

Pancreaticoduodenectomy for secondary periampullary cancer following extrahepatic bile duct cancer resection

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Purpose: This study addressed the feasibility and effect of surgical treatment of metachronous periampullary carcinoma after resection of the primary extrahepatic bile duct cancer. The performance of this secondary curative surgery is not well-documented.

Methods: We reviewed, retrospectively, the medical records of 10 patients who underwent pancreaticoduodenectomy (PD) for secondary periampullary cancer following extrahepatic bile duct cancer resection from 1995 to 2011.

Results: The mean age of the 10 patients at the second operation was 61 years (range, 45–70 years). The primary cancers were 7 hilar cholangiocarcinomas, 2 middle common bile duct cancers, and one cystic duct cancer. The secondary cancers were 8 distal common bile duct cancers and 2 carcinomas of the ampulla of Vater. The second operations were 6 Whipple procedures and 4 pylorus-preserving pancreaticoduodenectomies. The mean interval between primary treatment and metachronous periampullary cancer was 20.6 months (range, 3.4–36.6 months). The distal resection margin after primary resection was positive for high grade dysplasia in one patient. Metachronous tumor was confirmed by periampullary pathology in all cases. Four of the 10 patients had delayed gastric emptying (n = 2) or pancreatic fistula (n = 2) after reoperation. There were no perioperative deaths. Median survival after PD was 44.6 months (range, 8.5–120.5 months).

Conclusion: Based on the postoperative survival rate, PD may provide an acceptable protocol for resection in patients with metachronous periampullary cancer after resection of the extrahepatic bile duct cancer.

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Key Words: Extrahepatic bile duct, Cholangiocarcinoma, Metachronous neoplasms, Pancreaticoduodenectomy

INTRODUCTION

Cholangiocarcinoma is a relatively rare tumor with a poor prognosis and few long-term survivors [1]. Surgical resection remains the only potentially curative treatment, but many patients develop tumor recurrence [2]. Another biliary cancer, that is, multiple biliary cancer, have been found rarely after surgical treatment of cholangiocarcinoma, rather than recurrence. Some multiple gastrointestinal cancers have been reported. However, multiple cancers in the extrahepatic

bile duct (EHBD) have not been reported frequently. While synchronous multiple biliary cancers occur in 3.7%–7.4% of all surgically resected biliary tumors, metachronous multiple biliary cancers have not been reported frequently [3-5]. Moreover, treatment or outcome of metachronous biliary cancer has not been found precisely.

Local recurrence following resection of extrahepatic bile duct cancer is generally regarded as incurable, and secondary curative surgery as virtually impossible. However, metachronous biliary cancers with about 10 cases reported in the world literature

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were treated with curative resection [6-8]. Thus few studies have addressed the surgical treatment of secondary periampullary carcinoma after resection of the extrahepatic bile duct cancer and the role of this resection is not well-documented or established.

This study was conducted to examine the feasibility and effect of secondary curative surgery for metachronous periampullary cancer in the extrahepatic bile duct.

METHODS

Between October 1995 and December 2011, 455 patients with EHBD cancer underwent surgical resection in a tertiary institution. The EHBD cancers in the present study did not include gallbladder (GB) cancer or distal common bile duct (CBD) cancer. Lymph node dissection was performed for at least the hepatoduodenal ligament in all EHBD cancers. We excluded 40 patients who underwent palliative surgery for EHBD cancer in this study. Among the 415 patients who underwent surgical resection with curative intent for EHBD cancer, 245 patients (59%) had recurrence, including local recurrences ($n = 104$), intrahepatic metastases ($n = 61$), and systemic metastases ($n = 80$). Instances of local recurrence occurred in the following areas: hepaticojejunostomy site ($n = 34$), hepatic pedicle lymphadenectomy area ($n = 43$), liver resection margin ($n = 15$) and periampullary region ($n = 12$). In two of the 12 patients with periampullary recurrence, local recurrences consequently revealed duodenal cancer of primary origin, regardless of biliary tract involvement. Those two patients underwent palliative surgery, such as gastrojejunostomy, due to aggressive vascular invasion. Ten patients underwent pancreaticoduodenectomy (PD) for secondary periampullary cancer following EHBD cancer resection.

Follow-up studies after EHBD cancer resection included routine laboratory tests, serum CA 19-9, and abdominal CT in the first month after surgery and every 3–6 months for 2 years after surgery, every 6 months until 5 years, and then annually thereafter. All periampullary lesions were first detected with abdominal CT during follow-up for EHBD cancer resection. We checked preoperative magnetic resonance imaging scans and PET to evaluate resectability and seek evidence of distant metastasis. The criteria for resectability for secondary periampullary tumor were as follows: (1) absence of distant metastasis on imaging scans, (2) absence of intrahepatic metastasis, and (3) absence of clinically and/or radiologically evident lymphadenopathy in the para-aortic region.

We reviewed medical records, including surgeon's notes, radiologic images and pathology reports retrospectively. A pathologic examination was performed for all of the resected specimens. Preoperative interventions such as endoscopic retrograde cholangiopancreatography (ERCP), endoscopic

ultrasonography (EUS) and esophagogastroduodenoscopy (EGD) were performed to confirm preoperative pathologic status. Intraoperative frozen biopsy was performed to confirm margin status. The diagnosis of periampullary cancer was based on the histology obtained from the postoperative biopsy of the resected specimen. Time to metachronous disease was calculated from the date of EHBD cancer resection to the date when metachronous tumor was first diagnosed with interventional biopsy or imaging studies.

Tumor stage was based on criteria from the 7th edition of the American Joint Committee on Cancer (AJCC) cancer staging manual for ampulla of Vater (AoV) cancer, distal CBD cancer and hilar cholangiocarcinoma. Curative resection (R0 resection) was defined as no-residual-tumor status, whereas microscopic (R1 resection) and macroscopic residual tumor (R2 resection) were defined as noncurative resection. Postoperative pancreatic fistula was classified by definition of the International Study Group of Pancreatic Fistula [9]. The cumulative survival rates were calculated using the Kaplan-Meier method.

RESULTS

Clinicopathologic classification of the 10 extrahepatic bile duct cancers

The study group included 7 men and 3 women of mean age 61 years (range, 45–70 years). The EHBD cancers were 7 hilar cholangiocarcinomas, 2 middle CBD cancers, and one cystic duct cancer. In accordance with tumor location, 5 patients with hilar cholangiocarcinoma underwent hepatectomy with caudate lobectomy; 4 patients with hilar cholangiocarcinoma and middle CBD cancer and one with cystic duct cancer underwent bile duct segmental resection with hepaticojejunostomy. The TNM classifications and tumor stages of the EHBD cancers, based on the AJCC cancer staging manual, are shown in Table 1. Lymph node involvement was observed in only one patient. Perineural invasion was noted in 4 patients (40%). An R0 resection was achieved in 9 patients and an R1 resection in one. No patient underwent adjuvant therapy following EHBD cancer resection.

Clinicopathologic characteristics of the metachronous periampullary cancers

Clinical features of the 10 patients who underwent PD are shown in Table 1. Only in patient number 6, who had hilar cholangiocarcinoma, was margin status of the distal bile duct positive after EHBD resection, i.e., with focal high grade dysplasia. After 25.8 months, however, the metachronous cancer in this patient was detected in the AoV, not in the remnant bile duct. Resection margins at the first operation were free of tumor in 9 patients. Preoperative CA 19-9 before PD was high in 5 patients with 4 hilar cholangiocarcinomas and in one

Table 1. Clinical profiles of 10 patients who underwent pancreaticoduodenectomy

Case	Sex	Age (yr)	Primary cancer	1st Stage ^{a)}	Margin status ^{b)}	Preoperative CA19-9 (U/mL)	Metachronous site	Tumor size (cm)	2nd Stage ^{a)}	Time to metachronous disease ^{c)} (mo)	Follow-up ^{d)} (mo)	Status
1	Female	70	Middle CBD	IIIB (T1N1)	-	134.00	AoV	2.5	IIA (T3N0)	31.3	120.5	Alive
2	Male	69	Cystic duct	II (T2N0)	-	21.60	Distal CBD	5.0	IA (T1N0)	10.6	44.6	Dead
3	Male	45	Hilar CC (IIIA) ^{e)}	II (T2N0)	-	578.17	Distal CBD	2.0	IIB (T3N1)	12.9	32.7	Dead
4	Female	63	Hilar CC (IIIB)	I (T1N0)	-	32.30	Distal CBD	1.5	IA (T1N0)	26.4	38.5	Alive
5	Male	55	Hilar CC (II)	II (T2N0)	-	127.52	Distal CBD	3.5	IIB (T3N1)	21.7	8.5	Dead
6	Female	67	Hilar CC (IIIA)	II (T2N0)	HGD	145.32	AoV	1.0	IA (T1N0)	25.8	13.2	Dead
7	Male	63	Middle CBD	I (T1N0)	-	5.35	Distal CBD	1.5	IA (T1N0)	6.6	22.8	Alive
8	Male	63	Hilar CC (IIIA)	I (T1N0)	-	16.13	Distal CBD	3.5	IA (T1N0)	3.4	13.3	Alive
9	Male	53	Hilar CC (I)	I (T1N0)	-	50.60	Distal CBD	3.0	IA (T1N0)	31.1	12.5	Alive
10	Male	65	Hilar CC (I)	II (T2N0)	-	29.85	Distal CBD	4.5	IIB (T3N1)	36.6	18.5	Dead

CBD, common bile duct; AoV, ampulla of Vater; CC, cholangiocarcinoma; HGD, high grade dysplasia.

^{a)}Based on the American Joint Committee on Cancer 7th ed. ^{b)}Distal bile duct resection margin after primary resection. ^{c)}Interval between primary treatment and detection of the metachronous periaampullary cancer. ^{d)}Follow-up period after pancreaticoduodenectomy. ^{e)}Bismuth classification of the hilar cholangiocarcinoma.

with middle CBD cancer. The metachronous cancers included 8 distal CBD cancers and 2 AoV cancers. Interventional biopsies using ERCP, EUS, and EGD were preoperatively performed in 6 patients and cancer was confirmed. Following detection of the metachronous cancer progression, 10 patients underwent PD, including 6 Whipple procedures and 4 pylorus-preserving pancreaticoduodenectomies. In the 10 patients who underwent PD, the mean number of lymph nodes harvested was 6 (range, 0–13) while the mean number of lymph nodes involved was 0.8 (range, 0–6). The volume of blood loss was 586 ± 243 mL (range, 300–1150 mL). No patient underwent homologous blood transfusion during the perioperative period. The postoperative complications after PD included delayed gastric emptying in 2 patients and pancreatic fistula as grade B and C in 2 others. There were no intra- or postoperative deaths in this series. The mean interval between extrahepatic bile duct cancer resection and detection of the metachronous periaampullary cancer was 20.6 months (range, 3.4–36.6 months). The follow-up period after PD ranged from 8.5 to 120.5 months. Five of the 10 patients died during the follow-up period. Patients No. 2 and 3 died as cancer progression with multiple metastases to the lymph nodes, detected at 35 and 17 months after PD, respectively. Patients No. 5, 6, and 10 died through systemic recurrence with hepatic metastasis and peritoneal seeding, detected at 3, 5, and 16 months after PD, respectively. Patient No. 3 and 5, who had positive nodal disease, underwent adjuvant chemotherapy (5-fluorouracil based regimens). Patient No. 10, who also had positive node status, refused treatment with adjuvant chemotherapy. Palliative radiotherapy was administered to Patient No. 2 due to local recurrence around the hepaticojejunostomy site 35.5 months after the second operation.

Comparison of the histopathological findings

The histologic types, cell differentiation and gross types between the EHBD cancer and the metachronous periaampullary cancer were compared in Table 2. The degrees of cell differentiation were identical in the primary and secondary cancers of 9 patients but not in the cancers of Patient No. 6. Among the 10 patients, the gross tumor types were papillary in 4 patients. Mean distance from the resection margin of distal bile duct to the EHBD cancer was 1.7 cm (range, 1.0–2.5 cm) except in one case in which the resection margin was positive for tumor.

Survival

Median survival after EHBD cancer resection including the survival period after PD was 56.1 months (range, 18.6–152.7 months). Median survival after PD was 44.6 months (range, 8.5–120.5 months) (Fig. 1).

Table 2. Comparison of pathologic finding for extrahepatic bile duct cancers and subsequent periampullary cancers

Case	Extrahepatic bile duct cancer				Periampullary cancer		
	Histologic type	Grade	Gross type	Margin distance ^{a)} (cm)	Histologic type	Grade	Gross type
1	DAC	M/D	Nodular	1.2	AoV AC	M/D	Nodular infiltrating
2	DAC	M/D	Nodular	1.5	CBD DAC	M/D	Nodular
3	DAC	M/D	Nodular infiltrating	2.5	CBD DAC	M/D	Nodular infiltrating
4	IPC	W/D	Papillary	2.2	CBD IPC	W/D	Papillary
5	DAC	M/D	Sclerosing	1.5	CBD DAC	M/D	Nodular infiltrating
6	DAC	M/D	Sclerosing	0	AoV AC	W/D	Nodular
7	DAC	M/D	Papillary	1.7	CBD DAC	M/D	Papillary
8	IPC	M/D	Papillary	2.0	CBD IPC	M/D	Papillary
9	DAC	M/D	Papillary	1.3	CBD DAC	M/D	Papillary
10	DAC	M/D	Nodular	1.0	CBD DAC	M/D	Mass form

DAC, ductal adenocarcinoma; M/D, moderately differentiated; AoV AC, ampulla of Vater adenocarcinoma; CBD, common bile duct; IPC, intraductal papillary adenocarcinoma; W/D, well-differentiated.

^{a)}Distance from distal resection margin.

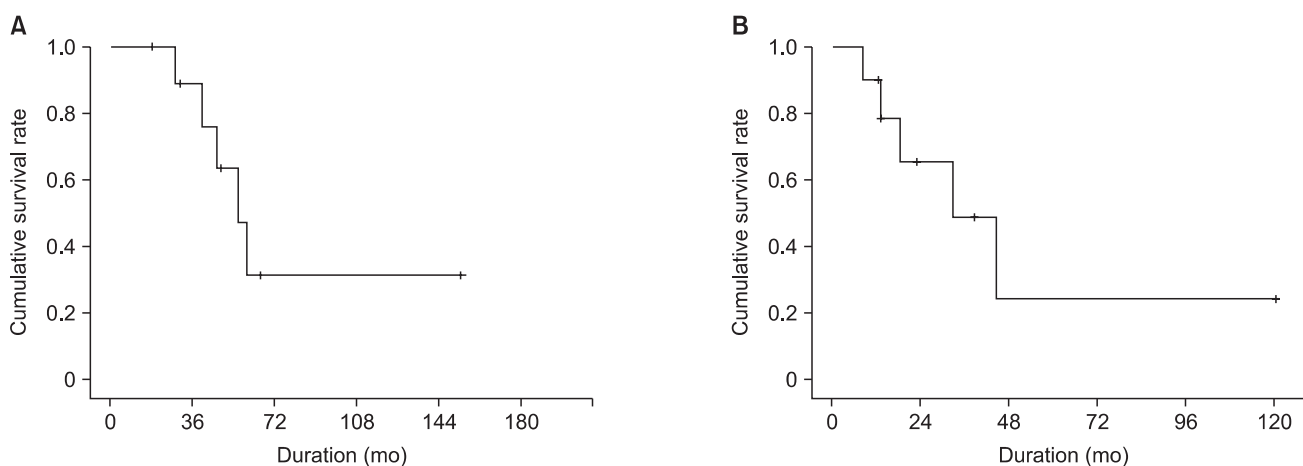


Fig. 1. Overall survival rates (A) after extrahepatic bile duct resection and (B) after pancreaticoduodenectomy for secondary periampullary cancer.

DISCUSSION

Surgical resection is the only accepted curative treatment for cancer of the EHBD. Nagakawa et al. [10] reported the resection rate and the curative rate for bile duct cancer as 67.0% and 30.4%, respectively. Multiple cancers in the EHBD have not been found frequently. In many such instances, there are double cancers of the CBD and the GB [3,6]. But, double cancers of the CBD are rare. Although the actual incidence of multiple malignant tumors in the bile duct is unknown, it is reported to occur in approximately 5%–10% of bile duct cancers [4,5]. When metachronous cancers are identified, the distinction between secondary primary cancer and recurrence is often clinically difficult. Warren and Gates [11] proposed the three still generally accepted criteria that had to be met in order to consider malignant tumors as multiple primary tumors rather than recurrence: (1) each tumor must present a definite

picture of malignancy, (2) each tumor must be distinct, (3) the possibility of one being a metastasis of the other must be ruled out. Gertsch et al. [5] suggested that the criteria for double primary cancer in the biliary tract was their location at separate sites with normal intervening tissue, together with histologic evidence sufficient to rule out submucosal to periductal lymphatic spread. Kobayashi et al. [12] demonstrated that multicentric adenocarcinoma of the biliary tract is more likely to be early cancer and papillary carcinoma with extensive dysplastic epithelium and is less likely to have lymph node metastasis.

In the present study, the sites of metachronous cancers in 2 patients were the AoV, not biliary tract. Conceivably, those two AoV cancers may be regarded as metachronous multiple tumors or derived by intraluminal tumor implantation rather than recurrence. Local recurrence usually originates from residual cancer cells at the surgical margins [13]. Based on

evidence from pathologic reviews, all of the primary tumors in this study were more than 1.0 cm distant from the distal resection margin except in one case. Although histologic types and grades in the primary and secondary tumors of 8 patients were matched, we could not rule out the occurrence of multiple malignant tumors solely on the following evidence: (1) negative resection margins of distal bile duct in fist pathology, (2) distance from primary tumor to resection margin, (3) secondary tumor sites in remnant distal bile duct being far from original resection margin. Moreover, as stated by Joo et al. [8] and Kobayashi et al. [12], the bile duct cancer resembled a primary tumor from evidence of dysplastic changes near the main mass. Extensive dysplasia in the biliary tract suggests that multicentric adenocarcinomas might arise from the carcinogenetic background epithelial dysplasia. Metachronous tumors of 5 patients in this study developed within 2 years following EHBD resection. In view of the recurrence, it should be noted that the remnant bile duct recurrence developed in a patient with synchronous multicentric cancer despite negative resection margin. This recurrence might be considered to be metachronous tertiary cancer even though it developed within 2 years after the prior surgery [12].

The cause of multiple biliary cancers has not been defined, but it is generally accepted that the anomalous pancreaticobiliary duct union (APBDU) plays an important role in the development of multiple biliary cancers. Previous studies describe the occurrence of multiple malignant tumors in association with APBDU [6,8,14-17]. It is reported that about 50% of cases of synchronous double biliary cancers were associated with APBDU [6]. The presence of APBDU was not evaluated in this series. Others have speculated that familial and genetic factors are associated with occurrence of multiple malignant tumors [7]. Three of the patients in this study had family histories of cancer; and two of these cancers involved gastrointestinal tissues, suggesting genetic predisposition. Upper biliary tract cancers and metachronous double biliary cancers might have a strong genetic predisposition such as loss of heterozygosity, point mutation of k-ras oncogene, or overexpression of the tumor suppressor gene p53 [3,8,18]. Multiple malignant tumors are rare, hence it is proposed that bile duct cancers are usually advanced by the time of diagnosis, and that when surgery is possible with curative intent, this should be performed with a wide surgical margin [7,19]. Papillary carcinomas of the EHBD tend to grow multiply and spread fairly long distances superficially, and appear to have better prognosis than do other types of EHBD cancer [12,20-22]. Kobayashi et al. [12] reported that early papillary adenocarcinoma in the biliary tract were associated with multicentric cancer. Although 4 of the tumors in this study were grossly of papillary type, we would not conclude from this that papillary carcinomas of bile duct are more likely than ductal adenocarcinomas to develop

metachronous cancer after surgical resection. Moreover, 4 of 5 survivors in this study had papillary carcinomas according to the gross tumor type and this may have contributed to the favorable survival rates observed.

Similar cases of metachronous bile duct cancer are reported [6-8,12]. In all of those reported cases, the metachronous bile duct cancers were treated successfully by surgery. Jung et al. [23] reported median overall survival after biliary tract cancer resection as 48.8 months. These results are similar with our results, although we observed longer median survival after the bile duct cancer resection. Previous studies report five-year survival rates of 11.0%–28.6% for hilar or superior bile duct cancer [24-26] and 21.0%–32.7% for middle and distal bile duct cancer after resection [2,27-29]. Median survival times after EHBD resection and the secondary operations were 56.1 and 44.6 months, respectively, in the present study. Based on these results, our suggestion is that development of surgical treatment permitting long-term survival for metachronous periampullary cancer is both feasible and necessary.

There is a wide variation in practice patterns between individuals and institutions, because no studies have compared high- versus low-intensity surveillance in patients after surgical resection for EHBD cancer. Follow-up management after EHBD cancer resection may contribute to prolonged survival. Triphasic CT scan of the liver (abdomen and pelvis) was performed as the usual follow-up imaging modality every 3–6 months for the first 2 years after resection and every 6 months thereafter. As for the follow-up of those patients enough to have a prolonged survival after surgical resection for metachronous periampullary cancer, we suggest an intensive role for CT scanning, especially in papillary carcinoma of the EHBD. Based on the overall survival rate after EHBD cancer resection in this series, follow-up duration should be maintained for at least 5 years.

Analysis for factors related to long-term survival was limited by the small number of patients in our study. However, the findings support the hypothesis that PD for secondary periampullary cancer, although a relatively aggressive treatment, may potentially extend patient survival.

In conclusion, because local recurrence after EHBD cancer resection is common, to achieve long-term survival in patients with extrahepatic bile duct cancer, and papillary carcinoma in particular, a second curative surgery should be considered. In metachronous periampullary cancer, following resection of the extrahepatic bile duct cancer, PD may provide a feasible and acceptable treatment.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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