Hepatic resection for hepatocellular carcinoma in cirrhosis

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Hepatocellular carcinoma is one of the most common cancers worldwide. Several treatment modalities have been proposed, but hepatic resection is still considered the first-line therapeutic option for most of the patient carries of HCC. The proper selection of patients candidate to hepatic resection for HCC and the eradication whenever is possible of the intrahepatic metastases are the most crucial steps for improving the surgical outcome in HCC. This article reviews the current state of the art of the surgical treatment of HCC.

KEY WORDS: Hepatocellular carcinoma, Hepatic resection, Vascular invasion

ABBREVIATIONS: HCC, Hepatocellular Carcinoma; ICG, Indocyanin Green; ICG R15, Indocyanine Green Retention at 15 minutes; PVE, Portal Vein Embolization; FLR, Future Liver Remnant; PVTT, Portal Vein Tumor Thrombus; TACE, Trans-Arterial Chemo-Embolization.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide with an incidence of 500,000-1,000,000 new cases per year [1]. Several treatment modalities have been proposed, but hepatic resection is still considered the first-line therapeutic option for most of the patient carries of HCC [2,3]. Liver transplantation is considered the optimal treatment for HCC because of the concurrent treatment of HCC and the underlying liver cirrhosis [4]. However, due to the shortage of donors liver transplantation can still be offered to a minority of patients.

A major concern in hepatic resection of HCC is the high incidence of postoperative recurrence, which is reported to be approximately 60% at 3-year after surgery [5-7]. Indeed, HCC has a tendency to recur in the liver because of the underlying liver cirrhosis, which represents the ideal background for the development of HCC, and because of the high propensity to invade the portal vein branches. In fact, the underlying cirrhosis, the vascular invasion and the intrahepatic metastases are the strongest determinants of long-term prognosis among the risk factors [8-14]. However, liver resection can offer survival benefits for these patients once the proper selection of patients candidate to hepatic resection is carried out, and surgery is performed with a radical oncological intent and a liver parenchyma sparing policy. This article reviews the current state of the art of the surgical treatment of HCC.

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Patients' Selection

Liver Functional Reserve

The evaluation of the hepatic functional reserve is the first step that should be performed in each patient candidate to hepatic resection for HCC. Generally, it is performed with the Child-Pugh classification, which was originally introduced for predicting the prognosis of patients with portal hypertension undergoing shunting operations and esophageal transection; however, this method does not allow to determine the amount of hepatic parenchyma that can be safely resected. The serum estimation of the indocyanine green retention rate

at 15 minutes (ICG-R15) allows to tailor the rate of liver parenchyma that can be safely removed (3). It is part of a simple algorithm which is also based on the presence or absence of ascites, and the total bilirubin level (3). The operability is established according to the former two parameters, while the total resectable liver volume is established by the ICG-R15 as follows: patients with ICG-R15<10%, 10–20%, 20–30%, and more than 30% are subjected to right hepatectomy or more, sectoriectomy, segmentectomy, and limited resection, respectively.

Portal Vein Embolization

Major hepatectomy produces sudden increment of the portal pressure due to the massive loss of the liver parenchyma. However, when the portal branches to the potion of the liver to be resected are obliterated preoperatively, the liver is adapted to the increased portal pressure and it proceeds the atrophy-hypertrophy process. To induce hypertrophy of the part of the liver that has to be preserved and atrophy of the contralateral part that has to be resected preoperative portal vein embolization (PVE) was invented. This safe procedure was at first systematically introduced for extended hepatic resection for hilar bile duct carcinoma (15), PVE is now worldwide adopted in case of HCC and colorectal liver metastases to enhance safety of hepatectomy. Indeed, PVE can be applied when the planned hepatectomy exceeds the resectable area determined by the ICG-R15. In case of HCC, PVE can be recommended when the future liver remnant (FLR) is expected to be below 40% of the whole normal liver or the liver volume to be resected is 40–60% of the whole liver with a 10–20% ICG-R15 value. PVE of one sectorial branch can also be performed when the ICG-R15 exceeds 20% and the planned operation is a total sectoriectomy. The hypertrophy of the FLR is expected approximately two-three weeks after the PVE, although in patients with almost normal liver, two weeks are generally enough time. At that time, the hepatic resection can be performed after the confirmation of the expected hypertrophy by the liver volumetry (16).

The drawbacks of the PVE are some technical-related complications, such as bleeding, hematoma, and inadvertent migration of the embolic material: these occurrences mainly depend on the expertise. Conversely, PVE allows, the reduction of postoperative complications in patients with chronic liver disease [17]. Moreover, PVE can be successfully applied in combination with trans-arterial chemoembolization (TACE), especially in case with large HCC. Indeed, a sequential approach with PVE and TACE allows to broaden the surgical indications and more importantly the safety of the subsequent major hepatic resection in patients with large HCC on a damaged liver [18]. TACE and PVE are two important surgical tools, which should be considered dynamically during the evaluation of patient carrier of HCC to establish the proper indications and timing of application.

Operative Procedures

Intraoperative Ultrasonography

Intraoperative ultrasonography (IOUS) is the last chance to stage the disease in patients with liver tumors including HCC. Several studies have documented its role in the management of new nodules detected during liver surgery, reporting benefits and drawbacks [19-21]. More recently the use of contrast-enhanced IOUS (CEIOUS), seems to improve the specificity of IOUS during surgery for HCC on cirrhosis [22,23].

More importantly, IOUS is essential to guide the resection. In patients with HCC and cirrhosis, the amount of liver to be resected must be determined carefully, and must be minimized to avoid the risk of postoperative liver insufficiency. It is almost impossible to correctly define the hepatic segmental boundaries without the IOUS as well as the boundaries of the tumor itself, especially in cirrhosis, because of the existing wide variations in the anatomy of portal vein branches (24). Therefore, IOUS should be systematically used during hepatic resection.

The main advantage of IOUS-guided resection is the modification of the traditional approach to liver tissue dissection, which involves dissection in vertical planes to avoid tumor exposure on the cut surface. With IOUS, the relationship between the dissection plane and the tumor edge can be followed in real time, and the direction of the dissection plane can be modified when needed. Versatile dissection planes around the tumors can avoid tumor exposure while sparing important vascular structures. This approach has been recently redefined by the authors “the radical but conservative approach”, and should be applied in liver surgery to maximize the results [25]. However, even in patients in whom major resections are required the IOUS allows better design of the dissection plane, which should run along the hepatic vein to be properly anatomic.

Specific and original IOUS-techniques have been developed and reported to help the surgeon during the operations, such as the ultrasound guided puncture for the systematic subsegmentectomy [26], the so-called hooking technique [27], the application of the color-Doppler IOUS in the evaluation of the outflow from the hepatic veins [28], the IOUS-guided finger compression for the subsegmentectomy [29], and recently a new valid IOUS classification of tumor-vessel relations [25,30]. All these procedures have the objective of minimizing the functioning liver parenchyma sacrifice without compromising the oncological radicality.

Anatomic versus Non-anatomic Resection

Because of the high likelihood of the cancer cells from HCC spreading through the portal venous system, resection of the tumor-bearing portal tributaries is theoretically the most proper approach for eradication of the intrahepatic metastases of HCC. However, excluding sec-

toriectomies and hemihepatectomies, in which the resection area can be recognized by demarcation once the portal and arterial branches feeding that part of the liver are ligated extra-parenchymally, other segmental and subsegmental area to be resected cannot be disclosed precisely on the liver surface. For this purpose, the so-called systematic subsegmentectomy was devised and consists in the puncture and dye-injection into the portal branches which feed the subsegmental area in which the tumor to be removed is located [26]: this modality, and the IOUS-guided finger compression [29] are the only methods described, which allows real subsegmental anatomical resection. As a consequence of that any other subsegmental resection which has been carried out without respecting precisely the tumor-bearing portal area should not be considered a real anatomical approach.
The potential superiority of anatomic resection for HCC, based on the aforementioned approach has been recently validated in a study comparing 156 anatomic resections versus 54 nonanatomic resections. In that study the patients treated with anatomic resections had better overall and disease-free survival over patients treated with nonanatomic resections [31]. Therefore, even if the debate of this issue is still open, anatomic resection should be considered as first-line treatment of HCC.

Liver Dissection

Intraoperative bleeding is one of the most important determinants of outcome after hepatic resection, and therefore its reduction is of paramount importance. Maintenance of low central venous pressure, usually less than 4 cmH2O, has been showed to reduce blood loss from hepatic veins and hepatic parenchyma during liver transection [32]: the collection of an amount of patient's blood corresponding approximately to the 0.7% of his body weight prior to liver dissection and its reinfusion at the end, seems to be an additional method for reducing the CVP and as consequence the backflow bleeding during transection [33], although has been only applied to donors hepatectomy for now.
Several methods designed to control intraoperative bleeding have been described and adopted [34]. However, the intermittent inflow clamping with the Pringle's maneuver [35,] by repeated 15-minute clamping of the hepatoduodenal ligament and 5-minute reperfusion, or with the hemihepatic or selective clamping by repeated 30-minute clamping, may minimize both intraoperative bleeding and circulatory and biochemical disturbances due to the warm liver ischemia and reperfusion [36,37]. Indeed, Man et al. [38] revealed in a prospective randomized trial that the postoperative outcome of patients who underwent liver resection with inflow occlusion was better than of those who underwent surgery without it. Moreover, Belghiti et al. [39] showed in a randomized controlled study that inflow occlusion was associated with less postoperative complications and shorter hospital stay over total vascular exclusion due to minor hemodynamic instability. In our experience, total vascular exclusion in patients with tumors involving the hepatic veins close to the caval confluence TVE is not generally considered [40]. Using these techniques of inflow occlusion, the blood transfusion rates can be drastically minimized [3] and as consequence the safety of the treatment increases and the long term survival improved [41]. Whether hepatic inflow should be occluded intermittently or continuously has been investigated by Belghiti et al. [42] that reported better tolerance with the intermittent over the continuous clamping. Moreover, the safety of the intermittent inflow occlusion has been also proved during donor hepatectomy for living donor liver transplantation [43].
Several developed devices, including radiofrequency coagulators and ultrasonic dissectors, have been proposed to reduce the blood loss during parenchymal transection. However, recent prospective randomized trials that compared different liver transection strategies failed to find any significant differences in terms of blood loss between resection performed using such new transection devices and the traditional crush-clamping technique [44-48]. Therefore, the crush-clamping technique is still the technique of choice for the hepatic parenchymal transection.

Discussion

Safety and radicality of the procedures selected for treating surgically the patients are the landmarks which should guide the surgeon for proposing this therapeutic option. Once, these two objectives are achievable, surgery remains the most radical treatment among the local treatments for HCC. Furthermore, once safety is warranted with mortality and morbidity rates below 1% the surgical treatment plays an important role also and moreover for those patients who may not be considered for any treatment such as those with multiple HCC or with HCC and macrovascular invasion.

Advanced HCC

The prevalence of macrovascular invasion in the portal or hepatic vein branches is reported up to 40% in patients submitted to hepatectomy for HCC [49]. The prognosis of those patients is quite poor: the median survival is only 2.4 months without intervention, while when resectable a 5-year survival rate of 42% could be expected [50]. The suggested selection criteria in patients with vascular invasion are: no more than two primary nodules, patent main portal trunk, and ICG-R15 <20%. It is generally recommended to perform preoperative TACE in patients with gross portal vein tumor thrombus (PVTT) to interrupt rapid growth of the thrombus, identify the presence of other liver tumors, and enhance atrophy of the portion of the liver parenchyma with PVTT.

RECURRENT HCC

As aforementioned, the recurrence rate in HCC patients after hepatic resection is reported to be very high, because of the development of intrahepatic metastases, and new primary lesions in the remnant liver [6]. Repeated resection may be selected as the primary treatment for recurrent HCC under the same indications of the first resection. With this policy survival benefits can be expected with a 5-year survival rate of 56% after repeated resection [51]. Absence of portal invasion at the 2nd resection, single HCC at primary hepatectomy, and a disease-free interval of 1 year or more after primary hepatectomy are favorable factors which allows survival of 86% after the 2nd resection. Furthermore, once a radical but conservative policy is adopted also for these patients a no-mortality approach can be obtained [51].

Conclusions

The proper selection of patients candidate to hepatic resection for HCC by accurate preoperative evaluation of hepatic functional reserve, systematic and extensive use of the IOUS guidance to minimize the extension of the resection and therefore maximize the sparing of functioning liver parenchyma or the selective use of PVE to enhance the safety of the resection, together with the control of intraoperative bleeding may lead to negligible rates of morbidity and mortality and long-term survival even in case of advanced HCC.

Riassunto

Il carcinoma epatocellulare è uno dei più comuni tumori al mondo. Sebbene siano stati proposti numerosi approcci terapeutici la resezione viene ancora ritenuta il trattamento di scelta per molti pazienti portatori di epatocarcinoma. L'appropriata selezione dei pazienti candidati alla resezione epatica e la radicalità del trattamento sono le assolute priorità perché si possano ottimizzare i benefici dell'approccio chirurgico. Questo articolo analizza lo stato dell'arte nella terapia chirurgica dell'epatocarcinoma.

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