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TOPIC HIGHLIGHT

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Principles of surgical resection in hilar cholangiocarcinoma

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Abstract

The aim of this article is to describe the surgical techniques for the treatment of hilar cholangiocarcinoma (HC). Resection with microscopically negative margin (R0) is the only way to cure patients with HC. Today, resection of the caudate lobe and part of segment Ⅳ, combined with a right or left hepatectomy, bile duct resection, lymphadenectomy of the hepatic hilum and sometimes vascular resection, is the standard surgical procedure for HC. Intraoperative frozen-section examination of proximal and distal biliary margins is necessary to confirm the suitability of resection. Although lymphadenectomy probably has little direct effect on survival, inaccurate staging information may influence post resection treatment recommendations. Aggressive venous and arterial resections should be undertaken in selected cases to achieve a R0 resection. The concept of "no-touch proposed" in 1999 by Neuhaus *et al* combine an extended right hepatectomy with systematic portal vein resection and caudate lobectomy avoiding hilar dissection and possible intraoperative microscopic dissemination of cancer cells. More recently minor liver resections have been proposed for treatment of HC. As the hilar bifurcation of the bile ducts is near to liver segments Ⅳ, Ⅴ and Ⅰ, adequate liver resection of these segments together with the bile ducts can result in cure.

Key words: Cholangiocarcinoma; Surgery; Technique

Core tip: The aim of this article is to describe the surgical techniques for the treatment of hilar cholangiocarcinoma (HC). In recent years, parenchyma-preserving hepatic resections have been proposed to treat high risk surgical patients without vascular infiltration. This type of liver resection must include segments Ⅰ, Ⅳb and Ⅴ. Radical surgery in patients with type Ⅰ or Ⅱ tumors should also include a right liver resection, except in the case of papillary HC and in high-risk surgical patients.

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INTRODUCTION

The aim of this article is to describe and discuss aspects of the surgical techniques used in the treatment of hilar cholangiocarcinoma (HC). No exhaustive survey of the results obtained by surgery will be made; this question is addressed in a separate section.

As is the case with the surgical treatment of other tumor diseases, the improvements introduced in recent decades have derived not from evidence obtained in clinical trials but from a better understanding of the pathways of tumor spread[1-11]. Furthermore, most of the publications on this subject are studies comparing the results in recent cohorts with historical data. Due to the rarity of HC, most surgical series have a long inclusion period[12,13]. As a result, changes in perioperative management techniques over the course of a study can introduce bias. All these features have complicated and delayed the introduction of new techniques and strategies in the surgical treatment of HC.

HC surgery remains one of the most technically challenging operations for hepatobiliary surgeons, due to the complex, intimate, and sometimes variable anatomical relations of the bile duct and vascular structures. Radical resection with a microscopically negative margin (R0) is the only way to cure patients with HC and is associated with marked survival advantages compared to margin-positive resections. Unfortunately, only 50%-70% of patients who undergo surgery are candidates for curative resection[14]. Over the last decades, various technical innovations have been introduced in order to increase the chances of achieving a negative resection margin, which is the only prognostic factor under the control of the surgeon. Today, resection of the caudate lobe and part of Couinaud's segment Ⅳ, combined with a right or left hepatectomy, bile duct resection, lymphadenectomy of the hepatic hilum and sometimes vascular resection, is the standard surgical procedure for HC.

In the early 1970s, Longmire[15] introduced the concept of partial hepatectomy in resection of HC. However, because of the poor postoperative outcomes, hepatic resection was not recommended during the two following decades. Starting in the 1990s, more partial liver resections were performed for HC and were routinely combined with complete excision of the caudate lobe which is now fully accepted[16-22]. Likewise, better outcomes were reported with more radical surgery. The Memorial Sloan-Kettering group found that a concomitant hepatectomy resulted in an R0 resection in 78% of the patients and it was the only independent predictor of long-term survival[14]. Today the reported resectability rate ranges between 28% and 95% and the radical resection rate varies from 14% to 95%[23-27].

Over this period, Japanese surgeons have adopted a more aggressive approach and have achieved a higher negative margin resection rate[28]. They have also published numerous "tricks" to increase the chances of achieving radical resection.

LAPAROSCOPIC ASSESSMENT

The goal of staging laparoscopy is to exclude peritoneal metastases and small liver metastases, for which other noninvasive tests lack accuracy. van Gulik *et al*[29] reported that laparoscopy avoided unnecessary laparotomy in 25%-40% of patients. However, the use of staging or preoperative laparoscopy for HC is not widely accepted. Regimbeau *et al*[30] observed that laparoscopic assessment was not routinely performed in France in 2008 and that the accuracy of this procedure even in selected patients appeared to be low. That series included 56 patients and only in one case was resection contraindicated due to peritoneal carcinomatosis. More recently, Ruys *et al*[31] evaluated the benefit of laparoscopic assessment in 195 patients treated from 2000 to 2010. They found that the yield and accuracy of laparoscopy were considerably lower than those reported in previous studies including one performed by their own team. Laparoscopy avoided unnecessary laparotomy in only 14% of patients, with an accuracy of 32%.

Explanations for these changes are the impact of new imaging techniques and a better selection of patients for laparoscopy. After their review, the authors recommended that laparoscopy should be performed only in patients with Bismuth type Ⅲ and Ⅳ and that it should be used preceding laparotomy in a single session.

INTRAOPERATIVE BIOPSIES OF BILIARY MARGIN

Intraoperative frozen-section examination of proximal and distal biliary margins is necessary to confirm the suitability of resection. If invasive cancer is observed in the examination, additional resection is recommended to complete tumor removal[24,32]. However, additional resection of a positive proximal bile duct is difficult, and, usually, only a few extra millimeters can be resected. Some evidence has suggested that this additional resection of the proximal bile duct margin does not confer any survival advantage[33]. However, Ribero *et al*[34] found that median survival after additional resection of an intraoperative proximal bile duct margin was similar to that observed after primary R0 resections (30.6 *vs* 29.3). Therefore, although the available evidence is inconsistent, it seems advisable to try to complete resection whenever possible. On the other hand, this additional resection is associated with increasing incidence of postoperative biliary fistula. Finally, it should be borne in mind that intraoperative frozen section analysis of proximal bile duct margin is misleading in 9% patients.

LYMPHADENECTOMY

Lymphadenectomy associated with resection of HC must include lymph nodes, lymphatic channels and nerves surrounding the portal vein and hepatic artery. Nodal invasion beyond the hepatoduodenal ligament, including para-aortic nodal metastases, has a dismal prognosis with a 5-year survival of 0%-12%[35,36]. Therefore, routine lymph node dissection beyond the hepatoduodenal ligament is not generally recommended[36,37]. Once HC has metastasized to lymph nodes, an extended nodal dissection can provide a more accurate staging of the disease, but cannot improve survival.

The intraoperative finding of lymph node metastases is not considered a reason for abandoning resection when lymph node metastases are confined to the hepatic pedicle or the hepatoduodenal ligament[29]. However, tumor positive lymph nodes along the common hepatic artery or celiac axis are usually considered a contraindication for resection.

Lymphadenectomy for HC is unlikely to provide any great clinical benefit. Recently, Kitagawa *et al*[35] analysed 110 patients with HC who underwent both regional and para-aortic lymphadenectomy. A median of 24 lymph

nodes were retrieved during surgery. The disease-specific survival of patients with para-aortic lymph node metastasis was similar to M1 patients, suggesting that survival is not influenced by the extent of lymphadenectomy but rather by the presence of metastatic disease. However the Nagoya group[35] reported the 5-year survival for patients with para-aortic nodal metastases to be 12.3%. The finding that long-term survival is possible in patients with para-aortic disease encouraged the authors to perform aggressive surgery with extended lymph node dissection in selected patients.

Some authors have reported changes in the extent of lymphadenectomy in successive historical periods. In the initial period[38] lymphadenectomy was regional. It was then extended to include para-aortic nodes from the level of the diaphragm to aortic bifurcation, but this was associated with high morbidity. Finally lymphadenectomy was reduced to include the para-aortic nodes from the level of the coeliac axis to the mesenteric inferior vein. However, in the elderly (> 70 years) lymphadenectomy was limited to regional nodes in order to reduce perioperative mortality.

Although lymphadenectomy probably has little direct effect on survival, inaccurate staging information may influence post resection treatment recommendations which in turn have the potential to affect outcome. The studies by the Memorial Sloan-Kettering Center[39,40] suggest that a minimum of seven lymph nodes are needed in the surgical specimen to obtain a correct staging.

VASCULAR RESECTIONS

The role of portal vein resection (PVR) is controversial. Although portal vein bifurcation invasion used to be considered a relative contraindication for resection, more recently some surgeons have advocated a more aggressive approach[41]. Despite recent advances in diagnostic imaging techniques, portal vein invasion is still a relatively frequent intraoperative finding. Surgeons should suspect the presence of this invasion if they find severe adhesions between the tumor and the portal vein bifurcation. In this situation, combined resection and reconstruction of the portal vein is necessary to obtain a negative surgical margin.

de Jong *et al*[41] recently published the results of an international, multicenter database from seven major hepatobiliary centers. They found that 30-d postoperative mortality was higher in the cohort of patients who underwent concomitant PVR (17.6% *vs* 10.6%, $P = 0.03$). However, no differences in long-term outcome were observed compared to patients who underwent hepatectomy without vein resection. The authors conclude that PVR should be undertaken when necessary to extirpate all disease.

Nagino[42] recommend PVR only when the vessel adheres to and cannot be freed from the tumor during skeletonization resection of the hepatoduodenal ligament. In contrast, Neuhaus *et al*[43] recommend routine resection of the portal vein to achieve more radical surgery. This latter strategy will be discussed in another section. However, there are no randomized studies to support it.

Advances in surgical technique have facilitated the performance of hepatic artery resection and reconstruction during surgical treatment of HC. However, most of the studies[44-46] have shown negative results and do not recommend a combined resection of the hepatic artery for biliary cancer. However, in 2010, Igami *et al*[47] reported their experience with major hepatectomies with resection and reconstruction of the hepatic artery. In this series of 53 patients (18%) undergoing concomitant hepatic artery resection with or without PVR, only one patient died in the postoperative period and two survived more than five years after surgery.

EXTENDED HEPATECTOMY FOR HC: NO-TOUCH CONCEPT

Extended right hemihepatectomy consists of the resection of the right liver, the inferior part of segment Ⅳ, the hilar plate, and the entire caudate lobe[48], while extended left hemihepatectomy consists of resection of the left liver, the hilar plate of the right paramedian sector, and most of the caudate lobe. Both are coupled with complete resection of the extrahepatic bile duct and porta hepatis lymphadenectomy. The choice of side is dependent on the predominance of the tumor, but an extended right-hemihepatectomy is indicated for centrally located tumors, because of the length of each hepatic duct, the location of the hilar common bile duct in the hepatoduodenal ligament, the ease of complete caudate lobectomy and portal vein reconstruction, and the frequent involvement of the right hepatic artery[9,32].

"No-touch" concept

Usually, resection of the portal vein is carried out when the vein is adherent to the tumor and cannot be freed. However, even in cases where negative margins are proven histologically, local or peritoneal recurrence may occur during the follow-up period. One possible reason for recurrence is the microscopic dissemination of cancer cells during dissection of the portal vein in the hilar region, where the bile duct involved lies very close to the portal vein. In fact, the distance between the tumor and the outer layer of the adventitia of the portal vein is less than 1 mm, even in cases without portal infiltration[6]. What is more, the majority of hilar malignancies have microscopic perineural infiltration of the tumor.

Ebata *et al*[6] reported that the intraoperative macroscopic diagnosis of portal infiltration, regardless of microscopic diagnosis, was a significant prognostic factor. This result probably confirms that exposure of the tumor may occur during portal dissection, even in a case without microscopic infiltration. In the operative field microscopic invasion cannot be distinguished from adhesion and perivascular fibrosis[49].

The concept of no-touch was proposed in 1999 by Neuhaus *et al*[50] as a result of a multivariate analysis of prognostic factors in 100 resected patients. Surgical radicality, lymphangiosis carcinomatosa, perineural sheath infiltration and histopathological grading were identified as independent prognostic variables for the entire group of patients. However, in patients with curative resection, the only independent prognostic variable was an additional resection of the portal vein bifurcation. After this, the authors decided to apply the principles of no-touch techniques to HC and combined an extended right hepatectomy with PVR and caudate lobectomy. This technique avoids the dissection of the right hepatic artery, which can easily be infiltrated by tumor, and obtains a wide tumor-free biliary margin, since the left hepatic duct measures up to 5 cm.

The goal of a no-touch technique and an *en bloc* resection can be achieved by placing vascular clamps on the left portal vein branch within the umbilical fissure as well as on the portal vein trunk, directly above the pancreatic head, and dividing the two vessels without dissecting the portal vein bifurcation. This strategy is facilitated by the anatomical characteristics of the left portal vein which runs transversely from the bifurcation to the umbilical portion. After this, an end-to-end venous anastomosis is performed. This reconstruction straightens the portal vein, avoiding the kinking frequently observed after right hepatic resections. Depending on the extent of tumor growth to the left, it may be impossible to keep the whole of segment IV. This increases the risk of postoperative liver insufficiency, but reduces the number of biliary orifices to anastomose.

In 2012, Neuhaus *et al*[43] compared the oncological results of hilar *en bloc* resection to that of major hepatectomy. The 5-year survival of patients who underwent *en bloc* resection was significantly superior (58% *vs* 29%, $P = 0.021$).

LEFT RESECTIONS

Right or extended right hepatectomy is not indicated in cases of HC extending far to the left, with atrophy of segments Ⅱ and Ⅲ and with vascular complications in the left hemiliver. In these situations left resections are indicated and represent about 25%-30% of all resections. Left hepatectomy is considered to be a more complicated procedure, than right hepatectomy[8,51] and requires greater skill, especially in cases involving PVR and reconstruction. Resecting the portal vein bifurcation when performing a left trisectionectomy is substantially more difficult because of the relatively short course of the right portal vein before branching. Surgical resection for Bismuth-Corlette type Ⅲb tumor with involvement of the portal vein bifurcation may not be feasible even in specialized centers because of the difficulty of portal vein reconstruction.

The distance from the principal biliary bifurcation to the sectional ramification in the right liver is much shorter than in the left[52]. Furthermore, there are many anatomical variations in the right sectional bile ducts[53]. These anatomical issues may increase the difficulty of achieving tumor-free stumps for right sectional ducts during left hepatectomy compared with right hepatectomy. Furthermore, the presence of more complex biliary anastomoses increases the risk of postoperative biliary leakage.

Another oncological problem with left or left-extended hepatectomy is the need to preserve the right hepatic artery and the right portal vein, which increases the risk of tumor cell dissemination.

To confirm whether a predominantly left-sided tumor is resectable with a left trisectionectomy, the surgeon can apply a combination of manual palpation, intraoperative ultrasound and dissection along the posterior aspect of the right portal pedicle. These maneuvers could help to determine whether the tumor has extended to the posterior division of the right pedicle[54]. Lowering the hilar plate would be very useful in this exploration, because the division occurs intrahepatically; however, this dissection would be too close to the boundaries of the tumor and is not recommended.

If the right hepatic artery is infiltrated by the tumor, it must be resected *en bloc* to achieve a radial R0 resection. In this situation reconstruction of the right hepatic artery is difficult and the risk of technical failure is high. Based on the knowledge of spontaneous arterial revascularization of the liver after ligation of the proper hepatic artery, it has been proposed that pre-operative embolization of the proper hepatic artery induces development of arterial collaterals through the hepatic ligaments, providing additional arterial supply to the liver. This will facilitate the performance of a R0 resection, as the proper, left and right hepatic arteries could be totally resected without vascular anastomosis.

Yasuda *et al*[55] reported the preoperative arterial embolization of the proper hepatic artery in six patients. In all patients, arterial flow signals were detected in the liver with Doppler ultrasonography. Three weeks after embolization, surgery was performed and in all cases a R0 resection was achieved. During surgery, intraoperative Doppler ultrasonography confirmed collateral arterial blood flow in the right anterior and posterior segmental branches of the right hepatic artery. During dissection of the hepatoduodenal ligament, the bile duct can be dissected in the right liver without risk of injury to accompanying arterial branches. However, mobilization of the right liver or division of ligaments must be avoided to preserve arterial revascularization.

In the study by Shimizu *et al*[56] R0 resection was achieved in all seven patients who underwent right trisectionectomy, but in only eight of 13 patients (61.5%) undergoing left trisectionectomy. This suggests that a more extended resection from the right side, but not from the left, may provide greater potential for cure.

Some authors[57] consider that extended left hepatectomy increases the extent of resection in the periphery

of the liver, but that the oncological benefit in the perihilar region is very limited. However Nagino[42] reported that left trisectionectomy increased the number of negative proximal ductal margins compared with left hepatectomy, leading to a high proportion of R0 resections, and improving survival for patients with advanced left-sided perihilar cholangiocarcinomas[58]. Therefore, these authors recommend left trisectionectomy in such cases, even if the tumor is deemed to be resectable by left hepatectomy.

Despite the difficulties associated with left liver resections, no other treatments achieve survival rates comparable to those of surgical resection. Therefore left or extended left hepatectomy should be aggressively performed for type Ⅲb tumor if curative resection is possible, even in cases with portal involvement.

STRATEGY WITH BISMUTH TYPE Ⅰ AND Ⅱ PATIENTS

Some authors[12,14,27] have considered that patients with Bismuth type Ⅰ or Ⅱ tumors can be treated with local or hilar resections including the extrahepatic suprapancreatic biliary tract. However, others[10] have recommended a left hepatectomy, because this procedure affords high resectablity, is safe and provides good quality of postoperative life. Finally, others[13,32] support the indication of a right hepatectomy because the right hepatic artery passes behind the common hepatic duct and, therefore, can be infiltrated by cancer.

Bismuth type Ⅰ and Ⅱ HCs appear less advanced on cholangiography and are easier to resect than Bismuth type Ⅲ and Ⅳ tumors. Therefore hilar resection is the procedure preferred by many surgeons. However, locoregional recurrence may be frequent[12,15] even after R0 resections. Moreover, Seyama *et al*[26] reported better prognosis in patients with Bismuth type Ⅰ and Ⅱ tumors who underwent right hepatectomy with caudate lobectomy. Histologic evaluation of the right hepatic artery showed that its infiltration is infrequent, but the distance between the edge of the cancer and the arterial adventitia was very short (1 mm in many cases). Therefore without right hepatectomy the resection margin could have been positive.

In the opinion of Ikeyama *et al*[59] the surgical approach to Bismuth type Ⅰ and Ⅱ HCs should be based on the macroscopic tumor type seen in the preoperative study. For nodular and infiltrating HCs, right hepatectomy offers the best long-term survival, whereas for papillary tumor bile duct resection with or without limited hepatectomy is adequate unless spread of superficial cancer is discovered preoperatively.

PARENCHYMA PRESERVING SURGERY

A reduction in morbidity and mortality after liver resection is the key strategy for improving the results of surgical treatment of HC.

Minor liver resection (three segments or fewer, according to the Couinaud nomenclature) may be one way to resolve the problem of the high mortality after major liver resections. As the hilar bifurcation of the bile ducts is near to liver segments Ⅳ, Ⅴ and Ⅰ, adequate liver resection of these segments together with the bile ducts can result in cure. For early tumor stage, minor resection of segments Ⅰ, Ⅳb and Ⅴ has been performed to excise the tumor with adequate margins; this is termed "central liver resection" by some authors[60].

A central hepatectomy for HC can preserve up to 35% more functional liver parenchyma than an extended hepatectomy. However, it has not been widely accepted as an alternative to extended hepatectomy because of its uncertain oncological equivalence and greater technical complexity[61,62].

The study by Chen *et al*[63] did not find differences in cumulative survival rates between major and minor liver resection in patients with HC. Furthermore, major liver resection was associated with higher operative mortality and morbidity rates than minor resection. Chen *at al*[63] hold that major resections should be reserved for Bismuth-Corlette type Ⅲ HC with vascular invasion, or type Ⅳ HC. In central liver resection for HC, many intrahepatic bile ductal openings are left behind, making the reconstruction very difficult; this is the main disadvantage of this procedure. However, using their own technique of hepatojejunal anastomosis the same authors reported a bile leak rate of only 14%[63].

OTHER SURGICAL "TRICKS"

Resection of middle hepatic artery in right hepatectomy

Frequently, the middle hepatic artery (MHA) runs in close proximity to the HC. In this case, preservation of this artery in a right hepatectomy may result in a positive resection margin. On the other hand, interruption of the arterial flow could cause postoperative complications related to biliary ischemia such as the disruption of the bilioenteric anastomosis and liver abscess.

A retrospective study by Hirano *et al*[64] investigated the anatomical variations of the MHA and also assessed the safety of resection of the MHA combined with right hepatectomy, caudate lobectomy, and bile duct resection. In this study of 61 patients with hilar biliary malignancies, the perioperative outcomes in patients in whom the MHA was resected were similar to those in whom it was preserved.

Anatomic study of the microcirculation of the liver revealed that the intrahepatic bile ducts are fed by a dense surrounding vascular plexus arising from the hepatic artery[65]. After a right hepatectomy, the peribiliary plexuses of the bile ducts from the left medial and lateral sections may retain their connections through the plate system, compensating for any loss of arterial blood supply. Compensatory arterial blood supply to the area fed by the interrupted artery may also derive from intrahepatic interconnecting arterial pathways or vessels connecting the hepatic artery and the portal system.

Portal vein arterialization

PVA has been used in patients with portal hypertension, liver transplantation and acute liver failure to solve the occlusion of the hepatic artery. In the context of HC this procedure can be used to allow radical resection in patients requiring an extended left hepatectomy who present encasement of the right hepatic artery[66]. The encasement of the hepatic artery can prevent its resection and anastomoses. The objective of the PVA is to ensure adequate oxygen delivery to hepatocytes and biliary ducts. Animal experiments have suggested that PVA can improve the microcirculation in the liver, but a sustained increase in portal pressure can promote hepatocyte apoptosis and inhibit liver regeneration[67]. Anastomoses with small arteries (< 3 mm) should reduce the risk of severe portal hypertension. PVA can be considered a salvage procedure in special situations[68], but has some drawbacks that limit its indications.

CONCLUSION

The goal of surgical treatment of HC should be an R0 resection. The planning of surgery should take into account the difficulties in establishing tumor boundaries intraoperatively and the close proximity to certain anatomical structures such as the caudate lobe and the right hepatic artery. Therefore, potentially radical intervention should include resection of the bile duct with lymphadenectomy of the hepatic hilum and right hepatectomy including the caudate lobe and part of segment Ⅳb. There is evidence that systematic resection of the portal bifurcation can decrease the risk of loco-regional recurrence. However, not all authors agree on this point.

When the HC mainly involves the left liver (Ⅲb type) a left or left-extended hepatectomy should be performed. These interventions are technically more difficult and potentially less radical. In selected patients, resection and reconstruction of the right hepatic artery may offer the possibility of radical surgery in patients with tumors that mainly affect the left liver. Portal arterialization may be a salvage procedure in these patients when resection and reconstruction of the right hepatic artery is not possible.

In recent years, parenchyma-preserving hepatic resections have been proposed to treat high risk surgical patients without vascular infiltration. This type of liver resection must include segments Ⅰ, Ⅳb and Ⅴ. Radical surgery in patients with type Ⅰ or Ⅱ tumors should also include a right liver resection, except in the case of papillary HC and in high-risk surgical patients.

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