Surgical Resection of Hepatocellular Carcinoma

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Background: Surgical management of hepatocellular carcinoma is challenging. Advances in patient selection and operative techniques are taking place in various parts of the world.

Methods: The literature on diagnosis, evaluation, and surgical treatment of hepatocellular carcinoma is reviewed and combined with the extensive clinical experience of the authors.

Results: While alpha-fetoprotein levels often are elevated in patients with large hepatocellular tumors, a combination of hepatic arteriography and Lipiodol computed tomography is the most sensitive imaging approach. An indocyanine green retention of more than 14% at 15 minutes predicts a poor outcome from surgery. Intraoperative ultrasound and ultrasonic dissector assist surgery. One-, three-, and five-year survival rates of 68%, 44%, and 35%, respectively, have been reported.

Conclusion: Methods to diagnose and assess the suitability of patients with hepatocellular carcinoma for surgical resection are now available, and operative and postoperative care has improved. Surgery remains the “gold standard” to which other treatments can be compared.

Introduction

Surgical resection of liver tumors is a challenge for many surgeons. In most Asian countries, the dominant primary malignant hepatic tumor is hepatocellular carcinoma (HCC). This article on surgical resection of HCC is a retrospective review of our experience in Hong Kong as well as a review of the literature.

HCC, a common tumor throughout the world, remains a major health problem in Asian countries, and its incidence is increasing in the Western world. In China, HCC accounts for approximately 100,000 deaths annually.[1] Hepatic tumor resection remains the only proven treatment that offers a meaningful chance of long-term survival. HCC, however, is associated with liver cirrhosis in 73% to 83% of cases,[2,3] most of which are related to viral hepatitis. Together with its multifocal nature, only approximately 20% of all patients with HCC are considered resectable at presentation. Underlying chronic liver disease also contributes to operative morbidity and mortality, especially after major heptectomy for HCC.

Recent advances have included more effective diagnostic techniques for earlier identification of tumors, more accurate preoperative evaluations, improved operative techniques, better measures to prevent recurrent lesion, and more effective nonoperative management for patients with advanced unresectable disease and recurrent tumors. Nonoperative management techniques, including percutaneous, ultrasound-guided alcohol injection and transarterial oily chemoembolization, could offer a comparable survival to that of heptectomy in selected patients. It is therefore relevant to review the current status of resection for HCC.

Preoperative Assessment and Perioperative Care

The objectives of preoperative investigations for patients with HCC include confirmation of the diagnosis, localization, determination of the local extent of the tumor, and assessment of the severity of underlying cirrhosis. Based on the initial assessment, resection (and its extent) or other forms of treatment are determined. The only well-established tumor marker for clinical application in the management of the patients with HCC is alpha-fetoprotein (AFP). While an elevated level is usually found in tumors of 5 cm or more in diameter, only approximately one third of patients with small HCC (less than 5 cm) have an elevated serum AFP above 200 ng/mL.[4] The trend of AFP titer is more informative than the absolute titer, and any continuous elevation of AFP titer above the diagnostic range should be considered as an early sign of occult HCC or recurrent tumor if heptectomy has been performed previously.

Percutaneous real-time ultrasound examination of the liver is noninvasive, inexpensive and, in experienced hands, highly accurate in the detection of HCC. The diagnostic accuracy can be further enhanced by the addition of AFP measurement.[5,6] Computed tomography is a useful diagnostic tool for preoperative assessment of patients with HCC. The combination of hepatic arteriography and Lipiodol computed tomography is perhaps the most sensitive diagnostic means for HCC presently available. When Lipiodol is injected into the hepatic artery, the lipid lymphographic agent is preferentially retained in HCC, probably as a result of the architectural deficiencies with enhanced permeability and the sluggish flow inside its well-developed neovasculature.[7] A homogeneous or dense patchy uptake of Lipiodol was usually found within the tumor when computed tomography examination was repeated at approximately two weeks later. The overall sensitivity and specificity of Lipiodol computed tomography examination for HCC are 97% and 77%, respectively.[8]

Knowledge of the hepatic vascular anatomy is helpful for surgical resection of HCC. The characteristic features of large HCC include increased neoplastic arterial blood supply, vascular lakes and channels, and arterioportal shunts. Localized stains in the capillary phase, however, may be the only angiographic feature of small HCC. The venous phase of the superior mesenteric arteriography is used to detect any tumor thrombus in the portal venous system.

Since postoperative liver failure is the major cause of mortality and morbidity after heptectomy for HCC, especially in cirrhotic patients, a careful preoperative evaluation of liver function is mandatory for the assessment of resectability. Routine laboratory tests including serum total bilirubin, serum albumin, and prothrombin time allow for the identification of only a few advanced cirrhotic patients. Measurement of the clearing capacity of the liver of sulfobromsulphalein sodium was reported to be a sensitive indicator of liver function. Patients with retention of more than 30% at 45 minutes are excluded from major liver resection.[9] Hasegawa and associates[10] have observed that patients with a high sulfobromsulphalein sodium clearance have a better outcome. Nevertheless, the follow-up period of the patients reported in this study is relatively short (7 months). Further study is needed to confirm the validity of this observation.

Conclusion: Surgical resection of HCC is a complex procedure that requires a multidisciplinary approach. The preoperative evaluation of the patient, the selection of the surgical procedure, and the perioperative care are crucial factors in determining the outcome of the operation.

References:
[2] Chung-mau Lo, MB, BS(HK), FRCS(Edin)
[3] Sheung-tat Fan, MS, FRCS(Glas), FACS

Clinical Image: Surgical Resection of Hepatocellular Carcinoma

Venice, Italy, 1996. Courtesy of Oscar F. Ballester, MD.
suggested that major resection should not be performed if the indocyanine green (ICG) retention at 15 minutes exceeded 10%. However, a more recent study[11] of 54 patients with cirrhosis who received major hepatectomy showed that an ICG retention of 14 at 15 minutes was the cutoff level that best defined the likelihood of survival or death of cirrhotic patients after operations. In addition, since surgery removes parts of functioning liver parenchyma, the volume of the remnant liver is also a determinant of the risk of postoperative liver failure.[12]

When an exploration is envisaged, the nutritional status of the patient is evaluated. Intensive nutritional support can reduce the net catabolic response to surgery and can improve protein synthesis and liver regeneration. A randomized control trial of 124 patients (most of whom had cirrhosis) who underwent hepatectomy for HCC has been conducted at Queen Mary Hospital in Hong Kong to investigate whether perioperative nutrition support could improve the outcome of these patients.[13] The study showed a reduction in the overall postoperative morbidity rate in the perioperative nutritional-support group compared to the control group, predominantly due to fewer septic complications. In addition, the supported group needed less diuretics to control ascites, and they experienced less weight loss after hepatectomy and less deterioration of liver function as measured by the change in the rate of clearance of ICG.

**Operative Technique**

Our operative techniques continue to evolve regarding the choice of incision, the modes of parenchymal transection, the mode of vascular control during the procedure, and the use of intraoperative ultrasonography.

While a thoracotomy was used extensively in the past, especially for the right hepatic resection, a bilateral subcostal incision with or without an upward midline extension is now more commonly used, regardless of the lateralization of lesion. For a right hepatic lobectomy, after initial control of the ipsilateral branches of the portal vein and hepatic artery at the hilum, parenchymal transection was conventionally used after the right lobe had been completely mobilized from the posterior abdominal wall. The right hepatic lobe would then be rotated anteriorly to allow an extraparenchymal control of the right hepatic vein and small caval branches leading to the back of the liver. After complete control of both the inflow and outflow vessels, the hepatic parenchyma is transected.

In some circumstances, however, the conventional approach for major right hepatectomy is not practical. Rotation of the right lobe is sometimes difficult because of tumor size or tumor infiltration into the surrounding anatomical structures such as the posterior abdominal wall, right diaphragm, or right adrenal gland. Rotation and mobilization of the right lobe of the liver are potentially hazardous when the lesion is compressing directly on the inferior vena cava. Even when mobilization is possible, twisting of the portal pedicle may render the contralateral hepatic lobe ischemic. Forceful retraction of a large HCC also can squeeze tumor cells into the circulation and sometimes cause intraoperative tumor rupture. Under these circumstances, an “anterior” approach has been adopted for major right hepatectomy in selected patients (Figs 1A- B).[14] After hilar dissection, the plane of transection is marked on Glisson’s capsule with the help of intraoperative ultrasonography (IOUS). Parenchymal transection is performed without prior mobilization of the right lobe of the liver. Using an ultrasonic dissector, the middle hepatic vein as well as the respective bile duct is exposed and controlled individually within the hepatic parenchyma. After complete transection of liver parenchyma, the anterior surface of the inferior vena cava is exposed, and the right hepatic vein can be encircled, clamped, and divided extraparenchymally. When the specimen is completely disconnected from the inferior vena cava, the right hepatic lobe is mobilized from the right abdominal cavity in the usual manner and delivered. Since 1992, approximately 30 patients at our center have undergone major right hepatectomy for HCC using the “anterior” approach. Preliminary analysis showed that, despite larger tumors in patients managed with the “anterior” approach group, satisfactory results have been obtained (comparable perioperative blood transfusion and fluid replacement without an increase in operative morbidity and mortality) compared to those managed with the conventional approach.

During parenchymal transection, portal clamping (Pringle’s maneuver) was employed by many surgeons to reduce blood loss. Its efficacy was shown in several retrospective studies,[15–17] but a prospective, randomized, comparative study to show its efficacy has not been reported. In our practice, portal clamping has been used with decreasing frequency because, in most instances, the hepatic veins was the source of bleeding. Furthermore, warm ischemia might have a harmful effect on the contralateral lobe of the liver.[18] This might adversely affect the recovery of liver function postoperatively, especially in patients with cirrhotic liver.

IOUS is an indispensable step in surgery for HCC and is considered to be not only the final diagnostic modality before resection, but also an operative guide for precise and safe liver resection. Since a high-frequency transducer (7.5, 10, or 13 MHz) can be used, IOUS allows better delineation and identification of small lesions when compared to preoperative ultrasound. Small daughter nodules and tumor thrombi in portal veins or hepatic veins are more readily identified with IOUS. The angle of scanning of the liver is unlimited with IOUS. It allows more precise localization of the tumor in relation to intrahepatic vascular structures and therefore is an important guidance for the line of parenchymal transection. In addition, guided biopsies of lesions of uncertain nature could be performed under IOUS guidance. With recent advances in preoperative diagnostic modalities, an increasing number of small HCCs are detected. In the presence of cirrhosis, the tumors often are invisible and nonpalpable during surgery. Thus, precise liver resection is not possible without IOUS in these cases. Approximately half of the neoplastic nodules measuring 3 cm or less in diameter would be overlooked without the use of IOUS.[19]

According to many investigators, intrahepatic and systemic metastases developed as a result of tumor spread along its portal venous tributaries. Based on this concept, routine removal of the entire tumor-bearing segment or subsegment was considered necessary for cure. The technical difficulty of delineating the boundary of individual hepatic subsegments was overcome by selective puncture of the portal vein branch followed by dye injection to map out the segment on the liver surface under IOUS guidance. IOUS also is helpful in identification of the inferior right hepatic vein during surgery so that right inferior segments (Couinaud segments V and VI) can be preserved to keep more functional liver mass even after transection of the right hepatic vein, which is removed together with the tumor.

The ultrasonic dissector was introduced in 1984 by Hodgson and Del Guercio[20] as an instrument for parenchymal transection during hepatectomy (Fig 2). The device has gained popularity among many liver surgeons. Use of the ultrasonic dissector appears to localize and control the branches of the hepatic vein more efficiently than the crushing clamp or finger fracture methods. Since bleeding from branches of the hepatic vein is the major source of bleeding during major hepatectomy, the use of the ultrasonic dissector may reduce blood loss and the need for blood transfusion. This has a beneficial effect on the operative outcome of patients, especially for...
Prognostic Factors

Different clinical, serological, gross pathological, and histopathological features are factors of probable prognostic importance for patients who are undergoing hepatectomy for HCC (Table 1).

Operative mortality of hepatectomy for HCC is increased for elderly patients, especially those with associated medical problems (e.g., diabetes mellitus and cardiac and pulmonary disease). One study[29] showed that the operative mortality rate increased to 19% for patients who were 65 years of age or older, and women were found to have a significantly better survival rate than men.[30-32] The mechanism for the difference is unclear, and a possible role of sex hormones is uncertain.

The potential role of hormonal receptors in the prognosis of patients with HCC has been examined. Estrogen receptors were found in approximately half of HCC patients in the cytosol of tumor cells.[33,34] However, survival rates were the same with or without estrogen receptors.[35] A significantly better survival rate was observed in patients with estrogen receptor-negative HCC.[36] Also, the prognosis was poorer for patients with raised serum AFP titers above 200 ng/mL than those with lower titers.[37] However, there is no consensus on the prognostic value of AFP.

Most investigators believed that the size of HCC predicts the long-term outcome of the patients regardless of the treatment received. An analysis of 144 patients with small HCC 5 cm or less in size reported five-year and 10-year survival rates of 67.9% and 54.3%, respectively.[38] The macroscopic appearance of the lesion (e.g., multinodular lesions, satellite nodules around the main tumor, irregular tumor outline, hilar lymph node metastases, and gross tumor infiltration of the portal venous system) may carry prognostic importance. Histological features associated with poor prognostic influence include lack of tumor capsule,[39] capsular invasion or portal vein invasion by tumor cells, presence of microsatellites, and poor differentiation of tumor. Conversely, the fibrolamellar variant of HCC is associated with a more favorable prognosis. This variant of HCC had a higher preponderence for women, and over 90% of them were 25 years of age or younger at presentation. A raised AFP titer and positive hepatitis B surface antigen were present in only approximately 10% of the patients. Very few of these patients had associated liver cirrhosis.

Postoperative Follow-up

A monitoring program following a successful hepatic resection is essential due to frequent recurrent disease, especially in the first two postoperative years. For careful disease surveillance, the patient should be examined approximately four weeks after the operation. Besides serum AFP levels and percutaneous ultrasound examination, angiography of the hepatic remnant may be helpful. Serum AFP titer and an ultrasound examination should be performed regularly at four-week intervals for the first postoperative year, every four months for the second year, and every three to four months thereafter. A persistent elevated titer of AFP above the normal range in the postoperative period may indicate residual disease, and a steady rise of AFP after initial normalization may indicate recurrent disease.

When recurrent disease is suspected, initial attention should be focused on the hepatic remnant. Percutaneous ultrasound examination followed by a hepatic arteriography of the hepatic remnant may be helpful. The relationship of tumor to major vascular structures, the location of the tumor, and the size of the hepatic remnant should be evaluated. If invasion or obstruction of the portal vein occurs, the possibility of liver transplantation should be considered.

Prognostic factors are important in determining the likelihood of recurrence. Among these factors, the size and location of the tumor, the presence of metastatic disease, and the degree of differentiation of the tumor are critical. Other factors that may influence prognosis include the patient's age, sex, and preoperative liver function. A recent study[36] has shown that patients with a macroscopic margin of 1 cm had a lower rate of recurrence than those with a macroscopic margin of 0.5 cm. Additionally, patients with elevated serum AFP levels at the time of diagnosis have a higher risk of recurrence and a shorter survival time.

Table 2. — Results of Hepatic Resections for Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Mortality Rate (%)</th>
<th>3-Year Survival (%)</th>
<th>5-Year Survival (%)</th>
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<td>1991</td>
<td>64</td>
<td>20</td>
<td>43</td>
<td>20</td>
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<tr>
<td>Bismuth[6]</td>
<td>1993</td>
<td>60</td>
<td>10</td>
<td>52</td>
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"Table 2. — Results of Hepatic Resections for Hepatocellular Carcinoma"

Those with liver cirrhosis. The ultrasonic dissector also allows precise division of the liver parenchyma along the plane determined by intraoperative ultrasonography. On the contrary, the finger fracture method is not precise. In patients with a large tumor, the transsection plane frequently enters the space between the tumor capsule and the uninvolved liver, thus rendering the tumor-free resection margin unsatisfactory. Although the pace of parenchymal transection may be slow when using the ultrasonic dissector, the transected surface is often completed quickly. Much time is spared in hemostasis after transection when compared to cases in which the crushing clamp or finger fracture method is used for transection.

In a retrospective study of 165 patients with HCC who underwent hepatectomy, Fan et al.[21] compared the results of hepatectomy using the crushing clamp and the finger fracture techniques (96 patients) with those using the ultrasonic dissector (69 patients). The groups were comparable in terms of preoperative liver function, tumor size and stage, incidence of cirrhosis, and proportion of patients undergoing major hepatectomy. Use of the ultrasonic dissector resulted in statistically significant lower mean blood loss, lower mean blood transfusion requirement, fewer patients requiring blood transfusion, and fewer postoperative complications. A wider tumor-free resection margin and lower serum bilirubin level throughout the postoperative period were also observed in patients who received hepatectomy using the ultrasonic dissector. Thus, the operative outcomes of hepatectomy for HCC are better with the ultrasonic dissector than with the crushing clamp or the finger fracture techniques.

Extent of Liver Resection

At the time of hepatectomy, the extent of resection to ensure a curative resection is uncertain. A resection margin that is free of tumor is considered necessary for curative resection of HCC and, according to many investigators, a macroscopic margin of 1 cm is adequate.[22-24] However, interpretation of the 1-cm resection margin may vary according to the size of the lesion. While a 1-cm margin of nontumorous liver was thought to be sufficient for small tumors of less than 5 cm, this might not be adequate for larger tumor. When a large HCC was examined histologically, residual disease could be found at a macroscopic surgical margin of 2 cm.[25]

As proposed by Makuuchi and associates[26] in the theory of systematic subsegmentectomy, intrahepatic metastasis of HCC is spread by invasion of the portal venous system. Therefore, the entire Couinaud segment of the liver supplied by the involved portal vein should be resected in order to achieve an adequate curative liver resection. Conversely, Ozawa et al.[27] advocated that the involved segment and the adjacent segment of the Goldsmith and Woodbourne classification[28] should be resected for cure if the liver function permits. The decision for the extent of liver resection is based on preoperative liver function, the relationship of tumor to major vascular structures, the I05 finding of additional tumor nodules near to the proposed transection margin and, most importantly, the status of uninvolved liver. In the case of cirrhosis, sacrificing a large volume of uninvolved liver in exchange for an adequate margin often results in difficulty with postoperative management and mortality. A positive margin is undesirable, but a wide tumor-free margin is not always protective of recurrence since liver cells in the liver remnant may undergo hepatocarcinogenesis any time after hepatectomy. Therefore, it is important to preserve as much liver parenchyma as possible in the case of cirrhosis.
Results

In recent years, operative mortality rates following liver resection for HCC have ranged from 9% to 23% (Table 2). Causes of perioperative mortality are liver failure, bleeding complications, and sepsis. Five-year survival rates as high as 49% have been reported. Comparisons of survival data are difficult and largely invalid because no universally accepted staging system is in use and also because many authors exclude perioperative mortality when reporting long-term survival. Many other factors including the incidence and severity of underlying cirrhosis, the size of tumors, and the extent of liver resection may affect the perioperative and long-term outcome of the patients.

From 1972 to 1994, 343 patients with HCC underwent hepatectomy at Queen Mary Hospital at The University of Hong Kong. The experience can be divided roughly into three time periods: 1972 to 1986, 1987 to 1991, and 1992 to 1994. Clinical parameters of the patients among these three time periods (eg, age, sex, percentage of patients with associated cirrhosis and hepatitis B, and tumor size) were all comparable. The resectability rate has risen significantly to 23% since 1992. The majority of the patients (73%) had major liver resection (defined as three or more of the Couinaud segments having been resected) regardless of the periods of hepatectomy. In the three time periods (1972-86, 1987-91, and 1992-94), improvements were seen in mobility rates (73%, 52%, 32%, respectively), in 30-day operative mortality rates (14%, 9.4%, and 4.5% respectively), and in hospital mortality (21.5%, 14.8%, and 6%, respectively). The survival rates also improved with one-, three-, and five-year survival rates of 68%, 44%, and 35%, respectively, for the 194 patients after 1987 compared to 48%, 21%, and 14%, respectively, for the 149 patients before 1987.

Many factors may have contributed to the recent improvement of the results of hepatectomy for HCC. Better technological support with IOUS and the ultrasonic dissector may decrease the risk of injuring major vascular structure because the intended plane of parenchymal transection can be adhered to accurately. Careful perioperative parenteral nutritional support also may affect outcome, especially in cirrhotic patients undergoing major liver resection. A bilateral subcostal incision provides satisfactory exposure without the need for a thoracotomy and also may eliminate the frequent postoperative pleural effusion. The lowered incidence of hemorrhage and intra-abdominal sepsis after surgery reflects the value of meticulous attention to guard against bleeding and bile leak. Also, better management of patients with recurrent disease contributes to the improvement of the overall survival. An adequate surveillance with a combination of serial AFP assay and percutaneous ultrasonography provides a satisfactory postoperative monitoring. The use of transarterial oily chemoembolization and percutaneous alcohol injection allows effective control of intrahepatic recurrences and thus a better survival. In selected patients, re-resection for localized disease, either within the hepatic remnant or in extrahepatic locations, may provide benefit.

Discussion

Although improved results have been obtained with surgical resection in recent years, most patients with HCC present with advanced disease, and the majority of them are unreatactable. While early diagnosis and intervention are important to the successful management of HCC, the widespread application of a well-developed screening program for early cancer detection is hampered by cost, even when applied to a population in endemic areas. Since the yield of mass screening is low in comparison to the efforts, routine screening should be restricted to high-risk patients such as hepatitis B carriers, patients with chronic liver disease, and family members of patients with HCC.

While favorable outcomes have been seen in elective hepatectomy for HCC, the mortality rate associated with emergency hepatectomy for ruptured HCC has been nearly 50%. Several factors contribute to the unsatisfactory results of emergency hepatectomy: (1) A thorough evaluation of the underlying disease is usually not possible because of the urgency of the situation. (2) The exact location of the disease, especially occult tumor nodules, is easily missed. (3) Detailed information of the hepatic reserve is largely unknown, and a history of hemorraghic shock would render the liver function worse than before the rupture. In addition, an analysis at our institution of 96 patients with large tumors measuring 5 cm or more indicates that a history of ruptured hepatic cancer does not increase the risk of postresectional tumor recurrence.[53] Given the major drawbacks associated with emergency hepatectomy, a two-stage treatment is the preferred approach. Initial hemostasis with the least invasive measure followed by definitive treatment is considered the safest strategy to pursue without compromising the chance of long-term survival. Initial treatment includes transcatheter arterial embolization and hepatic artery ligation. If the results of the subsequent workup are favorable, a hepatectomy can be offered at the second stage of the treatment. Favorable results were observed in 21 patients who underwent a second-stage hepatectomy for their ruptured tumor with a mean survival of 380 days and a three-month survival rate of 89.4%.

Multimodality treatment also may play an important role in providing favorable outcomes in the future. Preoperative arterial embolization alone or with portal vein embolization and preoperative transcatheter arterial chemoembolization have produced favorable survival results. The value of postoperative adjuvant chemotherapy has been controversial, but recent retrospective data suggest that either systemic or regional chemotherapy might be useful. Further prospective randomized trials are needed. Conversely, a recent study [56] from Japan reports on the effectiveness of polypropenoic acid to control recurrence and second primary tumors after hepatectomy for patients with HCC. This may enhance the long-term survival in patients who undergo surgical resection for HCC.

While hepatic resection has produced favorable outcomes, many patients present with unresectable disease. Development of nonresectional therapies (eg, percutaneous ethanol injection, transcatheter oily chemoembolization, hormonal therapy, and immunotherapy) is needed to effectively manage these patients. With a multidisciplinary approach involving surgeons, oncologists, and radiologists, better quality of life and improved survival in patients with HCC is a reasonable goal.

References


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