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MINIREVIEWS

Management of centrally located hepatocellular carcinoma: Update 2016

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Abstract

Centrally located hepatocellular carcinoma (HCC) is sited in the central part of the liver and adjacent to main hepatic vascular structures. This special location is associated with an increase in the difficulty of surgery, aggregation of the recurrence disease, and greater challenge in disease management. This review summarizes the evolution of our understanding for centrally located HCC and discusses the development of treatment strategies, surgical approaches and recurrence prevention methods. To improve patient survival, a multi-disciplinary modality is greatly needed throughout the whole treatment period.

Key words: Centrally located hepatocellular carcinoma; Hepatectomy; Combined treatment; Hepatic vascular occlusion

Core tip: Centrally located hepatocellular carcinoma (HCC) is situated in the deeper portions of the liver and adjoins main vascular structures. Due to this special location, the management of this group of patients is challenging. Low resection rates and high recurrence rates are two major problems that urgently need to be resolved. This review summarizes the evolution of our understanding for centrally located HCC and the development of disease management, and explores the possible strategies to improve overall patient survival.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide[1]. Traditionally, we describe centrally located HCC as being sited in Couinaud hepatic segments Ⅳ, Ⅴ or Ⅷ[2]. These tumors are often adjacent to main hepatic vascular structures and accept a dual blood supply from the right and left hepatic artery branches. Due to this special location, the management of this group of patients is still challenging. Low resection rates and high recurrence rates are two major problems that urgently need to be resolved. In this review, we focus on recently developed centrally located HCC classification, evaluation, surgical techniques and adjuvant treatments, and we explore the possible management strategies to improve overall patient survival.

DEFINITION AND CLASSIFICATION OF CENTRALLY LOCATED HCC

The traditional definition of centrally located HCC is based on Couinaud's segmental anatomy of the liver. In this system, the liver is divided into eight functionally independent segments. Each segment has separating vascular inflow, outflow and biliary drainage. Segments Ⅳ, Ⅴ and Ⅷ lie in the medial and make up the middle part of the liver. Tumors located in this area are called centrally located HCC. However, in clinical settings, the factor that determines the degree of surgical difficulty is not only the segment location of the tumor but also the proximity of the tumor to major vascular structures. To reflect upon its key clinical characteristics, we previously proposed a clinical definition of centrally located HCC based on the relationship between the tumor and vascular structures. This definition defines centrally located HCC as "carcinoma adjoined hepatic portals, less than 1 cm from major vascular structures (including the main portal branches, the main trunks of the hepatic veins as well as the inferior vena cava) which are usually located in Couinaud segments Ⅰ, Ⅳ, Ⅴ, Ⅷ, or at the junction of the central segments"[3].

More recently, a new classification system for centrally located HCC was proposed. Focusing on the involvement of resected areas and the anatomical location of tumors relative to the main vascular structures of the liver, this system divided centrally located HCC into four subtypes[4]. The first subtype is the tumors that are located in liver segment Ⅴ or/and Ⅳb. The second subtype is the tumors that are located in liver segment Ⅳa or/and Ⅷ. The tumors that are located in the connection of liver segment Ⅴ/Ⅳb and liver segment Ⅳa/Ⅷ are categorized in the third subtype. This subtype can be further divided into those that are superficially located and those that are deeply located. The latter is often closely adjacent to the inferior vena cava. The last subtype specifically describes the large tumors that are located in the middle of two hepatic portals. This classification system may help to plan the extent of resection or assess surgical risk, but its practical significance still needs to be further evaluated. The definition and classification of centrally located HCC, which not only rely on anatomic structures but also tumor behavior and treatment strategies, continue to evolve. We reported a single-center experience of the treatment of centrally located HCC in 2013[5]. Since then, many novel retrospective and prospective studies have been performed in this field. With a deeper understanding, the evaluation and management of the disease have also been changed greatly.

THREE-DEMENSIONAL IMAGING RECONSTRUCTION IN PREOPERATIVE EVALUATION

Centrally located HCC has complex adjacent structures. Consequently, the detailed preoperative evaluation of resectability is necessary. Besides liver function status, a clear image including tumors, blood vessels and bile ducts are essential. This preoperative evaluation is commonly obtained by multiphase contrast-enhanced computed tomography (CT), magnetic resonance imaging or ultrasound. However, because hepatectomy procedures need to be completed in a three-demensional (3D) setting, planning anatomic resections may be difficult when relying on 2D images. In 1995, van Leeuwen *et al*[6] reported depiction of the relationship between tumor and individual segmental anatomy in a 3D format. In 2005, Numminen *et al*[7] reported a 3D imaging technique, which was based on the data of multi-detector row CT scanning. So far the clinical value of 3D imaging systems in preoperative evaluations has been confirmed by a series of studies[8-12].

Currently, the 3D morphometric analysis system not only can precisely visualize tumors and adjacent vascular structures such as portal veins, hepatic veins and bile ducts from different directions in a screen but also can calculate the volume of the tumor and its surrounding areas and perform a virtual hepatectomy. Tian *et al*[13] reported a 3D morphometric analysis model of liver tumor image reconstruction with customized software for individual patients. This study included 39 patients with centrally located HCC. They all accepted a 3D image reconstruction and morphometric analysis before operation. The results demonstrated that the 3D model provides a quantitative morphometry of tumor masses. The predicted values were also confirmed by intraoperative conditions[13]. In clinical practice, 3D image morphometric analysis is often combined with liver function measurements such as Indocyanine Green (ICG) clearance test to determine the appropriate resection area. With the development of imaging techniques,

the usage of 3D imaging reconstruction systems in the surgical evaluation for centrally located HCC will be more and more promising.

INTRAOPERATIVE VASCULAR OCCLUSION TECHNIQUES

Centrally located HCC is situated in the deeper portions of the liver and adjoins main vascular structures, making hepatectomy difficult and time-consuming. Controlling intraoperative bleeding without excessive hepatic warm ischemia is a critical problem that has long perplexed liver surgeons. In 1908, James Hogarth Pringle described that occlusion of hepatic pedicle could help hemorrhage control[14]. Pringle's maneuver was then proposed to minimize blood loss during hepatic surgery. However, clamping of hepatic pedicle means occluding the total inflow of hepatic artery and portal vein. Clamping of hepatic pedicle carries potential hazards for liver function due to hepatic ischemia, while also contributing to intestinal congestion[15,16]. In addition, there has been a study that showed that Pringle's maneuver induces hepatic metastasis by stimulating tumor vasculature[17]. Especially in some HCC high incidence regions, where most patients have liver cirrhosis, long durations of hepatic pedicle occlusion should be treated with even greater care[18].

To resolve this problem, several selective hepatic vascular approaches have been described, represented by a hemihepatic vascular occlusion technique, which divides hepatic inflow into total right and total left Glisson sheaths[19]. In 2012, we proposed a concept named selective and dynamic region-specific vascular occlusion[20,21]. Before resecting liver tumors, a careful hepatic pedicle dissection was performed. The left or right hepatic artery and portal vein were dissected, exposed, and encircled with occlusion tapes. If caudate resection was needed, all short hepatic veins were ligated and dissected to free the caudate lobe from the inferior vena cava. For tumors involving the second hepatic portal or the trunk of the hepatic vein, the hepatocaval ligament was divided to make the root of the right hepatic vein stand out. If necessary, the common trunk formed by the middle and left hepatic veins also needed to be isolated to avoid fatal hemorrhage and air embolism. When liver parenchyma was dissected, we dynamically selected different regions for inflow or outflow blood occlusion according to tumor location. We have explored usage of this technique in the hepatectomy of complex centrally located HCC. Our study and other groups' studies showed that selective interruption of the arterial and venous flow to specified regions of the liver can satisfactorily control intraoperative bleeding, while also reducing ischemia-reperfusion injury of the whole liver. Most importantly, selective occlusion can maintain a fluent portal vein blood flow, which potentially avoids intraoperative gastrointestinal congestion and may accelerate postoperative recovery[20,22-24].

Given the complexity of centrally located HCC, there has been an upcoming consensus that the application of hepatic vascular occlusion needs to be more flexible in the hepatectomy. We believe the occlusion techniques not only include dissecting hepatic pedicle, hepatic veins or IVC, but also are embodied in each step of surgical procedure. For example, there is no need to occlude vascular structures when we dissect surface liver parenchyma. In some circumstances, the traditional sutures around the resection area of the liver, or even a simple hand pinching, could be effective to control bleeding. Appropriate occlusion methods can minimize intraoperative bleeding and maximize the protection of liver function. These methods allow surgeons to complete more complicated surgical procedures.

SURGICAL DETERMINATION AND RESECTION MARGIN

As a special type of HCC, the treatment choice of centrally located HCC is often challenging. Transcatheter arterial chemoembolization (TACE) is often recommended as the primary palliative treatment for unresectable HCC. This treatment is based on the fact that highly vascularized HCCs are mainly supplied by hepatic arteries, while normal liver parenchyma accepts blood supplies from both hepatic arteries and portal veins[25]. TACE was frequently performed in patients with centrally located HCC as a combined approach, but the efficacy of the treatment is still controversial. Mostly for unresectable centrally located HCCs, which are often associated with portal vein thrombosis (PVT), TACE in combination with radiotherapy has been reported to be therapeutically beneficial[26]. Chen *et al*[27] reported preoperative TACE in 89 patients with large centrally located HCC and compared their recurrence patterns and long-term outcomes. The results showed that preoperative TACE potentially improved resection rate and extended overall patient survival, but preoperative TACE also increased chronical inflammation, perihepatic adhesion and the likelihood of postoperative complications. Radiofrequency ablation (RFA) is another treatment choice for selected patients. Guo *et al*[28] reported 196 patients with centrally located small HCC (diameter < 5 cm), in which 94 patients accepted percutaneous RFA and 102 patients received partial hepatectomy. The results showed that RFA could get similar treatment efficacy as that of partial hepatectomy but with fewer complications in patients with small centrally located HCC. In this study, centrally located HCCs were defined as tumors located at Couinaud's segments Ⅳ, Ⅴ and Ⅷ. For the patient group that we discussed above, the tumor control rate of RFA is often disappointing due to potential injuries to adjacent main vasculatures and risks of bile leakage[29]. RFA can also be used to assist liver resection, which showed efficacy of reducing operation time and blood loss[30,31]. In addition, tumor ablation can be completed simultaneously in the operation. This new modality is worthy of being

Table 1 Surgical treatment of centrally located hepatocellular carcinoma

Years	Patients' number	Surgical approaches	Operative variables and outcomes
1993	19	Extended major hepatectomy or irregular hepatectomy (large tumor)	Mean operative blood loss: 1186.6 mL Mean operative time: 7.5 h One year overall survival rate: 84.2% One year recurrence-free survival rate: 73.7%[65]
1999	15	Mesohepatectomy	Mean operative blood loss: 2450 mL Hospital stay: 14.9 d Six year overall survival rate: 30% Six year recurrence-free survival rate: 21%[2]
2000	18	Mesohepatectomy	Mean operative time: 238 min Mean operative blood loss: 914 mL Hospital stay: 9 d[66]
2003	52	Central hepatectomy	Blood transfusion was needed: 1030 ± 1320 mL Bile leak occurred in 4 patients The median overall survival: 51 mo[35]
2007	246	Mesohepatectomy (larger tumor)	Mean operative blood loss (without pre-TACE): 420 mL Overall hospital mortality (without pre-TACE): 0.6% Five year overall survival rate (without pre-TACE): 31.7%[27]
2008	27	Central bisectionectomy	Median operative time: 330 min Twelve patients had postoperative complications and two died Bile duct injury was the most common complication[36]
2012	104	Hemi-/extended hepatectomy and central hepatectomy	Mean blood loss of hemi-/extended hepatectomy and central hepatectomy: 750 mL and 500 mL Five year overall survival rate for hemi-/extended hepatectomy and central hepatectomy: 66.2% and 53.1% Five year recurrence-free survival rate for hemi-/extended hepatectomy and central hepatectomy: 38.9% and 15%[67]
2013	292	Mesohepatectomy	Mean operative time: 259 min Mean operative blood loss: 634 mL Hospital stay: 10 d[68]
2014	350	Mesohepatectomy	Mean blood loss for large tumor: 950.7 mL Ascites was the most common complication Five year overall survival rate for larger tumor: 30%[69]
2014	24	Mesohepatectomy	Mean operative time: 238 min Mean operative blood loss: 480 mL Three year overall survival rate: 46%[70]
2014	198	Extended hepatectomy and mesohepatectomy	The biliary leakage incidence after mesohepatectomy: 10.2% Five year overall survival rate for mesohepatectomy: 28.9% Five year recurrence free survival rate for mesohepatectomy: 16.9%[71]
2014	119	Hepatectomy with narrow margin	Bile leak occurred in 4 patients Five year overall survival rate: 48.3% Five year recurrence-free survival rate: 27.8%[3]
2015	69	Hemi-/extended hepatectomy and central hepatectomy	Mean blood loss of hemi-/extended hepatectomy and central hepatectomy: 522.2 mL and 447.8 mL Hospital stay for hemi-/extended hepatectomy and central hepatectomy: 21.3 and 14.9 d Three year overall survival rate for hemi-/extended hepatectomy and central hepatectomy: 64% and 61%[72]
2016	353	Mesohepatectomy	Five year overall survival rate: 40.2% Five year recurrence-free survival rate: 30.7%[4]

TACE: Transcatheter arterial chemoembolization.

explored in centrally located HCC treatment. Liver transplantation is an ideal option, but the shortage of liver donors limits its applicability. Only a few patients can fulfill the strict selection criteria of liver transplantation.

Under these circumstances, surgical resection aimed at a total removal of the tumor mass remains the optimal treatment choice for selected patients with centrally located HCC. In early reports, extended major hepatectomy and mesohepatectomy were often recommended (Table 1). The reported overall survival of patients after surgery was much greater than the natural history of the disease[32,33]. However, the surgical procedures for centrally located HCC are still more technically demanding. As is shown in Table 1, the operation time was relatively long and the operative blood loss could be a severe problem, especially before 2000. In recent years, due to the fact that extensive hepatectomy removing the major part of live parenchyma was often difficult to achieve in clinical practice, several non-anatomic approaches of central hepatectomy have been proposed. Surgeons need to weigh the dangers of postoperative liver dysfunction against the radical major resection, especially in patients with chronic hepatic diseases. A surgical group from Japan reported a no-margin resection in HCC patients.

These tumors closely adhered to main hepatic vascular structures and were resected along the surfaces of tumors and vascular structures. There existed no significant differences in patient recurrence free survival and overall survival between this group and those who underwent regular hepatectomy[34]. Our group reported 118 patients with centrally located HCC, where the tumor is adherent to major hepatic vessels. These patients underwent comprehensive preoperative assessment. Unfortunately, most of them, especially patients with chronic liver diseases, would not have enough liver functional reserve to accept major hepatectomy based on ICG clearance test and 3D image reconstruction. To completely remove the tumor and preserve remnant liver function, we carefully exposed and resected the tumor from the vascular surface. This surgical approach increased the resection rate for patients with a special type of centrally located HCC. In combination with comprehensive adjuvant therapies, a five-year overall survival rate of 44.9% was reported, which is clearly superior to previously reported palliative strategies[35-38].

For a long time, the safe resection margin is one of the major disputes in the practice of HCC surgery. Several previous studies indicated that a resection margin of more than 1cm is an independent factor of improved recurrence-free survival[39-42]. But whether it can benefit all HCC patients is still controversial[43-47]. The clinical definition of centrally located HCC emphasizes the vicinity of liver tumor with major vascular structures. It is not easy to obtain a safe (> 1 cm) resection margin for this group of patients. More in-depth studies are needed to explore the possible ways to reduce postoperative recurrence and increase patient survival. It should be noted that HCC is a systematic disease; it would be impractical to prevent recurrence only by extending the resection region. We believe that the individualized surgical approaches, which are based on the patients' condition, liver function, and tumor location, are optimal for patients with centrally located HCC.

ADJUVANT THERAPIES FOR RECURRENCE PREVENTION

Recurrence disease is one of the main causes of long-term treatment failure for HCC patients. It was reported that the five-year risk of recurrence of HCC after hepatectomy could be as high as 70%[48]. Many factors are associated with tumor recurrence, such as tumor size, number, grade, vascular invasion, positive margin, cirrhosis and preoperative treatment[49-54]. Surgeons have long been searching for improved adjuvant therapies to reduce recurrence. TACE was investigated most in early studies and showed limited efficacy in preventing recurrence for selected HCC patients. Peng *et al*[55] reported that postoperative TACE enhances the effect of liver resection combined with PVT removal for HCC patients. Another study reported 115 Stage ⅢA HCC patients who underwent hepatectomy with adjuvant TACE or hepatectomy alone. The results indicated that hepatectomy with adjuvant TACE improved patients' recurrence-free and overall survival[56]. But for most HCC patients, the primary role of postoperative TACE is to detect and treat early metastasis, rather than extend patient survival[57]. Adjuvant intra-arterial injection of iodine-131-labeled lipiodol after resection of HCC also has been reported in recurrence prevention. However, the clinical value of this particular treatment is still uncertain[58-60].

As addressed above, the limited resection margin is a major concern for centrally located HCC. In clinical practice, we observed a higher recurrence rate for this group of patients[20]. In 2014, a randomized controlled study explored the safety and efficacy of adjuvant radiotherapy (RT) for centrally located HCC after a narrow margin (< 1 cm) resection[3]. The results showed that adjuvant RT for centrally located HCCs after narrow margin hepatectomy was technically feasible and relatively safe. The subgroup analysis demonstrated that postoperative region-specific RT remarkably increased patient recurrence-free survival. Patients with centrally located HCC are often at high risk of recurrence after hepatectomy. It is necessary to pay more attention to postoperative management. Regular follow-up, liver function monitoring, appropriate nutrition support and treatment of chronic liver disease (anti-virus) are important for improving patient survival[61]. Some recent studies have shown that integrative strategies, such as herbal medicine, could be effective in maintaining inner environment homeostasis and inhibiting tumor growth[62-64]. Integrative medicine focuses on restoring and maintaining a state of complete physical, mental and social well-being and not merely on the eliminating disease or infirmity. It will be interesting to explore these strategies in recurrence prevention. Currently, the development of novel treatment strategies, which incorporate molecular and immunological mechanisms, are underway and hold promise to be used for recurrence control in the future.

CONCLUSION

Over the past two decades, the management of centrally located HCC has evolved profoundly. Surgical indications, approaches, and techniques are greatly shifting. However, due to the complex procedure of centrally located HCC resection, obtaining high-level clinical evidence of surgical approaches on a large scale is still challenging. Dedicated clinical trials for this population with standardized classification are warranted. Currently, novel treatment options for HCC are constantly emerging. To elucidate which specific therapies or therapeutic combinations may be most beneficial for individual patients, a multi-disciplinary work team involving specialists in surgery, oncology, hepatology, radiology and integrative medicine is greatly needed during the whole treatment period. With more studies being involved, a general guideline for this special type of HCC can be expected and can further contribute to improving patient survival.

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