



REVIEW ARTICLE

Progress in hepatectomy for hepatocellular carcinoma and peri-operation management

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Abstract The global incidence of liver cancer continues to grow. Liver cancer, especially hepatocellular carcinoma, has high recurrence and mortality rates. Here, we review the past decade's diagnostic, therapeutic, and management strategies for hepatocellular carcinoma, and summarize new patient management approaches, including enhanced recovery after surgery, targeted therapy, and immunotherapy. We compare traditional and innovative management methods, which comprise developments in precision medicine, and consider their limitations. Ongoing innovation and technological advances enable surgeons to gain deeper understandings of the multidimensionality of hepatocellular carcinoma, thereby promoting the continuous development of precision therapy.

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Introduction

Liver cancer is a prevalent public health problem, and it is the fourth most common cause of malignancy-related death globally.¹ The World Health Organization

conservatively estimates that over one million people will die from primary liver cancer in 2030,² and that hepatocellular carcinoma (HCC) will account for 90% of deaths caused by primary liver cancer. Common causes of HCC include hepatitis B virus (HBV) or hepatitis C virus infection, fungal aflatoxins, alcohol abuse, metabolic syndrome-related diabetes, and obesity.^{3,4} Regardless of whether liver cancer is at an early or advanced stage and despite the availability of many nonsurgical treatments for HCC, liver resection remains the most effective treatment method.⁵

Hepatectomy, the mainstay of HCC treatment, has entered the new era of precision medicine. Achieving surgical precision, minimizing invasion, and rapid recovery are

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the goals of surgery in the twenty-first century.⁶ The key techniques that underlie hepatectomies for HCC have been refined over the past decade,⁷ and precision liver surgery has greatly facilitated more painstaking and precise hepatectomies. Currently, precision surgery is aided by technologies that include thin-layer scanning, and three-dimensional imaging and printing.^{8,9}

Despite the advantages of new technology, the effectiveness and precision of HCC resections remain unclear. In this review, we describe the past decade's diagnostic, therapeutic, and management strategies for HCC, new patient management approaches, including enhanced recovery after surgery, targeted therapy, and immunotherapy, and we compare traditional and innovative management methods, which comprise developments in precision medicine, and consider their limitations.

Progress in hepatic resection

Preoperative diagnoses, assessments, and preparatory surgical techniques

Liver failure is potentially fatal; hence, accurately assessing hepatic functional reserve before surgery may increase the likelihood of selecting the best treatment approach according to specific criteria, and determining the appropriate hepatectomy range, which, in turn, will reduce the incidence of postoperative liver failure.^{10–12} Conventional clinical evaluations of liver function include quantitative liver function tests, liver volume measurements, and the use of comprehensive clinical scoring systems, for example, the Child–Pugh scoring system.^{13–15} Liver function tests include assessments of the levels of aspartate transaminase (AST) and alanine transaminase (ALT), which are biomarkers of hepatocyte functional integrity in albumin production, bilirubin excretion, and cellular viability during acute and/or chronic liver injury.¹⁶ Persistent elevations of the AST and ALT levels indicate liver dysfunction, but they do not accurately reflect the liver's microenvironment. Although albumin and clotting factors are produced in the liver, they cannot be used to assess the status of the liver, because their serum concentrations are low.¹⁷ Moreover, serum bilirubin levels do not directly reflect the hepatic uptake, transformation, and excretion of bilirubin.¹⁸ Hence, while these conventional tests offer an insight into liver function, most fail to provide robust evidence of hepatic function and hepatic functional reserve. Consequently, the Child–Pugh classification system, which accounts for the total serum bilirubin levels, albumin levels, plasma prothrombin time, hepatic encephalopathy, and ascites, was developed to categorize liver function comprehensively.¹⁹ The Child–Pugh scoring system is suitable for patients who have undergone hepatectomy or liver transplantation. More importantly, it can predict high risks of mortality during surgery. Most patients with liver transplants are categorized as Child–Pugh classes B and C, and patients with hepatic metastases who have normal liver parenchymal function are categorized as class A. However, predicting postoperative liver failure in patients with class A disease is challenging, because the Child–Pugh score is unsuitable for patients without cirrhosis. Therefore, a

different approach is needed that accurately assesses liver function in patients with class A disease.²⁰ Several clinical staging systems have been developed for surgeons, including the Cancer of the Liver Italian Program score and the Barcelona Clinic Liver Cancer system, which consider more risk variables, including the Child–Pugh score, tumor morphology, the alpha-fetoprotein level, and the presence or absence of portal vein thrombosis. These clinical staging systems help to determine the preoperative liver status and accurately predict the outcomes of patients with HCC.^{21,22} Previous findings suggest that the end-stage liver disease model could be used to stratify patients with HCC.^{23–25} The continued development of these staging systems will improve the stratification of patients with advanced HCC, and surgeons will be better placed to select the most appropriate treatment approaches for individual patients.

Technetium-99 (^{99m}Tc)-labeled diethylene-triaminepentaacetic acid galactosyl-human serum albumin scintigraphy and hepatobiliary scintigraphy with ^{99m}Tc-labeled iminodiacetic acid are used to assess future remnant liver function preoperatively,²⁶ for follow-up assessments after preoperative portal vein embolization (PVE), and to evaluate postoperative liver regeneration.²⁷ The acids are not affected by high bilirubin levels; therefore, patients with biliary tract disease can be assessed preoperatively using these techniques.²⁸ However, these imaging techniques are currently used in Asia only.

Indocyanine green (ICG) is a fluorophore that binds to protein and emits light that peaks at about 840 nm upon illumination with near-infrared light at a wavelength of 750–810 nm, and it can penetrate tissues and organs.²⁹ Researchers have suggested that a hemihepatectomy or trilobal resection is feasible when the ICG retention rate at 15 min (ICGR15) is lower than 10%, a liver segment resection is indicated when the ICGR15 is between 10% and 20%, a single liver segment or subhepatic segment resection should be considered when the ICGR15 is between 20% and 30%, and no surgery is indicated when the ICGR15 is 30% and above.³⁰ ICG has been used for liver tumor detection, liver segmentation, biliary exploration, and liver function assessments in association with liver cancer surgery. Liver segments, hepatic portal vein branches, and peripheral veins can be visualized in three dimensions after injecting ICG.^{31–33} A dilute ICG solution (2.5 mg/mL) is sufficient to obtain color images and it can be detected using an imaging system, which improves the accuracy of the identification of the segmental anatomy.³⁴ However, this technology can only target superficial liver tumors that are approximately 5–10 mm wide.³⁵ Furthermore, false-positive results may occur in the ICG-exclusive region; these usually correspond to benign cells and cirrhotic nodules.³⁶

Digital imaging provides surgeons with critical information about the status of tumors and adjacent main blood vessels, and it has contributed to precise predictions about the sizes and locations of tumors. Conventional multiphase dynamic contrast-enhanced computed tomography scans or magnetic resonance imaging (MRI) can rapidly show heterogeneous arterial hypervascular liver tumors and elution in the venous phase.³⁷ Preoperative preparation involves assessing microvascular invasion during MRI, which helps to evaluate the outcomes of patients with hepatomas.^{38,39} Surgeons can calculate the volume fraction of the portal

vein perfusion area and quantify the hepatic vein drainage area. A liver surgery planning system that uses virtual three-dimensional models of hepatectomies can calculate the remaining liver volume. Three-dimensional models help surgeons determine spatial relationships between tumors and ducts multidimensionally, accurately identify anatomical structures, perform simulated surgeries preoperatively, adjust the pre-cut line, and calculate the residual liver volume.⁴⁰ Three-dimensional image reconstruction can help surgeons monitor a lesion's pathological changes during the intraoperative period, thereby reducing the operation time, the scope of the resection, and the amount of bleeding. However, this system is at an early stage of development, and more research is needed to confirm its reliability. This system is currently limited to three-dimensional imaging and virtual liver resections, and it cannot completely simulate the liver's physiological functions.

Recently, operative techniques have been developed that increase remnant liver function. PVE is the standard technique that is used to preserve the size of the future remnant liver (FRL) before major hepatectomies.⁴¹ However, the FRL often fails to support a patient's needs and it breaks down, and, ultimately, 20% of patients may be unable to undergo surgery. To resolve this issue, the associated liver partition and portal vein ligation for staged hepatectomy (ALPPS) technique has been developed that can increase the growth of the residual liver by changing the distribution of the portal vein blood flow. However, the growth of the remnant can take up to 6 weeks before an operation, and the final volume is often insufficient to fulfill a patient's needs. Moreover, several systematic reviews and meta-analyses have stated that ALPPS is not an effective solution, because most patients die from liver failure before the hepatectomy as a consequence of the technique's high complication and mortality rates that have greatly limited its development.

Anatomical challenges associated with surgery

To improve surgical safety, protect residual liver function, and reduce postoperative liver failure, surgeons must dissect the first, second, and third hepatic portal areas accurately to selectively obstruct the liver's blood flow, avoid the iatrogenic spread of tumors, reduce recurrences and metastases after resection, and improve the curative effect of hepatectomy for liver cancer.⁴² Intermittent Pringle maneuver (IPM) is a common surgical procedure and it is frequently used to block the first hepatic portal during liver surgery.⁴³ Several researches indicated that application of IPM has no significant difference in preoperative and postoperative survival rates. Furthermore, research does not recommend non-Pringle maneuver or selectively blocking the Glisson branch system.^{44–46} This is because the anatomical variation of bile duct in the hepatic segment is unpredictable and difficult to locate before and during surgery. If there is no intraoperative cholangiography, disconnection of bile duct from liver is not recommended to avoid the damage of bile duct.⁴⁷ Regarding the second hepatic portal area, ultrasound can be used to visualize the

middle hepatic vein in the liver parenchyma and accurately guide the liver parenchymal resection. The average length of the extrahepatic segment of the right hepatic vein is only 5.8 ± 3.5 mm, it is located at a specific angle to the inferior vena cava, and the separation and dissection of the extrahepatic segment of the right hepatic vein from the liver are undertaken on a patient-by-patient basis. In general, once the Makuuchi ligament is disconnected, the right hepatic vein is exposed.⁴⁸ For patients with challenging extrahepatic anatomies, radiofrequency ablation combined with transarterial chemoembolization or percutaneous ethanol injections is recommended.⁴⁹ Belghiti et al,⁵⁰ recommended using a liver suspension technique for the third hepatic portal area that creates a tunnel in front of the posterior inferior vena cava to facilitate hard-to-resect hepatectomies, especially for an anterior approach. If the distance between the left and middle hepatic veins is significant, the liver must be dissected to separate the left hepatic vein. Releasing the right hepatic vein involves its complete removal from the inferior vena cava ligament, which totally exposes the right and lower edges of the right hepatic vein, then it should be separated from the root of the right hepatic vein and the middle hepatic vein, beginning at the lower edge of right hepatic vein.⁵¹

Patients with liver cancer have different degrees of cirrhosis, and some tend to bleed more than others. Hence, strategies to reduce blood losses when clamping or compressing the liver parenchyma during hepatic transection are needed. Traditionally, Lin's liver clamp was used overcome blood losses as it gently presses on the liver parenchyma and intrahepatic vessels, and achieves hemostasis⁵²; however, limitations associated with this method led to its abolition many years ago. The Ultracision® harmonic scalpel and cavitron ultrasonic surgical aspirator are safer and more effective at reducing hepatic parenchymal hemorrhage and shortening the total operative time compared with traditional clamping methods.^{53–55} More recent techniques, that include using titanite clips, argon plasma coagulation, tissue cross-linking compounds, and bipolar coagulation, are used during liver resections to achieve hemostasis and end-to-end sutures.^{56–58} Emerging technologies for achieving hemostasis during liver surgery have helped surgeons shorten operation times and protect remnant liver function.

In this era of precision liver surgery, the numbers of patients who undergo minimally invasive surgery have increased exponentially, due in part to the minor systemic adverse effect and rapid postoperative recoveries following laparoscopic liver resection. Tumor size, lymph node involvement and dissections, and the anatomical relationships among the peripheral blood vessels are no longer contraindications for laparoscopic liver resection. Some of the limitations and drawbacks associated with traditional laparoscopy, including motion restrictions, the inability to insert sutures with high levels of precision, and surgeons' awkward body postures, have led to the introduction of the da Vinci robotic surgical system to overcome these difficulties. The da Vinci robotic surgical system allows surgeons to complete fine dissections and undertake precise intracorporeal suturing. The findings from studies in several research centers indicate that robotic surgical systems for

hepatobiliary oncology are feasible, and that surgeons can safely perform operations using the robotic hands once they have completed the training.⁵⁹ The use of robotic hands can benefit patients by avoiding laparotomies, reducing surgical trauma, shortening recovery times, and enabling the early implementation of postoperative adjuvant therapy.⁶⁰ Furthermore, there are no significant differences between robotic and laparoscopic hepatectomies with respect to the radical resection rate, overall survival rate, and recurrence rate.⁶¹

Perioperative patient management

Perioperative patient management programs aim to optimize patient rehabilitation; this underpins the enhanced recovery after surgery (ERAS) concept that was first proposed by Professor Henrik Kehlet in Denmark in 2001.⁶² Specifically, ERAS comprises a series of multimodal perioperative optimized management strategies that are based on medical evidence. Once the patients maintain normal physiological functions, they can reduce tissue damage, physiological and psychological stress, postoperative complication and mortality, achieve rapid postoperative recovery, reduce postoperative hospital stay, medical expenses and ultimately improve patients' satisfaction.^{63–66} Here, we retrospectively reviewed the multimodal management from the following three aspects:

Preoperative patient preparation

Doctors should inform patients the purpose and main goal of implemented ERAS program is to improve patients' compliance with the surgical plan, which can effectively alleviate patients' fear of disease and surgery.⁶⁷ For example, patients should consume semi-liquid nutrition 24 h before surgery and a 500 mL carbohydrate-loaded solution 2 h before surgery. As most liver surgeries do not involve gastrointestinal reconstruction, routine intestinal cleansing and nasogastric tube placement are not recommended. A nasogastric tube placed preoperatively can significantly increase the incidence of postoperative respiratory complications. Intestinal preparation greatly increases the intraoperative and postoperative infusion volumes, risks associated with anesthesia, and the incidence of postoperative intestinal paralysis.⁶⁸ Patients who are stressed and fast for a long time before surgery may be subject to a series of abrupt metabolic changes, including insulin resistance, which could cause hyperglycemia and increase the incidence of postoperative infectious complications and mortality.⁶⁹ Oral carbohydrates consumed 2 h before surgery do not exacerbate the effect of the anesthesia and hiccups, and they can significantly improve a patient's physical and psychological well-being preoperatively. Oral carbohydrate consumption enables the body to rapidly adapt from a starvation mode to an energy storage mode by stimulating the release of insulin and alleviating symptoms that include anxiety and thirst, which, in turn, reduces postoperative insulin resistance, helps to control serum glucose fluctuations, and maintains stability. By maintaining homeostasis, excessive fatty acid metabolism and tissue depletion can be avoided.⁷⁰

Intraoperative patient management

General anesthesia combined with thoracic epidural anesthesia, controlled reductions in the central venous pressure, target-guided fluid replacement, intraoperative warming, and incision anesthesia analgesia are highly recommended. Anesthesiologists use a target-oriented rehydration strategy to maintain a patient's central venous pressure at or below 5 cm H₂O; this affects the hepatic sinusoidal blood flow, achieves better control of intraoperative bleeding, and maintains a clear view of the intrahepatic portion of the vessel, which reduces the occurrence of intraoperative iatrogenic injury and postoperative complications. Liver surgery is usually associated with large surgical incisions and is time consuming. During surgery, the evaporation of fluid and heat loss from the patient's body are substantial, and this combined with the stress caused by surgical trauma and anesthesia, may cause a patient's temperature to drop by 1–3 °C below normal. Consequently, infections can occur at incision sites, drug metabolism may be reduced, and hypothermia may persist; therefore, applying external heat sources, for example, an insulation blanket, and using an infusion warmer and warm distilled water to flush the abdominal cavity are recommended. Other measures, for example, dynamically monitoring the nasal temperature, are required to monitor body temperature and ensure it is maintained between 36.5 °C and 37.5 °C. General anesthesia combined with epidural anesthesia can reduce the amount of anesthetic drugs used during surgery.⁷¹ These diverse optimization measures can significantly reduce the acute postoperative stress response, accelerate the recovery of a patient's nutritional status, reduce supplementation with albumin intravenously, and save valuable medical resources. Surgery without a drainage tube is safe and feasible, and the incidence of complications does not increase. Prophylactic drainage tube placement for liver surgery reduces the incidence of underarm abscesses and bile leakage, and if intraoperative injury control for patients at a high risk of severe liver cirrhosis and bile leakage is not ideal, drainage tubes can be placed to avoid postoperative abdominal adhesions. Leaks and postoperative infections do not lengthen hospital stays significantly.⁷²

Postoperative patient management

Resuming a normal diet, undertaking bed-based activities, and removing catheter and abdominal drainage tubes soon after the operation are recommended. Poor pain management and patient mobility limitations increase skeletal muscle depletion, which significantly increases the risk of deep vein thrombosis in the lower limbs and inhibits bowel motility. Early postoperative stress may contribute to intestinal mucosal congestion and hypoxia, and impair the intestinal barrier function, which is likely to cause bacterial translocation and microecological imbalances, all of which hinder early recovery.⁷³ Traditional treatment comprises analgesia, but most analgesic drugs are opioid-based, which suppress the cough reflex and cause constipation, thereby impeding the restoration of a patient's respiratory and intestinal functions.⁷⁴ The traditional treatment is not standardized and may have unknown effects. ERAS emphasizes multimodal analgesia, including thoracic epidural analgesia, a transverse abdominis plane block, and incision

anesthesia.⁷⁴ Thoracic epidural analgesia and a transverse abdominis plane block impede afferent nerve stimulation, reduce the sympathetic nervous stress response, reduce the release of catecholamines and cortisol, improve glucose tolerance, and provide analgesia, and they enable the parasympathetic nervous system to accelerate the recovery of intestinal function by controlling nausea and vomiting, thereby facilitating early enteral nutrition and cell metabolism.⁷⁵ General anesthesia combined with epidural anesthesia has obvious and long-lasting effects. Long-lasting anesthesia significantly reduces postoperative hospital stays and the incidence of complications, which facilitate patient recovery.⁷⁶ Additionally, incision anesthesia is an important part of multimodal analgesia management. Lowering incision pain can reduce the administration of opioids, prevent opioid-induced intestinal dysfunction, reduce local analgesia, and it lowers the incidence of postoperative urinary retention, accelerates the early removal of urinary catheters, and relieves patients' psychological and physiological stress.⁷⁷

In summary, ERAS is applied throughout the perioperative period and it provides the foundations for the successful implementation of other measures. An ERAS protocol is a component of precision medicine for liver cancer, because its implementation controls the pathophysiological response of the liver, reduces the depletion of tissue, and minimizes the response to trauma.

The challenge

HCC remains one of the most lethal cancers, and it has a high recurrence rate. While basic research into liver cancer has advanced our understanding of the disease, and new therapies and drugs have been introduced and applied, the 5-year overall survival rate for HCC is remains at 18% and the recurrence rate can reach 70%.^{78,79} The precise treatment of liver cancer faces two major challenges, namely, recurrence rate reduction and improving survival. Although hepatectomy benefits patients considerably, the high postoperative recurrence rate has created a bottleneck in relation to early liver cancer treatment.⁸⁰ On the other hand, surgery has not improved patients' long-term survival rates⁸¹; however, this is not devalue of surgery, and surgery remains as an important area of future research in liver cancer.

Future prospects

This section summarizes the current status of and challenges associated with liver cancer treatments. Technological advances and precision medicine have led to new treatment approaches for HCC. However, despite new insights into perioperative management and the ongoing innovation regarding molecular targeted therapy, could prognostically predict disease progression for patients with liver cancer.

Regarding treatment, postoperative systemic chemotherapy and HBV reactivation may be associated with liver.⁸² Targeted antiviral therapy can significantly reduce complications, including liver failure, cancer recurrence, and metastases. In addition, many potential treatments are

available for patients after hepatectomy. Targeted drugs, for example, sorafenib and regorafenib, treat patients with advanced HCC. One study's findings indicated that overall survival associated with lenvatinib (13.6 months) was not inferior to that associated with sorafenib (12.3 months), and that the study's other endpoints were better in the lenvatinib group than those in the sorafenib group. However, patients with HCC could become resistant to these targeted drugs, which could seriously affect their clinical efficacy.⁸³ Fortunately, the development of new immune checkpoint inhibitors has accelerated progress in HCC treatment by targeting cytotoxic T lymphocyte protein 4, programmed cell death protein 1 (PD-1), and programmed death (PD) ligand-1 (PD-L1). HCC often develops during chronic liver inflammation, and it is associated with immunosuppression in the microenvironment. PD-1 interacts with two ligands, namely, PD-L1 and PD ligand-2, to suppress normal immune function. Monoclonal antibodies to either PD-1, specifically, nivolumab and pembrolizumab, or PD-L1, namely, atezolizumab, avelumab, and durvalumab, have been approved for the treatment of a variety of malignancies.⁸⁴ Findings from the CheckMate 040 and KEYNOTE-224 clinical studies^{85,86} have shown that immune checkpoint inhibitors prolong the survival of patients who have failed to respond to first- or second-line treatment. The United States Food and Drug Administration has approved pembrolizumab and nivolumab as second-line therapy for advanced HCC. Studies' findings have shown that using PD1 and PD-L1, tumor mutagenesis, and tumor-associated T cell infiltration can predict the effectiveness of immune checkpoint inhibitors.⁸⁷⁻⁸⁹ Moreover, it may be possible to combine immunotherapy with targeted therapy to kill more tumor cells.^{3,78,90,91} However, to date, only a few patients have responded, and the new drugs can cause serious and potentially permanent side-effects in some patients. Specific markers are lacking that can be used to measure a drug's efficacy and its adverse effects. Therefore, research into biomarker-driven response recognition is needed to improve therapeutic decision-making about advanced cancer management and to create immunotherapies that are more feasible and reliable during the earlier stages of HCC.

To enhance precision medicine in liver cancer, treatment efficacy must improve. Future developments will involve a multidisciplinary treatment approach that will include specialists in medical care, molecular biology, and psychology. Multidisciplinary treatment will create personalized strategies for patients and transform HCC from a lethal disease to chronic disease.

Conclusions

In summary, the complexity and variability associated with HCC have led to less than ideal treatment outcomes and prompted physicians and scientists to gain a better understanding of the disease. Among the developments, the diagnosis of HCC has changed from traditional serology- and imaging-based approaches to embracing molecular biology and multiomics-based diagnoses. Treatment has progressed from unsophisticated surgical resection to refined surgery based on a tumor's anatomy and perioperative management. Additionally, molecular technologies and

immunotherapy have been developed to target tumors more effectively. Although many clinical experiments are being executed successively, the research findings must be verified and more research is required to detect new markers that can predict the reliability of these new therapies. All these advances have contributed to the development of precision medicine for liver cancer.

Conflict of interest

The authors have declared no conflict of interest.

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