Review

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Advances in the surgical treatment of liver cancer

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SUMMARY Liver resection is the standard curative treatment for liver cancer. Advances in surgical techniques over the last 30 years, including the preoperative assessment of the future liver remnant, have improved the safety of liver resection. In addition, advances in nonsurgical multidisciplinary treatment have increased the opportunities for tumor downstaging. Consequently, the indications for resection of more advanced liver cancer have expanded. Laparoscopic and robot-assisted liver resections have also gradually become more widespread. These techniques should be performed in stages, depending on the difficulty of the procedure. Advances in preoperative simulation and intraoperative navigation technology may have also lowered the threshold for their performance and may have promoted their widespread use. New insights and experiences gained from laparoscopic surgery may be applicable in open surgery. Liver transplantation, which is usually indicated for patients with poor liver function, has also become safer with advances in perioperative management. The indications for liver transplantation in liver cancer are also expanding. Although the coronavirus disease 2019 pandemic has forced the postponement of liver resection and transplantation procedures, liver surgeons should appropriately tailor the surgical plan to the individual patient as part of multidisciplinary treatment. This review may provide an entry point for future clinical research by identifying currently unresolved issues regarding liver cancer, and particularly hepatocellular carcinoma.

Keywords liver cancer, hepatocellular carcinoma, resection, transplantation, COVID-19

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most intractable cancers and is the fifth most common carcinoma worldwide. Moreover, it is the second most common cause of cancer-related deaths. Annually, 854,000 new cases are diagnosed, and 810,000 deaths occur. HCC accounts for approximately 90% of primary liver cancers. Regionally, incidence increases with age, peaking in the 70s. The number of HCC cases is increasing worldwide with population growth and aging, increasing 75% from 1990 to 2015. Medications for hepatitis viruses, a major cause of HCC, have also improved. However, HCC due to chronic liver damage caused by nonalcoholic fatty liver disease is on the rise (*1*). Surgery is the main form of treatment for HCC. The prognosis after surgery is 60-80%, which is better than that for unresectable HCC. HCC with distant metastasis is not an indication for surgery. Conversely, the indications for resectability differ in different countries and facilities. Surgery is usually indicated for patients with a tumor diameter of ≥ 3 cm and 3 or fewer tumors. In practice, liver resection (LR) can be performed in patients who exceed the aforementioned tumor criteria. Ablation is reported to have similar results for early-stage HCC. With advances in interventional radiology and systemic therapy, the opportunities for curative resection of initially unresectable HCC are increasing after down-staging. Liver transplantation (LT) can be performed in patients with a resectable tumor but is contraindicated for LR because of poor liver function such as Child-Pugh class C cirrhosis. LT has improved with advances in perioperative management, and the indications for LT for HCC are expanding.

This review outlines the advances in LR for liver cancer, and particularly HCC, over the past 30 years. It also aims to provide an entry point for future clinical research by identifying currently unresolved issues.

2. Reduction of intraoperative blood loss

2.1. Occlusion of inflow

Managing blood loss during LR affects both short- and long-term prognosis. Therefore, various efforts have been made to reduce blood loss. The Pringle maneuver reduces the blood inflow during hepatic dissection by simultaneously clamping the hepatoduodenal ligament. The procedure was originally performed in 1908 to control liver hemorrhage caused by trauma (*2*). Until the 1970s, however, occlusion of blood inflow was not widely used; it was considered to be contraindicated because the impaired liver is vulnerable to anoxia, and inflow blood deprivation contributes to postoperative liver failure. Makuuchi *et al*. (*3*) devised the hemiliver vascular occlusion method in 1987 to preserve liver function and reduce blood loss. Some surgeons in the 1980s considered the Pringle maneuver unnecessary. Thus, randomized control trials (RCTs) were conducted in the 1990s to confirm its usefulness. Man *et al*. (*4*) compared groups treated with (n = 50) and without (n = 50) the Pringle maneuver. The safety and efficacy of the Pringle maneuver were established with a lower bleeding rate per hepatic dissection area and a faster dissection rate. Intermittent clamping was used in that RCT. In 1998, Belghiti *et al*. (*5*) compared the Pringle maneuver using intermittent versus continuous clamping. Although the amount of blood loss during parenchymal dissection was significantly greater in the intermittent clamping group (n = 44) than in the continuous clamping group (n = 42), the incidence of postoperative hepatic dysfunction was significantly higher in the continuous clamping group. Both major postoperative liver failure (4/42, 9.5%) and surgery-related death (2/42, 4.8%) were noted only in the continuous clamping group. Moreover, intermittent clamping is better tolerated and remains a mainstay of the Pringle maneuver. In the intermittent clamping group in the RCT, clamping was performed for 15 min and the released for 5 min. Although the maximum continuous ischemic time was approximately 120 min, intermittent clamping did not cause hepatic failure in the normal liver, even after a cumulative clamping time of 322 min (*6*). The Pringle maneuver is now routinely performed, resulting in decreased blood loss during LR and improved surgical outcomes. Nevertheless, caution should be exercised in patients with HCC, as they often have pre-existing hepatic impairment. To minimize the effect on the remnant liver, selective clamping specifically of the blood inflow to the resected side may be effective.

2.2. Clamping the outflow

Partial or complete clamping of the hepatic vein or inferior vena cava is an effective technique for controlling bleeding from the hepatic vein. The total hepatic vascular exclusion (THVE) technique is the complete occlusion of blood inflow and outflow in the liver and was reported by Heaney *et al*. in 1966 (*7*). In 1974, Fortner *et al*. (*8*) reported a THVE technique performed under cooled perfusion of the liver. In 2015, Azoulay *et al*. (*9*) reported a 19.5% 90-day mortality rate in 77 patients who underwent LR using standard THVE with hypothermic portal perfusion and venovenous bypass, and they further recommended improvements to the method and patient selection. The necessity of cooling has also long been debated. In 1978, Huguet *et al*. (*10*) reported a THVE method involving cooling at room temperature. They also published a 25-case series in 1992, which indicated that an extracorporeal perfusion system is not necessary for at least 90 min of THVE for a healthy liver (*11*). Regardless of whether it is performed with or without cooling, the indications for THVE are limited to uncontrolled bleeding, large tumors, or the presence of a tumor thrombus in the hepatic vein or the inferior vena cava. Given the time and effort required for clamping, it is usually not necessary in hepatic resection. In fact, a systematic review of four RCTs by Rahbari *et al*. (*12*) found no benefit in performing hepatic vein clamping to reduce intraoperative blood loss.

2.3. Controlled low central venous pressure

Multiple RCTs have indicated that keeping the central venous pressure low during parenchymal dissection can reduce bleeding. Liu *et al*. (*13*) analyzed 18 RCTs involving 1,285 patients. That systematic review noted a 312-mL reduction in blood loss, a 59% reduction in patients requiring blood transfusions, and a significantly lower alanine transaminase level in the first 5 days after surgery in the low central venous pressure group than in the control group. Liu *et al*. also noted no significant differences in postoperative complications between the groups. Central venous pressure can be reduced in several ways, including reducing intraoperative infusions, phlebotomy, decreasing the tidal volume as part of ventilator management, and partial clamping of the inferior vena cava.

2.4. Hanging maneuver

In right hepatectomy, the basic procedure is to mobilize the liver before transection. However, the procedure may be difficult for large tumors or tumors involving the diaphragm. In such cases, the anterior approach is useful and should thus precede liver transection before mobilization. Belghiti *et al*. (*14*) introduced the hanging maneuver, in which the liver is taped between the dorsal side of the liver parenchyma and the ventral aspect of the inferior vena cava before hepatic transection. The advantages of this procedure are the easily understandable direction of transection, monitoring of the positions of the inferior vena cava and middle hepatic vein, an improved surgical field as a result of traction on the tape, and assessment of the effectiveness of compression hemostasis. Procedures to reduce blood loss during liver resection are summarized in Table 1.

3. Dealing with the insufficient future liver remnant

Table 1. Summary of procedures to reduce blood loss during liver resection

Procedures	Author	Year	Type of study	Results
Hemihepatic vascular occlusion	Makuuchi M, *et al*. (*3*)	1987	Historical cohort	Reduced intraoperative blood loss and postoperative hyperbilirubinemia
Pringle maneuver	Man K, *et al*. (*4*)	1997	RCT	Resulted in less blood loss, less blood transfused, and a shorter liver transection time
Intermittent Pringle maneuver	Belghiti J, *et al*. (*5*)	1999	RCT	Associated with an intraoperative blood loss comparable to that noted after continuous clamping, but with less severe parenchymal injury, especially in patients with an underlying liver disease.
Hepatic vascular exclusion	Rahbari N, *et al*. (*12*)	2009	Meta-analysis	Did not offer any benefit in terms of outcomes for patients undergoing hepatic resection compared to portal triad clamping alone.
Low central venous pressure	Liu TS, *et al*. (*13*)	2021	Meta-analysis	Reduced blood loss during liver resection, blood transfusions, and the number of patients requiring transfusion
Hanging maneuver	Belghiti J, *et al*. (*14*)	2001	Case series	Offered several advantages: *i*) smaller transection plane from the anterior surface of the liver to the anterior surface of the IVC, *ii*) upward traction on the tape pulls the liver up and allows better exposure, hemostasis of the transection surface, and protection of the IVC, and *iii*) applying leftward traction on the tape allows access to the transection plane, allowing safe isolation of the trunk of the middle hepatic vein.

RCT, randomized control trial; IVC, inferior vena cava.

3.1. Portal vein embolization

Postoperative liver failure is a fatal complication. If major LR is indicated but the future liver remnant is small, multi-step treatment is required. In patients with a small future remnant liver, portal vein embolization (PVE) is performed to promote the enlargement of the residual liver by embolizing the portal venous branch near the tumor before surgery, as first reported by Makuuchi *et al*. in 1982 in a Japanese population (*15-17*). The two types of percutaneous transhepatic approaches to PVE are the ipsilateral approach, in which embolization is performed from the side of the liver where the tumor is located, and the contralateral approach, in which embolization is performed from the side of the liver without a tumor. Although the ipsilateral approach is ideal to minimize the impact on the remnant liver, appropriate approaches should be selected depending on the circumstances of the case. Trans-ileocecal embolization can also be performed in open surgery. Before the widespread use of interventional radiology, ligation of the portal vein was performed in open surgery. However, PVE is superior given its minimal invasiveness and lower complication rate (*18,19*). PVE also results in greater hypertrophy than ligation (*20*). This may be because portal vein ligation produces more central occlusion of the portal blood flow, whereas PVE results in more peripheral occlusion. A study summarizing 319 cases at a single facility suggested that PVE is an effective technique for avoiding postoperative liver failure (*21*). The median waiting time from embolization to LR was 24 days. Nevertheless, 20% of patients were unable to undergo LR after embolization. This was mainly due to tumor progression, not the rate of hypertrophy. Hence, attempts are being made to shorten the waiting period. The rate of liver hypertrophy per week, referred to as the kinetic growth rate, may be more closely correlated with postoperative liver failure than the rate of hypertrophy of the remnant liver in colorectal liver metastases (*22*). This suggests that calculation of the liver volume alone is not sufficient to evaluate remnant liver function.

3.2. Sequential trans-arterial chemoembolization and portal vein embolization

PVE alone may not be sufficient to enlarge the future remnant liver, and especially in HCC. This may be the result of the following possible causes: (*i*) The background liver is often impaired or cirrhotic and may have already regenerated; (*ii*) a compensatory increase in arterial blood flow to the embolized liver may promote tumor progression; and (*iii*) if the HCC has an arterioportal shunt, PVE alone may be insufficient for embolization. Therefore, a sequential strategy was proposed in which transarterial chemoembolization (TACE) was performed before PVE. In 2004, Aoki *et al*. (*23*) reported 22 ± 4% hypertrophy of the non-embolized liver within 2 weeks of TACE+PVE in a case series of 17 patients. Moreover, the cumulative overall 5-year survival rate was 55.6%. In 2006, Ogata *et al*. (*24*) retrospectively compared TACE + PVE (n = 18) and PVE (n = 18) and noted a significantly better rate of liver hypertrophy in the TACE + PVE group. In addition, complete tumor necrosis after resection was achieved in 15 of 18 patients in the TACE+PVE group compared to 1 of 18 patients in the PVE group, and the 5-year recurrence-free survival (RFS) rate was significantly better in the TACE + PVE group. Conversely, this technique is theoretically contraindicated in patients with extensive portal thrombus or severe portal hypertension and after choledochojejunostomy (*25*).

3.3. Two-stage hepatectomy

Two-stage hepatectomy was proposed by Adam *et al*. (*26*) for multiple tumors in both lobes in 2000. Minor hepatectomy of the remnant liver is performed in the first stage, followed by major hepatectomy, often accompanied by PVE, in the second stage. Today, in hybrid operating rooms with interventional radiology capabilities, LR and PVE can be performed in the same operating room in a single stage. This contributes to a shorter waiting period for second-stage surgery (*27*).

3.4. Associating liver partition and portal vein ligation for staged hepatectomy

The associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure has further increased the rate of hypertrophy of the remnant liver by performing hepatic transection with PVE or ligation during the first stage of two-stage surgery. The goal is to complete the resection before tumor progression occurs (*28*). The novel ALPPS technique ignited excitement in the hepatobiliary surgery community because ALPPS challenged the idea of unresectability and it extended the limits of liver surgery. Moreover, liver hypertrophy of up to 80% was induced in a shorter time than PVE or ligation. Nonetheless, the ALPPS technique raised serious concerns due to the high morbidity and mortality (up to 40% and 15%, respectively) related to postoperative liver failure and bile leakage. Identifying the risk factors associated with ALPPS has opened up a new dimension in the field of ALPPS surgery to improve surgical outcomes through careful patient selection. The benefit of the ALPPS technique is enhanced when performed on young patients with a borderline future remnant liver. Technical modifications of ALPPS, such as middle hepatic vein preservation, surgical management of the hepatoduodenal ligament, the anterior approach, and partial ALPPS, may improve its performance. Few studies have noted the theoretical survival benefits of ALPPS (*29*). An RCT comparing ALPPS and two-stage hepatectomy in colorectal cancer liver metastasis noted a better rate of resection with ALPPS (*30*). In a 2021 study, long-term follow-up data indicated that the ALPPS group had a better prognosis than the two-stage hepatectomy group (*31*). However, a letter to the editor identified problems with the study design, an insufficient follow-up, and relatively poor results in the two-stage group compared to those in previous studies. In addition, although the indications and effectiveness of ALPPS have not yet been determined, it is performed not only in colorectal cancer liver metastasis but also in bile duct cancer and HCC in clinical practice (*32*).

3.5. Liver venous deprivation

In 2009, Hwang *et al*. (*33*) reported subsequent right hepatic vein embolization in 12 patients who had undergone right PVE for right liver resection. In 2020, Laurent *et al*. (*34*) evaluated the effects of simultaneous radiological portohepatic vein embolization before hepatectomy and reported a significantly better rate of postembolization hypertrophy of 61% in the portohepatic vein embolization group compared to 29% in the PVE alone group. A similar study confirmed the significantly greater kinetic growth rate in portohepatic vein embolization compared to PVE alone (*35*). Thus, portohepatic vein embolization is considered a safer procedure than ALPPS, but no clinical studies have directly compared it to ALPPS. Initial experiences with procedures to deal with the insufficient future liver remnant are summarized in Table 2.

4. Anatomic resection *vs*. non-anatomic resection

Since intrahepatic micrometastases can develop from HCC via the portal vein, anatomical resection depending on the distribution of the tumor-bearing portal vein should be performed to eradicate the tumor. Although left and right hepatectomies are anatomical resections, Makuuchi *et al*. (*36*) presented a case series of 57 patients who underwent systemic subsegmentectomy using intraoperative ultrasonography in 1985. This type of resection was performed in accordance with Couinaud's subsegmental boundaries, and Makuuchi *et al*. found that even patients with impaired liver function can safely undergo resection and that the resection is highly curative oncologically. In 2005, the same group reported long-term outcomes in 210 patients with solitary HCC (*37*). Multivariate analysis indicated that anatomical resection contributed to a risk reduction in both overall survival (OS) and RFS (hazard ratios [HR]: 0.57 and 0.65, respectively). In 2016, a study that performed propensity score matching indicated that anatomical resection contributed to prolonged RFS and decreased local recurrence in Child–Pugh

Table 2. Initial experiences with procedures to deal with an insufficient future liver remnant

Procedures	Author	Year	Number of patients	Results
PVE	Makuuchi M, *et al*. (*15*)	1982	14	Liver resection was performed after portal vein embolization and postoperative deaths were not noted.
Sequential TACE and PVE	Aoki T, *et al*. (*23*)	2004	17	Radical liver resection was completed in 88.2% of HCC cases. The 5-year overall and disease-free survival rates after curative resection were 55.6% and 46.7%, respectively
Two-stage hepatectomy	Adam R, *et al*. (*26*)	2000	13	Median survival was 31 months from the second hepatectomy in patients with colorectal liver metastases.
ALPPS	Schnitzbauer A, *et al*. (*28*)	2012	25	After a median waiting period of 9 days (range = 5-28 days), the median volume of the left lateral lobe increased 74% (range = 21-192%). Mortality was 12.0%.
Liver venous deprivation	Hwang S, *et al*. (*33*)	2009	12	Future liver remnant volume increased 14.2 ± 4.9% after PVE and 27.6 ± 8.6% after hepatic vein embolization. There were no serious adverse events.

PVE, portal vein embolization; TACE, transarterial chemoembolization, ALPPS, associating liver partition and portal vein ligation for staged hepatectomy

class A patients with a solitary HCC smaller than 5 cm. Liu *et al*. (*38*) performed a systematic review of 14 studies involving 9,444 patients. The anatomical resection group (n = 4260) had a significantly better 5-year OS (odds ratio [OR]: 1.19; $P < 0.001$) and RFS (OR: 1.26; $P < 0.001$) than the nonanatomical resection group. Anatomical resection was also associated with a longer operating time (mean difference: 47.08; $P < 0.001$), greater blood loss (mean difference: 169.29; $P = 0.001$), and wider surgical margins (mean difference: 1.35; $P = 0.04$). There were no significant differences in the rate of blood transfusions (OR: 1.16; $P = 0.65$) or postoperative complications (OR: 1.24, $P = 0.18$). However, most of the studies were from Asian countries such as China, Japan, and South Korea.

A Japanese multicenter RCT conducted in 2021 noted no significant difference in RFS between the LR and radiofrequency ablation groups in HCCs with a diameter < 3 cm and in those with three or fewer tumors (*39*). In this RCT, 69 of 150 patients (46%) underwent anatomical resection, but the prognostic impact of the technique was not studied.

5. Hepatectomy for highly advanced cancer

5.1. Portal vein tumor thrombus

Portal vein tumor thrombus (PVTT) is a common occurrence and a primary obstacle in the treatment of HCC with a high rate of recurrence and poor prognosis. No global consensus has been reached and no standard guidelines have been established regarding the management of HCC with PVTT. In Western countries, sorafenib and lenvatinib are the recommended first-line treatment options for HCC with PVTT, which is now regarded as Barcelona Clinic Liver Cancer Stage C, regardless of the type of PVTT. Relatively favorable results of hepatic resection have been reported in Asian populations. Kokudo *et al*. (*40*) used propensity score matching to compare 2,093 patients with PVTT in Japan who underwent LR and 4,381 who were treated otherwise. Results indicated that the median survival in the surgical group was significantly longer than that in the nonsurgical group (2.87 *vs.* 1.10 years; $P < 0.001$) with Child–Pugh class A disease. Further subgroup analysis indicated that LR could result in survival benefits as long as the PVTT is limited to the first-order branch of the portal vein (Vp1-Vp3). However, the benefit was not significant in patients whose PVTT affected the main trunk or contralateral branch (Vp4). A similar study in a Chinese population reported that as long as the PVTT was confined to the first-order branch of the portal vein, the patient may be eligible for resection (*41*). Resection most commonly precedes hepatic dissection. While emerging studies have suggested that the elimination of PVTT first may improve surgical outcomes, no conclusions have been reached with regard to better approaches.

5.2. Vascular resection and reconstruction

Hepatic resection with vascular resection and reconstruction is challenging. A limited number of high-level facilities are offering it because surgery with curative intent is currently the only treatment that can prolong long-term survival in advanced hepatic malignancy. Various studies on the hepatic artery, the portal vein, the hepatic vein, and the inferior vena cava have been published. If a direct anastomosis is not possible, a patch or graft should be placed on the defect. Depending on the facility and circumstances, the materials used for reconstruction include autologous materials or a homograft, xenogenous materials, and synthetic materials. In other words, material selection must consider the vessel diameter, the size of the defect, the risk of infection, the availability of anticoagulation therapy, operating time, and cost, among other factors. Naturally, familiarity with variations in anatomy is essential. Many vascular reconstruction techniques have been adapted from experience with LT. Moreover, approaches that involve a total hepatectomy for tumor resection as ex situ LR have been reported. Still, clinical questions remain, such as whether anticoagulation is needed after reconstruction and the steps to perform it, if needed (*42*).

6. Minimally invasive hepatectomy

6.1. Laparoscopic hepatectomy

Laparoscopic hepatectomy was reported in the 1990s based on the approaches used for other organs and is now widely performed for HCC and other diseases because of its established safety and efficacy. Hendi *et al*. (*43*) conducted a systematic review of 23 studies that involved 1,363 patients with HCC who underwent laparoscopic hepatectomy, of which 364 (27%) underwent major hepatectomies. Blood transfusions were required in only 4.9% of patients. Only 2 (0.21%) postoperative deaths were noted, and the overall morbidity was 9.9%. Tumor recurrence occurred within 6-25 months. The 1-year, 3-year, and 5-year RFS rates were 71.9-99%, 50.3-91.2%, and 19-82%, respectively. The 1-year, 3-year, and 5-year OS rates were 88-100%, 73.4-94.5%, and 52.6-94.5% respectively.

6.2. Laparoscopic donor hepatectomy

Laparoscopic hepatectomy has been adapted to donor LR for living donor LT at some facilities because of its improved safety. Gao *et al*. (*44*) reported that a laparoscopic donor hepatectomy group (n = 633) had a longer operating time than an open living donor hepatectomy group (n = 1368) but shorter postoperative hospitalization, less blood loss, and fewer complications.

6.3. Robotic hepatectomy

Robot-assisted LR has recently been introduced at some facilities as a minimally invasive procedure. Because of the use of highly movable arms, robotic surgery is considered easier to perform than laparoscopic surgery. The aim is to achieve better aesthetic outcomes, less pain and morbidity, and better quality of life without compromising safety. As with laparoscopic surgery, there are efforts to expand the indications for donor LR (*45*). However, understandably, publication bias exists, the surgical team needs to be experienced, and indications should be carefully determined. This is especially true for living donors, the safety of whom is important.

7. Simulation and navigation

7.1. Simulation using three-dimensional imaging

In addition to conventional preoperative imaging techniques, such as computed tomography and magnetic resonance imaging, three-dimensional imaging is also important in LR. The technology emerged in the 2000s as a method of virtually reconstructing anatomy and simulating surgery. Using specialized software, a more accurate calculation of the volume of the liver in sub-areas and even smaller units is now possible, as well as the estimation of the area of congestion in hepatic vein resection by calculating the venous return area. using A three-dimensional printer has also been used in attempts to create a three-dimensional model to confirm the surgical plan. These visualization techniques show potential as educational tools for physicians and medical students to facilitate their understanding of surgery and may be useful in the preoperative explanation of the surgical plan to patients. Challenges include the cost of implementation and the difficulty of fully simulating the actual surgery because of liver deformation during dissection (*46*).

7.2. Advances in intraoperative ultrasound

Similar to the techniques for preoperative simulation, intraoperative navigation techniques are also evolving. Intraoperative ultrasonography was first used in LR in the 1980s. Contrast-enhanced intraoperative ultrasonography was established in the 2010s to differentiate HCCs and identify new HCCs or colorectal liver metastases during surgery (*47,48*). The clinical applications of real-time virtual sonography, a technique that links preoperative computed tomography and magnetic resonance images with intraoperative ultrasound images, have become apparent in recent years (*49*).

7.3. Fluorescence imaging

The use of fluorescence imaging technology has advanced over the last few decades. Although various fluorescent agents are available, indocyanine green is the most commonly preferred, and especially in LR. Indocyanine green is used to evaluate liver function before LR, especially in Asian countries. During hepatectomy, fluorescence imaging in the near-infrared spectrum begins with the depiction of the biliary tract as a result of the uptake of indocyanine green into the biliary tract. This modality has been used to identify tumors, such as HCCs, and regional boundaries (*50*). Capturing fluorescence intraoperatively in real time is now possible using the Medical Imaging Projection System (*51*). It can accommodate liver deformities during surgical manipulation. Image-guided technology is considered especially important in laparoscopic and robotic surgeries, where palpation is not possible as it is in open surgery (*52*).

7.4. Augmented reality

A new technology that can be used in surgery creates three-dimensional stereoscopic images preoperatively and it projects them onto the actual surgical field intraoperatively as augmented reality. Augmented reality attempts to see through the tumor and vascular structures inside the liver. At present, this technology is only used to examine the position of port insertion in laparoscopic or robotic surgery and the puncture position in ablation; its use in actual clinical practice is still limited. It may be useful at ensuring an appropriate margin from the tumor and avoiding unnecessary damage to the vasculature. Novel techniques may not necessarily be needed by already skilled liver surgeons but may be beneficial for less experienced ones (*53*).

8. Evaluation of difficulty in hepatectomy

With the advent and widespread use of laparoscopic hepatectomy, surgical safety has become an issue. Attempts have been made to objectively classify the difficulty of hepatectomy. Ban *et al*. (*54*) scored surgical difficulty on a 10-point scale depending on tumor characteristics and the surgical procedure in 90 cases at three facilities in Japan and found that surgical difficulty was correlated with operating time and blood loss. Kawaguchi *et al*. (*55*) analyzed the rate of laparotomy conversion as an endpoint in 452 cases at a single French facility. Notably, resection of the posterosuperior segments is more difficult than that of the anterolateral segments, even with a limited hepatectomy, and the results agree with those from actual clinical practice. The classification of surgical difficulty is also applicable to open surgery (*56*) and is thus a by-product of the development of laparoscopic surgery. While it is not an advancement in surgical techniques or equipment, it should serve as a valuable reference in surgical education.

9. Role of surgery in multimodal treatment

9.1. Adjuvant therapy after hepatic resection

No standard adjuvant therapy after hepatic resection for HCC has been established. Several RCTs involving postoperative TACE were conducted in the 1990s, but consistent results were not obtained due to differences in patient characteristics (*57*). In 2006, an RCT involving oral uracil-tegafur noted no significant difference in both RFS and OS between the uracil-tegafur group (n = 79) and the control group (n = 80) (*58*). A phase 3 international multicenter trial (STORM trial) in 2015 found no significant difference in median RFS, with 33.3 months in the sorafenib group (n = 556) versus 33.7 months in the placebo group (n = 558) (*59*). An ancillary study examined differences in biomarkers but failed to find a group of patients who benefited from sorafenib (*60*). Ke *et al*. (*61*) conducted a meta-analysis of 1,333 patients in 12 studies to assess whether adjuvant hepatic artery infusion chemotherapy improved long-term prognosis. They found that both the OS rate and RFS rate in the adjuvant hepatic artery infusion chemotherapy group were better than those in the surgery alone group (HR = 0.56, 95% confidence interval (CI) = 0.41-0.77, P < 0.001; HR = 0.66, 95% CI = 0.55-0.78, P < 0.001, respectively). Moreover, they found that adjuvant hepatic artery infusion was particularly effective in patients with microvascular and macrovascular invasion. However, further studies are needed to determine the effects of adjuvant treatment.

9.2. Conversion surgery

Conversion surgery remains controversial in HCC treated with TACE, transarterial radioembolization with yttrium-90 microspheres, radiotherapy, systemic therapies, and combinations of multimodality treatment approaches. In recent years, hepatectomy has been performed to attain a radical cure and improve the prognosis for initially unresectable HCC (*62*). Sorafenib and lenvatinib have been commonly used as first-line therapies, followed by atezolizumab, a recently developed programmed death ligand-1 monoclonal antibody, and bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody. The median survival time has gradually improved to over 1.5 years (*63*). In a study by Shindoh *et al*. (*64*) 16 patients with advanced HCC were treated with lenvatinib after surgical intervention, including 9 patients undergoing curative LR. The conversion rate for curative resection was 8.4%. Such studies are expected to increase in the future.

9.3. Y-90 radioembolization

Radioembolization is a form of hepatic arterial therapy that provides high-dose brachytherapy by delivering yttrium 90 beta-emitting beads to the tumor. Conversion surgery after treatment with yttrium-90 radioembolization has also been reported (*65*). In a meta-analysis of 276 patients from 16 studies on yttrium-90 radioembolization, the 90-day mortality rate was 3.0% (95% CI 0.3-7.4%). The median time to resection after yttrium-90 radioembolization was 2.0-12.5 months in various studies. In all of the studies where resection was performed 8 or more months after yttrium-90 radioembolization, the 30-day mortality rate was 0%. A meta-analysis of grade 3 morbidity or higher overall revealed a rate of 26% (95% CI 16-37%). A meta-analysis yielded a pooled conversion rate of 11% (95% CI 5-17%). An interval of 8 months from Y-90 radioembolization to surgery may reduce mortality.

10. Indications for LT

Since Starzl (*66*) performed the first LT in 1963, transplantation has mainly been for patients with end-stage liver failure. However, since Mazzaferro *et al*. (*67*) proposed the Milan criteria in 1996, LT has been performed as a curative treatment for malignant tumors. They reported that patients with a solitary HCC with a diameter ≤ 5 cm or those with ≤ 3 tumors with a diameter ≤ 3 cm had a 4-year survival rate of 85% and RFS of 92% (n = 35). Currently, efforts are being made to further expand the indications for LT. Tumor characteristics, including serum alpha-fetoprotein, the presence of microvascular invasion, tumor grade or differentiation, and largest tumor size, are among the most important predictors of recurrence after LT (*68*). Bridging therapy to downstage the tumor before LT is also proposed. A study in 2020 found that atezolizumab plus bevacizumab resulted in a better progression-free survival than sorafenib (*69*). Immune checkpoint inhibitors may increase the risk of rejection, and debate has arisen regarding their impact on the perioperative period in LT and optimal immunosuppressant protocols.

11. COVID-19 pandemic

The coronavirus disease 2019 (COVID-19) pandemic has become a global health emergency that has also caused profound changes in the treatment of cancer. Liver cancer is no exception and requires prioritization since it is not a condition for which treatment can be postponed. However, the more invasive the procedure, the more likely it is to require postoperative intensive care units, ventilators, and blood transfusions, which may be affected by COVID-19 protocols. A general agreement has been made to delay non-urgent treatment for localized HCC by 8-12 weeks if oncological outcomes are unlikely to be affected. The tumor doubling time for patients with large tumors with alpha-fetoprotein of less than 20 ng/mL and non-viral cirrhosis is approximately 33 weeks. For incidental liver lesions <1 cm, imaging studies and liver biopsy can be delayed. If surgery cannot be delayed, other local treatments should be considered. For HCCs with a diameter < 3 cm and < 3 tumors, ablation can produce results comparable to surgery (*39*). For larger tumors, TACE may be considered as a bridging treatment until resection. Data from two international reporting registries indicated a high mortality rate of 39.8% in patients positive for COVID-19 with chronic liver disease. In symptomatic patients positive for COVID-19, treatment of COVID-19 should be a priority. In asymptomatic patients who are COVID-19-positive, surgery can be postponed reasonably until the patient is negative. The major guidelines are in favor of a temporary suspension of elective living donor LT due to lower priority for patients near the lower end of the Milan criteria, patients with compensated cirrhotic HCC, and patients who respond well to bridging therapy. The use of immunosuppressants after LT should follow the usual protocol. The impact of COVID-19 on posttransplant patients is unknown. With limited human and financial resources, a stratified risk model should be used for triage and prioritization (*70*).

12. Conclusion

This study has outlined the advances in surgical treatments for liver cancer. Over the last 30 years, the safety of hepatectomy has improved, and efforts have been made to further reduce the amount of bleeding. For HCC, anatomical resection along Couinaud's subsegmental boundary may increase oncological curability depending on the tumor's characteristics. PVE, two-stage hepatectomy, and ALPPS have been proposed for instances of a small future remnant liver. With advances in surgery, perioperative management, other local treatments, and systemic therapy, indications for LR and LT are expanding. However, appropriate patient selection is important to achieving long-term outcomes. Nevertheless, surgical equipment has made marked advances. Laparoscopic and robot-assisted hepatectomy have also become popular options due to their minimal invasiveness. Preoperative simulation and intraoperative navigation may help to reduce the experience gap between skilled and new surgeons and practitioners. the importance of a multidisciplinary approach tailored to each patient has only increased during the COVID-19 pandemic. Thus, liver surgeons should work as part of a multidisciplinary team.

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