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Review

Current status of hepatic resection for hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is one of the most common tumors worldwide. For this disease, a variety of therapeutic measures have been applied, including hepatic resections, total hepatectomy followed by allografting, transarterial chemoembolization, and percutaneous tumor ablative therapy by ethanol, microwave coagulation, and radiofrequency ablation. This article focuses on the current status of hepatic resections for HCC.

Key words: hepatocellular carcinoma, hepatic resection

Introduction

Hepatocellular carcinoma (HCC) is one of the most common tumors worldwide, with an estimated incidence ranging between 500 000 and 1 000 000 new cases annually. Historically, hepatectomy, either partial or total, has been considered the mainstay of surgical therapy. Liver transplantation, although known to have superior outcomes in patients with advanced concomitant cirrhosis, is often not feasible as the availability of hepatic allografts cannot meet demand; therefore, liver transplantation can be applied to a limited number of patients with HCC. To date, considerable knowledge and experience have been accumulated in resectional treatment for HCC, particularly in industrialized countries with a high incidence of viral hepatitis, and include the following:

1. Patient selection
2. Improved preoperative diagnosis of tumor size and location in relation to intrahepatic vasculature
3. Refined techniques for parenchymal dissection
4. Improved understanding of the oncological behavior of HCC
5. The influence of hepatic parenchymal inflammation on recurrence.

The purpose of this review article is to describe the current indications for and outcomes of resectional treatment for HCC.

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Preoperative evaluation

The accurate preoperative assessment of hepatic reserve as well as tumor size and distribution is important when considering surgery for HCC and include some or all of the following:

1. Radiological diagnostic tests: computed tomography (CT), ultrasonography (US), magnetic resonance imaging (MRI), angiography
2. Viral serological markers: hepatitis B virus (HBV), hepatitis C virus (HCV)
3. Tumor markers: alpha-fetoprotein (AFP), L3, protein induced by vitamin K absence or antagonist (PIVKA)
4. Assessment of cardiac disease, diabetes mellitus, ascites, icterus, nutrition
5. Assessment of hepatic reserve: indocyanine green retention rate

Among the radiologic diagnostic tests, helical triphasic CT is the standard study; ultrasonography is sensitive for small, early HCCs but is inherently subjective. Angiography gives accurate information on the anatomical variation of the inflow vessels (hepatic artery and portal vein) as well as portal vein thromboembolism. MRI allows an objective assessment of the intrahepatic vasculature, especially the hepatic veins as they relate to the tumor(s). Magnetic resonance cholangiography (MRC) gives information on the intrahepatic biliary

tree without the need for invasive studies such as endoscopic retrograde cholangiography (ERC) or percutaneous transhepatic cholangiography (PTC); however, the resolution of MRC does not produce the fine detail of the other two. Screening for hepatitis B and C should be performed. If HbsAg is positive, HbsAb, HbcAb, HbeAg, and HbeAb as well as blood HBV-DNA should be obtained. If HCVAb is positive, the quantitative viral load is assessed by blood HCV-RNA, and HCV serotyping is performed.

Strategy for hepatic resection

Because HCC usually develops in a cirrhotic or fibrotic liver, patient selection is of utmost importance. Preoperative selection criteria based on hepatic reserve consists of Child–Pugh classification and Indocyanine dye retention rate at 15 min (ICG R15).[1–3] Generally, patients should be in Child–Pugh class A or B, and the ICG R15 should be less than 35%. A value of less than 25 ng/ml for the lidocaine metabolism test with monoethylglycinexylidide (MEGX) has also been associated with safe hepatic resection.[4] Liver scintigraphy with 99 m-galactosyl-human serum albumin allows an assessment of hepatic reserve based on the selective uptake by asialoglycoprotein receptors on hepatocytes, which can be performed even in icteric patients.[5] Galactose elimination capacity has also been reported to predict complications and survival after hepatic resection.[6]

Of these studies, ICG R15 is the most frequently used determinant for the extent of hepatic resection and is utilized as follows: <15% for trisegmentectomy, <20% for lobectomy and anterior segmentectomy, <25% for posterior or medial segmentectomy, <30% for lateral segmentectomy, and <35% for subsegmentectomy or less.[7] To prevent postoperative hepatic failure, the preservation of hepatic parenchyma through the use of anatomical segmental or subsegmental resection as well as the judicious use of limited hepatic resection for small HCCs is advocated.

The spread of HCC is primarily through the bloodstream, first via the portal vein to cause intrahepatic metastases and later to extrahepatic organs such as the lung, bone, and adrenal glands. During the late phase of hepatic resection for HCC, tumor cells have been documented in the portal vein in 23% of patients whose tumor diameter exceeds 5 cm with macroscopic and/or microscopic vein invasion.[8] Therefore, inflow vessels should be occluded before hepatic mobilization or parenchymal dissection to minimize tumor cell dislodgment and spread.[9]

For resection of fibrotic or cirrhotic livers, conventional hilar dissection with separate control of the hepatic artery, portal vein, and bile duct of the segment or lobe to be resected often results in intractable ascites due to lymphorrhea. For this reason, hepatic inflow control is best achieved by en masse ligation and division of Glisson's pedicle of the hepatic segment or lobe that harbors HCC.[7–11]

When the HCC to be resected is located in the anterosuperior or posterosuperior subsegment, a thoracoabdominal or transdiaphragmatic approach may be required.[12,13] For resection of large HCCs, conventional inflow control and hepatic mobilization may be difficult or even dangerous. In such circumstances, it is best to start the transection of the hepatic parenchyma and control inflow vessels and hepatic veins as they are encountered during the parenchymal dissection.[14,15] For hepatic lobotomy or trisegmentectomy, residual liver size is an important determinant of early outcome.[16,17] Therefore, selected patients considered for extensive hepatic resection may benefit from preoperative portal vein embolization to induce compensatory hypertrophy of the unaffected liver.[18]

In cirrhotic patients, upper gastrointestinal endoscopy should be performed to evaluate esophagogastric varices before resectional therapy. In patients with a history of variceal hemorrhage and in those with large varices, endoscopic injection sclerotherapy or variceal ligation should be performed.[19,20] In selected patients with nonadvanced HCC, concomitant devascularization procedures may be performed during laparotomy.[20] Preoperative transarterial chemotherapy does not seem to improve the outcome of hepatic resection for HCC.[21,22] However, selected patients may become operable by preoperative systemic immunochemotherapy, including interferon.[23]

Perioperative management

Although the liver is a sterile organ, infectious complications are not uncommon following liver resection.[24] Preoperative nasopharyngeal culture or decontamination by mupirocine ointment is recommended. For prophylactic purpose, patients without obvious bacterial contamination are covered perioperatively with broad-spectrum antibiotics intravenously.[7]

Intraoperatively, ultrasonography is first performed to confirm the size and location of the tumor(s) and to identify their relationship to the intrahepatic vasculature; this allows determination of the hepatic resection plane.[25,26] During hepatic parenchymal transection, central venous pressure is preferably maintained below 5 cm H_2O to minimize blood loss.[27] For diaphragmatic invasion, combined resection of the diaphragm is a safe technique that can give long-term survival comparable to those cases without such invasion.[28,29]

Postoperatively, intravenous fluid of 5% glucose with electrolyte composition of quarter-normal saline is given sparingly to maintain a low central venous pressure. Hypovolemia is corrected by intravenous colloids rather than crystalloids to avoid tissue and liver edema. Generally, the nasogastric tube can be removed on the first postoperative day, and oral intake is resumed the next day to minimize bacterial translocation through the intestine.[7,30,31] For uncomplicated patients, the drains are removed by the fifth postoperative day. For patients with persistent bile leakage with or without signs of infection, the drains should be left in place until this subsides. Daily irrigation of the cavity and antibiotic therapy may required.

If signs of infection develop after the abdominal drains have been removal, CT with contrast is performed to rule out abscesses. If the tissue around the fluid collection exhibits enhancement, or if the fluid contains air–fluid levels or air bubbles, the fluid is drained percutaneously under ultrasound or CT guidance. Early recognition of intraperitoneal septic complications is important because uncontrolled infection among cirrhotics can lead to hepatic failure.[24]

Results of hepatic resection for HCC

Mortality and morbidity of hepatic resection

Early and late outcomes for both the Eastern and Western experience, respectively, are shown in the following tables.[32–37]

Improved patients selection, better understanding of intrahepatic vascular anatomy, and reduced intraoperative blood loss are clinically relevant factors responsible for the improvement in outcomes over the past one to two decades.[19,38]

Complications of hepatic resection include intraperitoneal hemorrhage, gastrointestinal bleeding, atelectasis, pleural effusion, ascites, wound infection, intraperitoneal septic complications such as subphrenic abscess, and liver failure. Mortality after hepatic resection for HCC is usually due to liver failure caused directly by excessive resection or indirectly following infectious and/or hemorrhagic complications. Once progressive hyperbilirubinemia with a ratio of direct : indirect serum bilirubin of 2 : 1 and hyperammonemia with poor synthetic function are observed, liver failure is usually fatal without urgent liver replacement.

Table 1. Mortality after hepatic resection

Author	Study years	No. of patients	No. with cirrhosis	Percent with cirrhosis	Mortality (%)
Eastern experience					
Takenaka[32]	1985–1993	280	146	52%	[6 (2%)][a]
Hsia[2]	1991–1996	168	79	47%	[3 (1.8%)][a]
Poon[40]	1994–1999	241	104	43%	6 (2.5%)
Hanazaki[33]	1983–2000	386	171	44%	27 (7%)
Imamura[37]	1994–2002	915	301	33%	0
Western experience					
Fong[35]	1991–1999	1540			7 (4.5%)
Grazi[36]	1992–2001	157	157	100%	3 (1.3%)

[a] [ ], 30-day operative mortality
[b] Cirrhotic patients only

Table 2. Long-term survival after hepatic resection

Author	Study years	No. of patients	3-year survival	3-year disease-free survival	5-year survival	5-year disease-free survival
Eastern experience						
Takenaka[32]	1985–1993	280	70%	41%	50%	29%
Makuuchi[3]	1990–1998	367	73%	32%	47%	13%
Hsia[2]	1991–1996	168	70%	49%	59%	40%
Poon[40]	1994–1999	241	62%	38%	49%	25%
Hanazaki[33]	1983–2000	386	51%	37%	34%	23%
Western experience						
Fong[35]	1991–1999	154	54%	—	37%	—
Grazi[36]	1992–2001	157	72%	49%	50%	28%

Table 3. Prognostic factors of hepatocellular carcinoma (HCC)

Tumor/patient characteristics	Risk of recurrence
Clinical factors	
Preoperative liver function status	Child–Pugh A < B or C
Sex	Male > female
Age	Young < old
Underlying liver disease	Hepatitis B < C
Diabetes mellitus	Yes > no
Rupture	Yes > no
Operative factors	
Number of tumors	Multiple > single
Size of tumors	Large > small
Surgical manipulation of tumors	Yes > minimal
Anatomical resection	Yes < no
Perioperative blood transfusion	Yes > no
Postoperative factors	
Interval to recurrence	Before or at 1 year > after 1 year
Concurrent extrahepatic recurrence	Yes > no
Type of treatment for recurrence	Transarterial oily chemoembolization > reresection
Pathological HCC factors	
Microvascular invasion	Yes > no
Satellite nodules	Yes > no
pTNM stage	III or IV > I or II
Nuclear grade	3 > 1 or 2
Fibrolamellar HCC	Yes < no
DNA ploidy	Diploid < aneuploid with multiple G_0/G_1 peaks
Mitotic count	High > low
Proliferative activity	High > low
Noncancerous parenchyma	
Inflammation in the liver remnant	Yes > minimal
Liver cirrhosis/fibrosis	Yes > no
Laboratory	
Preoperative blood values	
Serum AFP	Over 400 ng/ml > less than 10 ng/ml
Serum VEGF	Over > equal to or less than 500 pg/ml
Serum IL-10	Over > equal to or less than 12 pg/ml

Oncological outcome: prognostic factors

Prognostic factors of HCC after hepatic resection are listed in Table 3. Disease recurrence is related to advanced cancer stages as determined by tumor size and number, vascular invasion and growth pattern.

As previously stated, because HCC usually emerges in diseased livers with abnormal hepatic parenchyma, major hepatic resections are associated with the risk of postoperative liver failure. For this reason, a wide resection margin is often unadvisable to obtain. The significance of the resection margin as a prognostic factor remains controversial.[19,33,39] Poon et al. in 2000 reported that what seems to be a positive association between histological margin and local recurrence is usually due to the underlying venous invasion or intrahepatic microsatellites, and that the gross surgical margin does not seem to be crucial.[40] For HCCs located below the diaphragmatic dome, combined resection of the liver with diaphragm is safe and gives survival comparable to those without diaphragmatic involvement, probably because histological invasion is unusual.[28,29]

Gross portal vein tumor thrombosis is associated with poor prognosis.[41] Technically, however, removal of extensive tumor thrombi such as those extending into or beyond the portal bifurcation can be performed with acceptable mortality, which can lead to long-term survival in selected patients.[41–45] Extensive portal vein tumor thrombi often show invasion of the portal vein wall, for which resection rather than simple thrombectomy should be considered.[44] The clinical significance of portal thromboembolectomy for portal decompression with the resultant prevention of variceal bleeding has yet to be determined.

Biliary tumor thrombosis is a rare complication of HCC, which usually does not invade the bile duct

wall.[46,47] With appropriate management of jaundice, if present, hepatic resection with thrombectomy through a choledochotomy gives long-term survival comparable to conventional resection.

Effect of noncancerous hepatic parenchyma on recurrence

Active inflammatory and proliferative hepatitic activity of the noncancerous hepatic parenchyma seems to play a major role in intrahepatic recurrence.[48–51] Further, fibrosis or cirrhosis seems to be associated with poor survival beyond 5 years after surgery.[52]

Significance of palliative hepatic resection

Because the survival for patients with unresectable HCC is limited and can be associated with tumor rupture, palliative hepatic resection in combination with other therapeutic modalities such as intraoperative treatment of residual HCCs have been advocated to prolong survival.[53–55] Once ruptured, HCC is best treated by transarterial embolization followed by elective hepatic resection.[56,57] For cases of intraabdominal HCC rupture, peritoneal dissemination frequently follows successful resection.[57,58] Many other clinical, histological, oncological, viral, and laboratory parameters have also been correlated with recurrence of HCC.[59–68]

Prevention and treatment of recurrence after resection

The cumulative and disease-free survival of patients who underwent hepatic resection for HCC between June 1991 and December 2001 at the Department of Surgery II, Nagasaki University Hospital, Japan (Prof. Takashi Kanematsu) are shown in Figs. 1 and 2.[69]

The high incidence of recurrent HCC after hepatic resection is a universal phenomenon for which better treatment modalities are required. As shown in Fig. 3, the most common site of recurrence in this series was the remnant liver, which accounted for 88% of recurrence, followed by lung and bone.

Prevention of recurrent HCC after hepatic resection

Systemic or selective chemotherapy after hepatic resection of HCC has been associated with deterioration of long-term prognosis in cirrhotic patients.[70] Adoptive immunotherapy with autologous lymphocytes activated in vitro with recombinant interleukin-2 and antibody to

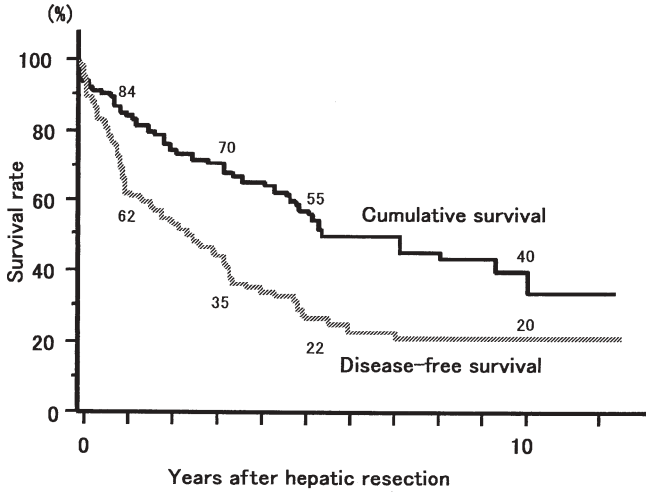

Fig. 1. Survival after hepatic resection for hepatocellular carcinoma[69]

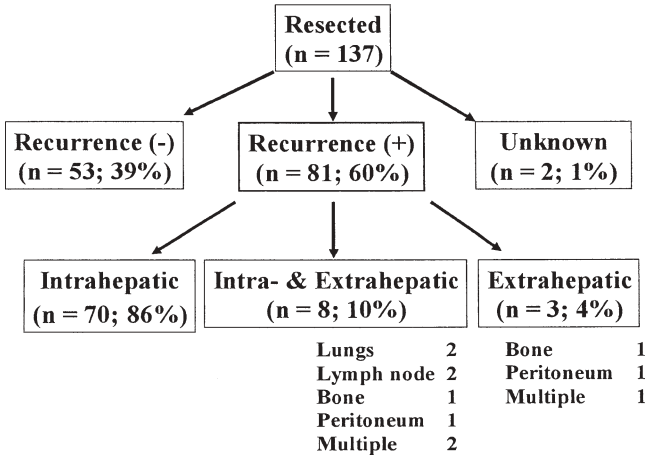

Fig. 2. Outcome of hepatic resection for hepatocellular carcinoma[69]

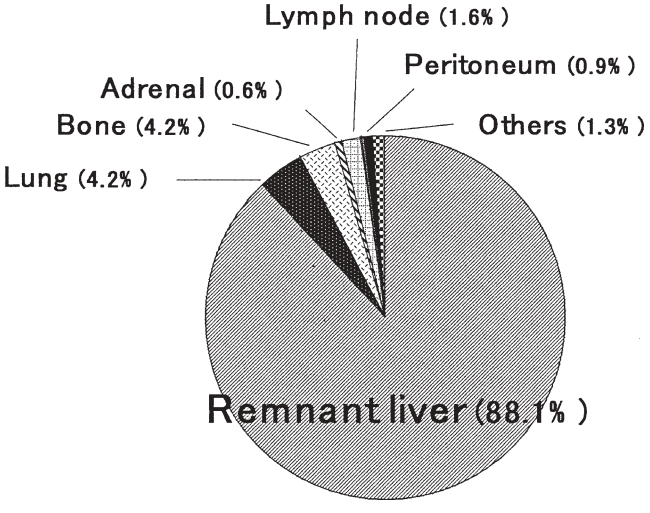

Fig. 3. Recurrence sites after hepatic resection for hepatocellular carcinoma[69]

CD3 or long-term postoperative interferon therapy may reduce the incidence of recurrent HCC.[71–73]

Treatment of recurrent HCC

Remnant liver

Recurrence in the remnant liver accounts for 75%–100% of the recurrences after hepatic resection worldwide, the etiology of which may be either intrahepatic recurrence or metachronous, multicentric HCC.[19,40,74] Current therapeutic modalities consist of repeat hepatic resection, transarterial chemoembolization or lipiodolization, and percutaneous needle ablative therapy; of these, repeat resection appears to be most the effective.[74–77] Patients with metachronous, multicentric HCCs seem to have a better survival compared to those with intrahepatic recurrence.[77]

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