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Chapter 5

Novel Techniques in the Surgical Management of Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy with cirrhosis preceding its development in most cases. Surgical resection remains the primary therapeutic option despite the recent emergence of locoregional therapies. Novel surgical techniques are being proposed to overcome the limitations of traditional anatomical open liver resection. Laparoscopic resection is a safe and effective alternative to open liver resection, especially for left lateral or peripheral segment tumors. It is associated with less postoperative morbidity, intraoperative blood loss, and medial hospital stay with no difference in oncological outcomes. Robotic-assisted liver resection overcomes the technically difficult resection of tumors located at the posterosuperior segments with similar outcomes to laparoscopic resection. Associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure allows resection in patients with HCC, and associated major vascular resection or small future liver remnant (FLR) with long-term results yet to be announced. For patients with small solitary tumors or poor liver function, non-anatomical liver resection is a feasible therapeutic option due to minimal postoperative morbidity and similar oncological results of anatomical resection.

Keywords: hepatocellular carcinoma, laparoscopic, robotic, ALPPS, novel

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third leading cause of cancer-related deaths worldwide [1]. Cirrhotic patients have the highest risk of developing HCC [2]. Numerous factors contribute to cirrhosis which precedes HCC development, including viral hepatitis, heavy drinking, and aflatoxin exposure. Hepatitis C epidemic in the Western world and Hepatitis B epidemic in China have attributed to the incidence of

HCC [3]. However, HCC has a dismal prognosis, mainly due to the early recurrence; about 40% of patients that have undergone hepatectomy develop recurrence within the first year after surgery [2].

Although liver transplantation is considered as the ideal treatment, hepatic resection remains the only curative method of therapy for HCC. Other methods of potentially curative therapy are radiofrequency ablation (RFA), microwave ablation (MWA), high power focused ultrasound ablation (HIFU), and transarterial chemoembolization (TACE) [4, 5].

Novel surgical techniques are being proposed to overcome the limitations of traditional anatomical open liver resection. Laparoscopic and robotic resection as well as nonanatomical resection and ALPPS procedure have emerged as new and effective ways of surgical therapy for HCC.

The aim of this chapter is to analyze the aforementioned novel surgical techniques in the management of HCC and present the results from the relevant studies.

2. Laparoscopic liver resection for HCC

Laparoscopic surgery has become widely accepted as a feasible alternative to traditional open surgery for many surgical indications. The first laparoscopic hepatectomy was performed in 1992, for a benign tumor by Gagner et al. [6], and the first laparoscopic resection for HCC was reported in 1995 [7].

The liver presents many and significant technical challenges for minimally invasive techniques. Its mobilization is difficult, the space is limited, its vascular and biliary anatomy is complex and the parenchyma is fragile, friable and often fibrotic or cirrhotic [8]. Nevertheless, numerous studies have already shown the feasibility and safety of wedge resections, single-segment resections, and left lateral sectionectomies [9, 10].

The first international consensus conference on laparoscopic liver resection (LLR) was held in Louisville in 2008. It was suggested that the best indications for laparoscopic excision were solitary lesions less than 5 cm, located in the anterior segments. Also, the resection should be far from the hepatic hilum and the vena cava [11]. The second international consensus was held in Morioka, Japan in 2014, stating that anatomical resection for HCC is standard of care procedure, but the laparoscopic version needs to be standardized to increase propagation [12].

There are many reasons why laparoscopic major hepatectomy has not been widely accepted and performed yet. There are technical difficulties related to liver mobilization, vascular control, inability for manual palpation, access to posterosuperior liver segments, and intraoperative hazards such as gas embolism, massive bleeding, and bile duct injury [13, 14].

The benefits of laparoscopic surgery, though, have long been proven. Early postoperative ambulation, decreased respiratory complications, minimization of blood loss, minimal abdominal trauma, and less postoperative pain are some of the accepted benefits of laparoscopic

surgery. For cirrhotic patients with HCC, the minimization of the surgical incision and the subsequent preservation of the abdominal wall circulation and lymphatic flow explains the decrease in postoperative liver failure and ascites formation [15].

The last decade, several meta-analyses of laparoscopic vs. open resection for HCC have been published [16–23]. These meta-analyses have analyzed and compared the results of many nonrandomized control trials and case-matched studies. Three categories of outcomes were used to compare the two operative techniques:

a. Operative outcomes, such as operative time, operative blood loss, and number of patients that needed transfusion.

b. Postoperative outcomes, such as morbidity, mortality, and hospital stay.

c. Oncologic results, such as pathologic resection margins, incidence of port-site recurrence, disease-free survival (DFS), and overall survival (OS).

Jiang et al. [16] reported the superiority of laparoscopic liver resection (LLR) concerning the reduced intraoperative blood loss and blood transfusion, the expansion of the pathologic resection margins, the increase of R0 resection, and the shorter length of hospital stay. Laparoscopic resection has similar OS, DFS, and recurrence rate as open liver resection (OLR).

Sotiropoulos et al. [17], in a recent meta-analysis of 44 studies, showed that laparoscopic resection is superior to open resection in terms of resection margin and R0 resection. It is possible that this difference in resection margin and R0 excision is due to the smaller size of tumors resected in the laparoscopic group. It was confirmed that the laparoscopic technique is strongly associated with less blood loss, fewer blood transfusions, less postoperative pain, faster recovery, and shorter hospital stay. Operative time and tumor recurrence were not statistically different between LLR and OLR as well as the long-term oncological results such as OS and DFS. These results confirm those of previous authors [15, 18, 21, 22]. Hand-assisted laparoscopic or laparoscopy-assisted resections (hybrid group) gain statistical advantage over the OLR group concerning the negative resection margin width and influence the results in favor of LLR. They, however, showed no difference as to the OS and 30-day mortality compared to the OLR group.

The main concerns about LLR are the inadequate tumor resection margins and the potential risk of port-site recurrence. Tumor recurrence is the main cause of death in patients with HCC. The adequate tumor-free margin is a prognostic indicator of HCC [23]. Due to the lack of tactile sensation in laparoscopic surgery, the tumor location is sometimes difficult to determine. Intraoperative ultrasonography is a useful tool for precise identification of lesions and its borders [24, 25]. Another concerning factor is the risk of tumor peritoneal dissemination and port-site metastases [26, 27]. Interestingly, there has not been any evidence so far of tumor peritoneal dissemination or port-site metastases [20, 22]. The use of a plastic bag to remove the specimen can help to prevent this complication.

Concern has also been raised about the safety of laparoscopic techniques in cirrhotic patients. A plethora of patients with HCC also suffer from cirrhosis. Portal hypertension is a major risk

factor for the development of postoperative decompensation [28, 29]. The benefits of LLR can be attributed to the preservation of the abdominal wall collateral circulation and the preservation of the round ligament which may contain significant collateral veins [18]. In a study by Tranchart et al., LLR had lower rates of liver decompensation, with the occurrence of postoperative liver failure and ascites ranging from 7 to 8% in LLR vs. 26–36% in OLR [30]. One study from Japan showed lower rates of morbidity, ascites formation, and shorter hospital stay following LLR with no difference in survival [31]. A recent meta-analysis presented intraoperative and postoperative outcomes of patients with known cirrhosis undergoing resection for HCC, comparing results for OLR and LLR [32]. This meta-analysis showed wider resection margins, reduced intraoperative blood loss and transfusion need, as well as reduced morbidity rates and shorter lengths of stay with the laparoscopic approach. Another study by Sotiropoulos et al. [33] mentioned the difference in results concerning cirrhotic patients that undergo LLR vs. OLR. The operative time was longer as anticipated, but the blood loss and morbidity had no statistical difference from the noncirrhotic group. The mortality rate was significantly lower in the cirrhotic subgroup when LLR was performed. Although patients with preserved liver function are the best candidates for LLR, cirrhotic patients benefit from LLR in terms of shorter hospital stay, complication rate, and long-term oncologic outcomes.

Tumor recurrence after primary HCC has been shown to be 30–70% at 5 years, limiting the overall survival of these patients [34, 35]. Numerous studies have been published reporting the results of repeat laparoscopic liver resection (RLLR) in patients with recurrent HCC [36–38]. A recent systematic review by Machairas et al. demonstrates RLLR as a safe and promising approach for the treatment of recurrent HCC, with significant benefits in terms of short-term outcomes with the oncologic adequacy not compromised [39].

The conversion rate has decreased from 5–15% [9, 40] to 4%, indicative of the surgeons' growing experience, with the most common causes being bleeding and failure to progress secondary to difficult exposure.

Overall, LLR can facilitate a safe and feasible approach to the surgical management of HCC. Major laparoscopic hepatectomy still remains a technically demanding procedure and should only be performed by highly experienced hepatobiliary surgeons with training in laparoscopic surgery. Longer follow-up periods are needed for more definite conclusions about the survival probability of the LLR vs. the OLR groups.

3. Robotic liver resection for HCC

Robotic liver resection (RLR) has been incorporated into clinical practice with increasing frequency since 2003 when the first report of a robotic liver resection was published by Giulianotti et al. [41].

Robotic technology was developed to overcome the technical difficulties of laparoscopic surgery; precision of movement, three-dimensional vision, magnification of the operative field, motion scaling, tremor filtering, and seven degrees of movement mimicking the human hand provide steady and careful dissection as well as prompt and precise endosuturing in case of

intraoperative bleeding. A major advantage of the robotic technology in liver surgery is the dissection of the hilum and the hepatocaval dissection in right hepatectomy [42] as well as the possibility of biliary reconstruction due to the microsuturing capacity of the robotic system [43].

All published liver resections were performed using the da Vinci Surgical System (Intuitive Surgical Inc., Sunnyvale, CA USA). The major disadvantage of robotic surgery is the high cost due to the longer operating time and the instruments required, in spite of the similar hospitalization costs [44]. The purchase and maintenance costs are significant, and that is the reason for the limited incorporation of the robotic system in many facilities.

A large series by Tsung et al. [45] compared RLR to LLR and with the exception of operative time, and they found no significant differences comparing operative and postoperative results of RLR and LLR. The R0 status did not change, and the oncologic margin was not compromised. It must be highlighted that using a minimally invasive technique, a greater percentage of minor and major hepatectomies was completed; 93% of RLRs were accomplished in a purely minimally invasive manner compared with 49.1% performed laparoscopically.

Chen et al. [46] compared RLR with OLR for HCC providing superior short-term outcomes for RLR (shorter length of stay and decreased need for patient-controlled analgesia) and similar long-term outcomes (DFS and OS) despite longer operative times for RLR. A substantial proportion of patients suffered from cirrhosis and half of patients underwent major hepatectomy. They reported a DFS in 1 year of 91.5% with the RLR, whereas DFS was 79.2%. Overall survival in 1 and 3 years did not differ between the two groups. The authors reported that the patients treated with RLR had significantly wider surgical margins compared with OLR. This matched comparison offers support for further RLR in patients with HCC, performed by experienced surgeons.

Another study by Lai et al. [47] presented the results of RLR vs. LLR for HCC. Robotic group had longer mean operating time (207.4 vs. 134.2 min). Both groups had similar blood loss (334.6 vs. 336 ml) and no difference in morbidity. Mortality rate was 0% in both groups. They reported a comparable 5-year DFS and 5-year OS between RLR and LLR (42 vs. 38% and 65 vs. 48%, respectively) in patients with HCC.

Salloum et al. [48] included 14 studies in their systematic review, with HCC comprising the majority of the malignant cases. Mortality was 0%, and overall morbidity ranged from 0 to 43.3%, results comparable to laparoscopy. The mean duration of LOS was similar in both techniques. There was no statistically significant difference between RLR and LLR concerning the surgical margins or R1 resections. No clear advantages of RLR over LLR were noted; therefore, it is difficult to establish the true indications for RLR. Nevertheless, RLR has the same advantages as LLR in terms of shorter LOS and postoperative return to normal activities. Also, it seems that the learning curve for RLR is shorter than that of LLR.

The most recent systematic review from Tsilimigras et al. [49] included 31 studies with HCC being the leading indication among malignancies, comparing RLR to LLR or OLR. Median operative time was 295.5 min, EBL was 224.5 ml, conversion rate was 5.9%, and complication rate was 17.6% in the RLR group. The complications were graded according to the Clavien-Dindo classification [50], with the most common complication being bile leak (2.9%). In minor

resections, the complication rate was 14.8% compared with the major resections, where the complication rate was 17%. Most of the studies show no benefit of RLR over LLR concerning safety and feasibility and multicenter, and randomized, prospective trials are needed to validate the exact indications and benefits of RLR.

Buchs et al. [51], in a systematic review of eight studies, compared RLR to LLR with the majority of the malignant cases being HCC (50.3%). There were minor and major hepatectomy procedures, and tumor size ranged from 8 to 120 mm. In the RLR group, there was no mortality, and the overall complication rate was 23.3% which fell to 19% when only postoperative complications were considered. A reduction of the conversion rate during major hepatectomy was reported as well. Overall, there was no clear outcome difference between RLR and LLR.

Ocuin et al. [52] included 14 major series in their review with the most common indication for resection being HCC. The estimated blood loss (EBL) ranged from 50 to 413 ml and transfusion rates from 0 to 44%. An overall conversion rate of 7% and an overall complication rate of 21% were reported. No perioperative mortality was associated with RLR. Length of stay (LOS) varied from 4 to 12 days. One study by Ji et al. showed a shorter LOS following RLR than OLR (10 vs. 7 days) [53]. Most series reported a high R0 resection rate with no port site recurrences. Recurrence rates following RLR were similar to those reported for LLR [9].

In conclusion, robotic liver resection is an acceptable alternative to open surgery with the robotic approach allowing an increased proportion of major hepatectomies to be performed in a minimally invasive manner [54]. These encouraging results should prompt the expansion of the robotic approach by highly specialized surgeons in experience centers worldwide.

4. Associating liver partition and portal vein ligation for liver surgery (ALPPS) for HCC

Surgical resection is the only potential curative treatment for hepatocellular carcinoma (HCC). In many cases, a major hepatectomy is required to achieve tumor-free surgical margins. However, the volume and functional reserve of the future liver remnant (FLR) are essential to avoid post-hepatectomy liver failure (PHLF), which is a crucial and important cause of morbidity and mortality after extensive liver resection [55]. In recent decades, some new strategies, such as portal vein embolization (PVE), portal vein ligation (PVL), and two-staged hepatectomy (TSH) have been developed to induce regeneration of FLR, minimizing the risk of PHLF and finally expanding the resectability criteria in HCC and generally in liver tumors [56]. Makuuchi et al. first introduced portal vein embolization into clinical practice in 1980s [57]. In 2015, a systematic review and meta-analysis from Pandanaboyana et al. compared PVL and PVE to assess the percentile increase of the

FLR, morbidity, mortality, and tumor progression [58]. This meta-analysis revealed that the difference in the mean percentile increase in the FLR between those two techniques was not statistically significant, with similar results in morbidity, mortality, and disease progression.

In 2000s, Adam et al. first described the two-staged hepatectomy for liver malignancies in which a single surgical procedure was not possible [59]. The primary reason for the failure of TSH is tumor progression between two stages or an insufficient hypertrophy in FLR after the first stage of the procedure (portal vein occlusion).

An innovative, accelerated two-staged technique utilizing PVL and in situ split (ISS) of hepatic parenchyma was first described in 2012 by Schnitzbauer et al. [60]. In the same year, De Santibanes et al. named this procedure as ALPPS procedure (associating liver partition and portal vein ligation for staged hepatectomy) [61]. In 2007, ALPPS was first performed by chance by German surgeon Dr. Schlitt [62, 63]. In an attempt to perform an extended right hepatectomy for a perihilar cholangiocarcinoma, he intraoperatively realized that FLR was inadequate. He resected the liver adjacent to the falciform ligament after performing a left hepaticojejunostomy. The right portal vein was also ligated for the purpose of left lobe hypertrophy. Out of curiosity, on postoperative day 8, he performed a computed tomography (CT) scan. To his surprise, the left lateral section had extensively grown in size. He successfully removed the diseased liver in a second operation.

ALPPS indications are an FLR < 30% in patients with a normal liver or an FLR < 40% in patients with a cholestatic, steatotic or fibrotic liver [64]. Therefore, ALPPS can be performed for marginally resectable or locally advanced tumors with an inadequate FLR. This technique constitutes a surgical strategy for colorectal liver metastases, hilar cholangiocarcinoma, and hepatocellular carcinoma [64]. On the other hand, contradictions for ALPPS procedure include unresectable liver metastases in the FLR, unresectable extrahepatic metastases, severe portal hypertension, high anesthetic risks, and a poor condition of the patient prior to this major operation [64]. Patients with cirrhotic liver are less capable for hypertrophy of FLR after portal vein obstruction (PVL or PVE) than patients with healthy liver parenchyma. Vennarecci et al. reported that ALPPS for HCC is safe even when performing a major hepatectomy in a cirrhotic liver. They also mentioned that ALPPS induces a significant increase in FLR between the first and the second stage of the procedure and after hepatectomy, either in healthy or cirrhotic patients [65].

It has been reported that postoperative morbidity and mortality after ALPPS are 16–64 and 12–23%, respectively, with the main cause of morbidity being bile leakage and sepsis and the main cause of mortality being PHLF [66, 67]. In the latest systematic review and meta-analysis by Zhou et al., 719 patients were included, and the aim was to compare the regeneration efficiency, safety, and complication rates of ALPPS and TSH. The degree of FLR regeneration in ALPPS was significantly higher than that in TSH, and the interval of the two stages in ALPPS was obviously shorter than that in TSH. Bile fistulas were much more common after ALPPS with the reason being the liver splitting that is mandatory during this procedure.

Although ALPPS had lower 1-year DFS rate, no significant difference in the 90-day mortality rate was discovered comparing the two techniques [66]. ALPPS was associated with a higher completion rate, a lower probability of tumor progression during the stage interval, and a lower insufficient regeneration rate; these findings are similar to those of previous studies [56, 67, 68].

Many variations of the ALPPS technique have been recently mentioned in the literature with the aim of improving safety and extending indications of hepatectomy. Modifications, such as avoiding liver mobilization and hepatoduodenal skeletonization, seem to prevent tumor spreading, adhesions, overall invasiveness, and parenchymal ischemia [69–73]. In addition, anterior approaches, portal vein embolization (PVE) as an alternative to ligation, partial liver splitting, tourniquet application or ablation procedures replacing parenchymal transection, and laparoscopic approaches represent fundamental modifications to the original ALPPS procedure that aim to improve safety [15]. The result of these modifications is the reduction of morbidity and mortality in this innovative surgical procedure. Furthermore, prospective controlled studies are needed to confirm which of these modifications should be considered as a reliable and safe alternative strategy to classical ALPPS.

5. Anatomical vs. nonanatomical resection for HCC

The incidence of HCC continues to increase due to the dissemination of hepatitis B and C virus infection. Hepatic resection is the gold standard treatment for HCC [74]. Nevertheless, postoperative recurrence of HCC, 3 and 5 years after hepatectomy is 50–60% and 70–90%, respectively [75, 76].

It is known that HCC invades mainly the intrahepatic vascular system and spreads along the portal and hepatic vein branches, producing intrahepatic metastases [77, 78].

Since Makuuchi et al. introduced the concept of anatomical resection (AR), the advantages of anatomic resection for HCC have been suggested in many studies [79]. On the other hand, limited nonanatomic resection (NR) with a minimal safety margin may be preferred for patients with impaired liver function [80]. Tanaka et al. showed that microscopic vascular invasion was more important than tumor size as a predictive factor for local recurrence [81].

Anatomical liver resection is a plausible option for patients with HCC, as HCC tends to cause intrahepatic metastasis through vascular invasion, and its advantages in improved OS or DFS for HCC patients have widely been reported [82].

In a systematic review of Cucchetti et al., AR seemed to yield improved 5-year OS and DFS compared to NR [83]. Zhou et al. [84] and Bigonzi et al. [85] presented significantly improved 5-year OS with AR.

Nonanatomic resection is recommended for patients with impaired liver function [86, 87]. The plausible reason is that NR can preserve as much functional liver as possible, with surgical curability and hepatic function equally important [87, 88]. The preservation of hepatic functional reserve allows effective treatment options in HCC recurrence, which may also improve the long-term prognosis [87, 89].

The superiority of anatomical resection (AR) over nonanatomic resection (NR) for hepatocellular carcinoma (HCC) remains controversial. Marubashi et al. reported no significant differences in OS, DFS or recurrence within 2 years after hepatectomy between the AR and NR groups [90]. Likewise, Tanaka et al. reported no outstanding difference in the recurrence rates and OS between AR and NR patient groups; it was also stated that survival rates after recurrence and median survival time after recurrence were higher in the NR group compared to the AR group for patients with a solitary HCC confined to 1 or 2 liver segments [91]. Chen et al. reported in their meta-analysis that AR contributed to better DFS, but did not improve OS [92]. Thus, the superiority of AR over NR is still controversial. Furthermore, Yamamoto et al. reported that AR is associated with more perioperative risks. The same study revealed significantly greater intraoperative blood loss and longer postoperative hospital stay for the AR group [82].

In 2010, Yamashita et al. [80] published a retrospective study of 321 patients with HCC. About 120 patients underwent limited nonanatomic resection (NR) for a single HCC < 5 cm. In noncirrhotic patients (n = 215), both 5-year OS and DFS rates in the AR group were considerably better than those in the NR group (87 vs. 76% and 63 vs. 35%, respectively). In cirrhotic patients (n = 106), both 5-year OS and DFS in the AR group were worse than those in the NR group (48 vs. 72% and 28 vs. 43%, respectively).

According to their results, the width of the resection margin did not influence postoperative recurrence, and major hepatic resections did not improve patients' survival. The main disadvantage of AR in comparison with NR is the limitation of a repeat resection, which would be the most effective treatment for recurrence, because of its disadvantageous effects on remnant liver function [93, 94].

In conclusion, there is a need for more, large, prospective, multicenter studies to confirm the data about any possible superiority of nonanatomic resection for HCC.

6. Conclusion

Hepatocellular carcinoma is a malignancy with an increasing incidence and a dismal prognosis. Patients are often referred to specialists in an advanced stage of the disease. Surgery is the primary treatment and novel surgical techniques are developed offering better perioperative and oncological results (**Table 1**). Nevertheless, prospective, randomized controlled studies have to be designed for the confirmation of such possible advantages of those new surgical techniques.

Technique	Advantages	Limitations	Reference
Laparoscopic resection	• Early ambulation • Decreased respiratory complications • Minimal abdominal trauma • Less postoperative pain • Decrease in PHLF • Reduced blood loss • Shorter length of hospital stay • Increase of R0 resection	• Technical difficulties • Vascular control • Difficult access to posterosuperior segments • Massive bleeding • No manual palpation • Longer operative time	[13–17, 23, 26, 27]
Robotic resection	• Precision of movement • 3-dimensional vision • 7 degrees of movement • Precise endosuturing • Dissection of the hilum • Biliary reconstruction • Shorter length of stay	• High cost • Longer operative time • Specialized surgeons	[42–44, 46, 54]
ALPPS	• Increase in FLR • Application to cirrhotic patients • Marginally resectable tumors • Locally advances tumors	• Severe portal hypertension • High risk patients • High rates of post-operative morbidity and mortality • Bile leakage • Sepsis	[64–67]
Nonanatomical resection	• Repeat resection • Impaired liver function • No difference in recurrence rates • Less intra-operative blood loss • Cirrhotic patients	• Worse 5-year OS and DFS • Width of resection margin • Microscopic vascular invasion	[80, 81, 83–85, 90, 91, 93, 94]

Table 1. Advantages and limitations of novel surgical techniques for hepatocellular carcinoma management.

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