History of Surgery in Hilar Cholangiocarcinoma

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17.1 Introduction

In 1965, Dr. Gerald Klatskin reported in the American Journal of Medicine an article "*Adenocarcinoma of the Hepatic Duct at Its Bifurcation Within the Porta Hepatis*" [1]. The purpose of this report by Dr. Klatskin on 13 patients was "to draw attention to the unusual features of adenocarcinomas that arise in the hepatic duct at its bifurcation within the porta hepatis". Thereafter, this tumor is named after him as Klatskin tumor. Actually, tumors of this type have been reported before him [2–7], but the distinctive manifestations of this tumor have not received sufficient emphasis. Dr. Klatskin stated in his paper that "tumors of this type are frequently overlooked during laparotomy …, death in this disease is usually attributable to hepatocellular failure and/or hepatobiliary infection secondary to unrelieved biliary obstruction rather than to massive invasion of the liver by tumor or to extrahepatic metastases, palliative surgery aimed at relieving biliary obstruction may restore the patient to a good state of health for a remarkable long period of time, and such palliation may be achieved by internal drainage of only one of the major intrahepatic bile ducts". Some of these observations are still true even today on these tumors which for one reason or another cannot be resected!

The development of biliary enteric anastomoses has been extensively reviewed and reported by Ahrendt and Pitt [8] and by Braasch [9]. At the time when Dr. Klatskin published this landmark paper, biliary surgery and imaging were both at their embryonic stages. The first cholecystectomy was carried out by Carl Langenbuch in 1882 [10]. The first use of contrast to show the gallbladder in humans as quoted by Braasch [9], was carried out in 1924. The bile ducts were first visualized by injection of contrast into a biliary fistula in 1918 by Reich [11], Mirizzi first reported the use of operative cholangiogram [12]. Frommhold in 1953 introduced intravenous cholangiography which is now rarely used [13] and cannot be used in patients with obstructive jaundice. After the study by Carter and Saypol in 1952, percutaneous transhepatic cholangiography (PTBD) started to become available clinically [14]. PTBD was, however sparingly used because of its serious complications until the introduction of the Chiba or "skinny needle" technique by Okuda et al. in 1975 [15]. The first cannulation of the ampulla of Vater was in 1968 by McCune et al. [16] Oi in 1970 [17] and other Japanese groups, working with instrument manufacturers developed endoscopic retrograde cholangiopancreatogram [9]. Ultrasonography gradually established its foot-hold in the investigation of biliary tract disease in the twentieth century [18].

17.2 Early Attempts of Surgical Treatment

Surgical treatment of hilar cholangiocarcinoma is technically challenging because of the central location of the tumor in the liver hilum and its intimate relationships with adjacent liver parenchyma, the portal vein and its branches, and the hepatic arteries. Furthermore, the diagnosis and the assessment of the extent of local tumor infiltration of hilar cholangiocarcinoma has been a constant challenge to surgeons since the first description of this tumor by Durand-Fardel in 1840 (as quoted by Rershaw in 1922) [2] and its detailed pathological and clinical description by Klatskin in 1965 [1].

The early attempts of surgical treatment of hilar cholangiocarcinoma aimed primarily at palliation, with generally poor long-term survival outcomes. However, the short-term outcomes were rewarding, with relieve of jaundice and its associated pruritus, and prolongation in survival. Moreover, laparotomy was also used to provide an opportunity to diagnose hilar cholangiocarcinoma in patients with obstructive

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jaundice "by retrograde probing and cholangiography through the common hepatic duct …. and transhepatic cholangiography at the time of surgery" (to avoid the serious complications of bile peritonitis and cholangitis of preoperative percutaneous transhepatic cholangiography) [1].

Klatskin [1], and the surgeons before his time [6, 7] usually drained "only one of the two major hepatic ducts within the liver … by internal drainage via a T tube or vitallium tube threaded through the constricted bifurcation from below, or external drainage via a catheter inserted proximal to the stricture". Surgical stenting of malignant biliary stricture was soon replaced by other less-invasive and safer alternatives. The period of 15 or 20 years from the mid-1970s saw the technical development and maturation of endoscopic biliary procedures [19]. Endoscopic papillotomy, bile duct exploration, biliary stenting and other biliary tract procedures were established. At around the same time, percutaneous transhepatic external/externo-internal/internal biliary drainage procedures were developed. Unfortunately, these stents/tubes often become obstructed by tumor or cause cholangitis as a consequence of the presence of foreign bodies. Although these stents/tubes can be changed, patients often require repeated admissions into hospitals to treat complications and to change the stents/tubes. The alterative to stenting is internal biliary-enteric bypass, which is more invasive than endoscopic/percutaneous stenting but it results in less requirements for subsequent readmission into hospital to deal with complications arising from stenting. The methods and the choice of internal biliary-enteric bypass procedures have been extensively reviewed [8, 9].

17.3 Local Resection of Hilar Cholangiocarcinoma

In the 1910s, surgical management of hilar cholangiocarcinoma gradually evolved from primarily palliative with stenting or internal biliary-enteric bypass to curative resection [20, 21]. Early reports of resection of hilar cholangiocarcinoma typically involved local resections of the bile duct with hepaticojejunostomy [22, 23]. This operation resulted in low R0 resection rates at the expense of significant perioperative morbidity and mortality [24]. In a recent article by Ito et al. [25], the authors concluded after reviewing the medical literatures that R0 resection remains the most effective and only potentially curative therapy for hilar cholangiocarcinoma, and negative resection margins are associated with improved outcomes.

Local excision of the bile duct is not an adequate curative operation for hilar cholangiocarcinoma [26], except perhaps for small papillary Klatskin tumors without bile duct confluence involvement (type 1, Bismuth-Corlette classification) [22] confined to the bile duct wall (Tis and T1, AJCC staging for extrahepatic cholangiocarcinoma [27]). This can be explained by the patterns of spread of cholangiocarcinoma. The mean length of longitudinal spread along the bile duct is 6–10 mm for invasive filtration and 10–20 mm of superficial spread [28]. Therefore, a gross surgical margin of more than 1 cm in the infiltration type and more than 2 cm in the papillary and nodular types is required to achieve a R0 resection [29]. Furthermore, about 75 % of hilar cholangiocarcinoma is associated with perineural invasion (a prognostic factor for poor survival) [30, 31], 80 % has extended into the liver parenchyma [32, 33], 30 % involves the portal vein [32, 33] and around 45 % has metastases to the lymph nodes [29].

A more aggressive surgical approach is required to achieve better long-term survivals for patients with hilar cholangiocarcinoma.

17.4 Local Resection Versus Hepatic Resection for Hilar Cholangiocarcinoma: Operative Safety and Effectiveness

As the pathologic characteristics and the local invasive patterns of hilar cholangiocarcinoma are better understood, it becomes obvious that local excision is inadequate for radical resection of this tumor. Over the past two decades, there has been an increase in the use of hepatic resection to treat hilar cholangiocarcinoma, aiming at a wider resection to cure the disease.

There is little doubt that local resection is safer than liver resection in patients with hilar cholangiocarcinoma [34–36]. In a review article published by Boerema in 1990, perioperative mortality was significantly lower after bile duct resection than after hepatectomy (8 % vs. 15 %) [37]. In 1992, the group from Memorial Sloan-Kettering reported no mortality and 25 % morbidity after local excision compared with 8 and 36 %, respectively, after extended procedures [38]. In 1996, Pichlmayr et al. reported mortality rates of 12.7 % after liver surgery associated with bile duct resection versus 3.3 % after local resection [35]. In the 1990s, surgeons argued that the higher mortality after liver resection was a clear indication that local resection was the operation of choice, even though associated liver resection could improve radicality because long-term benefits were lost in the high operative mortality rates in liver resection [26, 34]. With better patient selection and improvement in perioperative management, postoperative mortalities and morbidities have significantly improved in the past few years [39–43]. In 2000, Launois published a study on the French experience, operative mortality rates were high but similar in patients with and without liver resection (17 % vs. 14 %) [44]. In 2000, Tsao et al. compared the results of surgical treatment in a Japanese center (Nagoya) where liver resection was performed routinely, with those of an American Center (Lahey Clinic) where isolated bile duct resection was

Table 17.1 Association between hepatectomy rate and R0 resection rate for hilar cholangiocarcinomas

Series	Year	Hepatectomy rate (%)	R0 resection rate (%)
Tsao et al. [45] (Lahey)	2000	16	28
Cameron et al. [24]	1990	20	15
Hadjis et al. [48]	1990	60	56
Burke et al. [47]	1998	73	83
Lai and Lau [51]	2005	89	72
Tsao et al. [45] (Nagoya)	2000	89	79
Capussotti et al. [43]	2002	89	89
Nimura et al. [49]	1990	98	89

preferred. The short term outcomes were good and similar between the two groups: mortality rate 4 % vs. 8 % and morbidity 44 % vs. 51 %, respectively [45]. Some Japanese groups have reported no mortality after bile duct resection associated with hepatectomy [39, 41, 42].

There are enough evidence to support that the rate of R0 resection increases with the rate of associated liver resections for hilar cholangiocarcinoma [26, 46–51], although R0 resection can still be achieved in some patients with isolated bile duct resection (Table 17.1).

The caudate lobe ducts join the left and right hepatic ducts near to their conference, explaining why the lobe is involved by hilar cholangiocarcinoma in 40–98 % of patients [49, 52– 54]. Retrospective studies have shown a decrease in local recurrence [55] and improvement in 5-year survival [25, 56, 57] when concomitant caudate lobe resection is performed. Tsao et al. stated that combining hilar resection and partial hepatectomy with complete caudate lobe resection can be performed safely in the hands of experienced surgeons who are familiar with caudate lobe anatomy [45]. This operation is now adopted by most Japanese and some Western surgeons [58–60].

17.5 Combined Liver Resection for Hilar Cholangiocarcinoma

In the past two decades, there has been an increased use of hepatic resection in patients with hilar cholangiocarcinoma. Major hepatic resection with caudate lobectomy addresses both direct hepatic invasion and intraductal extension of hilar cholangiocarcinoma to achieve a wider and, therefore, a higher chance of negative radial and longitudinal resection margins. Incorporating a major hepatic resection as a fundamental surgical strategy for hilar cholangiocarcinoma has increased the R0 resection rate [32, 36, 60–62], improved recurrence-free survivals, and decreased the incidence of hepatic recurrence [62].

In the review article by Ito et al. [25], the published 5-year survival rates after surgical resection for hilar cholangiocarcinoma vary from 25 to 40 %. Clinicopathological factors which have been shown to have a positive impact on long-term survivals include negative histologic margin status, concomitant hepatic resection, lack of nodal involvement, lower AJCC T stage, well-differentiated tumor grade, papillary tumor morphology and lack of perineural invasion. Of these, complete resection with histologically negative margins is the only modifiable factor and should therefore be the primary goal of surgical therapy. If the histological margin is involved by tumor (R1 resection), it is still controversial in the surgical literature as to whether R1 resection provides any survival benefits to patients when compared with patients with unresectable disease [41, 45, 62–68].

Long-term survival data coming from a single institution comparing local bile duct resection with combined hepatectomy should be interpreted with caution as these data concern hilar cholangiocarcinoma with different extension into the bile ducts. Patients undergoing local excision probably had tumors without (or at the most with minimal) involvement of the bile duct confluence. This is not clearly defined in most of the published articles, and the treatment was most likely planned according to tumor location, and that liver resection was scheduled for patients with more extensive diseases. It is, therefore, not surprising to find reports showing no evidence of any statistical difference in long-term survival after local resection when compared with extended surgery with liver resection [34, 35, 37, 38, 44, 69–73]. On the other hand, studies from single institution reported significantly increased survival after associated liver resection [26, 32, 37, 42, 58]. The evidence supporting associated liver resection to treat hilar cholangiocarcinoma came from the study by Tsao on comparing oriental and US experiences, reporting on significantly better long-term survival in Japanese patients undergoing more aggressive surgical strategy (5- and 10-year survival rates were 16 % and 12 % vs. 7 % and 2 %, respectively) [45]. Additional supporting evidence came from the report in 2005 by Dinant et al. from the Netherlands. With a change in policy to treat hilar cholangiocarcinoma with aggressive surgery, there was a higher R0 resection rate and an improvement in long-term survival, with no increase in operative morbidity or mortality [58].

To clarify whether local resection may have a role in patients with hilar cholangiocarcinoma, Capussotti et al. reviewed the medical literature and focused their analysis on the reported results in Bismuth-Corletter (BC) types I to II hilar cholangiocarcinoma [26]. In selected cases, long term survival without recurrence was achievable with local resection [59, 71, 74]. However, the results of local resection have been reported to be poorer than with associated liver resection [26, 41–43, 75–77]. In the Neuhaus series, local resection achieved a R0 resection in two of six patients in BC type I, and one of four in BC type II tumors. However, no patient survived 5 years [75].

The Nagoya group reviewed 54 patients with BC types I, II tumors. Local resection was carried out in 14 patients.

Based on their experience, the authors suggested a surgical approach based on cholangiographic tumor type: extended hepatectomy was always necessary in the nodular or infiltrative tumor, while bile duct resection with or without limited hepatectomy could be performed in papillary tumor without superficial cancer spreading [78]. Capussotti et al., after reviewing the medical literature on local surgical resection of hilar cholangiocarcinoma, concluded that local resection should be scheduled only for small papillary Klatskin tumors without bile duct confluence involvement (type I) confined to the bile duct wall (Tis and T1). These tumours form a small minority of hilar cholangiocarcinoma. Extension of treatment should always be determined in accordance with the patient's condition [26]. To confirm histologically-negative resection margins, intraoperative frozen section examinations of the bile ducts have been advocated [29, 79, 80], especially in local resection, to plan the extent of surgical resection.

17.6 Developments in the Advances in Preoperative Management

Three major advances in the preoperative management of hilar cholangiocarcinoma need to be discussed in slightly more detail:

1. Preoperative Biliary Drainage
   The preoperative relief of obstructive jaundice and the reversal of its hepatic and systemic effects by biliary drainage have been proposed as a method to decrease the risk of surgery in patients with obstruction to the biliary system. In several prospective randomized studies, the routine use of preoperative biliary drainage, either in the form of percutaneous transhepatic or endoscopic, failed to show any benefit [81–84]. A meta-analysis concluded that preoperative biliary drainage increased rather than decreased overall complications and provided no benefit in terms of reduced mortality or decreased hospital stay [85] because postoperative septic complications were common after biliary drainage. A major criticism of these prospective studies is that the duration of preoperative drainage (10–18 days) were not long enough to reverse the metabolic and immunologic abnormalities associated with obstructive jaundice. However, for malignant obstructive jaundice, the wait for surgery cannot be too long or the tumor might have progressed and become unresectable. Another criticism is that the results of these studies may not be applicable to hilar cholangiocarcinoma as most of the patients in these studies received no liver resection, and liver resection is commonly used in hilar cholangiocarcinoma.

   A recently published systematic review on preoperative biliary drainage for resection of hilar cholangiocarcinoma concluded that there was no clinical benefit of using preoperative biliary drainage, and preoperative drainage resulted in significant increase in postoperative complication rates and postoperative infectious complication rates [86].

   Although all these data suggest that preoperative biliary drainage is not beneficial in the routine management of patients, preoperative biliary drainage may have some value in selected patients with advanced malnutrition, biliary sepsis, prolonged delay in surgery to wait for the effects of portal vein embolization or chemotherapy/radiotherapy.
2. Portal Vein Embolization (PVE)
   Most patients with hilar cholangiocarcinoma present with jaundice and are considered to have cholestasis-induced compromised liver function. Portal vein embolization should be considered for patients with potentially resectable tumors with compromised liver function when the anticipated future liver remnant is below 40 % of the total liver volume [25]. The potential benefits of PVE are its ability to induce hypertrophy in the future liver remnant (FLR), thereby reducing the risk of postoperative liver failure, and its ability to permit curative resection for patients who otherwise would be considered unresectable due to insufficient FLR. This strategy has been used prior to major hepatic resection for hilar cholangiocarcinoma [28, 63, 87–89]. Currently, there is no evidence to support the routine use of PVE for hilar cholangiocarcinoma. The major disadvantages of PVE in hilar cholangiocarcinoma are the waiting time for the FLR to hypertrophy, and the occasional difficulty in deciding preoperatively whether a right or a left hemihepatectomy will be required if the tumor is placed centrally at the hilus [25].
3. Staging Laparoscopy and Laparoscopic Ultrasound
   Despite exhaustive preoperative investigations, a significant proportion of patients are found to have unresectable disease at the time of laparotomy [32, 62]. Of the patients who are explored with curative intent, only 40–50 % are ultimately resectable [25]. The yield and accuracy of laparoscopy to determine resectability is between 25–42 % and 42–53 %, respectively [89–93]. Laparoscopy is more likely to detect occult metastases from T2/T3 extrahepatic bile duct cancer than T1 tumors (36 % vs. 9 %, respectively) [89]. Laparoscopic ultrasonography increased the yield of laparoscopy by up to 17 % [91].

17.7 Curative Surgery Beyond Liver Resection

Metastasis to regional lymph nodes is common and is an important prognostic factor for long-term survival after resection for hilar cholangiocarcinoma [25, 62, 64, 72, 94]. Studies showed poor survival for patients who had nodal involvement beyond the hepatoduodenal ligament with

5-year survival of 0–6 % [64, 72, 94]. Routine lymph node dissection beyond the hepatoduodenal ligament is not recommended. Patients with grossly involved lymph nodes beyond the hepatoduodenal ligament are considered to have unresectable disease [25].

Combined portal vein resection and reconstruction for hilar cholangiocarcinoma produce conflicting results [75, 95–97]. Several retrospective studies have shown combined portal vein resection does not add to the operative mortality [75, 96, 97]. The impact of combined resection of the portal vein on long-term survival is less clear [25]. Neuhaus proposed routine portal vein resection as part of "no touch" resection of tumor and adjacent tissue [75]. However, the 60-day mortality after portal vein resection was 17 % as compared with 5 % for patients without portal vein resection. When the 60-day mortalities were excluded, portal vein resections were identified as an independent positive prognostic factor in their multivariate analysis of patients undergoing R0 resection. Other authors show equivalent or worse survival in patients undergoing *en bloc* resection of the portal vein [96–99]. We need a properly conducted randomized clinical trial to find out whether routine resection of the portal vein as advocated by Neuhaus is beneficial or not.

17.8 Palliative Surgery

Patients with hilar cholangiocarcinoma who are not candidates for resection on investigation because of locally extensive disease, distant metastases or serious associated medical illness are usually treated non-surgically by percutaneous or endoscopic biliary stenting. Patients who receive chemotherapy or radiotherapy also require optimal hepatic function prior to these treatments, and thus require biliary drainage as well. An operative biliary decompression procedure is usually only performed for patients with locally advanced tumors who are found to be unresectable at laparotomy, and have therefore already encountered the potential morbidity of laparotomy [25]. In the absence of cholangitis, a unilateral biliary drainage is generally sufficient to relieve jaundice.

17.9 Ex Situ Ex Vivo Liver Resection and Autotransplantation

Ex situ ex vivo liver resection and subsequent autotransplantation was first carried out by Pichlmayr et al. in 1988 for a patient with bilateral liver metastases of a leiomyosarcoma [100]. This procedure was subsequently carried out five times up to the year 2003 for cholangiocarcinoma, and our group carried out the six cases with the longest survival [101, 102]. This procedure is technically difficult and few centers are experienced with this technique. Results with ex situ ex vivo liver surgery with hilar cholangiocarcinoma have generally been poor, and these patients often die of postoperative hepatic insufficiency [103]. This is believed to be due to the longstanding cholestasis associated with this disease which reduces the liver tolerance to ischaemia. Ex situ ex vivo surgery for hilar cholangiocarcinoma is an aggressive surgical treatment which should only be attempted in experienced centers on carefully selected patients.

17.10 Liver Transplantation

Orthotopic liver transplantation (OLT) offers the advantages of resection of all structures that may be involved by hilar cholangiocarcinoma including portal vein, bilateral hepatic ducts, atrophic liver lobes and hepatic artery. Total hepatectomy may therefore permit R0 resection for locally advanced tumors which are beyond the ordinary criteria for resection using partial hepatectomy. The early experience of OLT for hilar cholangiocarcinoma unfortunately was disappointing with early tumor recurrence and poor 5 year survival of 28–30 % [104–107]. As a consequence of these early results and the limited availability of cadaveric livers, hilar cholangiocarcinoma was considered to be a relative contraindication to OLT.

Recently a "Mayo protocol" has been developed to treat a highly selected group of patients with unresectable hilar cholangiocarcinoma or hilar cholangiocarcinoma arising from a setting of primary sclerosing cholangitis. There are very strict inclusion and exclusion criteria [103]. Patient received neoadjuvant chemoradiation and then a staging laparotomy to rule out metastatic nodal disease. Patients without disease progression undergo OLT. This highly rigorous selection process may result in a selection bias in favor of patients with biological favourable disease. Very encouraging results have been reported [108, 109]. At present OLT cannot be recommended for patients with resectable hilar cholangiocarcinoma. Further studies are required to fully define the role of OLT. As primary sclerosing cholangitis commonly develops into cholangiocarcinoma, OLT carried out for primary sclerosing cholangitis often has an associated high rate of unsuspected cholangiocarcinoma [110–112].

17.11 Conservative Combined Liver Resection

Surgical resection of hilar cholangiocarcinoma with adequate resection margins is the only form of treatment that offers the potential of cure. In an attempt to achieve a high rate of R0 resection, major hepatic resections such as left hepatectomy, right hepatectomy, left trisectionectomy and right trisectionectomy have been advocated [56, 73, 113–117]. However, major liver resection in patients with obstructive jaundice results in high surgical mortality and morbidity [98]. High operative mortality rate of 17 % for major liver

resection [50] and 23 % for left trisectionectomy have been reported.

As an alterative to using preoperative biliary drainage and portal vein embolization to reduce the perioperative risk of liver resection for hilar cholangiocarcinoma, we have been using a strategy of minor liver resection (defined as resection of less than three Couinaud liver segments) in selected patients with hilar cholangiocarcinoma, so that a sufficient hepatic mass is preserved after surgery [118]. As the hilar bifurcation of the bile ducts is near to liver segments 4, 5 and 1, adequate resection of these liver segments together with their bile ducts can result in cure in selected patients. For obvious reasons, for hilar cholangiocarcinoma that involves the right and left hepatic arteries, or portal vein, or for Bismuth-Corletter type IV tumors, the surgical option is to carry out a right/extended right or left/extended left hepatectomy. With a predetermined selection criteria to choose patients with hilar cholangiocarcinoma for minor or major hepatectomy, we were able to achieve a 0 mortality rate, and a 29.7 % morbidity rate. There was no significant difference in the 5-year survival rates of 34 % in the minor liver resection group compared with the major liver resection group. Although resecting Couinaud's liver segments 1, 4, 5 is called a minor liver resection in this study, this operation is technically more difficult than most of the major liver resections because it involved: (1) a mesohepatectomy with two liver transection planes and the need to preserve the blood supply to the left outer section (segments 2, 3) and the right posterior section (segment 6, 7) [119]; (2) many intrahepatic ductal openings are left in the remnant liver after liver resection and these ducts need to be anastomosed to a roux-en-y loop of jejunum. We have devised a special technique in hepaticojejunostomy to solve this problem [118, 120].

Central lobe resection (or mesohepatectomy) in selected patients with hilar cholangiocarcinoma requires good technical skills. The initial good results need to be confirmed by more studies.

Conclusion

The surgical treatment of hilar cholangiocarcinoma has evolved through many stages. The changes involved improve the immediate and long-term results of this tumour. Hilar cholangiocarcinoma is still a disease which is difficult to cure. Further studies are needed to further improve on the management of this disease.

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