable micrometastatic disease involving the peritoneum.

Following visual examination of the abdomen, intraoperative ultrasound (IOUS) can be used to assess extent of intrahepatic disease. It has been shown that the use of IOUS, either laparoscopically or open, has changed the operative course up to 50% of the time because of identification of previously unseen pathology, although this number is now probably less because of improvements in preoperative imaging modalities.^{14,15}

Following an IOUS to assess the extent of intrahepatic disease, vascular control of the inflow and outflow vessels is typically obtained prior to transection of the liver parenchyma. Once a safe and effective operation has been considered achievable, there are several options available to the surgeon, depending on the location of the tumor. For small, peripheral tumors, nonanatomic wedge resections (single or multiple) or sublobar segmental resections (single or multiple) can be performed. Larger and/or more central lesions may require a right or left hepatectomy or a right or left extended hepatectomy. These cases have traditionally been performed through a laparotomy or subcostal incision, although recently there have been several series reporting hand-assisted laparoscopic liver resections.¹⁶⁻²⁰ The main concern with the laparoscopic technique is the inability to control major hemorrhage should the need arise as well as carbon dioxide emboli from inadvertent laceration of the hepatic vein.

HEPATOCELLULAR CARCINOMA

The incidence of primary liver cancer, also known as HCC, is the fifth most common cancer worldwide and is among the most frequently encountered solid-tumors in the world, with ~250,000 new cases reported annually.²¹ HCC requires a multimodality approach to provide the best patient outcome. The severity of the underlying parenchymal disease is a complicating factor that may limit the therapeutic options in HCC patients. Nevertheless, it must be emphasized that liver resection,

Table 1 Morbidity and Survival Post-Hepatic Resection for HCC

Author	Year	Patients	Percent with Cirrhosis	Morbidity (%)	1 Year (%)	3 Years (%)	5 Years (%)
Fong et al ²³	1999	154	65	45	81	54	37
Llovet et al ²⁴	1999	77	100	—	85	62	51
Margarit et al ²⁵	2001	105	80	9	77	47	37
Kanematsu et al ²⁶	2002	303	55	—	84	67	51
Grazi et al ²⁷	2003	308	100	42	—	64	42
Ercolani et al ²⁸	2003	224	100	36	83	63	42
Minagawa et al ²⁹	2003	334	—	—	94	75	56

in the absence of extrahepatic disease, remains one of the fundamental tools in the multidisciplinary armamentarium, especially because median survival in untreated disease is low.²² In those patients who have severely altered liver function, liver transplantation may be the only surgical option.

In the United States, the Child-Turcotte-Pugh classification remains the method by which the majority of surgeons categorize liver dysfunction. Liver resection for HCC is generally offered to those patients who are classed as Child's A and very carefully selected Child's B patients. Despite improvements in perioperative care of these patients who undergo liver resection for HCC, morbidity after liver resections still remains high. This is primarily related to patient selection with regard to hepatic dysfunction and other intrinsic liver disease. Despite the level of liver dysfunction, 5-year survival rates remain between 37 and 56% (Table 1).^{23–29} When examining these data it must be kept in mind that the cirrhotic patients were all well selected, Child's A class individuals. Those that were Child's B/C patients did not qualify because of the level of liver dysfunction and therefore increased risk of postoperative morbidity and mortality. Predictors of poor outcome after hepatic resection are listed in Table 2. Other factors that may figure into postoperative performance are medical comorbidities, age, and perioperative transfusion.^{1,30–32} Absolute contraindications to operative resection include the presence of extrahepatic disease, poor hepatic functional reserve, multifocal disease, tumor location, and main portal vein involvement.

Partial hepatectomy has long been the gold standard of surgical treatment for HCC in patients

without any extrahepatic disease. Cirrhotic patients who have poor hepatic function and HCC have long been a challenge, and for them, liver transplantation is often the only choice. This treatment option, unfortunately, cannot be offered to all patients due to the limited number of donor livers that are available; many of these patients will have progression of disease while waiting for a donor liver. The poor outcomes of liver transplantation in the early 1990s led to the development of the Milan criteria to better define the patient population that would best benefit from the procedure. These include cirrhotic patients with a single tumor less than 5 cm, or less than three lesions none of which is ≥ 3 cm in size, no extrahepatic disease, and no vascular invasion.³³ For those who are selected, transplantation offers a chance for cure of the underlying liver disease, relief of portal hypertension, and prevention of metachronous liver lesions. Although this seems to be the ideal treatment choice, it is not without its downsides. There is a risk of recurrence because of immunosuppression and a risk of recurrence of the intrinsic liver disease, especially in those patients with concomitant hepatitis C infections.³⁴

Those patients who eventually develop recurrence in the liver remnant have very few therapeutic options as standard chemotherapeutic agents are not effective against HCC. There has been recent evidence that intra-arterial ¹³¹I-lipiodol may have some effectiveness in the adjuvant setting. It was shown that 3-year survival increased to 86% from 46% when comparing the treatment and control groups.³⁵ Transarterial chemoembolization is another technique being investigated for use in both the adjuvant setting as well as in an effort to convert previously unresectable patients to theoretically resectable patients by inducing tumor shrinkage.^{36,37} There is still controversy with regard to the effectiveness of this procedure because of conflicting reports in the literature with regard to whether or not there is any improvement in survival.^{38–41}

Table 2 Factors Associated with Adverse Outcome Following Resection for Hepatocellular Carcinoma (HCC)

Multiple lesions
Lesions > 5 cm
Alpha fetoprotein > 2000 ng/mL
Positive resection margins
Vascular invasion
Advanced tumor stages
Lymph node metastases

LIVER METASTASES

We categorize liver metastases into colorectal and non-colorectal groups. Noncolorectal hepatic metastases are

Table 3 Survival after Resection for Metastatic Colorectal Liver Lesions

Author	Year	Patients	5 Years (%)	10 Years (%)	Median (mo)
Scheele et al ⁴⁸	1995	469	33	20	40
Nordlinger et al ⁵⁰	1996	1568	28	—	—
Fong et al ⁵¹	1997	577	35	—	40
Jamison et al ⁵²	1997	280	27	20	33
Fong et al ⁴⁹	1999	1001	37	—	—
Choti et al ⁵³	2002	226	40	26	46

further divided into two subcategories, neuroendocrine and nonneuroendocrine. Our multidisciplinary team approach takes into consideration the natural history of disease as well as the current efficacious surgical and nonsurgical treatment options.

Colorectal Hepatic Metastasis

Metastatic colorectal cancer has become the most common indication for liver resection in the Western world, with 10 to 15% of the 50,000 to 70,000 colorectal patients developing liver metastases amenable to potential curative surgical treatment.⁴² Prior to being considered for surgical resection it must be shown that the patient has no extrahepatic disease and has intrahepatic disease that is easily and safely resectable; the patient must also be in good medical condition.

Once the patient has been deemed a surgical candidate, the same surgical principles as described above apply. Surgical resection of colorectal metastases has become an aggressively sought after option due to the demonstrated decreased mortality rates (<5%) and improved survival benefits from high-volume centers in properly selected patients.⁴³ Five-year survival among untreated stage IV colorectal patients is extremely rare, and median survival has been shown to be between 5 and 12 months.^{44–46} In comparison to 5-fluorouracil (5-FU)/leucovorin and CPT-11 (irinotecan), the most effective systemic chemotherapy to date, which shows a 14.5-month median survival, complete resection of hepatic metastases is associated with a 30- to 40-month median survival (Table 3).^{47–53} Although there have not been, and will probably never be, any prospective randomized trials comparing survival after hepatic resection and systemic chemotherapy with no treatment, several retrospective studies have shown superior 5-year survival rates with resection (25 to 38% versus 0 to 2.5%, respectively).^{48,54}

Even with careful patient selection, many individuals will experience a recurrence. Half of these recurrences will appear in the liver and the other half will appear in extrahepatic sites such as the lung and peritoneum. It has been postulated that the high rates of recurrence, even after an adequate resection by experienced surgeons, are due to tumor biology. There are now clearly defined

criteria that increase an individual's risk of recurrence following hepatic metastasectomy. Fong et al have defined a clinical risk scoring system to predict recurrence (Table 4). After analyzing 1001 patients, they identified five preoperative risk factors that were found to be independent predictors of outcome after hepatic resection for colorectal metastases.⁴⁹ It was found that those individuals with a score of 0 to 2 had a median survival of 47 to 74 months and 5-year survival of 40 to 60% versus those with a score of 3 to 5 who had a median survival of 22 to 33 months and 5-year survival of 14 to 20%.⁴⁹ Using this system preoperatively, realistic expectations for both the patient and the surgeon can be discussed.

The role of additional systemic therapy following hepatic resection for colorectal metastases is unclear.⁵⁵ Unfortunately, further systemic therapy after hepatic resection is often not an option because most of these patients are not chemotherapy naive and are therefore not considered candidates for adjuvant therapy, because if their disease has progressed on the agents previously used, then tumor biology dictates that it is probably resistant to the drug. Those patients who have not received previous treatment are often administered postoperative chemotherapy, but there is no data to support this as there have been no randomized trials to investigate the role of systemic therapy after hepatic resection. An option that is currently being explored is combination systemic therapy with 5-FU-leucovorin and regional hepatic artery infusion with 5-fluoro-2-deoxyuridine, a 5-FU analogue. One study showed that this therapy was associated with a significantly prolonged overall survival when compared with systemic therapy alone.⁵⁶

Table 4 Factors Associated with Increased Risk of Recurrence Following Resection of Colorectal Metastases

Clinical Risk Score
1. Lymph node positive primary
2. Disease-free interval < 12 month between primary and hepatic metastases
3. Tumor size > 5 cm
4. Number of liver tumors > 1
5. Preoperative CEA level > 200 ng/mL

Each criterion receives 1 point: score = sum. Data adapted from reference 49. CEA, carcinoembryonic antigen.

Table 5 Results of Hepatic Resection for Neuroendocrine Tumors

Author	Year	Patients	Cured	Operative Mortality (%)	Symptom Relief (%)	Survival (%)
Que et al ⁵⁸	1995	74	28	2.7	90	74 (4 years)
Dousset et al ⁵⁹	1996	17	12	5.9	88	46 (4 years)
Chen et al ⁶⁰	1998	15	15	0	N/A	73 (5 years)
Elias et al ⁶¹	1998	27	15	2	N/A	74 (5 years)
Chamberlain et al ⁵⁷	2000	34	15	6	86–100	76 (5 years)

Noncolorectal Hepatic Metastasis

Neuroendocrine hepatic metastases are generally slow growing and indolent but may present with a variable clinical course because of the number of different diseases that they encompass. Symptoms vary even with similar tumor types and do not always correlate with volume of disease. The most common neuroendocrine tumor with metastases to the liver is carcinoid tumors; gastrinomas and glucagonomas are the islet cell tumors that are most likely to metastasize to the liver but are extremely rare and follow a very indolent course. Hepatic metastases occur in 45 to 90% of neuroendocrine tumors, but interestingly, most patients rarely develop liver dysfunction. Mortality is generally a result of complications due to uncontrolled hormone secretion rather than liver failure. Extent of liver involvement is a predictor of survival, with those patients having over 75% liver involvement doing poorly compared with others and those with only unilobar disease demonstrating lower morbidity.

The success of resection of colorectal metastases has generated a significant interest in the resection of neuroendocrine metastases. Although cure after identification of these hepatic metastases is rare, prolonged survival after resection has been reported (Table 5).^{57–61} The goal of hepatic resection in this select patient population is amelioration of symptoms from hormone production, and surgical therapy is generally felt to be the best initial management. This includes complete resection, if possible, or debulking procedures for palliation. Resection for cure is possible in only 10% of these patients; even with complete resection, recurrence rates are 50 to 60%.⁵⁷ Total hepatectomy with trans-

plantation may be indicated in a very select group of young patients with unresectable disease limited to the liver. To date, there have been no randomized trials comparing management strategies.

Nonneuroendocrine metastases can be from several different sources with different natural histories and are usually treated nonoperatively. Survival in untreated patients is limited, with the median survivals being measured in months due to the aggressive nature of the primaries and limited response to chemotherapy. Hepatic metastases in these patients are often a manifestation of other systemic disease, and as such, surgery is not beneficial unless disease is limited to the liver and the primary disease site has been resected. The disease must also be in an anatomic location that is amenable to resection.

Strict patient selection is one of the cornerstones for good outcomes with these patients. Good candidates for resection of nonneuroendocrine metastases are those individuals with long disease-free intervals after primary tumor resection and those whose hepatic disease can be completely resected. Chemotherapy should be administered preoperatively to assess for response, because those that respond to chemotherapy will generally have a favorable biology and do better after liver resection. There are several reports showing survival improvement in select patients with hepatic metastases from both sarcoma and breast primaries, as well as other primary sites (Table 6).^{62,63} Regrettably, there are limited data on resection for individual nonneuroendocrine hepatic metastases to guide treatment, and further investigation in this area is needed.

Table 6 Results of Hepatic Resection for Nonneuroendocrine Tumors

Primary Tumor Type	Patients	5-Year Survival (%)
Breast	18	6
Soft tissue sarcoma	48	11
Renal cell sarcoma	15	27
Melanoma	21	10
Gynecologic cancers	15	27
Gastric	23	4

ABLATION

For those tumors that are deemed unresectable, ablative techniques are an acceptable alternative. Ablation of metastases may be performed alone or in conjunction with a liver resection. One of the oldest techniques is alcohol ablation, which may be done either percutaneously or intraoperatively. It is often used in patients who have contraindications to undergoing surgery or those who have small, unresectable lesions.⁶⁴ The ease of performance and low cost make this technique appealing, but unfortunately, it is associated with a high rate of

recurrence and often requires several sessions to adequately destroy the target lesions.

Another ablative technique that has been used is cryosurgery. This also can be used alone or in combination with resection. In the past, this technique required that a laparotomy be performed for access. It is associated with a significant risk of recurrence and can be complicated by postoperative bleeding. Although there have been no randomized controlled clinical trials to evaluate the effectiveness of cryosurgery compared with resection on survival rates, there are reports that it may be similar.⁶⁵

Radiofrequency ablation (RFA) has recently become a more popular technique because of its versatility and effectiveness. It can be performed percutaneously, laparoscopically, or surgically, and as of yet there has been no investigation into whether one approach is superior. There has also been no evidence to support RFA as having an improved complication rate, survival rate, or decrease in recurrence when compared with cryosurgery, but it has been shown to have a slight improvement in recurrence over ethanol injections.^{66,67}

CONCLUSION

With time, there has been dramatic improvement in the outcome of patients undergoing hepatic surgery because of advances in perioperative care. What was once a highly morbid procedure has now become a safe and effective treatment for individuals with either primary and metastatic hepatic malignancies. Surgical resection of hepatic malignancies remains the single best option for a potential cure. The best treatment of hepatic malignancies should be based on the conclusions drawn from the discussions of a multimodality team of specialists. Even so, recurrence rates with surgery remain high, and further research needs to be performed with effective systemic agents to improve survival. Once this occurs, the indications for the surgical treatment of both primary and metastatic hepatic malignancies will expand, perhaps even to those individuals who are now defined as having unresectable disease.

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