Surgical Outcome of Extra-hepatic Cholangiocarcinoma

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ABSTRACT

Extrahepatic cholangiocarcinoma is divided into two compartments, namely perihilar cholangiocarcinoma and distal cholangiocarcinoma. Hemihepatectomy and caudate lobectomy with resection of extrahepatic bile duct is usually performed for patients with perihilar cholangiocarcinoma, whereas pancreaticoduodenectomy is performed for distal cholangiocarcinoma. As pancreaticoduodenectomy has been a well-established and more commonly performed operation, distal cholangiocarcinoma was thought to have better outcomes as compared to perihilar cholangiocarcinoma. However, both cholangiocarcinomas originate from the bile duct epithelium and it is not clear if the malignant potential of perihilar cholangiocarcinoma and distal cholangiocarcinoma are different or not. Therefore, we analyzed 162 perihilar and 98 distal cholangiocarcinoma in our institution from 2002 to 2011, to clarify the actual overall survival, disease-free survival, and prognostic factors. The actual 5-year overall survivals of perihilar and distal cholangiocarcinoma were 39.8 % and 45.2%, respectively, and actual 5-year disease-free survivals were 29.6% and 38.4%, respectively. There are no significant differences in overall survival and disease-free survival between perihilar and distal cholangiocarcinoma. In both cholangiocarcinomas groups independent prognostic factors were distant metastasis, lymph node metastases, perineural invasion, and lack of R0 resection. In conclusion, the oncological outcomes of perihilar and distal cholangiocarcinoma are similar poor long-term outcome for both groups. Effective neoadjuvant and adjuvant therapies must be established to improve patients' prognosis.

Key word: distal cholangiocarcinoma, perihilar cholangiocarcinoma, biliary tract cancer, prognostic factor, overall survival

BACKGROUND

Extrahepatic cholangiocarcinoma is associated with poor prognosis and an over-all survival rate of 20-50 % (1,2). Extrahepatic cholangiocarcinoma consists of perihilar cholangiocarcinoma and distal cholangiocarcinoma. The surgical treatment for these two types of cholangiocarcinoma is quite different. In general, patients with perihilar cholangiocarcinoma undergo hemihepatectomy with caudate lobectomy and resection of the extrahepatic bile duct (3,4). Patients with distal cholangiocarcinoma usually undergo pancreaticoduodenectomy (5). Because the operation for perihilar cholangiocarci-

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noma is more technically demanding, it is thought that the surgical outcome of perihilar cholangiocarcinoma might be inferior compared to that of distal cholangiocarcinoma. Moreover, both cholangiocarcinomas originate from the epithelium of the bile duct and it is not clear if the malignant potential of perihilar cholangiocarcinoma is different from that of distal cholangiocarcinoma. In this paper, we describe our experience for resection of perihilar and distal cholangiocarcinoma. We compare the two types of extrahepatic cholangiocarcinoma to clarify similarities and differences of clinicopathologic characteristics and surgical outcome at a single institution.

PATIENTS AND METHODS

In this retrospective study, we reviewed all medical records for extrahepatic cholangiocarcinoma. From January 2002 to December 2011, we operated 276 consecutive cases of extrahepatic cholangiocarcinoma (excluding ampulla of Vater carcinoma) in our institution, Tohoku University Hospital. To clarify patients' oncological outcome after surgical resection, we analyzed 260 cases of extra-hepatic cholangiocarcinoma after exclusion of 16 cases in-hospital death. Those patients were divided into two categories, perihilar cholangiocarcinoma and distal cholangiocarcinoma, according to the Japanese classification of Biliary Tract Carcinoma (3rd edition) (6). The primary tumors were classified according to the Japanese classification of biliary tract carcinoma (6th edition). We analyzed overall survival and disease-free survival of the perihilar cholangiocarcinoma and distal cholangiocarcinoma with Kaplan-Meier analysis and Cox proportional hazards model.

RESULTS

According to the Japanese classification of biliary tract cancer (3rd edition), 162 (62.3%) of 260 extra-hepatic cholangiocarcinoma were perihilar cholangiocarcinoma and 98 (37.7%) were distal cholangiocarcinoma.

As shown in *table 1*, 81 of the 260 patients (31.2%) underwent pancreaticoduodenectomy (PD). Eight patients (3.1%) underwent right trisectionectomy with caudate lobectomy (CHx) and extrahepatic bile duct resection(BDR). Sixty-eight (26.2%) received right hepatectomy + CHx + BDR and 12 (4.6%) received right hepatectomy and PD. Six (2.3%) underwent left trisectionectomy + CHx + BDR, 56 (21.5%) underwent left hepatectomy +CHx + BDR, and 9 (3.5%) underwent left hepatectomy + PD. Remaining 20 patients (8.5%)

Table 1

Operation	n	
Pancreaticoduodenectomy (PD)	81	31.2 %
Right trisectionectomy	8	3.1 %
Right hepatectomy	68	26.2 %
Right hepatectomy with PD	12	4.6 %
Left trisectionectomy	6	2.3 %
Left hepatectomy	56	21.5 %
Left hepatectomy with PD	9	3.5 %
Others	20	8.5 %
Total	260	100 %

underwent other operation, such as resection of bile duct.

Patients characteristics

Of the 162 patients with perihilar cholangiocarcinoma, 111 (68.5 %) were male and 51 (31.5 %) were female (*table 2*). The mean age was 67.0 years (range 41-82). On the other hand, of 98 patients with distal cholangiocarcinoma, 66 (67.3 %) were male and 32 (32.7 %) were female. The mean age was 69.5 years (range 15-83). There are no significant differences of sex and age between perihilar and distal cholangiocarcinoma.

However, the histopathological status was quite different ($p < 0.0001$). In perihilar cholangiocarcinoma, most patients presented with a pT2 ($n=80$, 49.3%) or pT4 tumor ($n=52$, 35.2 %), whereas in distal cholangiocarcinoma, pT3 tumors were most frequently found ($n=59$, 60.2 %) with no patient presenting with a pT4 tumor.

Histopathologically positive lymph nodes were found in 46.9 % in perihilar cholangiocarcinoma and 31.6 % in distal cholangiocarcinoma ($p=0.0145$). The patients who underwent preoperative biliary drainage were 77.2 % in perihilar cholangiocarcinoma and 88.8 % in distal cholangiocarcinoma ($p=0.0028$). R0 resection rate was 71.6% in perihilar cholangiocarcinoma and 85.7 % in distal cholangiocarcinoma ($p=0.0175$).

Overall survival

The median follow-up time was 38.2 months for all cohort and the median follow-up time of survival cases was 68.7 months. The actual 5-year overall survival rates were 39.8% in perihilar cholangiocarcinoma and 45.2% in distal cholangiocarcinoma (*fig. 1*). The median survival time were 42.1 months in perihilar cholangio-

Table 2

	Perihilar (n = 162)	Distal (n = 98)	p value
Man / Woman	111 (68.5 %) / 51 (31.5 %)	66 (67.3 %) / 32 (32.7 %)	n.s.
Age <Median>	67.0 (41 - 82)	69.5 (15 - 83)	n.s.
pT (1/2/3/4)	8 / 80 / 17 / 57	10 / 29 / 59 / 0	<0.0001
pN (0/1)	86 (53.1 %) / 76 (46.9 %)	67 (68.4 %) / 31 (31.6 %)	0.0145
Biliary drainage	125 (77.2 %)	87 (88.8 %)	0.0028
R(0/1/2)	116 (71.6%) / 42 / 4	84 (85.7 %) / 12 / 2	0.0175

carcinoma and 51.9 months in distal cholangiocarcinoma. There is no significant difference between perihilar and distal cholangiocarcinoma.

Disease-free survival

As shown in *fig. 2*, the actual 5-year disease-free survival (DFS) rates were 29.6% in perihilar cholangiocarcinoma and 38.4% in distal cholangiocarcinoma. There is no significant difference between two cholangiocarcinoma.

Multivariate analysis

The results of multivariate analysis by Cox proportional

hazards model are shown in *fig. 3*. On multivariate analysis presence of distant metastases (HR 3.26; $p < 0.0001$), perineural invasion (HR 2.65; $p = 0.0003$), lymph node metastasis (HR 1.63; $p = 0.0067$), and positive resection margin (HR 1.64; $p = 0.0108$) were associated with poor survival. There were no significant association of pathological grading, T stage, preoperative biliary drainage, adjuvant chemotherapy, severe complication (Clavian-Dindo > 3) or tumor location with survival.

Survival was significantly difference between patients with pN0 and pN1 ($p < 0.0001$; log-rank test). The 5-year survival rate of the patients with lymph node metastases was 20.2% (median survival 27.3 months) was 55.8% (median survival 75.0 months) in patients without lymph node metastases (*fig. 4*). The 5-year

Figure 1 - Overall Kaplan-Meier curves of perihilar cholangiocarcinoma and distal cholangiocarcinoma. The outcome of distal cholangiocarcinoma was superior compared to perihilar cholangiocarcinoma, but there is no significant difference ($p = 0.1848$ by log-rank)

Figure 2 - Disease free survival curves of perihilar cholangiocarcinoma and distal cholangiocarcinoma

survival of the patients with R0 resection was 46.5% (median survival 54.4 months), whereas the 5-year survival after R1 and R2 resection were 26.6% (median survival 32.1 months) and 0% (median survival 19.1 months), respectively (fig. 5).

DISCUSSION

In this retrospective study, we analyzed the

oncological outcome of extrahepatic cholangiocarcinoma. Surgical resection is the only curative therapy for extrahepatic cholangiocarcinoma. The standard chemotherapy for unresectable extrahepatic cholangiocarcinoma is gemcitabine plus cisplatin with a median survival of 11.7 months and a 5-year survival rate of 0% (7).

Prior to this retrospective study, long-term outcome of distal cholangiocarcinoma was believed to be

Figure 3 - The results of Cox hazards model for prognostic factors for extrahepatic cholangiocarcinoma

Figure 4 - Overall survivals in patients with pN0 and pN1

Figure 5 - Overall survivals curves according to the curability (R0/R1/R2)

superior to that of perihilar cholangiocarcinoma, because of a more complex surgical approach is required to achieve complete tumor resection in patients with perihilar tumors. Indeed, the percentage of patients with negative lymph nodes and R0 resection

was higher in distal cholangiocarcinoma than in perihilar cholangiocarcinoma. However, neither overall survival nor disease-free survival were significantly different between perihilar cholangiocarcinoma and distal cholangiocarcinoma.

It needs to be noted that the staging system of perihilar cholangiocarcinoma and distal carcinoma is different. For example, pT4 stage in perihilar cholangiocarcinoma includes pT4a, which is Bismuth-Corlette classification type 4, and pT4b, which presents invasion to both or contralateral portal vein or hepatic artery. Many surgeons pointed out that most cases of pT4a and pT4b perihilar cholangiocarcinoma were resectable (8). On the other hand, pT4 distal cholangiocarcinoma invaded the celiac, common hepatic artery or superior mesenteric artery. pT4 distal cholangiocarcinoma is commonly considered an unresectable tumor.

In this study, the multivariate analysis revealed that the prognostic factors for extrahepatic cholangiocarcinoma were distant metastasis, perineural invasion, lymph node metastasis, and resection margin. Lymph node metastasis was one of the most important prognostic factors of extrahepatic cholangiocarcinoma (4, 9). Moreover, the number of involved nodes as a prognostic factor in distal cholangiocarcinoma (10) and perihilar cholangiocarcinoma (11). In our study, overall survival of patients with positive lymph nodes was significantly lower than those with negative lymph nodes. Lymph node metastasis was a strong prognostic factor in both perihilar and distal cholangiocarcinoma.

Some authors have reported perineural invasion as significant prognostic factor in cholangiocarcinoma (12-14). In line with these data in the present study, survival of patients with perineural invasion was worse than that of patients without perineural invasion. This association remained to be significant on multivariate analysis.

Many studies have reported that R0 resection is necessary for long-term survival (4,15,16). In our previous study, we revealed that R0 resection was among the strongest predictive factors and we concluded that the surgeon's goal for a patient's long-term survival is complete resection of the tumor with negative margins (3).

CONCLUSION

In conclusion, surgical outcome of both perihilar cholangiocarcinoma and distal cholangiocarcinoma are similar in this single institutional analysis. Perineural invasion, lymph node metastasis and positive resection margin are prognostic factors in patients who underwent resection with curative intent.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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