Is There a Place for Resection of HCC in the Presence of Liver Transplantation and Interventional Radiology in Cirrhotic Liver?

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ABSTRACT

Hepatocellular carcinoma is the fifth most common cancer worldwide and one of the leading causes of cancer-related mortality. The majority of patients with hepatocellular carcinoma have underlying liver cirrhosis as a result of hepatitis B or hepatitis C virus, and alcoholic hepatitis. Its management in the presence of liver cirrhosis is a complex condition. Selecting the appropriate treatment modality is dependent not only on tumor stage, but also on the severity of the underlying liver disease. Liver resection and transplantation remain the main course of treatment of HCC. However, liver transplantation is considered nowadays the standard of care for hepatocellular carcinoma because it removes both the tumor and the underlying cirrhotic liver; improving quality of life by restoring a normal liver status. However, the shortage of donors and high costs make liver transplantation less available. Therefore, liver resection remains the commonly used strategy for HCC patients with preserved liver functions. However, liver resection is associated with high peri-operative morbidity and mortality, and high incidence of HCC recurrence. Here, we review the role of liver resection in the era of liver transplantation and interventional radiology.

Key words: hepatocellular carcinoma, liver resection, liver cirrhosis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide (1,2) and one of the leading causes of death worldwide, representing a major health problem (3). The vast majority of patients with HCC have underlying liver cirrhosis (LC) as a result of hepatitis B virus (HBV), hepatitis C virus (HCV) infection, or alcoholic hepatitis (4). In Egypt, HCV is considered as the main predisposing factor for HCC. We previously investigated 1012 patients with HCC, in which HCV was found in nearly 79.6%, while mixed infection with HBV represented about 3.6% of cases (5). In another study, conducted also in Mansoura University, we observed aflatoxins as a significant contributing factor for HCC patients in the Delta region in Egypt as its level was 32.47 ± 92.46 vs. 7.33 ± 5.5 for the control group ($p < 0.0001$) (6). HCC can occur also in individuals without LC. The reported percentage of non-cirrhotic HCC ranges from 7 to 54%,

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depending on demographic area, underlying cause, and the sources of the specimen, such as liver biopsies, autopsies, or resected liver (7)(fig. 1).

It is established that both liver resection and transplantation are the cornerstones for management of HCC. However, LT is superior in its results because it offers a rich resection for cancer, removes the underlying cirrhotic liver; decreasing its future hazards as malignancy and returns the normal liver status. With the change in the criteria for patient selection (9,10), many authors estimated transplantation for even early HCC leads to very good results over liver resection (9,11,12) and similar to cases that underwent liver transplantation for nonmalignant diseases (9,10,13). However, the existing shortage of donors makes this option not applicable for all patients (14,15).

Liver resection is associated with high peri-operative morbidity and mortality, and high incidence of HCC recurrence; especially in cirrhotic liver. However, with the expected worse prognosis in comparison with LT, we raise a question: in cases with liver cirrhosis and developed HCC, does resection still pose a role in the era of liver transplantation and interventional radiology methods?

In cases with HCC within Milan criteria in cirrhotic liver in the waiting list of LT, LR can be offered as a bridge for liver transplantation. For large HCC (more

than 10 cm), LR remains the only curative treatment. Caudate lobe resection for HCC in cirrhotic liver is safe and feasible in experienced hands. For HCC cases with obstructive jaundice due to invasion of the extra-hepatic biliary system, resection may be the only curative treatment or as a bridge for liver transplantation.

DISCUSSION

Liver resection in the context of cirrhosis is associated with high incidence of operative difficulties, postoperative complications, and recurrence rates (14). Recent mortality rate following hepatectomy has been reduced significantly due to preoperative examinations, development of surgical techniques, and improved management of patients, resulting in an increased long-term survival rate (15). However, the 5-year recurrence rate of HCC after hepatectomy remains high at 77% to 100% (16).

Prognosis following LR in those patients with early HCC concomitant with LC may vary. The findings of Yeh et al. showed that HCC patients with LC who had an operation of hepatic resection should be stratified based on the tumor size, the high value of alkaline phosphatase, satellite lesions, and vascular invasion (17). Similarly, several factors have been documented to be responsible for possible reduced

Figure 1 - Large HCC in normal liver

survival after hepatic resection for early HCC (18,19).

In our study, done on 175 patients with HCC on top of cirrhotic liver, we concluded that LR in cirrhotic liver with preserved liver function can be performed safely, but is associated with high post-resection recurrence rates (20).

The restriction of surgical resection can be disputed for several reasons. First, the safety of liver surgery has markedly improved over the last years, making liver resection a technically feasible option even for patients with cirrhosis or large tumor lesions (15,21). Second, LT is a non-projectable therapy option comprising the risk of cancer progress while waiting for a suitable organ (22,23). Finally, the sensitivity and specificity of current diagnostic means are both limited (24), leading to erroneous classifications with serious consequences on therapeutic goals.

Resection as a bridge to liver transplantation for HCC in cirrhosis

The superiority of transplantation over LR has been proved through recurrence and survival numbers (9,11). However, the problems regarding short donors and long waiting lists made it an inapplicable choice for all patients (25,26). Therefore, resection is feasible for those patients planning for a transplant in case recurrence occurred (14, 15, 28).

This plan relies on theories that assume that a percent of these cases may live free of tumor after resection for years, and that transplantation as a second option in a bit more hazardous than if it was performed as a first option (29).

Bleeding was estimated to increase in secondary transplanted cases when compared with primary ones. Survival was also assumed to be affected greatly after secondary LT (39% versus 61% at 5 years). However, these hazards could be decreased using either transthoracic or laparoscopic approaches that usually results in less adhesions or by using other lines of treatments, such as percutaneous radiofrequency (29).

In practice, this 2-stage strategy should not be considered as routine practice: it should be reserved only for selected patients with low risk of recurrence after resection. On the other hand, cases that have factors affecting disease-free survival after resection should be excluded such as those with multi-nodular tumors (30) Child-Pugh score B or C (31,32), serum alpha-fetoprotein levels more than 32 ng/ml (23) or serum aminotransferase greater than twice the normal levels (33,34) hepatitis C-related HCC (35,36) microscopic vascular invasion (30,37). Primary transplan-

tation would be a more appropriate option for this subset of patients. Sometimes, we can apply this 2-strategy technique in patients planned for transplantation during the waiting time of LT to avoid tumor progression (38-40).

Large tumors

With the evolving number of HCV patients, we will not be able to perform screening to all cases; especially in developing countries due to increased costs of this procedure, leading to more patients that may be first discovered with a larger tumor burden (41).

Management tools for such huge tumors are limited. Such tumors pose higher probability for recurrence (42,43), may contain undetected small vessels invasion (44) and tend to have an aggressive course that may be due to unknown genetic factors (45). According to the experience of Mazzaferro et al., liver transplantation for such cases poses a bad outcome regarding liver function and incidence of recurrence (10). Also, application of interventional radiology methods for those cases were not preferred, as it showed the same worse prognosis (46). Chemoembolization was one of the methods that was tried for such category of tumors with shown poor short-term outcomes and unknown long-term results (47). Among all these options, resection appeared to be the best option in large tumors, with proven safety in high volume centers and acceptable morbidity (48-51) (*Fig. 2, 3*). Shah and his team performed a study to evaluate results of resection in large tumors and comparing them to cases posing smaller tumors (<10cm) and to detect the factors affecting the proposed incidence of recurrence (41). Their results showed that overall survival was not significantly different (54% vs. 53% at 5 years). In comparison, other articles reported lower overall survival rates for resection of such large tumors (48,49,52).

With accurate preoperative risk assessment, and advanced surgical techniques using recent technology for coagulation and vessel sealing, resection of such tumors can be done safely and with the least expected complications (53).

Caudate lobe HCC

The caudate lobe could be a primary site for HCC and also a site of metastatic malignancy (54). Caudate resection can be performed as an extension of a lobectomy or other types of hepatectomy or as isolated resection, which is the most demanding

Figure 2 - CT scan showing large exophytic hepatocellular carcinoma in cirrhotic liver. (a) - Large HCC right hemi-liver, (b) - Large exophytic HCC in left lateral section.

Figure 3 - Operative photos of large exophytic hepatocellular carcinoma. (a) - Exophytic bleeding HCC from left lateral section, (b) - Large exophytic HCC from segment VI, (c) - Exophytic HCC from segment VIII (d) - Large exophytic HCC from left lateral section.

from a technical standpoint (55). Therefore, surgery for HCC originating in the caudate lobe is challenging for hepatic surgeons (56,57). Non-surgical treatment such as percutaneous ethanol injection, RFA and TACE have been developed, but have been thought to be technically difficult. Also, the results are less certain than with surgery (58-60). Liver resection for caudate lobe tumors can now be performed in high-volume centers with an acceptable morbidity of 50%-60% and no mortality (61,62). In our series the rate of post-operative complications was 33% with no mortality which was comparable to other series (*table 1*) (63).

Thus, caudate lobe resection appears to be well-tolerated, even in patients with poor liver function. Ikegami et al. reported that limited resection of HCC in the caudate

lobe confers prognostic values similar to those obtained in other segments (59). Furthermore, other authors have reported comparable survival rates for patients with HCC in the caudate lobe and those with HCC in other locations (58,59). The previous reports were comparable to our series in which the overall survival rates after isolated caudate lobectomy were 62% and 34% at 1 and 3 years, respectively; for those after hepatectomy for HCC in other locations, the rates were 68.6% and 29.6%, respectively (20). We could conclude from our study that isolated caudate lobe resection is a feasible procedure and can be undertaken with low morbidity and nil mortality. It also maximally spares hepatic parenchyma in patients with hepatic dysfunction. Careful technique and detailed anatomic knowledge of the caudate lobe are essential for the safe use of this procedure (63)(*fig. 4, 5, 6*).

Table 1- Results of different studies for caudate lobe resection.

Study	Year	Number of patients	Morbidity (%)	Mortality (%)	Recurrence (%)	Survival
Yamamoto (14)	2004	15	13	0	66	70% at 3 years
Tanaka (10)	2005	20	60	0	50	25% at 5 years
Wen (16)	2008	11	45	0	54	48% at 16 months
Sakoda (17)	2009	12	16	0.08	41	50% at 3 years
Liu Peng (18)	2010	114	18	0	66	31% at 5 years
Wahab (62)	2011	30	33	0	40	11% at 5 years

Figure 4 - CT scan of large caudate lobe HCC, (a) - Preoperative, (b)- After isolated caudate lobe resection.

HCC invading the biliary tree

Jaundice is present in 19% to 40% of patients with HCC at the time of diagnosis. However, obstructive jaundice is uncommon as the main clinical feature of HCC (64). Jaundice in patients with primary HCC usually results from diffuse tumour infiltration, hilar invasion, severe cirrhosis, progressive liver failure, or a combination of these factors. The prognosis in these cases is dismal, and death follows in a short time. According to some recent literature, however, a phenomenon has

Figure 5 - CT scan of large caudate lobe HCC.

Figure 6 - Operative photos of resection of large caudate lobe HCC. (a) - After dissection of the porta hepatis from the tumor, (b) - Dissection of the tumor from the IVC, (c) - After removal of the tumor with empty space between porta hepatis and the IVC.

been found that patients with primary HCC and obstructive jaundice due to biliary tumour thrombus may benefit from surgical intervention, which may result in long-term resolution of symptoms and, occasionally, cure (*fig. 7*)(65–67).

Significantly, advances in diagnostic means have allowed increasingly accurate preoperative diagnosis of HCC with obstructive jaundice due to biliary tumor thrombi. The bile duct can be obstructed by tumor thrombi, hemobilia, tumor compression, or tumor infiltration. Biliary tumor thrombi have been identified in 2% to 9% of autopsy and surgical specimens.

Several reports on HCCs with biliary tumor thrombi have reviewed autopsy cases or patients who underwent palliative treatment (66,68,69). Few studies have investigated resection of HCCs with obstructive jaundice due to biliary tumor thrombi in regard to survival and found that LR is the only line of treatment of those patients (66,70-72).

Local recurrence after liver transplantation

After liver transplantation, recurrence of HCC is not that less; with reported cases in about 16% of patients. Such recurrence affects the outcome greatly. Management of such cases have attracted the attention of all experts in the field: this can be clearly

shown by the increased number of studies during the past years (73).

In spite of this increased number of publications, there are no RCT or even large cohorts addressing this issue.

According to many articles (73-78), time elapsed since LT and the appearance of recurrence is an important prognostic factor regarding survival, with worst prognosis expected with early HCC recurrence (within 24 months). Early HCC recurrence could be due to non-detectable extra-hepatic spread that was found before performing liver transplantation, and also as a consequence of circulating HCC cell clones engrafting and growing in a target organ in the post-transplant period (79).

On the other hand, late recurrence was explained to be due to late engrafting of HCC cells that remained latent and less numerous for a longer time after liver transplantation (75,79). In LT patients, immunosuppression is expected to have a major effect on the percent recurrence of HCC (80,81).

For both isolated hepatic and extra-hepatic metastases, surgical resection was found as the best treatment option offering longer survival chance (82-84).

Post-operative mortality and morbidity were very low in both resection of grafted liver and other organ metastases (e.g., lung, adrenal gland). Based on the

Figure 7 - Left lobe HCC in cirrhotic liver invading the extra-hepatic biliary system. (a) - ERCP photo showing large filling defect (arrow) inside the common bile duct, (b) - IO cholangiogram showing the same findings, (c) - Operative photo of distended common bile duct with tumor thrombus, (d) - After dissection of the distal common bile duct and both right and left hepatic ducts, (e) - After division of the distal common bile duct, (f) - Postoperative photo of resected left hemi-liver and extra-hepatic biliary system (CBD, common bile duct; RHD, right hepatic duct; LHD, left hepatic duct; GB, gall bladder).

current knowledge, surgery for HCC recurrence is a valuable option if performed in selected patients with curative intents, and we can offer it whenever possible. On the contrary, little is known about re-transplantation for intra-hepatic recurrent HCC, and it is currently considered not appropriate (85).

Unresectable but still limited HCC recurrence may undergo loco-regional therapy including TACE, SIRT, and RFA, with accepted survival rates (6). These treatments appeared to be safe and well-tolerated and may be repeated multiple times or combined in a multi-modality approach (86-88).

CONCLUSION

Liver resection should be considered when technically and functionally feasible, or after failure of non-surgical as palliative approach. In our hands, individual patient selection by an expert panel of experienced liver specialists appears to be more reliable than existing classification systems for the prediction of safe resection in HCC patients.

In the era of LT and interventional radiology as methods for HCC management in LC, LR still has a role. LR can be offered as a bridge for liver transplantation. In large tumors more than 10 cm, the only curative line of treatment is resection. Caudate lobe resection for HCC in cirrhotic liver is safe and feasible in experienced hands. For HCC cases with obstructive jaundice due to invasion of the extra-hepatic biliary system, resection may be the only curative treatment or as a bridge for liver transplantation.

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