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TOPIC HIGHLIGHT

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Surgical strategy for bile duct cancer: Advances and current limitations

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Abstract

The aim of this review is to describe recent advances and topics in the surgical management of bile duct cancer. Radical resection with a microscopically negative margin (R0) is the only way to cure cholangiocarcinoma and is associated with marked survival advantages compared to margin-positive resections. Complete resection of the tumor is the surgeon's ultimate aim, and several advances in the surgical treatment for bile duct cancer have been made within the last two decades. Multidetector row computed tomography has emerged as an indispensable diagnostic modality for the precise preoperative evaluation of bile duct cancer, in terms of both longitudinal and vertical tumor invasion. Many meticulous operative procedures have been established, especially extended hepatectomy for hilar cholangiocarcinoma, to achieve a negative resection margin, which is the only prognostic factor under the control of the surgeon. A complete caudate lobectomy and resection of the inferior part of Couinaud's segment Ⅳ coupled with right or left hemihepatectomy has become the standard surgical procedure for hilar cholangiocarcinoma, and pylorus-preserving pancreaticoduodenectomy is the first choice for distal bile duct cancer. Limited resection for middle bile duct cancer is indicated for only strictly selected cases. Preoperative treatments including biliary drainage and portal vein embolization are also indicated for only selected patients, especially jaundiced patients anticipating major hepatectomy. Liver transplantation seems ideal for complete resection of bile duct cancer, but the high recurrence rate and decreased patient survival after liver transplant preclude it from being considered standard treatment. Adjuvant chemotherapy and radiotherapy have a potentially crucial role in prolonging survival and controlling local recurrence, but no definite regimen has been established to date. Further evidence is needed to fully define the role of liver transplantation and adjuvant chemo-radiotherapy.

Key words: Bile duct cancer; Cholangiocarcinoma; Surgery; Liver transplantation; Hepatectomy; Pancreaticoduodenectomy; Adjuvant chemotherapy; Adjuvant radiation

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INTRODUCTION

Although bile ducts are anatomically classified as either in-

trahepatic or extrahepatic and cholangiocarcinoma refers to malignant tumors originating from epithelial cells lining both the intrahepatic and extrahepatic biliary trees[1], the term "bile duct cancer" usually refers to extrahepatic bile duct cancer. Histologically speaking, both extrahepatic and intrahepatic cholangiocarcinoma could be considered together, but they are usually discussed as separate entities based on critical differences in their clinical manifestations[2,3] and current prevalent staging systems describe these entities by completely different classifications[4,5]. Additionally, the term "extrahepatic cholangiocarcinoma/bile duct cancer" encompasses hilar cholangiocarcinoma and distal bile duct cancer[1-3].

In this review article, we describe the current diagnosis and treatments of "bile duct cancer", referring to extrahepatic cholangiocarcinoma, and focusing on the surgical treatment.

CLASSIFICATION OF EXTRAHEPATIC CHOLANGIOCARCINOMA

Anatomic classification

Extrahepatic bile duct cancer is further classified as hilar or distal. Hilar cholangiocarcinoma, also called a Klatskin tumor[6], is located within 2 cm of the bifurcation of the common bile duct and is further divided into four types by Bismuth and Corlette based on the anatomic location of the tumor[1,7]. Approximately 60% to 70% of cholangiocarcinoma is reported to be located at the hilum, 20% to 30% at the distal bile duct, and 5% to 10% intrahepatic bile duct[1,8,9]. The anatomic schema is presented in Figure 1. This classification, based on the longitudinal location of the bile duct cancer, defines the surgical strategy, including the operability and curability.

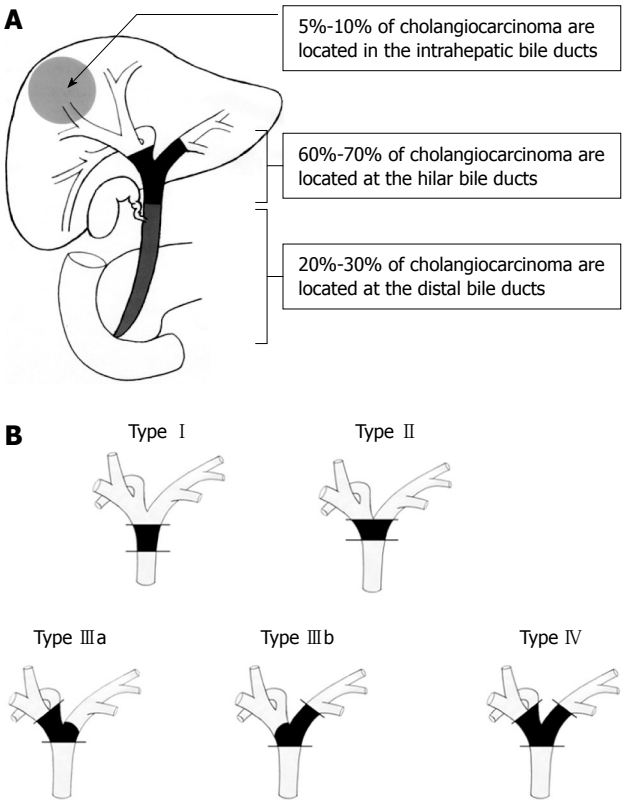

Figure 1 Anatomic classification of cholangiocarcinoma. A: The majority of cholangiocarcinoma (60%-70%) develop in the hilar bile duct and are called Klatskin tumors. The distal bile duct is involved in 20% to 30% of cases, while intrahepatic cholangiocarcinomas represent 5% to 10% of the tumors originating from the biliary tract; B: Bismuth-Corlette classification of hilar bile duct cancer. Type Ⅰ, cholangiocarcinoma confined to the common bile duct; Type Ⅱ, cholangiocarcinoma involves the bifurcation of the common bile duct; Type Ⅲa, cholangiocarcinoma involves the bifurcation and the right hepatic duct; Type Ⅲb, cholangiocarcinoma involves the bifurcation and the left hepatic duct; Type Ⅳ, cholangiocarcinoma involves the bifurcation and extends to both the right and left hepatic ducts.

Pathologic classification

Most cholangiocarcinomas are well-to-moderately differentiated adenocarcinomas with a tendency to develop desmoplastic reactions and early perineural invasion[1,2,10]. Macroscopically, extrahepatic cholangiocarcinoma develops sclerosing strictures, nodular lesions, or papillary growth[11]. The sclerosing type is the most common, while the papillary pattern is rare but associated with a more favorable prognosis[12,13].

MODE OF CANCER SPREAD AND INFILTRATION

Understanding the patterns of anatomic spread and infiltration of bile duct cancer is critical for planning treatment. Infiltration by bile duct cancer includes both longitudinal extension and vertical invasion. Longitudinal extension refers to the longitudinal spread of the tumor along the biliary tree, and vertical invasion refers to direct invasion of the surrounding pancreas or duodenum, infiltration into the hepatoduodenal ligament including the adjacent hepatic artery and portal vein, and direct invasion of the hepatic parenchyma[14-16]. Distant metastasis and lymph node invasion could be an extension of vertical invasion.

Longitudinal extension

The longitudinal spread determines the type of radical operation, including pancreaticoduodenectomy (PD), extended hepatectomy and hepatopancreaticoduodenectomy, and apparent infiltration beyond the secondary branches on both sides of the biliary tree is generally considered unresectable.

Microscopic extension of bile duct cancer beyond the tumor margin visualized by present diagnostic modalities or the margin observed macroscopically is often encountered. Longitudinal extension consists of superficial and submucosal infiltration depending on the tumor growth pattern, and sometimes includes direct infiltration along lymphatic and perineural tissues[13]. Sakamoto *et al*[17] reported a correlation between the gross tumor type and the pattern of infiltration, and demonstrated that mucosal extension predominantly occurs with papillary (intraductal) and nodular (mass-forming) tumors, while submucosal

extension mainly occurs with sclerosing (infiltrating) tumors. Tumor spread beyond the macroscopic margin is determined by the type of invasion, with a mean length of 6-10 mm for submucosal spread and 10-20 mm for mucosal spread[18]. Therefore, a gross surgical margin of more than 1 cm in the infiltrating type and more than 2 cm in the papillary and nodular types is recommended to obtain microscopically negative margins.

Vertical infiltration

The evaluation of vertical infiltration is critical to the patient's prognosis, because it usually defines resectability and curability. Apparent distant metastasis and para-aortic lymph node metastasis are absolute contraindications for radical surgery[19-21], while direct invasion of major vessels, regardless of the prognosis, present surgical challenges whose indication and operative procedures continue to be debated[22-28].

Patients with cancer invasion confined to the fibromuscular layer of the extrahepatic bile duct have a better postoperative survival rate (80%-100% 5-year survival), while those with cancer that extends beyond the fibromuscular layer have a poor prognosis[29-31].

Perineural invasion beyond the bile duct wall is a unique characteristic of cholangiocarcinoma that is observed in 75% of cases and has proved to be a significant prognostic factor for poor outcome[14,16,32].

Hilar cholangiocarcinoma easily infiltrates into the hepatic parenchyma and the hepatoduodenal ligament, in which the hepatic artery and portal vein are located adjacent to the bile duct, while distal bile duct cancer directly invades the pancreas or duodenum[33,34]. Up to 80% of hilar cholangiocarcinoma directly infiltrates the liver parenchyma and surrounding connective tissues of the hepatoduodenal ligament[34,35], thus necessitating meticulous three-dimensional knowledge of the hepatic hilum and challenging operations for this disease entity[36]. One of the most important points of anatomic consideration for the vertical invasion of hilar cholangiocarcinoma is the need for hepatectomy with complete caudal lobectomy. Hilar cholangiocarcinoma spreads not only longitudinally along the right and left hepatic ducts, but also in the cranial and dorsal directions along the thin bile ducts. Hence, it is necessary to remove the liver parenchyma adjacent to the hepatic hilum together with the hilar plate to achieve a complete curative resection. In this sense, complete caudate lobectomy and resection of the inferior part of Couinaud's segment Ⅳ coupled with right or left hemihepatectomy (according to the predominant tumor location) is the main goal of surgical resection of hilar cholangiocarcinoma[37-41]. Major hepatectomy with caudate lobectomy for hilar cholangiocarcinoma is associated with improved outcome[26,41-45].

PREOPERATIVE EVALUATION OF BILE DUCT CANCER

Preoperative evaluation of bile duct cancer in terms of radical resection consists of a multidisciplinary approach with ultrasonography (US), helical-computed tomography, magnetic resonance imaging (MRI) including MR cholangiography (MRC), direct cholangiography *via* endoscopic retrograde cholangiography (ERC) or percutaneous transhepatic biliary drainage (PTBD), intraductal US (IDUS), and bile cytology or biopsy[1].

Among these, dynamic multidetector row computed tomography (MDCT) is now widely used for the preoperative evaluation and staging of bile duct cancer, as it provides not only qualitative diagnosis and indicates the location of the tumor, but also shows the relationship between adjacent tissues, such as the hepatic artery, portal vein, and liver parenchyma[46-48].

Bile duct cancer is often revealed as a focal thickening of the ductal wall with various enhancement patterns[49,50]. The accuracy of the differential diagnosis of a malignant lesion from benign stenosis is reported to be over 90%[48], with satisfactory accuracy in evaluating major vessel involvement and liver parenchyma invasion[49-55]. Yet, lymph node metastasis is still difficult to diagnose preoperatively, even with the recent higher resolution of MDCT[51-54]. Some authors report that MDCT is effective for evaluating even longitudinal spread along the bile duct, demonstrating that the efficacy is equivalent to that of evaluation *via* MRC or direct cholangiography[56-62]. We reported that the evaluation of longitudinal tumor spread by MDCT was even superior to that of direct cholangiography and equivalent to histologic assessment of the specimen[62]; however, in cases with hilar cholangiocarcinoma, it seems still difficult to estimate the ductal spread precisely, even with the recent advancements of MDCT[53,63].

Additional important information obtained from MDCT and its three-dimensional reconstruction for surgeons is the precise arterial/portal/venous anatomy around the hepatic hilum/hepatoduodenal ligament/pancreas head/duodenum in relation to the tumor. Many authors have reported that MDCT is effective for preoperative planning and for navigation during the operation[46,59,62]. Figure 2 shows a multiple fusion image of a three-dimensional reconstruction of MDCT in a case of hilar cholangiocarcinoma.

MRI with concurrent MRC provides three-dimensional reconstruction of the biliary tree, and the diagnostic accuracy in evaluating cholangiocarcinoma is reported to be comparable to that of invasive cholangiography *via* ERC or PTBD[64-68]. MRI also facilitates the evaluation of vertical invasion of the tumor, similar to MDCT[65,69,70]. To exclude artifacts of biliary instrumentation and obtain precise images of ductal wall thickening and luminal stenosis/dilatation, both MDCT and MRI are strongly recommended before decompressing the biliary tree.

Despite the controversy regarding the necessity for preoperative biliary drainage to reduce surgical morbidity, direct cholangiography *via* endoscopic naso-biliary drainage (ENBD) tube or PTBD tube remains the gold standard for preoperative evaluation of ductal spread, especially in Japan[71-74]. A drawback of these invasive procedures is the risk of complications such as post-ERC pancreatitis[75],

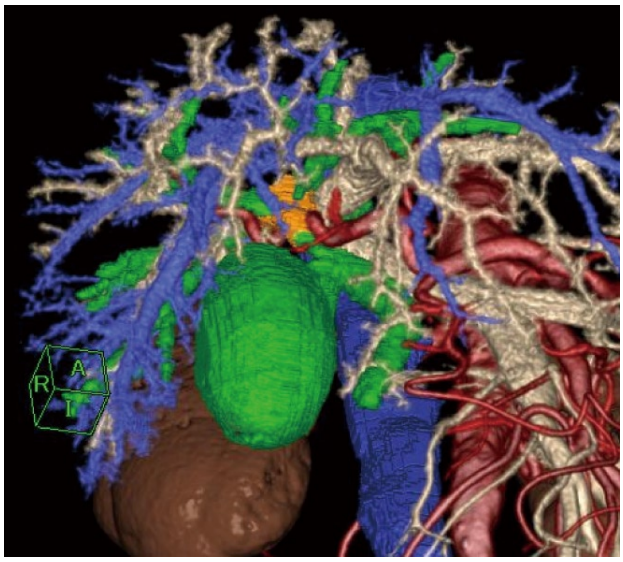

Figure 2 Hilar cholangiocarcinoma (Bismuth-Corlette type Ⅲa). Comprehensive multiphase fusion images of the tumor (orange), bile duct (green), and surrounding vessels including hepatic artery (red), portal vein (light yellow), and hepatic vein (blue).

bacterobilia and cholangitis[76], bleeding, sepsis, catheter tract seeding, and even death[77]. With the recent improvements in the diagnostic accuracy of other noninvasive imaging modalities, as mentioned above, these invasive procedures might soon not be essential, at least as preoperative diagnostic tools. On the other hand, ERC and PTBD have the advantage of enabling IDUS or choledochoscopy and of providing bile cytology, brushing cytology, and biopsy, which can confirm the diagnosis of cholangiocarcinoma[78]. Unfortunately, these histopathologic examinations yield low sensitivity, and non-diagnostic cytology or biopsy results may not rule out cholangiocarcinoma in the presence of appropriate radiologic findings[79,80]. In the absence of other explainable causes of biliary strictures, patients should be assumed to have cancer and operated on as such, accepting that 10% to 15% might prove to have a benign lesion on the final histologic investigation[81,82]. Fukuda *et al*[83] reported 100% sensitivity of bile duct biopsy by adding choledochoscopy to ERC, and a new technology such as SpyGlass®, which is currently under investigation, may soon improve the diagnostic accuracy of preoperative malignancy confirmation[84,85].

PREOPERATIVE TREATMENTS

Biliary drainage

The efficacy of preoperative biliary drainage for patients with obstructive jaundice remains controversial. Based on previous reports emphasizing the adverse effects of biliary drainage, such as pancreatitis, cholangitis, and tract seeding[76,86-91], and the recent meta-analysis comparing surgery with preoperative biliary drainage to that without drainage, which showed no beneficial effect of preoperative drainage[77], routine biliary drainage is not recommended for all jaundiced patients, especially for distal bile duct cancer without any complications[92]. Furthermore, preoperative biliary drainage seems to increase the risk of perioperative infections and a longer postoperative hospital stay[76,77]. Preoperative biliary drainage has proved to be beneficial, however, in the presence of cholangitis, severe malnutrition, and coagulation abnormalities[93,94], and it is absolutely indicated for patients requiring major hepatic resection for curative surgery[36,71]. Prolonged preoperative jaundice is associated with increased postoperative morbidity and mortality after hepatic resection due to severe cholestatic liver dysfunction[95,96]. When biliary drainage is performed for patients awaiting major hepatectomy, radical surgery should be postponed for several weeks until the serum total bilirubin is less than 2.0 mg/dL to allow for sufficient restoration of hepatic function[36]. The use of sequential liver volumetric analyses and hepatic functional studies is warranted when anticipating extended hepatectomy to secure a sufficient volume and function of the future remnant liver, thereby minimizing the risk of postoperative liver failure[97].

Portal vein embolization

As discussed above, hilar cholangiocarcinoma usually requires extended hepatectomy (i.e. extended right hepatectomy, and right or left trisegmentectomy), which is related with a rather high rate of perioperative mortality (0% to 19%)[98]. This is partly due to the increased rate of postoperative liver failure with major hepatic resection[99-101]. Portal vein embolization, which was first indicated for hilar cholangiocarcinoma by Makuuchi *et al*[102], is now widely accepted as a valuable preoperative measure in anticipation of extensive liver resection with a subsequent small liver remnant volume[103-108]. Compensatory hypertrophy of the remnant liver parenchyma, usually an increase of 8% to 20% within 2 to 6 wk, is induced in association with atrophy of the future resected liver by selectively occluding the main portal branch to the liver parenchyma to be removed. In general, portal vein embolization can benefit patients requiring a future liver remnant volume of less than 25% to 35% of the original liver volume, yet the indication is still controversial, especially for patients with normal liver function. Currently, there seems to be no objection to portal vein embolization for potentially resectable patients with normal liver function when the anticipated future liver remnant volume is less than 20% of the total liver volume, or in patients with compromised liver function when the anticipated future liver remnant volume is less than 40% of the total liver volume[98]. Once portal vein embolization is performed, sequential evaluation of liver function and volumetry is mandatory not to miss the optimal timing for radical surgery[109].

SURGICAL TREATMENT OF BILE DUCT CANCER

Considering that radical resection with a microscopically negative margin (R0) is the only way to cure bile duct cancer and is associated with marked survival advantages

Table 1 Review of the literature on pancreaticoduodenectomy for distal bile duct cancer

Author	Yr	Resections (*n*)	R0 resection (%)	Overall 3-yr survival (%)	Overall 5-yr survival (%)	R0 5-yr survival (%)	Operative mortality (%)
Kayahara *et al*[119]	1999	50	72	47	35	48	2
Suzuki *et al*[120]	2000	99	52	50	37	52	3
Yeo *et al*[21]	2002	49	NA	38	16	NA	3[3]
Yoshida *et al*[121]	2002	27	85	37	37	44	4
Sakamoto *et al*[122]	2005	55	84	52	26	NA	7
Jang *et al*[123]	2005	103	84	38	30	NA	5
Cheng *et al*[124]	2007	112	87	51	25	27	3
Murakami *et al*[125]	2007	36	81	54	50	62	0
Sasaki *et al*[126]	2007	77	92	NA	37	36[2]	NA
DeOliveria *et al*[127][1]	2007	239	78	35	23	27	3
Allen *et al*[128]	2008	98	85	45	43	42[2]	3
Bahra *et al*[129]	2008	95	81	36	29	34	4
Lee *et al*[116]	2009	149	NA	46	38	NA	NA
Hong *et al*[33]	2009	147	90	33	18	NA	NA
Nomura *et al*[130]	2009	57	61	NA	36	NA	2
Kawai *et al*[131]	2010	62	77	63	52	59	0

[1]Including palliative operations; [2]Including hilar cholangiocarcinoma; [3]Including operations for pancreatic cancer. NA: Not available; R0: Negative surgical margin.

compared to margin-positive resections (R1, microscopically positive; R2, macroscopically positive), achieving complete resection of the tumor is the most critical mission for surgeons. Many authors have reported meticulous operative procedures and their outcomes during last two decades with an attempt to achieve the most radical and safe resection of bile duct cancer.

Pancreaticoduodenectomy for distal bile duct cancer

Pancreaticoduodenectomy (PD), including pylorus preserving PD (PPPD) coupled with porta hepatis lymphadenectomy, is the standard treatment of choice for the complete removal of distal bile duct cancer, but extended lymphadenectomy including the para-aortic nodes is not justified because it does not provide a survival advantage and is associated with increased perioperative morbidity[20,21,110,111]. Both PD and PPPD provide equal outcome for distal bile duct cancer[20,21,112-114], while segmental bile duct excision is rarely an option because only 10% of patients undergoing bile duct excision alone obtain curative resection margins on final pathology[110,115]. Based on the equivalent outcome between segmental bile duct resection and PD recently reported by Lee *et al*[116], segmental bile duct resection with excision of surrounding lymph nodes and connective tissues seems to be a possible strategy[117], yet it is not accepted as a standard operation for distal bile duct cancer for obtaining a negative surgical margin[118].

Reports from high-volume centers during the last decade are summarized in Table 1[21,33,116,119-131]. The overall 3- and 5-year survival rates after radical surgery ranged from 33% to 63% and 16% to 52%, respectively. A recent meta-analysis by Japanese Biliary Tract Cancer Statistics Registry revealed that the overall 3- and 5-year survival rates of distal bile duct cancer after radical resection were 58% and 44%, respectively, among 779 patients who received PD or PPPD between 1998 and 2004 in Japan[132,133].

Extended hepatectomy for hilar cholangiocarcinoma

Based on the mode of tumor extension and the radicality and simplicity of the procedure, extended right- or left-hemihepatectomy is regarded as the standard radical operation for hilar cholangiocarcinoma[37-39,134], even for patients with Bismuth and Corlette type Ⅰ or Ⅱ[118]. 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, 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 coupled with complete resection of the extrahepatic bile duct and porta hepatis lymphadenectomy. "Right" or "left" is dependent on the predominance of the tumor, but an extended right-hemihepatectomy is preferentially indicated for even centrally located tumors, because of the length of each hepatic duct, location of the hilar common bile duct in the hepatoduodenal ligament, facility of complete caudate lobectomy, and the ease of portal vein reconstruction[39,135]. When the tumor spreads diffusely into the intrapancreatic bile duct, PD should be added to extended hemihepatectomy simultaneously[136-138].

Right or left trisegmentectomy is one of the most extensive hepatic resection procedures because of the massive volume loss of the liver parenchyma, and hilar cholangiocarcinoma invading the hepatic hilum sometimes requires trisegmentectomy for curative resection. Trisegmentectomy is advantageous in terms of obtaining a negative margin of the bile ducts[139,140]. A negative ductal margin is achieved in 75% and 88% of cases with left and right trisegmentectomy, respectively, both of which are higher than the negative rate obtained with extended hemihepatectomy[139,140]. On the other hand, minimally invasive procedures, including parenchyma-preserving hepatectomy and bile duct segmental resection without hepatectomy, could be an option for Bismuth-Corlette type Ⅰ and Ⅱ or

Table 2 Review of the literature on hepatectomy for hilar bile duct cancer

Author	Yr	Resections (*n*)	Major hepatectomy (%)	R0 resection (%)	Overall 3-yr survival (%)	Overall 5-yr survival (%)	R0 5-yr survival (%)	Operative mortality (%)
Neuhaus *et al*[26]	1999	80	85	61	NA	22	37	8
Todoroki *et al*[142]	2000	101	58	14	NA	28	38	4
Lee *et al*[73]	2000	111	99	78	52	22	NA	6
Nimura *et al*[71]	2000	142	90	61	43	26	27	9
Capussotti *et al*[146]	2002	36	83	89	41	27	29	3
Seyama *et al*[147]	2003	87	67	64	55	40	46	0
Kawasaki *et al*[135]	2003	79	87	68	NA	22	40	1
Rea *et al*[148]	2004	46	100	80	39	26	30	9
Hemming *et al*[149]	2005	53	98	80	60	35	45	9
Dinant *et al*[150]	2006	99	38	31	37	27	33	15
Sano *et al*[151]	2007	126	100	56	44	35	NA	4
Baton *et al*[152]	2007	59	100	46	45	20	22	5
Hasegawa *et al*[153]	2007	49	90	78	50	40	50	2
Allen *et al*[128]	2008	106	82	77	45	29	42[1]	4
Ito *et al*[45]	2008	38	53	63	65	33	60	0
Hirano *et al*[154]	2009	146	90	90	53	36	NA	3
Lee *et al*[155]	2009	302	89	71	41	33	47	2
Young *et al*[156]	2009	51	92	57	36	20	40	8
Igami *et al*[157]	2009	298	98	74	49	42	52	2
Miyazaki *et al*[158]	2009	107	91	59	45	28	33	2
Unno *et al*[159]	2009	125	100	63	37	35	46	8
Murakami *et al*[160]	2009	42	86	74	42	30	NA	7

[1]Including distal bile duct cancer. NA: Not available; R0: Negative surgical margin.

cancer of the middle bile duct, but in terms of obtaining R0, those procedures are indicated for strictly localized tumors or for patients with a poor general condition or high-risk factors[36,41,116,117]. Many authors report improved survival with complete caudate lobectomy and major hepatectomy[26,41-45].

Metastasis to regional lymph nodes is one of the most important prognostic factors influencing survival after resection for hilar cholangiocarcinoma[45,141]. Patients with nodal involvement beyond the hepatoduodenal ligament, including para-aortic nodal metastases, were shown to have dismal prognosis with a 5-year survival of 0% to 12%[141-144]. Therefore, routine lymph node dissection beyond the hepatoduodenal ligament is not recommended. On the other hand, portal vein resection and reconstruction has been performed for hilar cholangiocarcinoma with conflicting results[145]. With recent technical advances, several retrospective series have shown no difference in surgical mortality between patients undergoing major hepatectomy with portal vein resection and without it, advocating routine resection of the portal vein for en-bloc, "no-touch" resection[25,26], but the impact of portal vein resection on long-term survival seems to be less clear. Moreover, other studies have shown equivalent or worse survival in patients undergoing portal vein resection[23,27,28]. When there is severe adhesion between the tumor and portal vein, combined resection and reconstruction is necessary to obtain a possible negative surgical margin, yet routine resection of the portal vein might not be recommended unless supported by findings from a randomized clinical trial.

Reports from high-volume centers during the last decade are summarized in Table 2[26,45,71,73,128,135,142,146-160]. The overall 3- and 5-year survival rates after radical surgery ranged from 37% to 60% and 20% to 42%, respectively. A recent meta-analysis by the Japanese Biliary Tract Cancer Statistics Registry revealed that the overall 3- and 5-year survival rates of hilar bile duct cancer after radical resection were 47% and 39%, respectively, among 255 patients who received major hepatectomy during 1998 and 2004 in Japan[132,133].

Liver transplantation for hilar cholangiocarcinoma

For the treatment of locally advanced hilar cholangiocarcinoma beyond the indication for resection, orthotopic liver transplantation (OLT) may offer the advantage of resection of all structures involved by the tumor, including vessels within the hepatoduodenal ligament, all intra- and extrahepatic bile ducts, and whole liver parenchyma. Patients requiring a total hepatectomy to achieve a negative margin and those with underlying liver failure precluding hepatic resection are possible candidates for OLT, but early experience with OLT for hilar cholangiocarcinoma was disappointing with early recurrence rates of more than 50% and a 5-year survival rate of 10% to 20%[161-164]. Recently, in highly selected patients undergoing neoadjuvant protocols, improved survivals were reported with a 5-year survival rate of 30% to 45%[165-167]. More recently, the so-called "Mayo protocol" was reported with the intent of treating a highly selected group of patients with cholangiocarcinoma with a strict regimen of preoperative staging and neoadjuvant chemoradiation followed by OLT[168-170]. The inclusion criteria of this protocol are as follows, (1) locally advanced unresectable disease with positive intraluminal cytology or biopsy, or CA19-9 >100 with radiographic

features of malignancy; (2): primary sclerosing cholangitis with resectable bile duct cancer; and (3): absence of medical contraindication for OLT. Eligible patients receive neoadjuvant chemoradiation therapy comprising external radiation of 4500 cGy with concomitant fluorouracil, and transcatheter Iridium-192 brachytherapy of 2000-3000 cGy, followed by oral capecitabine as tolerated until OLT. Additionally, patients should undergo a staging laparotomy to rule out metastatic disease prior to OLT. In 38 patients who underwent this protocol, an 82% 5-year disease free survival was reported. Currently, the indication for OLT for the treatment of cholangiocarcinoma is reserved for highly selected patients in specialized centers.

PROGNOSTIC FACTORS AFTER SURGICAL RESECTION

A variety of clinicopathologic factors have been reported as prognostic factors in previous studies after curative intent surgery for bile duct cancer. Among those, the most frequently reported factors with a negative impact on patient survival are as follows: positive surgical margin[26,34,45,96,119,121,126,127,129,130,135,141,144,149,152,153,155,157,159], nodal involvement (including numbers of metastatic lymph node)[19,23,26,32,34,45,110,111,117,119,121,123-127,130,131,135,141-144,147,150,152,153,155,171], histologic morphology of the tumor[12,13,23,26,34,45,96,123,127,141,142,144,148,159], perineural invasion[14,26,29-33,117,122,131,159], and limited resection of the bile duct[34,41-45,150]. Of these, complete surgical resection with a microscopically negative margin is the only factor under the control of the surgeon and is therefore the most important goal of surgical treatment. A recent study emphasized the significance and accuracy of intraoperative assessment of bile duct margin[172], while a positive bile duct margin itself seems to have minimum impact on patient survival[12,173,174]. As noted above, there is a close association between the extent of the hepatic resection and the rate of negative margins in hilar cholangiocarcinoma[175]. These factors all warrant an aggressive surgical approach to bile duct cancer.

ADJUVANT THERAPY

Because of the high rate of recurrence and poor survival after radical surgery, postoperative chemotherapy, radiotherapy, and chemoradiation have been evaluated in terms of improving patient survival after resection of bile duct cancer[176].

Adjuvant chemotherapy

A previous randomized trial revealed that chemotherapy significantly improved survival and quality of life compared to best supportive care for unresectable cholangiocarcinoma[177]. The most extensively studied agents in unresectable cholangiocarcinoma are fluorouracil (5-FU) and gemcitabine, which have been investigated as a single agent[177-179] and in combination with other drugs, such as mitomycin C[178], leucovorin[180], cisplatin[181], capecitabine[182], epirubicin[183], and oxaliplatin[184]. Eckel *et al*[185] conducted a pooled analysis of 104 chemotherapy studies in advanced bile duct cancers, which suggested that gemcitabine combined with cisplatin or oxaliplatin resulted in the best response without significantly improved survival. On the other hand, reports on adjuvant chemotherapy after resection are scarce (Table 3). A recent multicenter randomized trial evaluated the effect of adjuvant chemotherapy with mitomycin C and 5-FU *versus* surgery alone for patients with pancreato-biliary malignancies, in which no survival benefit was seen for 139 patients with R0 resection for cholangiocarcinoma[186]. Recent institutional retrospective experiences found that gemcitabine-based adjuvant chemotherapy after curative-intent surgery significantly improved patient survival[160,187]. In summary, gemcitabine in combination with cisplatin or oxaliplatin seems to be the most efficacious regimen in cholangiocarcinoma, but adjuvant chemotherapy alone cannot yet be considered standard therapy after resection.

Adjuvant radiotherapy

Several studies have described adjuvant external beam radiotherapy, with or without dose escalation by intraluminal brachytherapy (Table 3). One prospective study and some retrospective studies found no survival benefit of adjuvant radiotherapy in patients who received a curative intent resection for cholangiocarcinoma[188-190]. In contrast, several large retrospective series suggested a survival benefit with adjuvant radiation. Todoroki *et al*[191] demonstrated a significantly higher 5-year survival of 34% in patients with R1 resections with adjuvant radiotherapy (intraoperative and extra beam) compared to 14% with surgery alone. Similarly, Cheng *et al*[192] and Schoenthaler *et al*[193] reported the efficacy of adjuvant radiation for the survival of patients with R1 or R2 resections. Other authors have corroborated the improved survival with adjuvant radiotherapy[194-197]. Although the bulk of retrospective data suggest that improved survival may be achieved with the use of adjuvant radiation, one prospective study was negative for survival benefit in a selected group of patients with hilar cholangiocarcinoma. Further prospective investigation is required to clarify the role of adjuvant radiation after resection.

Adjuvant chemoradiation therapy

The radiosensitization effect of chemotherapy has led to the investigation of concurrent chemoradiation as an adjuvant for resected cholangiocarcinoma. The most commonly utilized agent is 5-FU. Previous retrospective data revealed favorable outcomes of adjuvant chemoradiation (Table 3). Adjuvant chemoradiation has a survival benefit over adjuvant chemotherapy, adjuvant radiation, and surgery alone, especially in distal bile duct cancer[198-201]. Recently, three retrospective studies emphasized a comparable outcome of adjuvant chemoradiation for patients with non-curative surgery when compared to patients with curative surgery alone[202-204].

CONCLUSION

Several advances have been made in the surgical man-

Table 3 Review of the literature on adjuvant therapy for surgically resected bile duct cancer

Author	Yr	Background			*P*-value	Comments
Chemotherapy			Without chemotherapy	With chemotherapy		
Takada *et al*[186]	2002	Curative-resection	28% 5-yr OS	41% 5-yr OS	0.48	Two courses of mitomycin C plus infusional 5-FU, followed by oral 5-FU until tumor progression; 40% received a non-curative operation
		Non-curative resection	16% 5-yr OS	8% 5-yr OS	0.300	
Yubin *et al*[187]	2008	Hilar cholangiocarcinoma	37 mo MS	43 mo MS	< 0.05	Infusional gemcitabine based; no discrimination between curative and palliative resection; some of patients received radiation but the contribution of radiation was not analyzed
Murakami *et al*[160]	2009	Hilar cholangiocarcinoma	23% 5-yr OS	57% 5-yr OS	0.026	Infusional gemcitabine and oral S-1, every 2 wk
Radiation			Without radiation	With radiation		
Pitt *et al*[188]	1995	Hilar cholangiocarcinoma	20 mo MS	20 mo MS	NS	
Cameron *et al*[189]	1990	Hilar cholangiocarcinoma	21% 3-yr OS	21% 3-yr OS	NS	
Zlotecki *et al*[190]	1998	Bile duct cancer	19% 5-yr OS	35% 5-yr OS	NS	
Heron *et al*[195]	2003	Distal cholangiocarcinoma	63 mo MS	MS not reached (> 129 mo)	NS	
Gonzalez *et al*[194]	1999	Hilar cholangiocarcinoma			0.023	
		Hilar cholangiocarcinoma	8 mo MS	19 mo MS	0.001	
Schoenthaler *et al*[193]	1994	R1 resection	11 mo MS	22 mo MS, X-rays	0.010	
				61 mo MS, charged particles	0.001	
Cheng *et al*[192]	2007	Hilar cholangiocarcinoma	HR 4.3, 95% CI 3.6-4.9		< 0.01	Radiation was significantly helpful for R1/2 resection patients
Todoroki *et al*[191]	2000	Bile duct cancer	14% 5-yr OS	34% 5-yr OS	0.010	Radiation was significantly helpful for R1 resection patients
Gerhards *et al*[197]	2003	Hilar cholangiocarcinoma	8 mo MS	24 mo MS	< 0.05	
Chemoradiation			Without chemoradiation	With chemoradiation		
Nakeeb *et al*[198]	2002	Bile duct cancer	11 mo MS (Chemotherapy alone) 8 mo MS (Radiation alone)	16 mo OS	0.020	Chemotherapy; 5-FU
Kim *et al*[199]	2002	Bile duct cancer	9% 5-yr OS (Radiation alone)	41% 5-yr OS	0.0005	Chemotherapy; 5-FU, $P = 0.14$ in multivariate analysis
Serafini *et al*[200]	2001	Bile duct cancer	29 mo MS (Surgery alone)	42 mo MS	0.07	Chemotherapy; 5-FU; when stratified by location, only distal tumors significantly benefited (41 mo MS *vs* 25 mo MS, $P < 0.05$)
Hughes *et al*[201]	2007	Distal cholangiocarcinoma	22 mo MS (Surgery alone)	37 mo MS	0.04	Chemotherapy; 5-FU

MS: Mean survival; NS: Not significant; OS: Overall survival; R1: Microscopically positive margin; R2: Macroscopically positive margin; HR: Hazard ratio; CI: Confidential interval.

agement of bile duct cancer within the last two decades. Surgical morbidity and mortality have been dramatically decreased, but the long-term outcome remains poor. Among several generally accepted prognostic factors, a negative resection margin is the only factor under the control of the surgeon, which has resulted in many meticulous endeavors to establish safe curative procedures and to achieve improved outcome. Further evidence is needed to fully define the role of liver transplantation. Additionally, advances in adjuvant therapy are warranted for improvement of the long-term outcome.

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