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A Review of Resection and Surgical Ablation for Primary and Secondary Liver Cancers

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Abstract

The surgical management of primary and secondary liver tumors is constantly evolving. Patient selection, particularly with regard to determining resectability, is vital to the success of programs directed toward invasive treatments of liver tumors. Particular attention should be paid toward determining whether patients are best served with surgical resection or ablative therapies. A multidisciplinary approach is necessary to provide optimal care to patients with liver malignancy.

Keywords
- liver resection
- liver ablation
- liver-directed therapy
- surgery
- hepatocellular carcinoma
- liver metastases

The surgical management of liver tumors is an increasingly complex topic that is difficult to cover in any summary article. In this article, we aim to define main principles behind determining the appropriate surgical approach—including the decision-making process for choosing parenchymal resection versus ablation, either percutaneous or laparoscopic—and consider nuances of anatomy, technique, patient selection, and biology. Ultimately, strong collaboration between surgeons, interventional radiologists, and other multidisciplinary colleagues should be the mainstay of treatment for patients with primary or secondary liver cancers.

Defining Resectability

While the resectability of liver tumors is determined by anatomic considerations and hepatic function, the safety and appropriateness of resection is determined by patient fitness for surgery, performance status, underlying liver disease, and the expected oncologic or palliative benefit of any proposed procedure.[1] In all circumstances, patient considerations take precedent, sometimes making non-operative treatment of an otherwise resectable liver tumor the best treatment option.

Anatomy and Terminology

Anatomic considerations require an understanding of the segments of the liver, which are each supplied by inflow from the portal vein and hepatic artery, have their venous outflow into the hepatic veins, and their biliary drainage through the hepatic radicals. The most definitive description of the liver and its segmental anatomy was described by Couinaud in 1954.[2] He described the segments of the liver based on their relationship with the bifurcation of the portal vein and their relationship with the three hepatic veins (left, middle, and right). In the years following Couinaud, surgeons identified discrepancies and imprecision in the terminology used to describe liver resections, resulting from the simultaneous use of objective internal descriptors of anatomy (relationship with portal vein, hepatic vein, bile duct, etc.) and somewhat more subjective descriptions and eponymous terminology used to describe liver surface anatomy. In 1998, the International Hepato-Pancreatico-Biliary Association developed the Brisbane classification to resolve these discrepancies and this now serves as standardized terminology that should be used when describing or reporting resections.[3] Updates were recently made to the Brisbane classification (2020), to define subsegmental resections.[4]

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Functional Considerations

The Future Liver Remnant

In pre-operative planning, the surgeon first determines which segments or non-anatomic portions of the liver will be resected to achieve adequate oncologic resection, usually based on a goal of microscopically negative margins. The surgeon then evaluates whether an adequate future liver remnant (FLR)—the liver that will remain in situ following resection—exists. The FLR is of critical significance, as its volume and quality are predictive of the patient's risk of post-hepatectomy liver failure (PHLF), which is the leading cause of mortality following liver resection.[5] For patients with normal liver function, a FLR of 20% is the minimum acceptable FLR[6]; however, centers and providers may vary their cutoffs between 20 and 30%. Patients with decreased liver function—for example, patients with fibrosis or chemotherapy-induced liver injury—typically are held to a minimum FLR of 30%. Certain patients with Child-Pugh Class A cirrhosis may be candidates for resection if they have preserved liver function and a FLR of >40%.[7,8]

Calculation of the FLR

Assessment of FLR is undertaken using volumetric calculations and functional calculations. Volumetric assessments are based on CT- or MRI-guided calculations of body surface area, while functional assessments are performed using technetium-labeled mebrofenin (hepatobiliary scintigraphy), indocyanine green clearance, or LiMAx.[9,10] A combined assessment of both volume and function is more predictive of PHLF than is volumetric assessment alone.[11] In practice in the United States, most providers will clinically screen for concerns of function but largely rely on volumetric assessments, although, for patients with known diminished liver function, the combination of volumetric and functional tests should be strongly considered.[12]

Patients with Inadequate FLR

Diminished liver function is common in patients planned for liver resection—this is usually related to the indication for resection (cirrhosis and hepatocellular carcinoma [HCC] or prior chemotherapy for metastatic tumors, etc.). Patients with HCC have underlying cirrhosis and may have been pretreated with transarterial radioembolization (TARE) and yttrium-90 (Y-90) radioembolization, both of which are associated with minor decrements in liver function—TARE with radiation-induced hepatotoxicity and Y-90 with elevated bilirubin and ascites in select cases with poor outcomes.[13–16] For patients with metastatic disease, most have received chemotherapy. The most common chemotherapy regimens used for colon cancer are known to be hepatotoxic: oxaliplatin may result in steatohepatitis and sinusoidal injury ("blue liver"),[17,18] while irinotecan is associated with steatosis and steatohepatitis that has been associated with increased morbidity following major hepatectomy.[19,20]

Management of Inadequate FLR

In patients for whom the planned resection leaves an inadequate FLR, the FLR can be increased with techniques to stimulate hypertrophy of the remnant liver. Portal vein embolization (PVE) has been used to achieve increases in FLR to an acceptable volume for resection. Yttrium-90 (Y-90) has also been used to increase the FLR by using Y-90 sectionectomy techniques.[21] In some centers, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is done; however, this procedure is performed only at experienced centers due to high morbidity and mortality. To assess the success of these techniques in liver hypertrophy, the liver volume and growth rate are assessed following the procedure. Adequate hypertrophy of the anticipated remnant liver is measured by calculating the kinetic growth rate (KGR), a simple assessment of the increase in volume per unit of time.[22] A rate of >2% increase in volume per week following PVE is considered encouraging that the underlying liver is healthy enough to support regeneration, increase to a sufficient FLR, and could tolerate aggressive resection with a lower likelihood of PHLF. KGR is typically measured at 1 month post-intervention; any additional growth is less likely at or beyond 8 weeks following the intervention. The importance of the KGR is its applicability to patients with or without liver dysfunction. Importantly, patients with biliary obstruction should undergo biliary decompression prior to attempting procedures to induce liver hypertrophy; in prior studies, PVE has not been associated with significantly increased rates of post-procedural biliary or infectious complications when done at high volume centers, although cholangitis and related sepsis are not uncommon.[23] Patients may be at increased risk for post-procedural complications and should be carefully monitored or followed up. In addition, KGR may be reduced or otherwise affected by underlying liver dysfunction, age, etc.

The Decision-Making Process

When considering the approach to a liver procedure, be it surgery versus ablation or which ablation approach to take, the primary technical considerations must include pathology, tumor location, tumor size, and predicted FLR. Patient-specific factors are important but are discussed in the final section. This section will focus on reasons to choose resection or ablation and how to approach using percutaneous or surgical ablation. The details of ablation—settings, microwave versus radiofrequency, etc.—are discussed elsewhere in this issue.

Decision-Making: Ablation versus Resection

Tumor Location

Ablation is generally preferred for tumors where resection would result in substantial parenchymal loss, either from a standpoint of surgical risk and adequate FLR or from a standpoint of parenchymal preservation for pathologies where repeat ablations or resections may be needed for recurrent disease. One example of this is colorectal liver metastases (CRLM), where patients have excellent survival but fairly high recurrence rates (50% at 5 years) that might require additional interventions.[24] Similarly, a patient with cirrhosis and a tumor near the right and middle hepatic veins is better served by ablation than extended hepatectomy. Subcapsular or perivascular and peribiliary locations may be associated with either inadequate or incomplete burns, in which case surgical resection may offer improved outcomes.[25,26]

Tumor Size

Tumor size as a selection criterion for ablation versus resection is subjective, as large tumors can successfully be treated with appropriate ablation techniques including the selection of the probe, number of probes, probe placement within the tumor, and probe settings (wattage and duration of burn). Although there are reports of successful treatments of large tumors, most proceduralists will agree that local treatment failure rates may increase when tumors larger than 3 cm are ablated.[27,28]

Outcomes

Heterogeneity across studies and non-standardized reporting make retrospective trials difficult to compare outcomes of ablation versus resection. In part, this is difficult because surgical resection allows evaluation of pathology while ablation does not. Isolated studies can be used to compare specific clinical outcomes, as demonstrated by a 2021 multi-institutional study from South Korea, which demonstrated that liver resection resulted in improved rates of local tumor control for lesions known to be challenging to treat with ablation, particularly for RFA as reported in this case series, including subcapsular tumors, perivascular tumors, and tumors near adjacent organs.[26] To date, a lone randomized trial, COLLISION, has been initiated to compare resection versus ablation, with results expected soon.[29] Non-randomized data have been released regularly, including a recent report of the MAVERRIC trial, which demonstrated non-inferior survival with lower morbidity and fewer retreatments for microwave ablation (MWA) when compared with resection for CRLM.[30] Both treatments are safe and can be effective, but continued reporting from prospective trials and results from randomized studies are needed to better understand long-term local recurrence or failure rates.

Decision-Making: Percutaneous Ablation versus Surgical Ablation

Location

Tumors not easily or safely amenable to percutaneous ablation—for example, tumors high on the dome of the liver near the diaphragm or near other organs like the stomach or heart—are generally easily addressed using surgical approaches. Intraoperative techniques to increase access to these locations include carbon dioxide insufflation of the abdomen to increase room between the liver and the diaphragm, adjusting the patient's positioning during the procedure, direct manipulation of adjacent tissues, and mobilizing the triangular and coronary ligaments of the liver to gain easier access to tumors or protect other structures.[31] While hydrodissection and other maneuvers are commonly used to increase the safety of percutaneous ablation, they may add unnecessary complexity to a case that could be performed surgically. Surgical ablation—either minimally invasive (mostly laparoscopic) or "open" (via laparotomy)—does have the clear disadvantage of incisions, which are minimized with minimally invasive surgery with a trade-off of the patient needing to be able to tolerate abdominal insufflation with CO_2. Our group prefers laparoscopic ablation wherever possible, during which all segments of the liver are easily accessible and treatable during a single outpatient procedure. Patients with significant cirrhosis with poor liver function and/or ascites are generally poor candidates for surgery but may be able to tolerate a percutaneous procedure. Other considerations for patients include prior intra-abdominal operations leading to a significant burden of intra-abdominal adhesions—these may render percutaneous maneuvers more difficult to achieve safely. Our group has reported excellent minimally invasive success rates and long-term outcomes for surgical ablations performed where the lesion was deemed inaccessible percutaneously.[32] Central tumors within 1 cm of the biliary hilum are not amenable to ablation regardless of the approach, due to hilar stricture or central vascular injury. Notably, some groups have reported improved outcomes with surgical ablations for tumors in locations near major vascular structures.[33,34]

Tumor Size

Tumor size is typically not a major consideration when determining whether percutaneous versus surgical ablation is preferred. If there is concern about the safety of providing an adequate burn due to size or location percutaneously, surgical ablation should strongly be considered if any of the maneuvers described above can improve safety in delivering a treatment of a sufficient effect size. Increasing tumor size is often cited as a risk factor for recurrence, although the ablation zone margin may be a better measure of recurrence risk instead of initial tumor size.[25,35]

Outcomes

No randomized studies exist comparing percutaneous and surgical ablation. Ablation devices and probes are similar regardless of the approach; so, comparable outcomes could be achieved assuming equivalent skill and safe access to the tumor. Tumor size and ablation margin—frequently determined by cross-sectional imaging obtained a few weeks after the procedure—have been identified as significant factors in incomplete ablation and local recurrence, which historically has been reported to be as low as 4% with MWA.[35,36] Retrospective analyses and meta-analyses have regularly evaluated this clinical question. One recent meta-analyses of 740 patients from 10 retrospective studies of ablation in HCC demonstrated significantly lower tumor recurrence rates and greater 5-year disease-free survival in the surgical ablation group despite larger tumor sizes in this group.[37] Heterogeneity across studies and non-standardized reporting make retrospective trials difficult to compare.

Cost

The lower cost of treatment is often cited in support of percutaneous ablation, although some cost data has been accompanied by higher failure rates with this approach.[38] Additionally, select literature has compared percutaneous approaches to open—not minimally invasive—surgical ablations, with obvious between-group differences for those cohorts.[39] Our group performs laparoscopic MWA on an outpatient basis, significantly reducing the cost differential between surgical and percutaneous approaches with low morbidity. One final point is that a substantial degree of ablation literature incorporates RFA; surgeons and interventional radiologists must reliably report their outcomes to ensure that prior studies and opinions remain supported by data now that MWA has supplanted RFA as the primary hepatic ablation modality.

Decision-Making: Using Tumor Biology to Determine When Surgical Intervention Is Appropriate

Surgery historically was the mainstay of oncologic treatment prior to the introductions of anti-neoplastic drugs and radiation. As a result, there is a lack of prospective data that has demonstrated that surgery is superior to other treatment modalities. In fact, over time, surgical trials have trended toward less and less surgery (e.g., sentinel lymph node biopsy rather than axillary dissection in breast cancer, or wide local excision rather than amputation for extremity sarcoma). Nonetheless, surgery offers the optimal chance for cure for primary, secondary, or even recurrent disease. Surgery is not universally offered, however, based on several variables including an assessment of resectability (see above) and the underlying pathology- and patient-specific factors outlined below.

Hepatocellular Carcinoma

The timing and choice of specific interventions in the management of HCC is best determined in a multidisciplinary fashion. HCC arising from a background of hepatitis and/or cirrhosis should be considered a sign of a “field defect” where the entire liver is at-risk of tumorigenesis; localized treatments to known existing cancers may do very little to influence the risk of cancer arising elsewhere in the same liver. This is why transplantation has taken on such a prominent role, as it resets this field defect. Although liver transplant has not been compared with hepatic resection prospectively, retrospective studies have clearly demonstrated improved recurrence-free survival and overall survival relative to outcomes after hepatic resection.[40–42] As a result, the timing and choice of liver-directed therapy for cirrhotic patients is often planned around whether or not the patient is a transplant candidate. Transplant candidacy in the United States is quite complex and is beyond the scope of this review but, in general, candidacy for transplant is based on clinical severity of disease and exception points for malignancy. Exception points are used because the Model for End-State Liver Disease-sodium (MELD-Na) score for clinical severity may underestimate short-term mortality in patients with a known malignancy (HCC or intrahepatic cholangiocarcinoma).[43,44] However, this exception point system is not without controversy and continues to evolve. Clinical severity is often defined using the MELD-Na score and candidacy is often defined using the Milan criteria.[45–47] For patients within Milan criteria (one tumor <5 cm, or three tumors <3 cm) and otherwise eligible for transplant, these patients will often be directed to therapies that can serve as a “bridge to transplant,” meaning these treatments will treat existing lesions or at least delay progression and allow for the patient to get listed for and wait for a transplant. These “bridge” treatment options frequently include ablation, selective radioembolization, or TACE. Surgical resection can be considered for all patients but most often for patients outside of Milan criteria or otherwise ineligible for transplant. However, resection is generally only viable for patients with liver function no worse than Child-Pugh classification A due to expected postoperative morbidity.[48–51] The complexity of decision-making for HCC is ultimately beyond the scope of this article but is well-summarized by consensus guidelines and algorithms including the often-used Barcelona Clinic Liver Cancer prognosis and treatment strategy.[52]

Importantly, this field-defect perspective does not apply to cases of HCC arising from a non-cirrhotic liver, which has an estimated incidence of roughly 20% of all cases of HCC.[53,54] In these instances, hepatic resection is the treatment of choice for localized resectable disease and can have a substantial positive impact on recurrence rates and survival.[55]

Hilar Cholangiocarcinoma

To some extent, the treatment of hilar cholangiocarcinoma has changed greatly in the past several years. Resection remains the standard-of-care but is accompanied by major complications due to the significant extent of hepatic resection often required and by high recurrence rates ($>75\%$).[56] The exact sequence of therapies can become complex. Patients with biliary obstruction should undergo decompression of, at minimum, whatever liver segments can be spared after a margin-negative resection. The exact method of decompression—percutaneous versus endoscopic—is a topic of great debate that ultimately seems to have minimal long-term consequences.[57] Patients may need preoperative strategies to improve their FLR, and neoadjuvant systemic therapy may be considered while a patient receives all of these interventions awaiting the ability to undergo surgery.[58,59] Finally, liver transplantation after strict protocols of staging and neoadjuvant treatments has recently demonstrated acceptable long-term outcomes for patients with small but unresectable disease.[60,61]

Intrahepatic Cholangiocarcinoma

Upfront resection is preferred for intrahepatic cholangiocarcinoma, as current standard-of-care chemotherapy for intrahepatic cholangiocarcinoma including immunotherapy has a limited response rate of around 27%.[62] These tumors can be asymptomatic and frequently present as large and unresectable, for which neoadjuvant therapy can be used in an attempt to convert a patient to resectability.[63]

Colorectal Liver Metastases

The timing and sequence of resection and systemic chemotherapy for patients with CRLM can vary significantly on a case-by-case basis taking into account the sequence of presentation (synchronous or metachronous metastases), the burden of disease, prior treatments, disease-free intervals, and tumor biology and tumor genetics.

Emerging data have demonstrated that resection of the primary colorectal tumor is not necessary in Stage IV disease if the patient does not have intestinal obstructive symptoms, although this depends on whether the burden of metastatic disease is resectable or unresectable.[64,65] For cases with resectable metastatic disease, staged or simultaneous approaches to primary and metastasis resection in combination with systemic chemotherapy are acceptable.[66]

Patients with CRLM are at risk of progression of disease and liver failure, a major cause of mortality for these patients.[67,68] For both of these reasons, aggressive liver-directed therapy is often recommended, with substantial debate about the utility of chemotherapy around or after these procedures for patients with liver-only metastases.[69,70] Both resection and ablation are appropriate treatment options for CRLM. Patients with liver and lung metastases are eligible for local interventions with curative-intent, although a low proportion of patients actually complete the course of initially intended curative-intent procedures.[71]

Other Less Common Pathologies

In general, many secondary liver cancers represent Stage IV disease best treated by systemic chemotherapy without any anticipated benefit from the morbidity of hepatic resection. However, there are certain pathologies that are beyond the scope of this review where hepatic resection may offer survival relative to what can be gained from systemic therapy alone. Specific areas lacking a consensus include the management of metastatic neuroendocrine tumors, gastrointestinal stromal tumors, and isolated metastases from breast cancer, gynecologic cancers, and melanoma, among others.

Perioperative Considerations

Preoperative Preparation

Preoperative planning involves an assessment of resectability (see above) and an assessment of preoperative medical fitness for surgery. Specific medical conditions relevant in pre-operative assessment include underlying liver disease (as discussed above) and underlying cardiopulmonary disease.[72] Additionally, frailty is becoming increasingly relevant as a predictor of adverse outcomes in the growing population of elderly patients with cancer and should be addressed preoperatively.[73] The proposed extent of the procedure plays a significant role in patient selection. In general, all patients need to be able to tolerate general anesthesia and should have an extensive preoperative discussion about possible risks of surgery including their medical fitness to tolerate postoperative complications (see below). Anticoagulants are discontinued in advance of surgery, as are chemotherapeutic or other immunosuppressive medications, usually around 4 weeks before surgery depending on the drug.

Intraoperative Principles

Intraoperative success relies on adequate preoperative planning. On or before the day of surgery, the surgical plan should be communicated to the anesthetists to make plans for intraoperative monitoring. Historically, low central venous pressure (CVP) was recommended to reduce intraoperative blood loss by reducing intrahepatic venous pressure.[74,75] However, select data including recent randomized trials have failed to support superiority of this approach over goal directed therapy or intraoperative visual or ultrasound-based assessment of volume status by the surgeon, leading to a movement away from invasive CVP monitoring without any noted consequence in meaningful clinical outcomes.[76–78] Alternative metrics such as stroke volume variation (SVV) can be used, particularly for minimally invasive surgery where CO_2 insufflation of the abdomen can alter cardiac preload.[79] Techniques of parenchymal transection and inflow control are important but are beyond the scope of this review. Hemodynamic monitoring during MWA is less critical, although generous fluid resuscitation should be considered to prevent ablation-induced kidney injury.[80,81]

Postoperative Considerations

Postoperatively, care pathways and protocols such as those supported by the Enhanced Recovery After Surgery (ERAS) Society have taken the forefront in the perioperative management of patients undergoing major abdominal surgery including hepatectomies.[82] Morbidity after hepatic surgery can be as high as 40%, with common complications including ileus, bleeding, and bile leak, and many patients experience postoperative fluid shifts that may be associated with temporary kidney injury and electrolyte disturbances.[83–85] The most concerning postoperative complication is PHLF, defined as the inability of the liver remnant to maintain its synthetic, excretory, and detoxifying functions on or after postoperative day 5 using increased INR and bilirubin levels.[86] The incidence of PHLF varies substantially based on procedure- and patient-specific variables but remains the predominant cause of post-hepatectomy mortality, which can range from 1 to 10% depending on the extent of surgery among other variables.[84,87]

Conflict of Interest
The authors declare no conflicts of interest relevant to the material presented herein.

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