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Surgical Management of Hepatocellular Carcinoma

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What is already known on this topic?

- *Proper classification of hepatic function is one of the most important initial steps in preparing the patient for surgery.*
- *A patient-tailored approach is established in the management of HCC and these include radiofrequency ablation, transarterial chemoembolization, cryoablation, microwave ablation, radiotherapy, and chemotherapy.*
- *Various surgical techniques such as anatomical and non-anatomical resection can be performed.*

What this study adds on this topic?

- *This is a current review of the surgical management of HCC as we have summarized the recently used clinical biomarkers, imaging modalities, and the most commmonly (and controversial) used surgical techniques.*

Abstract

Hepatocellular carcinoma (HCC) is a common primary liver tumor that often develops after chronic liver disease. Main risk factors include hepatitis B and C, alcoholic liver disease, and non-alcoholic steatohepatitis. Despite advances in technology in prevention, incidence and mortality due to HCC continue to rise. Various screening and diagnostic modalities exist, and diagnosis can be established without the need for pathological examination. In the management of HCC, a thorough evaluation of hepatic function is crucial, and various treatment options are available that can be potentially curative. A patient-tailored approach is established in the management of HCC since there are different treatment modalities. These include radiofrequency ablation, transarterial chemoembolization, cryoablation, microwave ablation, radiotherapy, and chemotherapy. Different surgical techniques such as anatomical and non-anatomical resection can also be performed. Although nonsurgical approaches can be used for certain tumors, surgery is often curative, and various classification systems can be used to stratify patients in order to choose a treatment option that is best suited for them.

Keywords: Hepatocellular carcinoma, anatomical resection, liver surgery, minimally invasive surgery

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver tumor that usually develops after chronic liver disease. The main risk factors for the development of HCC include cirrhosis, hepatitis B and C, alcohol consumption, non-alcoholic fatty liver disease, diabetes mellitus, obesity, and metabolic syndrome.[1] Screening and diagnosis of HCC are usually accomplished by ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and serological markers such as α-fetoprotein.[1]

Various treatment modalities are available, while chemotherapy and radiotherapy are usually ineffective in HCC. The most commonly used medical treatment is sorafenib, which is a tyrosine kinase-inhibiting systemic agent. Interventional treatment depends on the tumor's location, size, presence of extrahepatic disease, and the current functional status of the liver.[2] Surgical resection and liver transplantation can be curative. Other treatment options include trans-arterial chemoembolization (TACE), radiofrequency (RF) ablation, microwave ablation, percutaneous ethanol injection, and cryoablation.[2,3]

Diagnosis of Hepatocellular Carcinoma

There are various diagnostic approaches with regard to HCC, and it often varies depending on the presence of an underlying chronic liver disease. Also, various serum markers have been recently developed for early detection of HCC.

Serum Markers

Alpha-fetoprotein (AFP) is the most commonly used glycoprotein that is used as a tumor marker for HCC. This widely used biomarker is a protein produced in the early years by the liver and the yolk sac, and it is elevated in patients with HCC. With regards to HCC diagnosis, the sensitivity and specificity often vary depending on the cut-off value. Also, it may not be a good surveillance test since it is elevated in other diseases such as cholangiocarcinoma and acute or chronic viral hepatitis.[4,5] A level

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above 20 ng/mL is used as the threshold to consider HCC in diagnosis.[6] When a cut-off level of 10-20 ng/mL is used, the sensitivity and specificity of diagnosing HCC are 60% and 80%, respectively.[7,8] In a meta-analysis by Zhang et al, researchers studied various AFP threshold values with regard to their accuracy. It was found that AFP levels showed good accuracy in diagnosing HCC when a threshold of 400 ng/mL was used compared to 200 ng/mL in terms of sensitivity and specificity.[9] Because of varying sensitivity and specificity with different threshold values, AFP is often used with other tests to diagnose and manage patients with HCC.

Biomarkers for Early Detection of Hepatocellular Carcinoma

Various biomarkers have been developed that have been used in conjunction with AFP. These include des-gamma-carboxy prothrombin (DCP), plasma microRNA expression, methylated DNA markers, and circulating tumor DNA.

Des-gamma-carboxy prothrombin is a type of prothrombin produced by the liver, and it is secreted by the tumor cells. The sensitivity and specificity of DCP have been shown to be 83% and 96%, respectively, and it has been reported to show moderate ability to diagnose HCC.[10] Circulating plasma microRNAs have also been used as a diagnostic tool. Various subtypes of microRNAs were found to be higher in patients with HCC, while some subtypes can be lower when compared with healthy individuals.[11] Methylated DNAs include a genetic modification sequence where methyl groups are added to cytosine molecules without altering the DNA sequence.[12] These novel biomarkers have been used lately for the diagnosis of early stage HCC.[12] Advances in molecular techniques have led to the development of the detection of circulating tumor cells via liquid biopsy. Various studies have pointed toward its utility in HCC with regard to obtaining cancer-specific genetic information.

Imaging Modalities

Various imaging modalities are available for diagnosing HCC. These noninvasive tests include contrast-enhanced and non-contrast ultrasonography, contrast-enhanced CT, and MRI. The definitive diagnosis can be established by tissue biopsy, which differentiates HCC from other primary and secondary tumors of the liver.

Computed Tomography

The contrast-enhanced CT of the abdomen is one of the methods to diagnose HCC where the tumor is observed through various phases (arterial, venous, and delayed). The hallmark feature to diagnose HCC is hyperenhancement, or the "wash-in" period, during the arterial phase, which is then followed by a washout period during the venous or delayed phases.[13] Early stage HCC may be hypoenhancing or isoenhancing in the arterial phase while late-stage HCC often appears as hyperenhancement.[13] However, this finding of hyperenhancement can be nonspecific since hyperenhancement is also observed in changes in perfusion, hemangiomas, focal nodular-hyperplasia-like lesions, fibrosis, atypical cirrhotic nodules, or neuroendocrine carcinomas.[14,15] During the washout period, there is a marked decrease in enhancement during the later phases, which leads to venous hypoenhancement. This is also nonspecific for HCC as it can be observed in cirrhotic nodules and dysplastic nodules.[13] Despite the nonspecificity, the combination of hyperenhancement during the arterial phase and washout appearance during the venous and delayed phases is specific to HCC in patients diagnosed with cirrhosis or other risk factors that predispose them to HCC.[13,16-18] In terms of HCC, this pattern in CT has a specificity of 90% in patients with 10-19 mm tumors, and a specificity of 100% in tumors larger than 20 mm.[13,16,18,19] In late-stage HCC, there is also a hyperenhancement of the capsule's peripheral rim during the venous phase or the delayed phase.[20] Despite these features, however, a large number of HCCs do not display the typical hallmarks on CT scans, leading to missed diagnoses. In a meta-analysis by Nadarevic et al, when using CT to detect HCC of any size and stage, 22.5% of people with HCC were missed, and 8.7% were treated unnecessarily.[21] Advanced imaging techniques such as contrast-enhanced ultrasonography, dynamic contrast-enhanced MRI, diffusion-weighted imaging, and radiomics have led to improved diagnostic accuracy in detecting HCC.[22]

Magnetic Resonance Imaging

The MRI with gadolinium or gadoxetate disodium contrast is another imaging modality to diagnose HCC. Wang et al[23] have shown that MRI had better sensitivity (79% vs. 62%) and diagnostic accuracy (78% vs. 67%) when compared with CT.[24] Overall, the diagnostic efficacy of MRI has been shown to be superior to that of CT in diagnosing HCC. With regards to small HCCs, however, there has been controversy regarding the superiority between MRI and CT.[23,25] On the MRI scan, HCCs appear hypointense on T1-weighted images, moderately hyperintense on T2-weighted images, display contrast enhancement on the arterial phase, and washout in the venous or delayed phase.[26]

Ultrasonography

The Liver Imaging Reporting & Data System (LI-RADS) is a classification system with standardized criteria for liver lesions on imaging modalities to predict the probability of a lesion being HCC.[27] This classification can be used in CT images, MRI images, as well as contrast-enhanced ultrasonography. Based on the imaging observations, the LI-RADS system is categorized into 5 groups. Benign lesions are grouped under LI-RADS 1, probable benign lesions are grouped under LI-RADS 2, lesions with intermediate probability are grouped under LI-RADS 3, lesions that are probably HCC are grouped under LI-RADS 4, and lesions that are definitely HCC are grouped under LI-RADS 5.

Under contrast-enhanced ultrasonography, in order to be definitely considered HCC (or LI-RADS 5), the tumor should be ≥10 mm, display non-rim arterial phase enhancement (APHE), and show mild and late washout.[28] There are 3 scenarios in contrast-enhanced ultrasonography that makes the lesion "probably HCC" (i.e., LI-RADS 4)[28]:

1) A tumor that is ≥10 mm displays non-rim APHE and does not show washout of any type.
2) A tumor that is <10 mm displays non-rim APHE and shows mild and late washout.
3) A tumor that is ≥20 mm does not display APHE and shows mild and late washout.

The observation in CT and MRI images is different in the LI-RADS 4 group and of those that are categorized as LI-RADS 4, only 74% are diagnosed as HCC, and about 81% are malignant.[29] In the LI-RADS 5 group, about 95% of the lesions are HCC, and 98% are malignant.[29] Under CT or MRI, in order to be definitely considered HCC (or LI-RADS 5), the lesion should be ≥20 mm, display non-rim APHE, and display washout.[29]

Another category, LI-RADS M, is the case when the lesion is probably or definitely malignant but it may not definitely be HCC. These lesions often require biopsy, and there is a 33% chance that these tumors are HCC.[30]

Further Management

In any imaging modality, tumors that are diagnosed as LI-RADS 3, LI-RADS 4, and LI-RADS M require additional work-up to diagnose HCC. The options include either the combination of other imaging modalities or tissue biopsy. Most LI-RADS 3 lesions are observed as benign but still require additional diagnostic work-up to diagnose HCC at an early stage. Usually, these patients are followed up with MRI or CT scans. For LI-RADS 4 and LI-RADS M lesions, the possibility of HCC is still a matter of concern, so tissue biopsy can be essential in the diagnosis.

Liver Biopsy

Biopsy is the management of choice in cases where the lesion is indeterminate. Usually, core needles or fine-needle aspiration are used to obtain liver tissue. Procedure-related complications include bleeding, infection, seeding of the tumor along the needle track, pain, and injury to adjacent organs.

Liver biopsy is indicated in LI-RADS 4 and LI-RADS M lesions. A LI-RADS 5 lesion does not require a biopsy since this lesion is radiologically diagnosed as HCC. However, a biopsy performed on a LI-RADS 5 lesion may allow for molecular subcategorization.[31] A repeat biopsy is required when the initial biopsy is nondiagnostic or the initial biopsy is discordant with imaging and biomarkers.[31]

Non-Surgical Approach to Hepatocellular Carcinoma

Transarterial radioembolization (TARE), TACE, immunotherapy, and systemic therapies are available for the non-surgical treatment of HCC. The TARE procedure involves the intra-arterial injection of a radiolabeled embolizing agent, yttrium-90 (Y90). Since the radioactive material is targeted toward the arterioles that feed the tumor, systemic irradiation is limited, and the minimal damage occurs toward the healthy liver. Transarterial chemoembolization, on the other hand, uses chemotherapy and embolic agents in the arteries that feed the tumor in order to block the tumor's blood supply. As a result, these agents trap the chemotherapeutic drug within the tumor. Recently, research in immunotherapy toward HCC has gained tremendous interest. These are drugs that target the immune microenvironment of the tumor. The immune checkpoint inhibitors include anti-PD-1 or anti-PDL-1 antibodies and anti-CTLA-4 antibodies.[32] Immune cell therapies have also been introduced, including CAR-T cell therapy, activated lymphocyte therapy, natural killer cell therapy, and dendritic cell therapy.[32]

Surgery for Hepatocellular Carcinoma

Eligibility

Surgical intervention for HCC includes either a partial liver resection or liver transplantation. Both can be curative; however, only a small portion of patients are eligible for liver transplantation. Patients have to fulfill certain criteria to be eligible for hepatectomy. In patients with HCC who have a Child–Pugh A or B score without distant metastasis or vascular invasion, liver resection or RF ablation can be performed for up to 3 tumors that measure ≤3 cm.[33] Liver resection and TACE can also be performed in patients with 3 tumors that measure >3 cm.[33] Liver resection is also reserved for patients with HCC together with vascular invasion and no distant metastasis.[33]

Surgical resection is preferred in patients with a good compensation of liver disease and in the absence of cirrhosis. The 5-year postoperative survival rates vary between 40% and 70% but recurrence can be observed up to 70%, especially in patients with cirrhosis.[34] For this reason, liver transplantation is recommended for patients with cirrhosis and HCC.

In general, patients with the absence of extrahepatic metastasis, compensated cirrhosis, absence of portal hypertension, and normal underlying liver function are eligible for surgical resection.

There are also other criteria that can be applied for liver transplantation. The University of California San Francisco (UCSF) criteria are presented in Table 1.[35] The Tokyo criteria refer to the size and number of HCC for liver transplantation. In this criteria, the "5-5" rule is described in which up to 5 nodules with a maximum diameter of 5 cm should be included.[36]

Depending on the stage of HCC, treatment varies according to different guidelines. The Barcelona Clinic Liver Cancer (BCLC) staging system is widely accepted since it takes into consideration the liver function, performance status, and tumor stage when offering different therapeutic approaches. The BCLC guidelines for the treatment of HCC are listed in Table 2.[37]

Besides BCLC, stage-dependent treatment recommendations have been offered in the treatment of HCC according to international guidelines. These recommendations are listed in Table 3.[38-40] Based on the modified Union of International Cancer Control staging system, the Korean guidelines recommend liver resection or TACE for stage 1 tumors, transplantation, liver resection, or TACE for stage 2 lesions, TACE, systemic therapy, or transplantation for stage 3 tumors, and systemic therapy for stage 4 tumors.[41]

Classification of Hepatic Function

Classification of hepatic function is one of the most important initial steps in preparing the patient for surgery. It is used to predict the prognosis of chronic liver disease, especially cirrhosis. The Child-Pugh classification is the most widely used to categorize hepatic function. A total score is calculated by adding the individual scores of 5 different factors such as serum bilirubin, serum albumin, prothrombin time, ascites, and hepatic encephalopathy. It is, therefore, a combination of clinical factors and laboratory parameters. Dysfunction in the liver is categorized into Child–Pugh groups A (mild dysfunction), B (moderate dysfunction), and C (severe dysfunction). Groups A, B, and C are a result of the sum of the points given for each factor resulting in 5-6, 7-9, and 10-15 scores, respectively. As a result, the patient's current hepatic functional state, whether compensated or not, can be categorized and survival can be predicted. Each of the 5 factors that are used to calculate the Child–Pugh score, however, is not specific to the liver. Bilirubin, for example, can increase in cholestasis or hemolysis,

Table 1. The University of California San Francisco Criteria for Liver Transplantation

A single tumor smaller than 6.5 cm
Maximum of 3 tumors with none exceeding 4.5 cm
Cumulative tumor size less than 8 cm
Absence of vascular invasion or extrahepatic metastasis

Table 2. The Barcelona Clinic Liver Cancer Staging System for the Treatment of Hepatocellular Carcinoma

Stage 0 and A	**Liver Resection, Ablation, Liver Transplantation**
Stage B	TACE*, liver transplantation, and systemic therapy
Stage C	Systemic therapy

*TACE, transarterial chemoembolization.

Table 3. Stage-Dependent Treatment Recommendations for Hepatocellular Carcinoma

	AASLD	APASL	EASL
BCLC stage 0 and A	Liver resection, ablation, liver transplantation	Liver resection, ablation, liver transplantation	Liver resection, ablation, liver transplantation
BCLC stage B	Locoregionel therapy	TACE, selective internal radiation therapy, radiotherapy	Locoregionel therapy
BCLC stage C	Systemic therapy with atezolizumab plus bevacizumab	Systemic therapy with atezolizumab plus bevacizumab	Systemic therapy, sorafenib, regorafenib (second-line)

AASLD, American association for the study of liver diseases; APASL, Asian Pacific Association for the Study of the Liver; BCLC, Barcelona clinic liver cancer; EASL, European Association for the Study of the Liver; TACE, transarterial chemoembolization.

and albumin levels can fluctuate when there is an underlying inflammation.

The Model For End-Stage Liver Disease (MELD) score is another prognostic scoring system that measures the severity of a patient's liver disease. The score ranges from 6 to 40 points based on factors such as bilirubin, serum sodium, creatinine, and international normalized ratio (INR). The patient becomes more urgent to receive a liver transplant as this score becomes higher.

Albumin-bilirubin score (ALBI) is another model that predicts survival in patients with HCC. It is calculated by using a formula that involves serum albumin and serum bilirubin levels. Although there are studies that show the superiority of one model over another, combination with other liver cancer staging systems can provide a more accurate result in predicting the survival and prognosis of the patient so that better patient-tailored management can be established.

Liver Resection vs. Transplantation

There have been advances in the treatment of HCC, but patients have to fulfill certain criteria to undergo either resection or transplantation. Patients with small tumors that are less than 5 cm can undergo either liver resection or liver transplantation.[42] However, larger tumors such as those greater than 10 cm are not suitable for resection since these patients have a morbidity rate of up to 50% and a mortality rate of up to 8%.[42]

The presence of portal hypertension is a crucial determining factor for deciding between resection and liver transplantation. Thrombocytopenia, ascites, bleeding esophageal varices, encephalopathy, edema, and jaundice are all signs of portal hypertension. The scoring systems that measure hepatic function are inadequate for determining portal pressure. To accurately predict the portal pressure, hepatic venous wedge pressure and hepatic gradient must be measured.[42] However, it is uncommonly performed since it is an invasive procedure. According to Kow, the key aspects to consider between the 2 surgical procedures in patients with HCC are the presence of cirrhosis and basal liver function, the availability of organs, and the long-term recurrence risk of HCC.[42]

In patients with well-compensated cirrhosis due to hepatitis C resulting in hepatocellular carcinoma, liver transplantation offered better overall survival compared to hepatic resection.[43] Liver transplantation was also superior to resection in terms of oncological outcomes in hepatitis B-related HCC patients.[44] It is quite difficult to compare the 2 treatment modalities since patients undergoing liver transplantation have different indications and characteristics in their tumor staging as well as liver function. When compared with liver transplantation, mortality can be up to 50% and the risk of recurrence can be threefold in hepatic resection of HCC.[45] Overall, clinical studies have shown that disease-free survival is more favorable after liver transplantation when compared with resection.[46] Salvage living donor transplantation was also found to be superior to repeated liver resection for transplantable, recurrent intrahepatic HCC, even in patients with cirrhosis with a Child–Pugh class A.[47]

Minimally Invasive Liver Surgery

Minimally invasive liver surgery caught the attention of surgeons in the late 1990s and early 2000s with the introduction of laparoscopic liver surgery and robotic liver surgery. Although it has advantages for the patient, such as smaller incisions, early recovery and discharge, and less postoperative pain, the learning curve can be quite difficult due to the necessity of technical skill and experience. Laparoscopic surgery has become the standard of liver surgery in most centers. Patients with peripheral liver lesions smaller than 5 cm, far away from the major vessels and anticipated transection planes, are suitable for laparoscopy.[48] However, there are centers that perform laparoscopic surgery regardless of this rule.

These patients experience less perioperative blood loss, decreased postoperative pain and narcotic use, and shorter hospital stays.[48]

Current literature and meta-analyses show favorable outcomes for robotic liver surgery. Although it has a longer duration of operative time, there was no significant difference in the duration of stay, perioperative blood loss, and the incidence of conversion.[47] Studies have shown robotic hepatectomy to be safe, effective, and feasible compared with laparoscopy.[49]

Although robotic surgery is an effective alternative to laparoscopic surgery, more results are needed to show its superiority. It offers the advantages of improved optic visualization, dexterity, and simpler dissection techniques and suturing.

Anatomical vs. Non-Anatomical Resection

Two different surgical techniques have evolved for the curative resection of HCC. Anatomical resection was introduced with the idea of resection depending on liver segments. With this technique, one of Couinaud's segments of the liver containing the tumor together with its portal vein branch can be completely excised. Non-anatomical resection focuses on the parenchyma rather than anatomical segments. The parenchyma is preserved by achieving at least 1 cm of tumor-free margin.

Literature shows controversial results regarding the 2 techniques. Although some studies have shown anatomical resection to be superior to non-anatomical resection, others have shown non-anatomical resection to be similar to anatomical resection in terms of survival outcomes.

Liver failure during the postoperative period is one of the most feared outcomes for a patient scheduled to undergo surgery. Preoperative liver functional capacity scores are therefore crucial in patients undergoing liver resection. There seems to be no overall consensus in deciding between an anatomical resection vs. a non-anatomical resection. One might predict that to prevent postoperative liver failure, the non-anatomical technique would be the way to go since it preserves the maximum amount of parenchyma. There seems to be no standardization in terms of leaving an adequate tumor-free margin. There is also controversy in this matter. A resection margin of 2 cm around the tumor was shown to be favorable and safe to perform since these patients had less postoperative recurrence and improved survival.[50] However, some studies contradict this and state that a wider margin might not be protective. Even with a margin of 1 cm, Poon et al have shown similar recurrence rates between patients with a narrow margin (<1 cm) removal and wide margin (>1 cm) removal.[51] It was believed that venous invasion or microsatellites were related to recurrence, which wide resection was not able to prevent. It, therefore, becomes difficult to form a consensus on which technique to perform in a heterogeneous group of patients.

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