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Surgical Resection of High-Risk Hepatocellular Carcinoma: Patient Selection, Pre-Operative Considerations, and Operative Technique

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the 5th most common malignancy worldwide and in some parts of the world, such as sub-Saharan Africa and Southeast Asia, HCC is the most common cancer overall. The varying incidence of HCC in different countries varies depending on the prevalence of the major causes. Such causes include chronic infection with HBV which itself is responsible for over 50% of all cases of HCC, chronic infection with HCV, chronic liver disease with subsequent cirrhosis secondary to alcohol use, hemachromatosis, alpha-1-antitrypsin deficiency, and other rare metabolic disorders. There is also a significant population of non-cirrhotic HCC patients whose pathogenesis remains uncertain.

Various treatment modalities have been applied to HCC dependent on the stage of the disease as well as the overall functional capacity of the non-cancerous liver ranging from local ablative therapies such radiofrequency or cryoablation, regional trans-arterial infusion/embolization, external beam radiation therapy, formal hepatic resection, orthotopic liver transplantation, and finally systemic chemotherapy. The selection of patients who should undergo aggressive resectional surgical therapy has changed considerably based on evolving data from multiple centers as well as with advancing technology which has helped to augment our surgical techniques. Although the standard management of typical HCC is not without significant debate, the appropriate management of what we define as the oncologically high-risk patient is certainly contentious. This review will focus on and discuss our institutions multidisciplinary approach to the surgical management of oncologically high-risk HCC patients. The definition of high-risk HCC in this article includes any one of the following requiring formal hepatic resection with or without chronic liver disease: tumors larger than 5cm in diameter, multi-nodular disease, and major vascular invasion.

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PATIENT SELECTION

LARGE HCC

Large HCC (>5cm in diameter) are still common at initial presentation despite increasing use of ultrasound and alpha-fetoprotein screening in high risk populations worldwide. These tumors typically present in the absence of underlying cirrhosis and can grow to large size (10cm) in the absence of symptoms. These larger tumors have historically been considered high-risk for intrahepatic or extrahepatic spread, moreover increasing tumor size has been found to directly correlate with incidence of vascular invasion which in itself has been associated with inferior outcomes as will be soon discussed.[1, 2] The other non-resectional treatment options previously mentioned are contraindicated as locoregional therapies are not effective for particularly large tumors and liver transplantation only reporting acceptable outcomes in small, early lesions in those centers following either established Milan criteria or even the new extended guidelines due to previous poor results and high recurrence rates in significantly larger lesions, thus an inappropriate use of limited donor resources.[3, 4] In addition the considerable technical challenges associated with major resection of these massive cancers are well documented and associated with higher perioperative complications such as significant bleeding and tumor rupture. As a result patients with larger tumors are often denied aggressive curative therapy and certain groups have even advocated that large size (>5cm) be a contraindication to liver resection.[5] With this being said, we do not consider size alone as a contraindication to surgery as liver resection is the only viable option for patients presenting with large HCC.

Earlier published large-series single-institutional studies looking at outcomes after resection in patients with HCC >5cm reported modest 5yr overall survival after resection ranging from 16.7% – 33%.[6–11] Most of these data were accumulated in earlier decades prior to advent of modern liver surgical techniques and other contemporary methods such as portal vein embolization. More modern data have challenged these outcomes and in fact resection of solitary large HCC without vascular invasion has been documented to result in favorable outcomes with 5-year survivals of >70% in selected cases.[12] A more recent report looking at resection in HCC classified as giant (>10cm) found overall and disease-free 5yr survival of 45% and 43% respectively.[13] Although data from the International Cooperative Study Group on HCC looking at resection of HCC in over 400 patients from multiple high volume centers did identify a significantly worse overall 5yr survival (39% vs. 58%) comparing large (>5cm) to small (<5cm) tumors, the perioperative outcomes were comparable to those of patients with small HCC.[14] Moreover those survival outcomes compare superiorly to those reported in the literature that used non-surgical modalities for patients with similarly staged HCC. Furthermore another series of 300 patients undergoing resection for HCC with tumors larger than 10cm reported perioperative mortality of 5% with the majority (60%) of those patients undergoing major or extended hepatectomy, proving that although technically challenging, large HCC can be safely removed.[15]

The advent of portal vein embolization (PVE) has also contributed significantly to improved outcomes in patients with large HCC. A recent publication looking at resection in large HCC (>10cm) found overall 5yr survival of 45%.[16] When they examined those patients

undergoing major hepatectomy in combination with PVE the overall 5yr survival in that subset was significantly higher at 58% suggesting better outcomes with PVE in patients with large tumors. Earlier studies have confirmed that major hepatic resection after portal vein embolization with complete surgical margins should be performed in patients with large tumors to allow optimal outcome.[17] Large HCC (>5cm) certainly are high-risk tumors, however when adequately selected, patients can be offered potentially curative resection with lasting results.

MULTINODULAR HCC

Multinodular HCC has traditionally been considered a contraindication to resection as it is associated with a significantly worse prognosis than solitary tumors. As a result multinodularity has been integrated into all known HCC staging and classification systems. The early literature would suggest that transplantation alone is the only modality that can offer long term survival in patients with multinodular disease.[3, 18] Initial work looking at outcomes in patients following resection of multinodular HCC compared to solitary tumors identified that only up to 25% of multinodular patients can experience long term survival after resection [2, 19] Another more recent study looking at 599 patients undergoing hepatectomy for multinodular HCC revealed the 3 and 5 year survival rates were 69.2% and 58.4% for single-tumor HCC, and 55.5% and 29.9% for multi-tumor HCC.[20] Thus it is true that multinodularity does portend more advanced disease and subsequent worse prognosis. However given the limited supply of donors for transplantation, the significant number of patients who do not meet either the Milan or the extended UCSF criteria for transplantation, and the fact that approximately 20% of transplant candidate patients drop out due to progression of disease while awaiting transplantation, offering formal liver resection as the only chance for cure is appropriate for the majority of these patients. As a result we do not consider multinodularity a contraindication to resection.

Recent data have shown significant improved outcomes even in this cohort of high-risk patients. Our own multi-institutional database results reveal that hepatic resection can be safely performed in patients with multinodular HCC, with an overall 5yr survival rate of 39%.[14] Another study looking at 126 patients with multinodular disease found 5yr overall survival of 58%.[21] In that series, at a major hepatobiliary center, although 5yr recurrence was high >70%, at least 20% of those recurrences were able to undergo re-resection for even further improved survival of >70% at 3 yrs. Thus even multinodular disease, in the era of modern surgical technique and appropriate patient selection, is not contraindicated for formal liver resection.

MAJOR VASCULAR INVASION

As previously stated major vascular invasion is classically one of the most important poor prognostic factors attributed to HCC, associated with an increased risk of intrahepatic and systemic metastases and having been found to be an independent predictor of outcome after resection.[22, 23] Intrahepatic dissemination of the tumor via the portal circulation is thought to be the mechanism of the large majority of in-liver recurrences. As neither ablative therapies, transplantation, or systemic chemotherapy have been shown to offer any significant survival benefit, and the fact that the natural history of untreated disease leads to

death usually within months, surgical resection remains the only therapeutic option that may offer any survival benefit.[3, 24–26] This logic and this aggressive approach had been challenged by various authorities in the past.

In contradistinction, early reports and updated series from single institutions have proven the feasibility and oncologic appropriateness of resection in selected patients and have in fact have been able to stratify risk based on the location of the portal vein tumor thrombus.[27] They reported 5yr overall survival of 63% and 46% in those without or with vascular invasion, respectively, and have subsequently shown that patients with invasion to the second or third peripheral portal vein branches had significantly improved survival than those with invasion to the main portal trunk, contralateral portal vein, or invasion to the first branches (right or left) portal vein. Although initial resection in these patients is almost universally associated with recurrence in the majority, secondary treatments for recurrence either with re-resection or local-regional therapy have led to satisfactory survival rates. Others have even shown that major vascular invasion to first portal branches can be treated with transarterial chemoembolization (TACE) combined with subsequent hepatectomy resulting in 42% overall survival in highly selected patients compared to 7% for those not undergoing resection.[28] Subsequent multicenter data including our own have confirmed that surgical resection of HCC with major vascular invasion can be performed relatively safely with an acceptable mortality of 5.9% and in fact can lead to long-term survival in a small subset of patients which is far superior to nonsurgical therapy.[29] The concept of gross versus microscopic invasion is significant. A very recent study looking at a cohort of patients undergoing resection with subsequent vascular invasion confirmed earlier data and found overall survival differed significantly with microscopic vascular invasion (~40%) versus gross vascular invasion (~20%) as expected.[30] However they also subdivided those with microscopic invasion to invasion of vessels with a muscular wall as well as invasion to vessels more than 1cm from the primary tumor, both of which were independent predictors or recurrence and worse survival. Keeping all this in mind, although not a formal contraindication, resection of high-risk patients with major vascular invasion is palliative in the majority of cases, however can offer significant benefit in certain highly selected patients.

PREOPERATIVE CONSIDERATIONS

CHRONIC LIVER DISEASE

The majority of patients with HCC seen at our institution have associated liver cirrhosis which presents a major challenge to treatment. There exists a spectrum of disease from no fibrosis to non-bridging fibrosis to frank cirrhosis with associated severe fibrosis/cirrhosis being an independent predictor of outcome after resection for HCC.[31] As the presence of underlying liver disease influences the survival duration of patients undergoing hepatic resection for HCC, this suggests that cirrhosis, hepatitis activity, or degree of fibrosis may predispose patients to multi-centric hepatocarcinogenesis by way of a field defect.[32, 33] In fact death due to HCC is rare in long-term survivors after resection in the absence of fibrosis or cirrhosis suggesting that late death due to HCC is a result of new primaries developing in a precancerous liver.[34] Unfortunately the preoperative sampling variability of fibrosis is a

significant limitation in the preoperative assessment of fibrosis with liver biopsy.[35] Patients with associated decompensated liver failure are more likely to die from progression of their liver disease than from HCC, thus treatment of this malignancy has to take into consideration the residual functioning liver reserve.

Our standard criteria for minor resection of HCC in patients with chronic liver disease are presented in Table 1. The presence of portal hypertension (PHT) does not preclude minor hepatic resection for HCC in our institution. Data looking at 66 Child-Pugh A patients with portal hypertension undergoing resection revealed similar overall 5yr survival (40%) as well as similar mortality, morbidity, and transfusion rates compared to a cohort without portal hypertension.[36] Similarly others have reproduced excellent results for Child-Pugh A patients with PHT undergoing resection for HCC with 5yr overall survival of 56%.[21] For those patients with liver disease requiring major liver resection, our selection criteria narrow and we also consider preoperative portal vein embolization.

PORTAL VEIN EMBOLIZATION

The development of significant postoperative liver failure after liver resection is the greatest determinant of postoperative mortality and morbidity in those patients with chronic liver disease and/or cirrhosis. Preoperative assessment of liver function has been accomplished by numerous methodologies varying according to geographic region as well as individual surgeon preference and familiarity in an effort to determine the functioning capacity of the future liver remnant (FLR) that will remain after resection. None have proven superior. As a result techniques have been developed to improve the function of the remaining liver parenchyma after resection.

The clinical observation that portal vein tumor infiltration results in ipsilateral hepatic atrophy and contralateral hepatic hypertrophy led to the first use of portal vein embolization in resection for HCC.[37] PVE reduces the risk of postoperative hepatic insufficiency by inducing atrophy of the embolized tumor-bearing lobe with compensatory hypertrophy of the nonembolized FLR. In patients who are candidates for major hepatectomy, the FLR size varies, and the safe minimal size for FLR is not well defined or universally accepted. Thus estimation of total liver volume (TLV) is necessary before major hepatic resection is considered which may result in a small FLR leading to postoperative liver failure. CT-volumetry has been shown to accurately assess the extent of liver resection.[38] FLR volume (which is not compromised by tumor) is directly measured by computed tomographic three-dimensional reconstruction. TLV is adequately calculated based on BSA as we have previously proven and validated.[39, 40] This method allows for a uniform comparison of FLR volume before resection with or without preoperative portal vein embolization. PVE is becoming standard of care in patients with extensive tumors requiring extended resections or with patients with chronic liver disease requiring standard lobectomy. PVE should be considered in patients whose FLR is estimated to be less than 40% of TLV.[38] In patients with chronic liver disease, the hypertrophy of the FLR induced by PVE decreases significantly the rate of postoperative complications.[41] Furthermore there is a considerable amount of data emerging regarding the significance of the degree of hypertrophy after PVE to predict postoperative outcome however the specific cutoff values

have not been universally accepted or defined. In our experience >5% hypertrophy after PVE is predictive of success however this has not been validated. Our standard criteria for major resection of HCC in patients with chronic liver disease are presented in Table 1. We do incorporate clinically relevant elevated portal pressure into our decision making for major resection in chronic liver disease. This is defined as either hepatic venous pressure gradient greater than 10 mm Hg, presence of esophageal varices, or splenomegaly with platelet count less than 100,000/mm. Others have found that clinically relevant portal hypertension in the presence abnormal liver function testing (i.e. elevated bilirubin) leads to significantly shortened survival as well as major postoperative morbidity due to decompensated liver failure.[42, 43] Furthermore we do not offer extended hepatectomy to patients with evidence of chronic liver disease for similar reasoning. In those patients with hepatocellular injury (i.e. AST elevations) from active hepatitis, we have found that treatment with interferon therapy in the interval weeks after PVE and before resection can be of significant benefit. For those patients without chronic liver disease in whom we anticipate extended right hepatectomy, we recommend embolization of segment 4 branches as well, as we have had improved post-PVE hypertrophy of segments 2/3 with this approach. Furthermore, because the main blood supply for HCC is the hepatic artery, PVE results in increased hepatic arterial flow and theoretic accelerated tumor growth. As such PVE can also be combined with trans-arterial chemo-embolization (TACE) for additional benefit as TACE eliminates the arterial blood supply to the tumor and embolizes potential arterio-portal shunts in cirrhotic livers that can attenuate the effects of PVE. This assumption is supported by previously reported data in which patients who undergo TACE before PVE have significantly increased FLR hypertrophy (>20%) as well as improved disease-free survival (up to 56%) than patients who underwent PVE alone.[44, 45] Such innovative measures allow broadening of typical surgical indications as well as increased safety of major hepatic resection.

Our group has recently reported results following right hepatectomy for HCC in patients undergoing PVE compared to non-PVE.[46] Excluding perioperative deaths, overall survival rates at 3 and 5 years were 82% and 72%, respectively, in the PVE group and 63% and 54%, respectively, in the non-PVE group, which were not statistically different. Similarly, disease-free survival (DFS) rates were not significantly different, with 3 and 5 year DFS of 56% and 56%, respectively, in the PVE group and 49% and 49%, respectively, in the non-PVE group. Furthermore the postoperative mortality and major morbidity rates were significantly higher in non-PVE than PVE group with the majority of the complications attributed to postoperative liver dysfunction. These results suggest that PVE increases the safety of major hepatectomy in patients with HCC without compromising long-term oncologic outcomes.

SYSTEMIC THERAPY

The use of multi-agent systemic chemotherapy in an effort to downstage large or locally advanced HCC to allow resection has been attempted as single-agent regimens have had limited responses.[47] Using PIAF (cisplatin, interferon, doxorubicin, and fluorouracil) in selected locally advanced HCC, 15 of 149 (10%) patients with advanced HCC were successfully downstaged, with 8 of these patients found to have complete pathological tumor

response.[48, 49] The 3-yr survival was 53% in those following surgical resection and a higher response to neoadjuvant chemotherapy was found in patients with less severe liver disease. Systemic therapy overall however has little net benefit in terms of overall or disease-free survival in the majority of patients with potentially resectable HCC. Newer biological agents have also not been found to increase the response rates in advanced HCC. Although, a recent multicenter trial found that Sorafenib, a small molecular inhibitor of several tyrosine protein kinases unique in targeting the Raf/Mek/Erk pathway (MAP Kinase pathway), was found to significantly improve overall survival and time to progression.[50] However none of these patients experienced significant response to allow resection. Overall some selected patients may benefit but the role of various combinations of systemic, regional, and subsequent resection remains to be elucidated in advanced high-risk HCC.

OPERATIVE CONSIDERATIONS

TECHNIQUE

Significant advances have been made in operative technique for major liver resection such that overall mortality has declined significantly over the past 2 decades. Methods such as low CVP anesthesia, portal inflow occlusion, vascular isolation, and numerous coagulating, dissecting, and stapling instrumentation have made excessive blood loss and the resulting need for transfusion with attendant decrease in long-term survival the exception rather than the rule. When discussing high-risk HCC, particularly large or multinodular cancers requiring extended resection in the presence of chronic liver disease additional maneuvers are necessary to perform safe surgery in these patients. The anterior approach without mobilization of the right lobe has been found to be associated with significantly less operative blood loss (8.3% vs. 28.3%) as well as significantly improved overall survival (68.1% vs. 22.6%) in a randomized controlled trial.[51] Interestingly however this trial did not find differences in disease-free survival (16% and 14%) suggesting that this approach leads to better perioperative outcome due to lower perioperative mortality but the long-term oncologic benefit being inconclusive. Our group has found that the liver hanging maneuver, initially described in 2001 by Belghiti, allows direct exposure, balanced countertraction, and controlled hemostasis and is our preferred approach to all high-risk HCC. [52, 53] This technique allows resection of intra- and extrahepatic RUQ tumors, it allows total vascular exclusion after parenchymal transaction, and other advanced techniques such as IVC resection and thrombectomy are more easily and safely performed.

CONCLUSION

There are an increasing number of patients with HCC that do not meet traditional criteria for standard curative therapies due to historical poor outcomes. These oncologically high-risk patients having either large tumors, multinodular disease, or major vascular invasion can still be offered aggressive surgical therapy with acceptable outcomes in selected patients. This requires adequate preoperative evaluation as well as multidisciplinary postoperative care provided in a major hepatobiliary center that can offer modern surgical care for the patient affected by HCC.

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Table 1

MDACC Criteria for Resection in Chronic Liver Disease

Minor Resection:
Child-Pugh A
Normal Liver Function Tests (Bilirubin ≤ 1.0 mg%)
Absence of Ascites
Platelets > 100,000/mm
Major Resection:
Criteria for Minor Resection +
Absence of Portal Hypertension
Portal Vein Embolization (PVE) for FLR <40%