Review Article on Current Management of Upper Gastrointestinal Malignancies

Surgical approach to achieve R0 resections in primary and metastatic liver tumors: a literature review

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Background and Objective: Primary and metastatic liver tumors are a significant cause of mortality worldwide. Regardless of the etiology of the tumor, macro- and microscopically clear margins (R0) while preserving adequate function of the remaining organ are the main goals after liver resections. However, technically challenging procedures are required to achieve R0 resection. Currently, there is no consensus of which should be the ideal minimal safety margin for liver tumor resections, with contrasting reports in regards of safety, tumor recurrence and overall outcomes following R0. Therefore, we aim to review current worldwide surgical practices to achieve R0 resections for primary and metastatic liver tumors in challenging surgical techniques and their reported outcomes.

Methods: PubMed database, Google Scholar, and OVID Medline were searched for peer-reviewed original articles related to surgical techniques performed to achieve R0 resections in the setting of primary and/or metastatic liver tumors. An up-to-date review of English-language articles published between 2015 to July 2022 was performed.

Key Content and Findings: Primary and metastatic liver tumors can be effectively treated using hepatic resection. Current literature highlights that tumors involving major vascular structures are not uncommon. Surgical advances have allowed for vascular control techniques, as well as vascular resections to be performed in a feasible and safe manner to achieve R0 resections. Complex resections combining surgical techniques can be performed in certain population after a detailed evaluation. Liver transplantation (LT) have been used with varying degrees of success for treatment of patients with hepatocellular carcinoma, cholangiocarcinoma (CCA), colorectal liver metastases (CRLM), non-resectable CRLM and metastatic neuroendocrine tumors.

Conclusions: Safety and feasibility of R0 resections have been reported for multiple techniques. Technical complexity should not be a limitation to achieve or pursue R0 tumor resection. However, there has to be a balance between patient risk/benefit in attempting R0 resections. Adequate training of surgeons on implementation of complex techniques, as well as transplant oncology techniques applied to hepato-pancreato-biliary (HPB) surgery represents as a promising path to improve short and long-term outcomes for liver-related oncology patients.

Keywords: Liver malignancies; resection margins; hepatic resections; complex surgical techniques; transplant oncology

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Introduction

Liver cancer is one of the most common cancers around the globe and has the second-highest cancer mortality rate in the world (1). Primary liver tumors, including hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (CCA), represents the majority (>95%) of all primary malignant liver tumors (2). On the other hand, metastatic liver tumors originate in other organs and spread to the liver, generally through hematogenous routes due to the rich vascularization of the liver. According to the origin site, tumor biology and behavior, liver metastasis can be divided amongst others in colorectal liver metastases (CRLM), metastases from endocrine tumors, and nonendocrine/noncolorectal liver metastasis (3). Although, each subtype differs in pathogenesis, tumor behavior, and prognosis, surgical treatment modalities have become the gold standard for curative treatment for liver malignancies (3). Characterization of surgical treatment available for liver malignancies can be discussed by liver tumor etiology/disease, or by technique. As the scope of this review, we find it best to present the current discussion by technique, with a particular focus in current strategies to achieve R0 resections in challenging surgical procedures. Anatomical and non-anatomical liver resections are vastly discussed elsewhere (4-7). Therefore, are not included in the present review.

Regardless of the etiology of the tumor, and following the principles of surgical oncology, achieving macro- and microscopically clear margins (R0), while preserving adequate function of the remaining organ, are the main goal after liver resections (2,7). However, in order to achieve R0 resections very often technically challenging approaches are required. Alternatively, R1 resections-defined as those with clear macroscopic margins, but with evidence of microscopic positive margins (8) have been reported (9). In addition, advances in different systemic treatments have allowed for an expanded patient population with more advanced and complex disease to be offered aggressive surgical treatment (2). Hence, pushing the safety limits to a higher extent and imposing an even higher challenge for the hepato-pancreato-biliary (HPB) surgeon.

Nevertheless, there is no consensus of which should be the ideal minimal safety margin for liver tumor resections (3), with contrasting reports in regards of safety, tumor recurrence and overall outcomes following R0 resections. Therefore, we aim to review current worldwide surgical practices to achieve R0 resections for primary and metastatic liver tumors and their subsequent reported outcomes in particularly challenging surgical techniques (*Table 1*). We present this article in accordance with the Narrative Review reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-778/rc).

Methods

PubMed database, Google Scholar, and OVID Medline were searched during June 1st to July 20th, 2022 for peer-reviewed original articles related to surgical techniques performed to achieve R0 resections in the setting of primary and/or metastatic liver tumors. In order to present an up-to-date review, articles published between 2015 to July 2022 were preferentially included. The following search terms were used: Resection margin primary liver tumor, R0 resection primary liver tumor, R0 resection metastatic liver tumor, vascular control, In situ liver resection, ante-situm liver resection, vascular involvement liver tumor R0 resection, surgical technique liver tumor resection. English-language literature including retrospective/prospective studies, clinical trials, single/multicenter cohorts, case reports, as well as systematic reviews and meta-analysis were reviewed. The search strategy summary is described in *Table 2*.

Tumors involving vascular inflow/outflow

Hepatic resection can be complicated by tumors involving the major vascular structures of the liver affecting the inflow (hilar structures: portal vein, hepatic artery), outflow [inferior vena cava (IVC) and/or hepatic veins], or in some cases, both. The degree of invasion of vascular structures varies according to tumor microenvironment, histologic and clinicopathological characteristics, and can involve the vascular wall or present as intravascular extension (tumor thrombosis) (10). Therefore, achieving an R0 resection becomes even more technically challenging. This requires a careful balance between aggressive surgical techniques and consideration of patient safety to minimize risks of bleeding and embolic complications (11-13). Although previously considered unresectable, advances in the surgical field have allowed surgical management of liver tumors with vascular invasion. Vascular reconstructions are crucial in these cases as they allow for preservation of adequate liver function postoperatively and reduction of postoperative complications. Such procedures require careful preoperative

Table 1 Summary of available surgical approaches to achieve R0 resections for primary and metastatic liver tumors in particularly challenging surgical techniques

Structure/region involved	Suitable subjects	Required conditions	Advantages	Shortcomings	Precautions	Key points/ recommendations
Tumors involving vascular inflow/outflow						
Inflow: vascular resection and reconstruction of hilar structures						
Portal vein	Patients with tumors involving the portal vein system	Primary or metastatic liver tumors involving the portal vein system	Graft interposition not necessary unless portal vein resection >6 cm; thrombectomy followed by resection is a feasible option for complex cases	Extent of tumor thrombosis and spread dictates treatment options; metastatic liver tumors often present with microscopic invasion of the portal vein; complex procedure with limited research on outcomes	Risk of intraoperative thrombus rupture	Tumors which were previously deemed unresectable due to involvement of the portal vein can now be operated on using advanced reconstruction techniques; further research is needed to guide individualized treatment options for patients
Hepatic artery resection	Patients with tumors involving the hepatic artery	Preferably performed when liver parenchyma transection is completed, but can be done before if necessary	Can treat tumors involving the hepatic artery, including HCC and CCA	High risk procedure with limited research on outcomes	Risk of derangement of the anastomosis and remnant liver ischemia	Hepatic artery resection and reconstruction remains controversial with better understanding of best practices needed
Outflow: vascular resection and reconstruction of IVC and/or hepatic veins						
IVC	Patients with tumors involving the IVC or hepatocaval confluence	Control of suprahepatic and infrahepatic IVC with vascular clamping, resection, and reconstruction	Many different techniques available to approach IVC resections; peritoneal patches have been safe and effective for previously unresectable reconstruction cases	No current consensus on which technique to use for suprahepatic IVC control	High risk of vascular complications	Variety of techniques used to treat complex tumors involving the IVC with further research needed to determine risks/benefits
Hepatic veins	Patients with tumors invading large hepatic veins, especially in the posteromedial portion of the liver such as intrahepatic CCA	Control of suprahepatic and infrahepatic IVC with vascular clamping, resection, and reconstruction if necessary	Help limit postoperative complications related to lack of collateral circulation	Requires careful consideration of individualized patient anatomy	Risk of intraoperative bleeding	Preoperative evaluation is critical to determining the need for hepatic vein reconstruction, since it is not always necessary if there is adequate collateral circulation

Table 1 (*continued*)

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Structure/region involved	Suitable subjects	Required conditions	Advantages	Shortcomings	Precautions	Key points/ recommendations
Ex-vivo liver resections	Patients with complex liver tumors	Proficiency with transplant oncology techniques	Access anatomically difficult tumors; high R0 resection rates; can be used for a variety of liver tumors	High rates of tumor recurrence, morbidity, and mortality	Requires surgeon to be proficient in both transplant surgery and surgical oncology techniques	Merges transplant techniques with oncology principles in order to access anatomically difficult tumors
In-situ liver resections with hypothermic perfusion	Patients requiring complex vascular outflow reconstruction	Hypothermic perfusion	Can be used for long operations; has demonstrated effectiveness in complex cases of tumors invading major vascular structures	Longer operations carry more risk	Risk of ischemia and reperfusion injury	Hypothermic perfusion can be used to improve outcomes for complex vascular reconstruction cases
Ante-situ liver resections	Patients with otherwise unresectable liver tumors	Ante-situm liver positioning	Better access and exposure to the tumor; can be used with total vascular occlusion; allows for possibility of R0 resection	High rates of tumor recurrence and mortality; technically challenging procedure limited to high volume surgical centers	Complex vascular reconstruction procedure with high risk of complications	Improved access to tumor via an ante-situm approach comes at the cost of relatively poor outcomes
Additional techniques						
Staged resections	Patients with primary or metastatic liver tumors	Embolization of portal vein ipsilateral to tumor, followed by regeneration of contralateral lobe	Established technique that can be used for primary or metastatic tumors; improved R0 resection rates and long-term outcomes compared to simultaneous resections	Not as effective as transplantation for extensive CRLM; expected FLR varies based on preoperative liver function	Careful selection of patients required for progression to second stage	Staged resections can help improve the resectability of complex tumors
ALPPS procedure	All patients with complex tumors except the elderly and those with poor functional status	Liver mobilization with clearance of disease from the FLR and right portal vein ligation; after a brief 1–2 week interval to allow for FLR hypertrophy, the right bile duct, hepatic artery, and the right hepatic vein with or without the middle hepatic vein are ligated and divided	Improved progression to second stage of hepatectomy compared to PVE; increased FLR hypertrophy compared to PVE; can be used in combination with minimally invasive techniques	High morbidity and mortality rates; limited research on outcomes	Not recommended for elderly patients or those with poor functional status	ALPPS modifications have yielded improved R0 resection rates and expanded treatment options for patients with complex tumors

Table 1 (*continued*)

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Structure/region involved	Suitable subjects	Required conditions	Advantages	Shortcomings	Precautions	Key points/ recommendations
RAPID procedure	Patients with CRLM or unresectable HCC	Transplant the patient with a small auxiliary left liver graft (left lateral segment or left lobe) and ligation of right portal vein, followed by transplanted graft hypertrophy and subsequent second stage hepatectomy	Expanded donor pool for liver transplantation; predictive models being designed to evaluate prognosis	Increased risk of small-for-size syndrome; lack of prospective clinical trials evaluating safety and efficacy	Still an experimental technique requiring additional research	Expanded donor pool improves treatment options for patients with complex tumors
Liver transplant and oncology— "transplant oncology"	Patients with primary or metastatic liver tumors	Must meet required transplant criteria	Effectively cure cancer; gold standard for patients meeting requirements	Risk of rejection; long-term immunosuppression; lack of donors	Limited donor pool requires careful patient selection	Transplant oncology is an interdisciplinary field that combines surgical oncology and transplantation medicine to improve outcomes and quality of life for cancer patients

HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; IVC, inferior vena cava; CRLM, colorectal liver metastases; FLR, future liver remnant; PVE, portal vein embolization; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; RAPID, resection and partial liver segment transplantation with delayed total hepatectomy.

Table 2 The search strategy summary

Items	Specification
Date of search	June 1–July 20, 2022
Databases and other sources searched	PubMed, Google Scholar, and OVID Medline
Search terms used	Resection margin primary liver tumor, R0 resection primary liver tumor, R0 resection metastatic liver tumor, vascular control, In situ liver resection, ante-situm liver resection, vascular involvement liver tumor R0 resection, surgical technique liver tumor resection
Timeframe	2015–2022
Inclusion and exclusion criteria	Inclusion criteria: peer reviewed original articles, systematic reviews and meta-analysis, case reports, clinical trials, English language
	Exclusion criteria: Studies published before 2015 (unless deemed important for background), studies not reporting outcomes of R0 resections, reports of other abdominal metastasis only, reports of secondary resections-secondary surgery, other language
Selection process	Conducted by author PAV and ND. Consensus whether to include or exclude a study was made by all authors

planning, including volumetric assessments ensuing a future liver remnant (FLR) volume of ~40% when possible (14). Techniques achieving R0 resection and acceptable postoperative outcomes have been described for hepatectomies with vascular reconstructions including the portal vein (PV), hepatic artery, IVC, and hepatic veins, and are described below.

Inflow: *vascular resection and reconstruction of hilar structures*

PV system involvement can be seen with primary and metastatic liver tumors. If involvement is present and resection and reconstruction is needed, PV reconstructions are usually performed using end-to-end anastomosis with continuous suture and oblique cut of the vein to minimize size discrepancy or the standard main-to-left PV reconstruction with or without an interposed graft (15,16). The long extrahepatic course of the left PV allows for an easier resection and reconstruction when compared to the right PV shorter length (16). The use of graft interposition is usually not necessary unless the resected portion of the PV is significant (exceeding ~6 cm). In such cases, grafts using autologous (internal jugular, left renal, splenic, iliac or saphenous vein) or synthetic materials [ringed/not-ringed 10 mm polytetrafluoroethylene (PTFE) or polyethylenterephthalat (PTE)] can be used for reconstruction (16). Recently, Conticchio *et al.* reported the use of Rex-shunt for reconstruction of the left PV in patients with hepatic malignancies requiring right or extended right hepatectomies and resection of the bifurcation or main PV. The authors found the procedure to be feasible and reproducible, and conclude that it can be used to achieve R0 resections or in cases where the standard main-to-left PV reconstruction is not a suitable option (15).

In the presence of tumor thrombosis, consideration for surgical resection is usually based on its extension. Currently, Cheng's classification of PV tumor thrombosis and The Japanese Vp—PV invasion—classification of PV tumor thrombosis classification are widely used to determine the best surgical approach (17,18). For primary tumors, tumor thrombosis of the PV is usually seen in ~40% of HCC patients (17). Thrombectomy is usually the preferred treatment option, unless the tumor thrombus is strongly attached to the vessel's wall, in which PV resection is then required (17). When the PV tumor thrombus is located in the main PV, the bifurcation or the contralateral PV, performing a thrombectomy first, followed by liver resection has shown improved survival outcomes in patients with Cheng's III and IV classification (17). On the other hand, PV involvement with metastatic liver tumors, including CRLM and CCA, present mostly with microscopic tumor invasion affecting the intrahepatic PV, while macroscopic tumor thrombus in the portal branch are rarely seen (19,20). In these cases, vascular resection and reconstruction are needed to achieve R0 resections. Nevertheless, reports of outcomes after this challenging procedure in metastatic liver tumors are scarce.

Surgical techniques for hepatic artery resection and reconstruction due to tumor involvement are complex and their use is controversial (16). In order to maintain arterial blood flow to the remnant liver, and avoid derangement of the anastomosis, hepatic artery resection and reconstruction is preferably performed when liver parenchyma transection is completed (16). Nevertheless, this procedure can be performed prior or after transection based on a case-by-case level (16). Most commonly, strategies for arterial reconstruction include direct end-to-end anastomosis if possible, and vascular interposition grafts (saphenous vein, gonadal vein, splenic artery, radial artery or inferior mesenteric artery). Additional techniques include transposition of another artery by end-to-end anastomosis between a reversed splenic artery, left gastric or gastroduodenal artery and the hepatic artery stump (16). Lastly, in cases where all possible reconstruction techniques are not feasible, PV arterialization can be performed as a salvage procedure for dearterialized grafts (16,21). This technique has been particularly useful in cases where there is hepatic artery encasement by the tumor as well as CCA involving the bile duct and biliary confluence. Successful PV arterialization with achievement of R0 resection was recently reported as salvage inflow surgical technique in a 78-year-old woman with CCA originating from the cysto-choledocal junction (21). The group performed surgical resection of segments 4b/5 *en-bloc* with the gallbladder, biliary confluence and common bile duct. For PV arterialization, the right hepatic artery stump was mobilized to reach the portal plane and the anastomosis between the right hepatic artery and the right PV was completed using a termino-lateral interrupted suture. The patient recovered uneventfully and was discharged at postoperative day 10 (21). Nevertheless, available reports following this technique are scarce and more studies reporting short- and long-term outcomes after this approach are needed.

Outflow: vascular resection and reconstruction of IVC and/or hepatic veins

The adequate surgical approach for tumors invading the IVC will mostly depend on the degree and location of the obstruction by the tumor. Tumors involving the hepatocaval confluence require a more technically challenging procedure when compared to tumors with tangential infiltration of the IVC (16). Nonetheless, when facing these challenging cases, three important surgical steps must take place: (I) control of suprahepatic IVC, (II) control of infrahepatic IVC and (III) vascular clamping + vascular resection and reconstruction.

Generally, when the IVC segment affected by the tumor is below the hepatic veins, an abdominal incision will allow for control of the supra e infrahepatic IVC in a sufficient and safe manner. Control of the infrahepatic IVC is achieved above the confluence of the left renal vein. For suprahepatic IVC control a number of techniques have been described. Broadly, methods to expose the suprahepatic IVC include those in where the IVC is clamped in the abdominal cavity at the infradiaphragmatic/infrapericardial region, and those with IVC clamping performed in the thorax at the supradiaphragmatic region/intrapericardial IVC level (22,23). However, there is no current consensus on which technique ensures the safest approach to expose and clamp the suprahepatic IVC and that will probably depend on the location and size of the tumor. Full liver mobilization and ligation of the diaphragmatic veins bilaterally is generally adequate for less complex cases, with resection of the retrohepatic IVC usually performed *en-bloc* with the liver tumor (16). On the other hand, the thoracic approach is usually the preferred technique in cases with large tumors with a short intraabdominal suprahepatic IVC, tumor thrombosis of the retrohepatic IVC and/or hepatic veins, or when the tumor encase the hepatocaval confluence (22). In these cases, total hepatic vascular exclusion (THVE) with preserved liver remnant perfusion and standard THVE with or without venovenous bypasss and *in-situ* cold perfusion represents the only way to achieve total tumor resection (16,22,24-26). Despite being a challenging approach, available reports show evidence of its safety and feasibility when carefully performed (22,23,26,27). Although reports have shown feasibility of the procedure, THVE should be performed in cases with a detailed preoperative planning, interdisciplinary pre-operative assessment and availability of cardiovascular and thoracic surgeons if the supradiaphragmatic region/intrapericardial technique is being considered.

Recently, Tohyama *et al.* (22) described a transmediastinal, intrapericardial IVC approach for hepatectomy and resection of the hepatic confluence or tumor thrombectomy of the suprahepatic IVC performed in five patients. Indications for this procedure included an expected R0/R1 status after hepatectomy and tumor thrombectomy in HCC patients with tumor thrombus in the supra-hepatic IVC and in patients with liver tumors invading the hepatic vein confluence, or anticipation of an adequate residual liver volume to achieve appropriate liver function. In order to secure the supra-diaphragmatic intrapericardial IVC, the authors performed a vertical incision in the diaphragmatic pericardium towards the ventral side of the intrapericardial IVC. Adjacent vasculature was excluded when possible, and clamping of the preserved hepatic veins to prevent backflow from the residual liver was also performed. Optimal resection site was confirmed by transesophageal echocardiography, and after hemodynamic stability was confirmed, the ICV wall was resected. The nine-step detailed procedure is reported by the authors (22).

Reconstruction of the IVC can be performed by primary closure by a running suture in cases where the wall defect is ≤30% of the IVC circumference (16). Patch repair with autologous patches can be used as a measure to prevent stenosis, or in cases with larger defects and involvement up to 30% (16). Recent studies suggest that peritoneal patch represent a safe and effective option for venous reconstruction during hepatectomy for liver tumors, even allowing for reconstruction of cases deemed to be unresectable (28). Alternatives reconstruction options include the use of prosthetic replacement, particularly in cases with segmental resection of the IVC distant to the hepatocaval confluence or as an alternative to patch repair in extensive resections (>60% of IVC diameter) (16). PTFE grafts and 18–20-mm ringed Gore-Tex grafts are usually recommended (16). In addition, performing a caval shift procedure is suggested to avoid infection of the synthetic graft when performing these particular cases (16).

Hepatic veins can be infiltrated by tumors located medially and in the posterior portion of the liver, as seen in intrahepatic CCA (29,30). In these cases, an approach of suprahepatic and/or infrahepatic IVC control as described above are also usually required. If collateral circulation is present, reconstruction is not necessary for hepatic vein tributaries that demonstrated limited contribution to venous drainage during preoperative evaluation. However, in cases where no collateral circulation—large inferior hepatic vein draining segment VI—reconstruction of the right hepatic vein is crucial to avoid congestion in segments VI and VII and prevent detrimental postoperative complications (30). As observed during living donor liver transplantation (LDLT), it is recommended to perform reconstruction of vascular outflow when large tributaries (>4 mm) are present (31). Commonly used grafts for hepatic vein reconstruction include autologous grafts, cryopreserved or prosthetic vascular grafts (30).

In particular cases, primary or metastatic tumors involving outflow and/or inflow structures present with such complexity that the abovementioned techniques become unfeasible. However, surgical advances and the possibility to merge techniques across surgical disciplines have open the door to provide alternative treatment options for these complex patients. Such is the case of *ex-vivo*, *in-situ* and *ante-situ* liver resections.

Ex-vivo liver resections

Ex-vivo liver resection is a complex procedure that involves complete hepatectomy, liver resection outside of the body, and auto-transplantation of the remnant liver. This procedure merges transplant techniques with oncology principles in order to access anatomically difficult tumors and improve treatment options for complex patients (32). Currently, there are no guidelines for indications and technical considerations for these techniques. Therefore, its use is based on a case-by-case strict approach, and include patients with malignant and non-malignant tumors (33). A recent meta-analysis evaluated outcomes after *ex-vivo* resections in 29 studies with reports of 215 patients (33). As expected, R0 resections rate was 100%. Overall mortality rate at 90-day was 11.6%, and mean overall survival was 55.8%, with both parameters being lower in patients undergoing *ex-vivo* resections for malignant tumors that those with non-malignant tumors, in alignment with previous reports (34). Importantly, in patients undergoing *ex-vivo* resections for malignant tumors, there was a significant relationship between the maximum tumor size and postoperative liver failure and 90-day mortality rate (33). Feasibility of the technique has been also reported in smaller series including its use for advanced CCA (35) and sarcoma-like tumors (36) with acceptable immediate liver function. However, high rate of tumor recurrence, morbidity and mortality have been reported (32-36).

In-situ liver resections with hypothermic perfusion

When prolonged operative time is expected due to complex vascular outflow reconstruction, the use of hypothermic perfusion appears as a promising technique to reduce the risk of ischemia and reperfusion injury (37). The procedure includes adequate tumor location by direct ultrasound and hepatic transection; preparation of the graft to be use for reconstruction; total hepatic vascular occlusion, tumor resection, graft placement, and hepatic reperfusion (37). Organo-protective and cell-protective solutions such as the histidine-tryptophan-ketoglutarate-Brettschneider or University of Wisconsin solution are the preferred solutions for perfusion of the liver (16). Feasibility of this procedure have been reported previously in cases requiring vascular reconstruction and resection of tumors with complete invasion of the hepatic veins (37), as well in even more complex cases including tumor invasion of the IVC and hepatic veins with concomitant use of extracorporeal membrane oxygenation (38).

Ante-situ liver resections

This complex procedure involves complete dissection of the hepatic venous confluence from the IVC, as well as complete detachment of the liver from the IVC in order to rotate the liver ante-situm allowing for better access and exposure to the tumor (16). The liver is then packed in sterile ice ante-situm followed by perfusion of the PV with cold preservation solutions (16). Ante-situm liver resections are performed with or without venovenous bypass, with the latter being the preferred method if the patient's hemodynamic status allows it. Ye *et al.* (39) published a case series of 23 patients with unresectable HCC who underwent ante-situm resections and reported 1-, 3-, 5-, and 10-year survival rates of 65.2%, 56.5%, 50.9%, and 20.3%, respectively. Nevertheless, reports of poor outcomes including high rate of tumor recurrence and high mortality rate have been also reported, particularly in patients with malignant tumors (36). Similarly, Oldhafer *et al.* (11) reported the use of a modified ante-situm resection technique using total vascular occlusion (median time of 23 minutes) without cold perfusion or veno-venous bypass to treat eight patients with tumors invading the hepatocaval confluence. Vascular replacement was performed using allogeneic donor veins or PTFE grafts. An R0 resection was achieved in 6 cases (75%) with a median overall survival of 33.5 months (11). However, the authors noted the technically challenging nature of the procedure that limits it to experienced surgeons and high-volume surgical centers.

The overall promising results highlight the fact that although *ex-vivo*, *in-situ* and *ante-situ* liver resections are extremely challenging procedures, the different technical variants allow the execution of potential curative resections in patients with lesions deemed unresectable otherwise. As there is no current consensus on recommendations for which technique to apply, knowledge of interdisciplinary techniques, in conjunction with a detailed pre-surgical planning and availability of a multidisciplinary surgical team is crucial for successful performance of these types of complex resections.

Additional techniques

Staged resections

A relatively established procedure in the field of hepatic resection is the two-stage hepatectomy, which helps increase resectability of complex tumors. In this procedure, the tumors in each hepatic lobe (if both lobes involved) are resected in distinct stages, with an interval to reduce the risk of liver failure (40). This procedure takes advantage of the liver's unique ability to regenerate following PV ligation or portal vein embolization (PVE). Generally, the PV branch ipsilateral to the tumor is embolized, either through percutaneous, transhepatic, or transileocolic routes, allowing for atrophy of the diseased liver (41). Various embolic materials, including absolute ethanol, fibrin glue, and N-butyl cyanoacrylate, have been used for PVE. However, no material has demonstrated a significant advantage clinically (41). Regeneration of the contralateral lobe generally takes place 4–8 weeks following PVE due to the release of growth factors and hormones from the atrophied lobe (2). Because PVE is performed before planned hepatic resection, its indications can vary based on the extent of liver disease and the planned operation. Current guidelines state the FLR should be anticipated to be 25% for patients with healthy livers, >30% in patients with liver disease, and >40% in cirrhotic livers (41). On the other hand, a study by Dueland *et al.* (42) involving 103 patients found that LT was more effective than PVE and hepatic resection for patients with extensive CRLM. These findings suggest that transplantation should be prioritized over two-stage hepatectomy when possible due to increased chance of cure and lower complication rates.

Feasibility of staged resections for CRLM is a topic of increased research interest with promising results. A recent multicenter study across the United States evaluated outcomes of 196 patients who underwent a two-stage hepatectomy for bilateral CRLM (40). R0 resections were achieved in 157 patients (84.4%) in the first stage and 174 patients (92.1%) in the second stage. Reported overall morbidity rate was 47.4% after the second stage, and 90-day mortality rate was 4.5%. The authors demonstrated the safety and feasibility of two staged hepatectomies in complex patients when carefully selected, as the group only proceeded with a second stage in patients with favorable biology (40). Importantly, it was observed that overall survival was negatively affected by positive surgical margins after the second procedure as well as increased estimated blood loss (40). When compared to simultaneous resections, staged CRLM have shown improved long-term survival, comparative peri-operative mortality and reduced mortality rates (43,44). In a recent population-based cohort study including and 776 (62%) staged and 442 (38%) simultaneous resections, the reported median overall survival was 78 (95% CI: 59–86) *vs.* 40 (95% CI: 35–46) months, respectively (43). Nitsche *et al.* reported their single center experience of 72 patients following staged resection *vs.* 68 following simultaneous resection. The authors found longer cumulative operation time in patients with staged resections *vs.* those undergoing simultaneous resections (460 *vs.* 299 minutes, respectively; P=0.003). Nonetheless, similar perioperative mortality was found between groups [2 (3%) *vs.* 1 (2%), respectively; P=0.25)]. In addition, liver-related morbidity rates and liver-related complications according to Clavien-Dindo classification were similar between groups. When exploring colorectal-related morbidity rates, the authors found significantly lower rates of complications grade 2 in patients following staged *vs.* simultaneous resections [2 (7%) *vs.* 11 (19%), respectively; P=0.001] (44). Nevertheless, further studies are needed in order to fully elucidate the benefits of a staged resection for CRLM when compared to simultaneous resections.

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure

ALPPS is a relatively new technique that aims to increase the potential for hepatic resection by stimulating FLR augmentation (45). First performed by Dr. Hans Schlitt in 2007, the idea for this technique is derived from the concept of PV occlusion, in which portal venous blood flow is redistributed to the liver in order to promote FLR hypertrophy (45). As hepatic resection is limited by the amount of liver parenchyma left behind, ALPPS helps expand treatment options for patients. ALPPS has been used to treat primary and metastatic liver tumors, with improved outcomes after prudent patient selection and technical experience (46).

The first step of the ALPPS procedure involves liver mobilization with clearance of disease from the FLR (if any). The structures within the porta hepatis are skeletonized and the right PV is ligated and divided while preserving the right hepatic duct and right hepatic artery. After a brief 1–2 week interval to allow for FLR hypertrophy, the right bile duct, hepatic artery, and the right hepatic vein with or without the middle hepatic vein (depending on the type of resection—right hepatectomy or extended right hepatectomy) are ligated and divided (46). Various alterations have been made to this original procedure, including tourniquet, radiofrequency-assisted liver partition, and segmental modifications. Thus far, no particular technique has emerged as the standard of care, and outcomes still have room for improvement (45). Currently, the use of ALPPS is limited to two-stage hepatectomy and is not recommended for elderly patients and those with poor functional status due to high complication rates (45). In a recent publication by Chan *et al.* (46), ALPPS demonstrated comparable outcomes, with no significant differences in morbidity or mortality when compared to PVE for hepatitis-related HCC. Furthermore, only 1 out of 46 patients (resection rate: 97.8%) who underwent ALPPS failed to proceed to resection, as compared to 33 out of 102 patients (resection rate: 67.7%) who underwent PVE. This suggests improved outcomes using current surgical practices and carefully selected patients. Although ALPPS stimulates increased FLR hypertrophy compared to PVE, higher morbidity and mortality rates have limited its feasibility at the beginning of its implementation (45). A better understanding of such complex procedure, in alignment with improved and adequate surgical training have allowed for improved outcomes in present times. In addition, current strategies involving minimally invasive techniques are being implemented to improve postoperative outcomes following ALPPS (47,48). Similarly, ALPPS modifications have led to improved R0 resection rates up to 100% (49), including feasibility when combined with techniques such as *ex-vivo* resections (32,50).

Resection and partial liver segment transplantation with delayed total hepatectomy (RAPID) procedure

The principle of the RAPID procedure is to transplant the patient with a small auxiliary left liver graft (left lateral segment or left lobe) and ligation of right PV, followed by transplanted graft hypertrophy and subsequent second stage hepatectomy (51). This approach basically combines principles of the ALPPS procedure, two stage hepatectomies, liver transplantation (LT) and LDLT. For example, the RAPID technique allows for an expanded donor pool for patients with CRLM through the use of small segmental auxiliary grafts and more recently for cirrhotic patients with unresectable HCC (51,52). The small graft used in the RAPID technique may be more susceptible to small-for-size syndrome, in which portal hyperperfusion leads to microvascular damage and subsequent liver failure (51,52). Outcomes may yet be improved by predictive models such as the one designed by Golse *et al.* (53). The RAPID procedure, while still experimental in nature, represents an exciting new option of expanding the donor pool for LT. In addition, refinement of the technique and surgical advances have allowed to implement RAPID in even more complex cases as seen in the first report of a successful RAPID procedure with a graft from a living liver donor performed in a patient with liver cirrhosis and HCC (54) and the first report of a successful RAPID procedure in a patient with non-resectable CRLM (55). Further studies, especially prospective clinical trials, are needed to optimize its effectiveness and reduce complication rates.

Liver transplant and oncology—"transplant oncology"

Hepatic resection is often considered a second-line treatment if transplantation is possible, as patients generally have underlying liver disease which limits the feasibility of long-term remission. LT is the only solid organ transplant that has been able to effectively cure cancer. This unique potential led to the development of transplant oncology, a new interdisciplinary field that combines surgical oncology and transplantation medicine to improve outcomes and quality of life for cancer patients (56). Currently, LT represents one of the most effective treatments for early-stage HCC, and current efforts are aimed at expanding the potential pool of patients who are eligible for transplant (57). The acceptable survival rate has been a matter of debate. Some have suggested a 5-year-survival rate of 50%, while others advocated for a more stringent 10-year-survival rate of 50%. Estimates of risk have greatly improved and there is now a risk estimation of tumor recurrence after transplant (RETREAT) score which has been validated by the United Network for Organ Sharing (UNOS) database (56).

LT is also an option for early-stage intrahepatic CCA, although resection is more common as the disease often presents late and consequently carries a poor prognosis (58). In addition, it has been used with varying degrees of success for HCC, CRLM, and metastatic neuroendocrine tumors (59). Recently, efforts have been towards implementation of LT in patients with advanced HCC and unresectable CRLM (18,60-63). The SECA-II arm D study evaluated survival of 10 patients with unresectable CRLM after LT using extended criteria for patients and donors. Although, a relative short disease-free and overall survival (4 and 18 months, respectively) was found, the authors conclude that using extended criteria donors could allow LT to be an option for selected patients and with it, improve long-term overall survival after LT (62,63). In addition, improvements in patient selection have led to improved outcomes for hilar CCA and early-stage intrahepatic CCA transplantation (64). Further research is needed to better understand tumor immunology and its impact on transplantation outcomes (65), as well as additional ways to take advantage of merging such interesting fields in medicine. Such advantages will subsequently translate into improve long and short term outcomes for liver-related oncology patients, with an improved recurrence free time and better quality of life for these patients.

Important considerations

Currently, there is no definite tool to assess tumor prognosis after liver resections. Kim *et al.* (66) found that the 2019 World Health Organization classification was not associated with post-resection prognosis of combined HCC and CCA. Nevertheless, clinical assessment and strict follow-up aid in clinical decision and prognosis assessment. A recent study by Zhang *et al.* (67) investigated 2,509 HCC patients who underwent R0 hepatic resection in 1,104 (44.0%) patients had microvascular invasion on the resection biopsy. The study found that preoperative hypercoagulability was associated with a poor prognosis in HCC patients with microvascular invasion after resection as the international normalized ratio level independently affected overall survival and recurrence-free survival. In addition, extremely high preoperative α-fetoprotein level was associated with increased rates of R1 resection and vascular invasion (67). In another report, preoperative model of end-stage liver disease, grade of post hepatectomy liver failure and HCC recurrence were independent predictors for patient survival (68).

A better understanding of the factors that influence prognosis following R0 hepatic resection for primary and metastatic liver tumors will allow for better preoperative planning and postoperative outcomes and should be a focus of future research efforts. It is important to highlight, that most of these complex patients are deemed unresectable, limiting the therapeutic options to palliative chemotherapy. Under this premise, these challenging procedures represents an alternative therapeutic option and therefore, attempting R0 resections in complex cases would be a justifiable approach.

Conclusions

Regardless of the surgical approach used to treat primary and metastatic liver tumors, the common end goal is achieving an R0 resection. Safety and feasibility of R0 resections have been reported for multiple techniques. However, success and postoperative outcomes are determined by a detailed preoperative assessment, taking into account tumor biology, disease burden, patient status, surgeons' proficiency and multidisciplinary care. Technical complexity should not be a limitation to achieve or pursue R0 tumor resection. Development of new systemic treatments, complemented with aggressive surgery offers the possibility of prolonged patient survival. However, there has to be a balance between patient risk/benefit in attempting R0 resections. Adequate training of surgeons on implementation of transplant oncology techniques, as well as minimally invasive techniques applied to HPB surgery represents as a promising path to improve short and long-term outcomes for liver-related oncology patients.

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