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Perihilar cholangiocarcinoma: paradigms of surgical management

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Abstract Cholangiocarcinoma is a lethal disease with increasing incidence worldwide. Perihilar cholangiocarcinoma represents the most common type of cholangiocarcinoma. Despite major development on surgical strategies over the past 20 years, the 5-year survival rate after surgery has remained below 40%, often in the vicinity of 20%. Most perihilar cholangiocarcinomas, however, are unresectable at the time of the diagnosis. The recent use of aggressive approaches based on better image modality, specific perioperative management, and a multidisciplinary approach have enabled to convert the use of palliative therapies to more radical surgery. This review focuses on the recent advances in surgical treatment for perihilar cholangiocarcinoma including liver transplantation with their respective impact on patient survival.

Cholangiocarcinoma originates from the epithelium of the bile duct, representing approximately 3% of all gastrointestinal tumors.[1] The anatomic distribution of cholangiocarcinoma is represented by intrahepatic, perihilar, or distal type (Fig. 1).[2–4] Intrahepatic cholangiocarcinoma represents 6% of the cases, while perihilar and distal types represent, respectively, 60% and 27% of all cholangiocarcinomas.[5]

Bile duct cancers were first described by Durand-Fardle[6] in 1840, but the entity of hilar cholangiocarcinoma was recognized only much later by Klatskin[7] in 1965. Subsequently, several major changes in the surgical therapies have occurred. Complete surgical resection of perihilar cholangiocarcinoma remains one of the most challenging procedures, mainly because of the topography and frequent invasion of vascular structures in the hepatic hilum.

Currently, surgical resection is the only possible chance of cure. The persistent efforts to increase the rate of R0 resection has eventually succeeded over the last 15 years, but with the drawbacks of higher incidence of severe postoperative complications and, so far, better survival benefit.[3] The aim of this review is to enable better understanding about the impact of aggressive surgical approach for perihilar cholangiocarcinoma.

From Palliation to Resection

Surgical palliation

Up until the mid-1970s, persisting painless jaundice was recognized as the guiding symptom of this disease, alone justifying an indication for exploratory laparotomy.[8–10] As high-resolution preoperative imaging was not part of the diagnostic arsenal at that time, surgeons were unaware of

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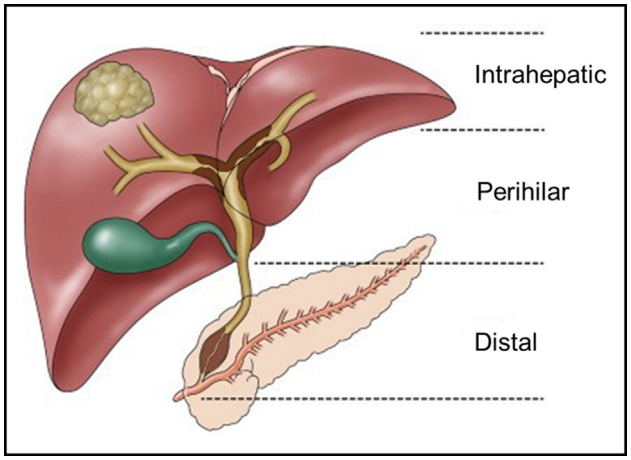

Figure 1 Cholangiocarcinoma subtypes. (Reproduced with modification from Rizvi & Gores[4] by the American Gastroenterological Association with permission from W. B. Saunders Co).

the extent of the disease before surgery. The only diagnostic tool consisted of intraoperative cholangiography associated to tumor biopsy.[11–13] Consequently, this entity was usually considered unresectable, and only palliative approaches became the standard of care for this disease. As an exception, Brown and Myers[14] described 2 cases of local bile duct resections for biliary tumors in 1954. Subsequently, Klatskin[7] presented a more detailed description of the disease in a synopsis of 13 cases of palliative treatment such as biliary drainage, and this entity was named Klatskin tumors.

During this time, surgery was mainly restricted to biopsies, cholecystectomy, and unilateral drainage of the major intrahepatic bile ducts by a T-tube drain (Fig. 2).[10,15] The armamentarium of palliative procedures consisted of bilioenteric anastomosis, transtumoral intubation, or later percutaneous placement of catheters[16,17] with the main goal of offering better quality of life for patients with tumoral bile duct obstruction.

With growing technical experience and better knowledge of the anatomy from the mid-1970s, reports of attempted tumor resections became more frequent.[11–13,18] A new guideline for surgical technical options of perihilar cholangiocarcinoma, still in use today, was proposed by Bismuth and Corlette[19] in 1975 through an anatomical classification depending on the tumor infiltration in the bile duct.[20] Finally, this concept challenged the former standard resignation of offering only palliative approaches.

A retrospective comparison of curative resections and surgical palliative procedures (bilioenteric bypass, palliative resection, bile duct intubation) highlighted less complications with curative approaches.[21] Unfortunately, postoperative mortality for curative resections reached 40% and was drastically increased when combined with additional liver resection. Of note, palliative resections or bilioenteric anastomosis reached mortality rates of up to 75% (Table 1). Other groups reproduced the same findings and pointed out palliative resections or bilioenteric bypass surgery as the most harmful procedures to treat perihilar

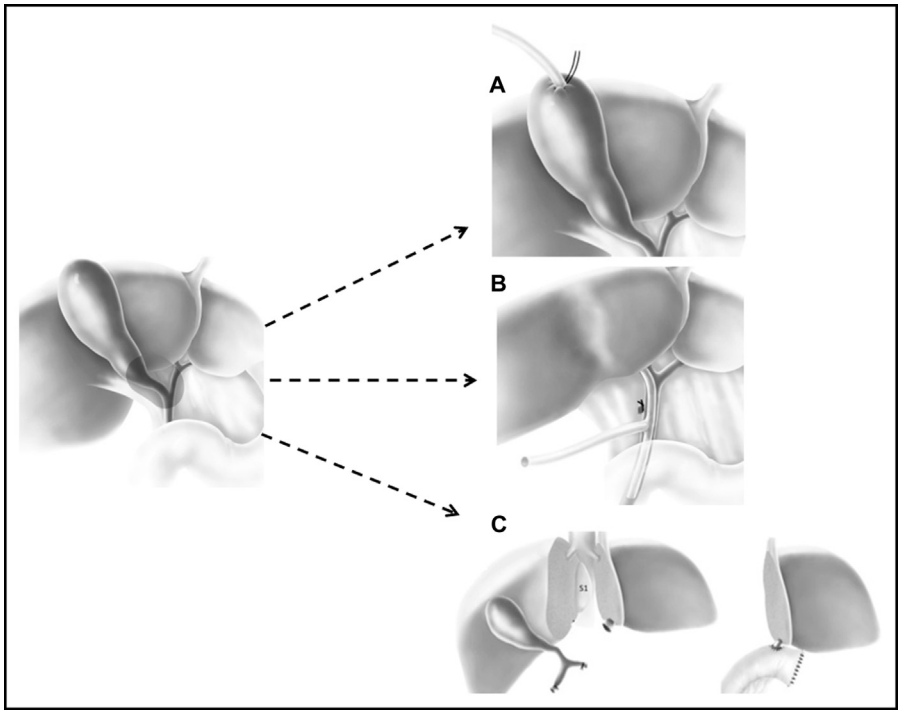

Figure 2 Progress of surgical approaches for perihilar cholangiocarcinoma. Palliative surgical treatment for perihilar cholangiocarcinoma: (A) biopsy and drainage through cholecystostomy; (B) cholecystectomy and t-tube insertion; (C) radical surgical treatment for perihilar cholangiocarcinoma: extended right hepatectomy with caudate lobectomy, bile duct resection; Roux-Y reconstruction hepaticojejunostomy.

cholangiocarcinoma (Table 1).[22–24] A new era with more radical surgical approaches was initiated.

Bile duct resection associated to hepatectomy

Bile duct resection alone gained popularity and showed acceptable mortality rates in specialized centers of less than 10%.[25] But surgeons were confronted with a low resectability (10% to 50%)[20,26–29] and high recurrence rates (50% to 70%)[2,30,31] besides poor long-term survival.[28,32–35] Advances in histological analysis of surgical specimen demonstrated a positive correlation between the absence of residual tumor and longer disease-free survival.[20,36] Hence, the achievement of R0 resection became the new defined aim of most teams. Likewise, Launois et al[11] observed an increase in mean survival from 6 to 17 months when associating liver resections for perihilar cholangiocarcinoma. Subsequently, other groups[37,38] confirmed a survival benefit for patients undergoing hepatic resections. Bismuth et al[20] defined the best approach for each perihilar cholangiocarcinoma type as follows: bile duct resection for type I and II tumors, hepatectomy with hepaticojejunostomy, type IIIa and IIIb and type IV were categorized as unresectable. In this study, local excision achieved an R0 rate of 40% to 60% for type I and II tumors, while association of hepatectomy for type III brought enthusiastic results of R0 resection in 63% of all patients. Of note, Bismuth et al[20] reported a mortality of 0% in his series, while the majority of the early studies were dominated by mortality rates up to 50%[12] and a low rate of hepatectomy as 20% to 25% (Table 2).[8,10–12,18,20–23,36–40]

Evolution toward major hepatectomy

Several advances in technical skills and in the perioperative management of hepatic resections, including anesthesiology and fluid management, reduced blood loss by parenchymal transection under low central venous pressure, and nutritional support resulted in an improved outcome after hepatic surgery.[41–44] The perioperative mortality could be drastically reduced from 90% to less than 10%. This positive development encouraged many centers to perform more radical liver resections for perihilar cholangiocarcinoma (Table 3).[3,20,27,28,32–35,45–63]

Table 1 Comparison of curative resection and surgical palliation for perihilar cholangiocarcinoma (from 1981 to 1991)

		Mortality (%)	
Author	Year	Curative resection	Surgical palliation
Blumgart[22]	1984	11	44
Lai[21]	1987	40*	75
Cameron[9]	1990	2	7
Reding[24]	1991	16	31

*With hepatic resection.

As a pioneer of aggressive treatment for perihilar cholangiocarcinoma, Nimura et al[48] introduced the concept of routine caudate (seg I) segmentectomy for perihilar cholangiocarcinoma. This idea is supported by the infiltration pattern, which spreads along the biliary tree and particularly the caudate branches leading to tumoral recurrence. This oncological landmark was followed by an improved 5-year survival rates in patients undergoing segmentectomy I (40%), when compared with those without (5%).[48,64,65] Several centers demonstrated an increased rate of R0 resections without any considerable increase in mortality when using this approach routinely.[64–67]

As the other side of the coin, the enthusiasm for a more aggressive hepatic resection with higher mortality rates was counter balanced by an increased incidence of liver failure.[68] Nevertheless, the distribution pattern of perihilar cholangiocarcinoma barely allows to achieve R0 resection with a future remnant liver of greater than 40%, which is widely used as a threshold for resection of cholestatic livers.[69] Therefore methods for preoperative induction of liver growth and improvement of liver function to enable a safe liver resection were developed.[70]

Biliary drainage and portal vein embolization

The role of preoperative biliary drainage was first considered unnecessary based on randomized controlled studies from the Western countries showing increased rate of infection for patients with perihilar cholangiocarcinoma undergoing extended hepatic resection.[71,72] However, those series presented low number of major hepatectomy (15%) and therefore the results were mostly based on palliative resection. These results were challenged by Eastern centers, in which a high mortality rate was observed in patients with jaundice undergoing extended liver resection.[73,74] Since then, preoperative biliary drainage before aggressive surgery for perihilar cholangiocarcinoma became a key step to ameliorate liver function and to decrease postoperative complications.

In 1982, Makuuchi et al[75] was the first to introduce portal vein embolization to prevent liver failure after major hepatectomy. This method results in compensatory growth of the nonoccluded future remnant liver. Subsequently, the indication of portal vein embolization was based on the criteria by Kubota et al[76] which depend on the results of the indocyanine green test and volumetry of the future remnant liver. Of note, this test is mostly performed in Asia and some centers in Europe, but rarely in America. Meanwhile, several publications have shown higher rate of resectability, as well as lower rate of morbidity, when performing portal vein embolization before major hepatic surgery for perihilar cholangiocarcinoma.[77–82] The Nagoya group[82] reported one of the largest series with 353 perihilar cholangiocarcinoma

Table 2 Early (1965–1991) surgical experience for perihilar cholangiocarcinoma

Author	Year	Patients	Resectability	Hepatic resection	Mortality
Quattlebaum[10]	1965	8	—	2 (25%)	1 (50%)
Klippel[18]	1972	32	1 (3%)	—	0
Longmire[13]	1973	13	—	—	5 (39%)
Fortner[12]	1976	26	9 (35%)	6 (67%)	3 (50%)
Launois[11]	1979	19	11 (61%)	6 (55%)	2 (18%)
Evander[8]	1980	80	—	15 (56%)	3 (11%)
Blumgart[22]	1984	94	18 (19%)	12 (67%)	9 (30%)
Beazley[36]	1984	64	16 (25%)	12 (75%)	3 (19%)
Langer[39]	1985	54/90*	12 (22%)	—	—
Mizumoto[40]	1986	32	24 (75%)	—	1 (4%)
Lai[21]	1987	97	29 (30%)	5 (17%)	2 (40%)
Pinson[38]	1988	83	8 (10%)	9 (36%)	1 (4%)
Bengmark[37]	1988	22	—	22 (100%)	6 (27%)
Cameron[23]	1990	96	39 (41%)	—	2 (5%)
Bismuth[20]	1991	136	23 (17%)	13 (57%)	0
Reding[24]	1991	307/552†	—	47 (48%)	15 (16%)

*54 perihilar cholangiocarcinoma.
†307 perihilar cholangiocarcinoma.

patients treated with portal vein embolization before extended hepatectomy. Resectability rate was 83% (n = 292), while mortality was 4% with 5-year survival rate of 40%.[82] The utilization of preoperative biliary drainage and portal vein embolization before major hepatic resection contribute to a safer management of perihilar cholangiocarcinoma patients with a preinterventional future liver remnant below 40%.[77,78,83] Therefore, preoperative strategies for safer major hepatectomy should be part of the arsenal for management of patients with perihilar cholangiocarcinoma.

Recent Advances for Perihilar Cholangiocarcinoma

Vascular resection

In early reports, most tumors were considered unresectable when they encased the proper hepatic artery, the main trunk, or both branches of the portal vein.[22] Therefore, early publications about vascular resections with complex reconstructions were limited to few cases.[11,22,36] In 1984, Beazley et al[36] reported his early experience of 3 portal vein reconstructions in a series of 16 patients with a perioperative mortality of 30%.[36]

Over time, portal vein resection gained popularity in many centers.[61,82,83] Ebata et al[81] postulated an increase in 5-year survival from 10% to 37% for perihilar cholangiocarcinoma patients undergoing portal vein resection. In contrast, another group pointed out a higher mortality rate ranging from 12% to 18% associated to portal vein resections.[61] Although there is an increasing acceptance in performing vascular resection for perihilar cholangiocarcinoma, the true benefits still remain controversial.

"Hilar en bloc" technique

As the concept of portal vein resection evolved, Neuhaus et al[35] introduced a new technique to achieve a radical surgical therapy for perihilar cholangiocarcinoma, and simultaneously to avoid manipulation with consecutive spreading of tumor cells: The so-called "hilar en bloc" resection or "non-touch" technique[35] combines an extended right hepatectomy with pre-emptive portal vein resection and reconstruction. After promising preliminary experience,[35] the same group reported a beneficial effect on 5-year survival for hilar en bloc resection, when compared with major hepatectomy (58% vs 29%, $P = .02$).[58] Drawbacks of this technique are a high postoperative mortality rate of 12% and the limitation to right-sided tumors.

Combined portal vein and arterial resection

Although portal vein resection and reconstruction is feasible and generally accepted, the need for arterial resection is still highly debated. In 2010, Nagino et al[84] reported an analysis of a single-center experience with simultaneous resection of portal vein and hepatic artery. The author demonstrated that this surgery can be performed with an acceptable mortality of 2% and postulates better chances of long-term survival for selected patients.[84] In contrast, Miyazaki et al[85] and others[86] indicate that such an approach is not justified because of lacking benefit for survival.

Role of lymphadenectomy in liver resection and liver transplantation

The most significant prognostic factors for perihilar cholangiocarcinoma are negative resection margins, as well

Table 3 Series of hepatic resection for perihilar cholangiocarcinoma

				30-day mortality (%)		5-year survival (%)	
Author	Year	*n*	HR (%)	LR	HR	LR	HR
Boerma[45]	1990	389	48	8	15	70	17
Bismuth[20]	1992	23	57	0	—	—	—
Baer[46]	1992	23	48	0	9	—	—
Pichlmayr[47]	1996	125	76	3	13	29	26
Launois[34]	1999	36	69	0	16	27	60
Neuhaus[35]	1999	80	83	0	9	0	57*
Kosuge[27]	1999	65	80		9	—	—
Nimura[48]	2000	108	93	0	6	16	26.0
Launois[34]	2000	98	48	14	17	—	—
Jarnagin[28]	2001	80	78	6	11	0	37
Capussotti[32]	2002	36	89	0	3	0	37
Kondo[50]	2004	40	78	0	0	—	—
Jang[33]	2005	48	48	0	0	28	48
DeOliveira[3]	2007	173	21	—	5†	—	—
Hirano[51]	2010	146	94	3	4	—	36
Lee[52]	2010	302	89	2	2	18	36
Unno[53]	2010	125	100	—	8	—	35
Ercolani[54]	2010	51	100	—	10	—	34
Shimizu[55]	2010	172	100	—	6	—	28
Giuliante[56]	2011	56	100	—	8	—	—
Young[57]	2011	83	100	—	7	—	20
Neuhaus[58]	2012	50	100	—	11	—	58/29‡
Ribero[59]	2012	75	100	—	10	—	28
Cannon[60]	2012	59	83	—	5	—	—
de Jong[61]	2012	305	73	1	7	—	20
Matsuo[62]	2012	157	82	4	9	8	38
Cheng[63]	2012	171	100	—	3	—	14

HR = hepatic resection; LR = local resection.
*Extended right hepatectomy.
†Hepatic and local resections.
‡Nontouch technique versus major hepatic resection.

as negative lymph nodes.[27,35,47,52,55,87–90] The indication of lymphadenectomy is widely recommended for staging purposes, but any benefit for extended lymphadenectomy is controversial. Early reports of lymph node involvement show rates ranging between 18% and 30%; nevertheless, the high rate of R1 resections was the predominant prognostic factor, which led to poor outcomes.[20,37] Neither the exact number of retrieved lymph nodes nor the extent of dissection was reported in detail.

Some studies revealed that a nodal invasion para-aortic lymph nodes present 5-year survival rate ranging from 0% to 12%.[27,87] Whereas retrospective series showed comparable survival rate for patients with regional nodal metastases and para-aortic nodal metastases (14.7 vs 12.3%).[53,54,91,92] Another important factor is the different recommendations proposed by the American Joint Committee on Cancer (AJCC) sixth and seventh editions. While the sixth edition described a minimal number of 3 lymph nodes retrieval for appropriated staging, the 7th edition increased this requirement for 15 lymph nodes. This new recommendation has triggered criticisms by experts because of the requirement of additional major dissection.[92] Different groups addressed this issue and reported a more moderate recommendation for adequate lymph node retrieval ranging from 3 to 10 total lymph node counts.[91–93] In summary, a certain threshold of lymph node retrieval has to be guaranteed, but a general recommendation for extended lymphadenectomy cannot be given yet. Hence, the extended lymphadenectomy is actually applied for staging purposes and as a prognostic tool only.[53,54,87]

Lymph node status has been a key factor for patient selection for liver transplantation after neoadjuvant chemoradiotherapy. The successful protocol of Mayo Clinic used for patients with unresectable perihilar cholangiocarcinoma achieved better 5-year survival (82% vs 21%, $P = .02$) with less recurrence (13% vs 27%) than surgical resection.[94] The neoadjuvant regimen consists of external beam radiation associated to chemotherapy and intrabiliary brachytherapy. Despite this great achievement, liver transplantation cannot be used widely and should follow the Mayo Clinic protocol, which implicates strict selection criteria. Briefly, the tumor size must not exceed 3 cm, absence of distant metastasis must be guaranteed,

and lymph nodes must be negative. To better evaluate the lymph node status, patients are submitted to staging laparotomy with lymphadenectomy. Only those with negative lymph nodes may qualify for entering the waiting list and subsequent liver transplantation. A recent multicentric study analyzed 287 patients from 12 large volume transplant centers and confirmed that patients outside these criteria show significantly poorer 5-year survival rates after transplantation (32 vs 69%).[95]

Laparoscopic surgery for perihilar cholangiocarcinoma

Several recent publications present their first experiences with laparoscopic and robotic-guided resections.[96,97] Nevertheless, only small series are reported and quality in terms of oncological long-term survival has not been proven yet.

Perihilar cholangiocarcinoma new staging system

In a consensus conference, the European–African Hepato-Pancreato-Biliary Association[98] pointed out the shortcomings of all available staging systems and formulated the urgent need for a modified staging system. Subsequently, a more detailed classification for perihilar cholangiocarcinoma was proposed by an international group of experts.[99] The main concept is to standardize the way of reporting perihilar cholangiocarcinoma surgical treatment allowing comparison among centers. This new system uses the Bismuth classification for bile duct infiltration, extent of tumoral involvement in portal vein and/or hepatic artery, lymph nodes status, tumor size, and the presence of underlying liver disease. In addition, it emphasizes the relevance of liver remnant volume with consequent choice of surgical strategy. In addition, this system can readily be used for recording the data of patients with unresectable disease, but within Mayo Clinic Criteria for Liver Transplantation. Most recently, an international perihilar cholangiocarcinoma registry (www.cholangioca.org) was offered to the surgical community to use such tool on large scale to contemplate a more precise classification system that may allow an estimation of resectability and prognosis for perihilar cholangiocarcinoma.

Conclusion

The development of refined surgical techniques, including liver transplantation after neoadjuvant chemoradiotherapy, has increased the arsenal of surgical options to treat patients with perihilar cholangiocarcinoma. However, prognosis remains overall poor with the exception of a few series. Further therapeutic advances by individualized target therapy may improve prognosis for patients with perihilar cholangiocarcinoma.

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