Review Article

Surgical resection for hepatocellular carcinoma

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Abstract: The incidence of hepatocellular carcinoma (HCC) is growing in the United States due to increasing rates of cirrhosis from viral hepatitis, alcohol, and fatty liver disease. The elevated incidence, along with the associated high mortality rate for patients with this diagnosis, highlights the importance of an understanding of the optimal management of HCC. Surgical resection and liver transplantation offer the only options for long-term cure. However, without careful patient selection, meticulous intraoperative technique and perioperative management, liver resection in patients with underlying cirrhosis is associated with a significant risk of postoperative morbidity and/or mortality. This article will describe key considerations in patient selection and recent improvements in surgical technique and peri-operative management that have increased the safety of liver resection in patients with HCC, particularly those with underlying cirrhosis.

Keywords: Surgical resection; hepatocellular carcinoma (HCC); liver transplantati; intraoperative technique; perioperative management; liver resection

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Background

Worldwide, hepatocellular carcinoma (HCC) is the 6th most common cancer and has the 3rd highest mortality of any cancer (1). While the burden of HCC is highest in developing countries, the incidence is rising in the United States and is expected to continue to rise for the next two decades (2-4). Approximately one-third of patients with cirrhosis due to hepatitis C will eventually develop HCC (5). Obesity also appears to be an emerging significant risk factor for the development of HCC and interacts synergistically with both alcohol and tobacco use to further increase the risk (6,7). For patients affected by this often devastating disease, surgical therapy represents the only hope for cure.

Over the last 20 years, significant advances in both surgical technique and peri-operative care have resulted in improvements in morbidity and mortality rates after major liver resection. Despite these advances, a recent analysis of the SEER-Medicare database suggests that surgical therapy remains widely under-utilized in this patient population (8). Educating the healthcare community about the role of surgical therapy in the management of patients with HCC is likely the most effective means of increasing its utilization, and by extension, improving life expectancy for these patients.

Methods

Articles for this review were chosen by performing a PubMed search for relevant English language articles using keywords including HCC, surgery, hepatectomy, and related topics. Preference was given to randomized controlled trials for topics for which those were available. For topics for which no randomized controlled trials were available, the methodology of available articles was reviewed to determine the quality of evidence. Preference was given to those studies with prospective data collection and then to carefully conducted large retrospective studies.

Pre-operative assessment of resectability

While determining which patients are appropriate candidates for surgical resection can be challenging for many malignancies, this task can be especially difficult in the case of patients with HCC because the majority of them have some degree of compromised liver function that may represent a contraindication to an otherwise anatomically feasible resection. For this reason, a careful pre-operative assessment is critical for these patients and must include an evaluation of medical comorbidities, tumor location, baseline liver function and tumor biology.

The same medical comorbidities that would render a patient unsuitable for major abdominal surgery are applicable in patients being considering for hepatectomy for HCC. Determination of the anatomic resectability of an HCC requires careful consideration of technical factors (9). In general, liver tumors are technically resectable if they can be removed with negative margins while preserving a liver remnant with adequate hepatic arterial and portal venous inflow, venous outflow, biliary drainage, and sufficient parenchyma to support critical liver functions (10). While this axiom holds true for HCC, determination of what constitutes 'sufficient remnant parenchyma' necessitates an understanding of the patient's baseline liver function.

The incidence of death from postoperative liver failure after right hepatectomy has been shown to be significantly higher in patients with fibrosis or cirrhosis compared to patients with normal background liver parenchyma (11). Prior studies have also shown that for patients with normal livers a functional liver remnant of 20% of standardized liver volume is adequate to avoid postoperative liver-related mortality (12,13), but for patients with cirrhosis, a 40% remnant is generally accepted as the lower limit of what is necessary for a safe resection (14,15). Although these percentage point thresholds are useful as guidelines, they are not a direct reflection of liver function. In some areas, ICG retention testing is available as a direct measure of liver function. In the absence of this test, patients with marginal functional liver remnant are recommended to have preoperative portal vein embolization performed, as this allows the surgeon to test the regenerative capacity of the liver prior to operative intervention.

In cirrhotic patients being evaluated for possible liver resection, the presence of portal hypertension is one of the strongest predictors of poor outcome (16,17). Frequently, patients with advanced cirrhosis and portal hypertension will describe a history of hepatic encephalopathy, gastrointestinal bleeding, easy bruisability, and ascites. These signs and symptoms should be sought in all cirrhotic patients and combined with the prothrombin time and serum albumin to determine a Childs-Turcotte-Pugh score (18). Portal hypertension is also characterized by a hepatic venous pressure gradient ≥10 mmHg, the presence of esophageal varices or splenomegaly and thrombocytopenia (platelet count < $100{,}000/mm^3$). Preoperative imaging should be carefully evaluated for the presence of varices and/or splenomegaly and in patients at high risk of portal hypertension, direct measurement of the hepatic venous pressure gradient should be considered (19).

The Model for End-Stage Liver Disease (MELD) score was originally developed as a tool to predict the survival of cirrhotic patients after transjugular intrahepatic portosystemic shunt placement, but was subsequently shown to be predictive of survival in patients with cirrhosis and has been adopted as a means of prioritizing patients for liver transplantation (20). It is calculated by the formula: $9.57 \times \log_e(\text{creatinine mg/dL}) + 3.78 \times \log_e(\text{bilirubin mg/dL}) + 11.2 \times \log_e(\text{INR}) + 6.43$ and, therefore, does not rely on any tumor characteristics for predicting prognosis. Despite this limitation, its powerful stratification of severity of liver disease makes it useful for the majority of patients with HCC. One of the first studies correlating MELD score with postoperative outcomes after resection of HCC in patients with cirrhosis was from the Mayo Clinic. This study showed that liver resection patients with MELD scores of 9 and higher had significantly higher perioperative mortality (29% *vs.* 0% for patients with lower MELD scores) and significantly lower 5-year survival rates (21). Another more recent retrospectively study of MELD scores in patients with HCC who underwent liver resection corroborated a MELD cutoff of 9 as an independent predictor of higher perioperative mortality and lower 3-year postoperative survival (22).

Several oncologic factors should also be considered when evaluating a patient's appropriateness for resection of an HCC. In many cases, the first challenge may lie in determining whether a suspicious lesion in a patient with chronic liver disease truly represents a cancer or just a regenerating nodule. For cirrhotic patients with suspicious lesions measuring 1-2 cm, the EASL-EORTC clinical practice guidelines for the management of HCC support either pathologic confirmation with biopsy or the presence of arterial phase contrast uptake with venous phase contrast washout (i.e., the radiological hallmark) on two concordant imaging techniques as diagnostic criteria (16,23). Once a diagnosis of HCC has been established, the next factor that should be evaluated is whether any extrahepatic disease is present. Both of these factors can be accurately assessed with magnetic resonance imaging (MRI) and/or computed tomography (CT) (17).

Regarding evaluation of intrahepatic disease burden, the joint consensus statement from the Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract recommends MRI as the preferred preoperative imaging for HCC because of its performance characteristics (17). Accurate preoperative imaging is essential for determining the number and location of tumors as well as the relationship of the tumor(s) to the major vascular structures within the liver. As a final assessment of resectability, intraoperative ultrasound (IOUS) should be utilized to confirm the number and location of the tumor(s) as well as the anatomy of the major vascular structures within the liver immediately prior to resection.

Staging

Clinical staging systems rely on non-pathologic tumor and/or patient characteristics. These systems aim to stratify patients by anticipated survival and suitability for different treatment modalities and are applicable for all patients with HCC, regardless of the extent of disease (18). Among the clinical staging systems for HCC, only the Barcelona Clinic Liver Cancer (BCLC) staging system has been widely tested, externally validated (19,24,25), and recommends appropriate treatment strategies for specific prognostic classifications (16,26). For these reasons, the EASL-EORTC Guidelines for the management of HCC recommend it as the preferred clinical staging system. The BCLC system classifies patients into 5 stages (0, A, B, C, and D) based on tumor-related variables (number, size, presence of vascular invasion, involvement of lymph nodes, and presence of metastases), liver function (Child-Pugh score), and patient functional status (ECOG) (27). Patients classified as stage 0 are Child-Pugh A with an ECOG of 0 and have a single tumor <2 cm in size. Such patients are appropriate candidates for liver resection. Stage A patients are Child-Pugh A or B with a performance status of 0 and have 1-3 tumors, all ≤3 cm. These patients are candidates for resection, liver transplantation, or ablative therapies. Together these two groups of patients have an expected median overall survival of 60 months or longer (27). Stage B patients are also Child-Pugh A-B with a performance status of 0, but have multinodular tumors and so are not candidates for curative therapy and have an expected median overall survival of about 20 months. Patients in this class are most frequently treated with chemoembolization. Patients who are stage C are also Child-Pugh A-B, but have a lower performance status of 1-2 and have portal vein invasion, positive lymph nodes, or metastatic disease and thus, have an expected median overall survival of only 11 months. Such patients would be considered for treatment with sorafenib (27). Stage D patients are terminal patients with a performance status >2 and Child-Pugh C, have a limited survival <3 months, and should be treated with best supportive care (27).

Preoperative preparation

Portal vein embolization

Portal vein embolization (PVE) is an important adjunct procedure in patients requiring major hepatectomy that provides an assessment of the ability of the future liver remnant to hypertrophy after hepatectomy. This ability closely correlates with avoidance of liver failure after hepatectomy in cirrhotic and noncirrhotic patients (28). A prospective clinical trial of PVE prior to right hepatectomy stratified patients by those with normal livers and those with chronic liver disease (29). All the patients in this study with chronic liver disease were undergoing hepatectomy for treatment of HCC. The authors found that while patients with chronic liver disease were slightly less likely to experience hypertrophy after PVE (86% *vs.* 100% of patients with normal livers) and had a lower median absolute increase in functional liver remnant percentage (9%±3% *vs.* 16%±7% for patients with normal livers), the use of portal vein embolization in patients with fibrosis due to chronic liver disease significantly lowered the rate of postoperative complications, improved postoperative liver function tests, and shortened intensive care unit and hospital lengths of stay (29). This study established that PVE was feasible, safe, and beneficial in patients with HCC and severe fibrosis/cirrhosis. The authors also hypothesized that a lack of hypertrophy in the future liver remnant after PVE was a sign that the underlying liver parenchyma lacked the ability to regenerate and so should be considered a contraindication to major hepatectomy (29), a theory that has since become widely accepted (14,28). Subsequent retrospective studies have corroborated the safety of PVE in patients with HCC and cirrhosis and have also found equivalent overall and disease-free survival rates for patients undergoing lesser hepatectomy for HCC without pre-operative PVE as for those requiring PVE for major hepatectomy (30,31). Patients with HCC and advanced forms of chronic liver disease may have physiologic and anatomic factors that represent a contraindication to use of PVE, including portal vein invasion, portal vein thrombosis, tumor extension into the functional liver remnant, uncorrectable coagulopathy, renal failure, and portal hypertension (28). In most cases, these same features contraindicate any resectional therapies and serve as guideposts for the dangers of local therapy of any type.

TACE + PVE

Concerns have been raised about a compensatory increase in hepatic arterial blood flow within the embolized liver of patients with chronic liver disease who undergo PVE, a physiologic change which might either limit the hypertrophy of the future liver remnant or result in increased blood flow to the tumor, potentially speeding growth (32). Combining PVE with transcatheter arterial chemoembolization (TACE) has been suggested as an approach to address these concerns. The use of this combination of procedures for patients with HCC and cirrhosis has been reported in retrospective studies, two of which have compared results after the combined procedure with those after PVE alone and have shown a higher mean increase in the percentage of the future liver remnant volume, a lower incidence of postoperative liver failure, higher rates of complete tumor necrosis, and higher recurrence-free and overall survival rates for the patients treated with the combined procedure versus those treated with PVE alone (32,33). Although the efficacy of the dual procedure has yet to be proven in prospective trials, the results from these studies suggest this approach warrants continued consideration.

Technical considerations

Open resection

Non-anatomic *vs.* anatomic resections

HCC tumors have a propensity for local portal vein invasion with extension toward the main portal vein, indicating that anatomic resection of the segmental, sectional, and lobar vascular structures, depending on the site and size of the tumor, may improve outcomes. A Japanese study compared results for 207 patients undergoing either anatomic (based on vascular pedicles) or non-anatomic resections for HCC and found that anatomic resection was an independent predictor of improved recurrence-free survival (34). A smaller French study reported similar results with the anatomic resection group having significantly improved disease-free survival rates (35). For this reason, anatomic resections are recommended in the EASL HCC guidelines as the preferred approach provided that adequate remnant liver volume can be preserved (16).

Margins

Micrometastases are frequently found within the region surrounding HCCs, providing support for the use of wide resection margins for these tumors (36). The aim of adequately treating micrometastatic disease, however, must be balanced against the need to preserve a maximal volume of functional liver parenchyma to minimize the risk of postoperative liver insufficiency (particularly in patients with underlying cirrhosis) and to preserve options for future treatment of recurrent disease. In an effort to balance these competing aims, a prospective randomized controlled trial was undertaken to compare 1 *vs.* 2 cm margins for patients with solitary resectable HCCs (37). This trial, in which anatomic resections were performed in the majority of patients, found that 2 cm gross resection margins were associated with improved overall survival rates and that assignment to the wide margin group was an independent predictor of lower risk of death in multivariate analysis. In addition, higher recurrence-free survival rates were seen in the patients in the wide margin group, as were lower rates of recurrences at the resection margins and lower rates of multifocal recurrences. Multivariate analysis of factors associated with tumor recurrence showed that the only two independent predictors were the presence of micrometases and the width of the final resection margin. Patients in the wide margin group also had significantly higher 1- and 2-year survival rates after tumor recurrence (37). These results provide compelling evidence favoring the use of anatomic resections with 2 cm margins, when feasible, for patients with solitary HCCs.

Low central venous pressure (CVP) anesthesia

Recognition of the relationship between CVP and blood loss during parenchymal division has been one of the key factors contributing to the improvement in the safety of liver resections in recent years. A prospective study from Australia examined the relationship between CVP and blood loss during hepatectomy (38). This study found that patients with a mean CVP during parenchymal transection of 5 cm H_2O or less had a median blood loss of 200 versus 1,000 mL in patients with a CVP higher than 5 (P=0.0001) and a 5% transfusion rate versus a 48% transfusion rate. Maintenance of a low CVP can typically be accomplished by fluid restriction, but in cases where this strategy is inadequate, use of vasodilators or diuretics may also be effective.

(Vascular inflow occlusion) Pringle maneuver

The use of the Pringle maneuver (hepatic artery and portal vein clamping) as a method of minimizing blood loss during hepatectomy has been evaluated in a randomized controlled trial (39). This trial showed that intermittent use of the Pringle maneuver (20 minutes of clamp time followed by a 5-minute clamp-free period) decreased the blood loss per cm^2 of transection surface, reduced the transection time and resulted in lower early postoperative serum bilirubin levels and higher postoperative transferrin levels in cirrhotic patients without significantly changing the morbidity or mortality rates or the 15-minute ICG-retention rate on postoperative day#8. This finding is significant because other studies have shown that increased intraoperative blood loss is an independent predictor of postoperative morbidity after hepatectomy and correlates with shorter overall and recurrence-free survival for patients with HCC (40,41).

Cross clamping of the infrahepatic vena cava is another means of decreasing blood loss during parenchymal transection. This technique has been compared to a strategy of maintaining a low CVP by using anesthetic techniques (fluid restriction, diuretic administration, use of vasodilators) in a randomized controlled trial without routine use of portal triad occlusion (42). This trial found that infrahepatic vena cava clamping was associated with significantly lower total intraoperative blood loss, lower blood loss during parenchymal transection, and less intraoperative hemodynamic instability than anesthetic interventions to maintain a low CVP. The group of patients in whom vena cava clamping was utilized, however, also had a significantly higher rate of pulmonary embolism, which limited the authors' enthusiasm for routine implementation of this strategy (42). A second randomized trial also compared these two strategies in combination with portal triad occlusion (43). This trial also found that vena cava clamping reduced blood loss during parenchymal transection and resulted in fewer hemodynamic changes, but in contrast to the earlier trial, also found that it was associated with a more rapid improvement in postoperative bilirubin levels. This trial reported similar rates of complications in the two groups without specific mention of whether any patients suffered a pulmonary embolism. In addition, it specifically examined results in the subgroup of patients with moderate to severe cirrhosis and found that the effect on blood loss during parenchymal transection was also significant for this high-risk subgroup (43). Combined, these data indicate that judicious use of perihepatic vascular control maneuvers can improve outcomes in cirrhotic liver resection patients by limiting blood loss.

Laparoscopic resection

While no randomized controlled trial has compared laparoscopic versus open approaches to resection in patients with HCC, four meta-analyses of nonrandomized studies have examined both short-term postoperative and longer-term oncologic outcomes after laparoscopic and open liver resection for this group of patients (44-47). Each of these meta-analyses found that laparoscopic resection was associated with significantly less blood loss, lower transfusion requirements, lower overall morbidity, and shorter length of hospital stay without a significant difference in length of operation, surgical margin status, or tumor recurrence rates. The two meta-analyses which examined postoperative mortality also found no significant difference after laparoscopic versus open resection (44,45). Specific types of postoperative complications were also examined in two of the studies, with both finding that laparoscopic resections were associated with significantly lower rates of pulmonary complications, ascites, and lower rates of liver failure, although this reached significance in only one of the two studies (44,45). While these results provide compelling evidence that laparoscopic resection is safe for patients with HCC and likely improves short-term postoperative outcomes, it should be kept in mind that the studies included in these meta-analyses included few major hepatectomies and few tumors in segments VII and VIII, so caution should be taken in applying these results to more challenging liver resections.

Radiofrequency ablation (RFA)

The use of percutaneous RFA for treatment of solitary HCCs ≤5 cm has been compared to surgical resection in a prospective randomized controlled trial (48). In this trial, ultrasound was utilized to confirm that ablation achieved a hyperechoic treatment zone that was larger than the target HCC. With this meticulous RFA technique, 1-, 2-, 3-, and 4-year overall and disease-free survival rates were achieved that were equivalent to those after resection. A second randomized controlled trial compared percutaneous RFA to hepatectomy for HCCs within the Milan criteria (solitary tumor <5 cm or up to 3 tumors all <3 cm) (49). In contrast to the earlier trial, this study found lower rates of 1-, 2-, 3-, 4-, and 5-year overall and recurrence-free survival for the patients treated with RFA. A third randomized controlled trial compared RFA and resection for HCCs up to 4 cm in diameter with one or two tumors and found that the difference in overall and recurrence-free survival between the two groups was not statistically significant (50). While the existing data are inconclusive as to whether results after RFA for small HCCs are as good as those after resection, they do suggest that RFA is a reasonable treatment strategy for such tumors, particularly in patients who may be at higher risk after resection or who prefer not to undergo a major operation.

Management of patients with major vascular invasion

Portal vein thrombosis and major vascular invasion have been shown to be robust prognostic factors for increased mortality in patients with cirrhosis and HCC (51,52). Even after resection the 5-year survival rates of patients with macroscopic invasion of the 1st order branches or main portal or hepatic vein trunks are only about 10-12% (53,54). In addition, reported median survival rates for these patients after treatment with transarterial chemoembolization, chemotherapy, or radiation rarely exceed 12 months, likely because of the high incidence of rapid development of extrahepatic metastatic disease after major vascular invasion/tumor thrombus (55). The most promising results for patients with major vascular invasion have been reported in a retrospective study of patients treated with preoperative transcatheter arterial chemoembolization followed by hepatectomy (56). In this study, the 18 patients who received both therapies had an 82% 1-year and 42% 3- and 5-year overall survival rates. While these results have yet to be confirmed in a large, prospective trial, at present, this combined therapy seems to be a reasonable approach, when technically feasible, for this high-risk group of patients.

Resection *vs.* transplantation

Although surgical resection has never been directly compared to liver transplantation for HCC in a randomized clinical trial, a 1999 study from the BCLC attempted to answer the question of which provides superior survival with a retrospective intention-to-treat analysis comparing patients who underwent resection with those who were listed for liver transplantation (57). The results of this study showed similar 1-, 3-, and 5-year intention-to-treat survival rates for both groups, but they also showed that in later years of the study, when rates of drop out on the transplant waiting list were higher, intention-to-treat survival rates decreased for the transplant group. Although the results of this study are difficult to interpret because nearly all the patients in the resection group were Child's A, compared to less than 1/3 of the patients in the transplant group and the authors acknowledge that patients who were felt to be unsuitable for resection (largely on the basis of elevated portal pressures) were referred for transplant evaluation, this study does highlight the importance of considering waitlist dropout rates when selecting transplantation as the preferred treatment strategy for a patient with HCC.

In another recent intent-to-treat retrospective analysis of resection *vs.* transplantation for solitary small HCCs, transplantion was found to result in improved outcomes for patients with tumors >2 and <5 cm (58). It should be taken into account, however, when interpreting these results that the waitlist time in the study was shorter than that expected at most U.S. transplant centers. In a subset analysis, the authors of this study found that even with a short waitlist time, patients with tumors ≤2 cm had equivalent survival rates after resection and transplant evaluation (58). Among patients who experienced recurrence of HCC after resection (the majority of whom had hepatitis C), only 22% were eligible for salvage transplantation. Others have proposed strategies for combining resection and transplantation for HCC such as immediately listing patients with high risk pathology for post-resection transplantation or using resection as a bridge therapy for patients likely to have a long waitlist time (59).

Complications

Although postoperative mortality after major hepatectomy has declined significantly with improvements in surgical and anesthetic techniques, complications after hepatectomy for HCC continue to occur in up to 50% of patients and have been shown to correlate with a lower overall survival rate (60,61). While patients undergoing hepatectomy for HCC are susceptible to the same cardiopulmonary, infectious and bleeding complications as patients undergoing other types of major general surgical procedures, they are also susceptible to specific liver-related complications, which are worthy of further discussion.

A recent retrospective study reported a 12.8% incidence of bile leak following hepatectomy for HCC (62). This study identified repeat hepatectomy and prolonged operative time as independent risk factors for bile leak and showed that occult biliary strictures as a result of previous therapy for HCC and intraoperative hepatic duct injury during repeat hepatectomy were the main factors associated with bile leakage that required either percutaneous transhepatic biliary or endoscopic retrograde biliary drainage for definitive management.

Postoperative liver insufficiency is closely associated with high mortality rates following major liver resection (28). Many definitions of posthepatectomy liver failure have been used in the literature and although recently a standardized definition has been proposed, it has yet to significantly impact the literature, making it difficult to understand the true incidence of this complication (63). Nonetheless, it is critical to recognize that this entity is characterized by persistently high bilirubin levels and abnormal coagulation studies, is typically associated with large volume ascites, and it puts patients at high risk of subsequent episodes of sepsis, multisystem organ failure, and death (64). The most effective treatment for this often devastating complication is prevention through careful selection of patients for resection, particularly in the setting of underlying cirrhosis, and judicious use of PVE for patients requiring major hepatectomies for treatment of their tumors.

Subsequent followup

Survival after resection and risk factors for recurrence

Five-year overall survival rates of 40-50% have been reported in modern series of patients treated with hepatectomy for HCC (52,65). Most factors predicting poor overall survival are associated with poor tumor biology (high AFP levels, large tumor size, major vascular invasion, extrahepatic metastatic disease, and positive margins) (52). Patients who have undergone hepatectomy for HCC are at high risk of developing recurrent disease, with 40-80% of patients recurring within five years of resection (65,66). The most significant risk factor for recurrence in patients with HCC is the presence of underlying cirrhosis (67) and active hepatitis. For patients with cirrhosis, genetic alterations frequently exist that represent a field defect that puts the entire liver parenchyma at risk for development of cancer. In addition, the presence of satellite nodules and venous invasion in the primary tumor also increase a patient's risk of developing recurrent intrahepatic disease (68). At a minimum, patients with a history of resected HCC should undergo surveillance with liver ultrasound and an alfafetoprotein level every six months.

Management of recurrence

Two different types of intrahepatic recurrences from HCC have been identified—those due to intrahepatic metastases and those due to multicentric occurrences (69). Intrahepatic metastases result from spread of the primary tumor to other parts of the liver, predominantly due to dissemination via the portal vein, whereas multicentric occurrences are *de novo* primary tumors arising within a high-risk parenchyma. As might be expected based on these different etiologies, the timing of recurrence and the prognosis following recurrence differs for the two types. Multiple studies have shown that survival after repeat resection of intrahepatic metastases is worse than after repeat resection for multicentric recurrences (69,70). One carefully conducted retrospective study of repeat hepatectomy for HCC found that the most reliable clinical factor for differentiating between intrahepatic metastases and multicentric recurrences was the time between the initial resection and the discovery of the recurrence, with 18 months being the cutoff point that most accurately differentiated the two types (70). Although management of recurrence should be individualized to patient circumstances, those patients with early recurrence after resection are generally recommended to have TACE, radioembolization or systemic therapy, while those with longer disease free intervals may benefit from repeat resection.

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