

Original Paper

**An Experience of Hepatopancreatoduodenectomy
in Patients with Hepato-Biliary Malignancies**

Atsushi Nanashima, MD, Toshiya Nagasaki, MD, Yori-hisa Sumida, MD,

Takafumi Abo, MD, Syuuichi Tobinaga, MD, Hiroaki Takeshita, MD,

Takashi Nonaka, MD, Shigekazu Hidaka, MD, Terumitsu Sawai, MD,

Toru Yasutake, MD, Takeshi Nagayasu, MD

Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki
University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki
852-8501, Japan

Running title: HPD in hepatobiliary malignancy

Corresponding and reprint requests to: Atsushi Nanashima, M.D.

Division of Surgical Oncology, Department of Translational Medical Sciences,
Nagasaki University Graduate School of Biomedical Sciences,
1-7-1 Sakamoto, Nagasaki 852-8501, JAPAN

Tel.: +81-95-819-7304 , Fax: +81-95-819-7306

E-mail: a-nanasm@net.nagasaki-u.ac.jp

ABSTRACT

Background/Aims: In the advanced stage of hepatobiliary malignancies, concurrent hepatopancreatoduodenectomy (HPD) is necessary to accomplish curative resection, even though high rates of morbidity and mortality still remain. **Methodology:** We examined the surgical records and outcome in 11 patients undergoing HPD. **Results:** In 11 patients, diseases included bile duct carcinomas in 7 patients, gallbladder carcinomas in 3, and ampullar carcinoma in one. Hemi-hepatectomy with resection of the caudate lobe was performed in 8 patients and resection of segment 4 and 5 of the liver in two. Pancreatoduodenectomy (PD) was performed in 3 patients and pylorus preserving PD in 8. Curative resection was accomplished in 8 patients. Two patients underwent adjuvant photodynamic therapy because of a cancer-positive margin. Morbidity rate was 36% but no hospital deaths were reported. The tumor recurrence rate was 73% and 8 patients died of cancer. Patient prognosis of gallbladder cancers (12 ± 1 months) tended to be shorter than in patients with bile duct cancers (19 ± 11 months) ($p=0.15$). Three patients with bile duct cancers survived without tumor relapse over 12 months. **Conclusions:** Complete surgical resection (R0) by HPD could be safely performed for diseases of the hepatobiliary malignancies, which achieved longer survival in some patients.

KEYWORDS: hepatectomy, pancreatoduodenectomy, biliary malignancy

ABBREVIATIONS: Bile duct carcinomas (BDC), gallbladder carcinomas (GBC), hepatopancreatoduodenectomy (HPD), pancreatoduodenectomy (PD)

INTRODUCTION

In recent years, surgical resection is the only curable treatment for advanced biliary malignancies, and a concurrent hepatopancreatoduodenectomy (HPD) is often necessary to accomplish complete (R0) resections (1-4). The resectability of hepatobiliary malignancies has markedly improved with the improvement of operative techniques (5, 6). However, physical stress in patients is severe and postoperative morbidity and mortality rate are still not low (7, 8). Therefore, the indication for HPD should be carefully decided. In the present report, we examined our results of HPD in patients with biliary malignancies at a Japanese single cancer institute and discuss the clinical status and problems.

METHODOLOGY

Patients

We analyzed 11 patients with biliary malignancies who underwent surgical resection in the Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS) between 1996 and 2006. The study design was approved by the Human Ethics Review Board of our institution. Informed consent for data collection was obtained by each patient during this period. Anesthetic and patient data were retrieved in the NUGSBS database. Tumor stage and curability was followed by the *Classification of Biliary Tract Carcinoma by the Japanese Society of Biliary Surgery* (9).

Operative indications, procedures and follow-up

The indication of HPD at our institute was described as follows: 1) malignant biliary diseases needing hepatic resection, which extends to duodenum and pancreatic head, 2) biliary malignancies with remarkably metastatic lymph node at peri-pancreatic head, 3) cases where cancer lesions could be completely (= radically) resected by HPD without liver metastasis, peritoneal dissemination, para-aortic lymph node metastasis or more distant metastasis, and 4) good general conditions and liver functions but border of patient age was not decided.

In liver resection, the volume to be resected is estimated preoperatively based on the results of indocyanine green retention rate at 15 minutes (ICGR15) using Takasaki's formula (10). The liver volume, excluding tumor volume (cm³), is measured by CT volumetry (11). We routinely clamped the hepatoduodenal ligament to occlude total inflow to the liver during transection (Pringle's maneuver). We also routinely used the forceps fracture method (12) and an ultrasonic dissector (USU MH-207, Olympus, Tokyo, Japan) for the transection of liver parenchyma. In pancreatic resection, pancreatoduodenectomy (PD) was usually performed in HPD. Pancreatic functions were not considered as operative indications.

After discharge from hospital, the patient status, laboratory data, and disease recurrence were checked every 2 to 3 months.

RESULTS

Patients included 6 men and 5 women with a mean age of 67.3 ± 8.0 years (\pm SD, range, 54-77 years) (**Table 1**). Diseases included bile duct carcinomas in 7 patients, gallbladder carcinomas in 3, and ampullar carcinoma in 1 patient. Reasons for liver resection were direct hepatic invasion of gallbladder carcinoma in 3 patients, extended hilar bile duct carcinoma in 7 and superficially wide extension to hilar bile duct of the ampullar carcinoma in 1 patient. Reasons for pancreatic resection included lymph node metastasis involving pancreatic head of gallbladder carcinoma in 3 patients, superficially wide extension of bile duct carcinoma to lower bile duct in the pancreas head in 7 patients, and advanced ampullar carcinoma in 1 patient.

Right hepatectomy with resection of caudate lobe was performed in 5 patients, left hepatectomy with resection of caudate lobe in 3, and partial resection of segment 4 and 5 of the liver in 2 patients. PD was performed in 3 patients and pylorus preserving PD in 8 patients. All patients underwent loco-regional lymphadenectomy (**Table 2**). The operation time ranged between 494 and 984 minutes (mean was 703 ± 144 minutes) and blood loss ranged between 910 and 2920 minutes (mean was 1778 ± 654 mL). Tumor stage with stage IV was observed in 8 patients (73%). Curability A and B was accomplished in 8 patients and 3 had curability C due to positive cancer margin at hepatic cut end, which caused superficial extension of carcinoma along the intra-epithelium. Two underwent adjuvant photodynamic therapy after surgery in patients with curability C.

Postoperative complications were observed in 4 patients (36%) but no hospital death. These complications subsided within a few weeks (**Table 3**). Duration of hospital stay

ranged between 35 and 76 days (mean was 51 ± 14 days). In 8 patients (73%), tumor recurrence was observed and liver metastasis was dominant. These 8 patients died of cancer recurrence. Compared between diseases, the survival period in patients with gallbladder cancer (12 ± 1 months) tended to be shorter than that in patients with biliary malignancies (19 ± 11 months) ($p=0.15$). Three patients with bile duct cancers survived without tumor relapse at 15, 12, and 12 months at this stage.

DISCUSSION

Nowadays, aggressive surgical exploration for hepatobiliary malignancy combined with hepatic resection and pancreatoduodenectomy is performed (1-4). However, the usefulness of such an aggressive approach remains controversial because highly advanced tumors are dominant in such cases (13). As the techniques and perioperative management have improved remarkably, our group has actively performed HPD for complete tumor resections (R0) during the last decade. Based on previous reports, the usefulness of HPD has been mainly reported by Japanese surgeons since the 1990s (1-4, 7, 8). This operative procedure is usually performed for bile duct carcinoma and gallbladder carcinoma (1-8). In our series, bile duct carcinoma was dominant. One ampullar carcinoma extended to the hilar bile duct by skip infiltration, which has not been reported previously. Widely intramural extensions of bile duct carcinoma between intra-hepatic bile duct and intra-pancreatic bile duct can be completely resected by HPD (8, 14-16), which is the best indication of this procedure. Other indications are direct invasion or

lymph node metastasis around the pancreatic head of gallbladder carcinoma (8, 15-17). In these indications, the usefulness of PD for lymphadenectomy was still limited (18). In the advanced stages of gall bladder carcinomas, extended surgical resection might provide a survival benefit, based on recent reports (15, 19, 20). In our series, 3 patients with gall bladder carcinomas underwent HPD for lymphadenectomy; however, tumor recurrence in the liver and lymph node were observed early on.

In the present series, right hepatectomy with caudate lobe resection was performed for bile duct carcinoma in 5 patients. HPD with right hepatectomy might be risky for post-operative hepatic failure because of a large volume of resection (21). In such cases, preoperative portal vein embolization might prevent such a lethal complication (22, 23). By applying this technique, we can safely perform HPD with right hepatectomy at present. In the present series, pylorus preserving PD was mainly performed. Pylorus preserving PD is physiologically better for post-operative nutrition than the usual Whipple's procedure (24). For the purpose of lymphadenectomy, Whipple's operation should not be necessary in many cases because peri-pancreatic head lymph node dissection is preferred over peri-pylorus lymph node dissection in biliary malignancies (25). In 3 patients with Whipple's operation, enlarged lymph nodes were observed at peri-pylorus lesions, and metastasis was suspected in 1 case, and ischemia of the duodenum near the pylorus was remarkable in 2 cases. Operating time and blood loss gradually improved by improvement of surgical techniques in our series. However, HPD is still a high level operation in the upper abdomen. HPD was performed to accomplish curative operation;

however, 3 patients showed curability C. Unexpected wide extension of intramural carcinoma in the intrahepatic bile duct was found in these cases, even after HPD was performed. In cases with remnant cancer cells at surgical cut end of the bile duct, additional local treatment is necessary to avoid tumor relapse. In 2 patients, photodynamic therapy, which is a cancer-specific treatment (26), was performed after the operation. As a result, local tumor recurrence has not been observed in these patients.

Post-operative complications were observed in 4 patients, but the complications were not severe, and there were no hospital stay deaths. Morbidity and mortality rates were still high, particularly in cases with combined vascular resections at this stage (4, 8, 15, 16, 27). Hospital stay was longer than in patients undergoing other abdominal surgeries. To tolerate such an aggressive operation, the indication of HPD should be carefully considered and selected (8). With respect to long-term prognosis, tumor relapse was frequent even after the aggressive resections, particularly in gall bladder carcinomas, in the present series. The usefulness of PD for lymphadenectomy in gall bladder carcinomas was reported (20); however, locally advanced carcinomas, such as cases accompanied with bile duct infiltration, might be avoided because of extremely poor prognoses (28). On the other hand, longer prognosis would be expected in bile duct carcinomas with wide extension by complete and aggressive resection (16, 29).

In conclusion, major surgical resection with simultaneous hepatic resection and pancreaticoduodenectomy (HPD) was performed in 11 patients with biliary malignancies at a single cancer center over the past 10 years. HPD could be safely performed because of

low morbidity rate and no mortality at this stage. In patients with bile duct and ampullar cancer, long-term survival could be obtained in some cases and, therefore, the indication of HPD should be considered for widely extensive bile duct cancer. On the other hand, the indication of HPD for patients with gallbladder cancer with peri-pancreatic lymph node metastasis should be carefully considered because of early recurrence.

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Table 1. Patient demographics

	Age	Gender	Diseases	Reasons for hepatectomy	Reasons for pancreatoduodenectomy
1	54	Male	GBC	Hepatic invasion	Lymph node metastasis
2	69	Male	GBC	Hepatic invasion	Lymph node metastasis
3	73	Male	BDC	Extension to hilar BD	Extension to intra-pancreatic BD
4	67	Male	AC	Extension to hilar BD	AC
5	55	Female	BDC	Extension to hilar BD	Extension to intra-pancreatic BD
6	71	Female	BDC	Extension to hilar BD	Extension to intra-pancreatic BD
7	58	Male	BDC	Extension to hilar BD	Extension to intra-pancreatic BD
8	72	Female	GBC	Hepatic invasion	Lymph node metastasis
9	69	Male	BDC	Extension to hilar BD	Extension to intra-pancreatic BD
10	77	Female	BDC	Extension to hilar BD	Extension to intra-pancreatic BD
11	75	Female	BDC	Extension to hilar BD	Extension to intra-pancreatic BD

GBC; gallbladder cancer, BDC; bile duct cancer, AC; ampullar cancer, BD; bile duct

Table 2. Surgical findings and tumor staging

	Operation	Operation time (minutes)	Blood loss (ml)	Tumor stage*	Curability*
1	PD + extended RH	565	2920	IVa	B
2	PPPD + resection of segment 4 and 5	615	1892	IVa	A
3	PPPD + extended LH	715	910	IVa	B
4	PPPD + right lateral sectionectomy	615	2050	IVb	C
5	PPPD + extended RH	623	1620	II	B
6	PPPD + extended LH	494	2000	III	B
7	PPPD + extended RH	695	2500	IVa	C
8	PD + resection of segment 4 and 5	730	1000	IVb	B
9	PD + extended LH	827	2200	III	B
10	PPPD + extended RH	867	950	IVa	C
11	PPPD + extended RH	984	1520	IVa	B

PD; pancreatoduodenectomy, PPPD; pylorus preserving pancreatoduodenectomy
 RH; right hepatectomy, LH; left hepatectomy

* *Classification of Biliary Tract Carcinoma by the Japanese Society of Biliary Surgery*

Table 3. Patient outcomes

	Complications	Hospital stay (days)	Tumor recurrence	Prognosis (months)
1	Pancreatic fistula	76	Liver	Cancer death (12)
2	None	35	Liver, lymph node	Cancer death (13)
3	Pancreatic fistula	47	Liver	Cancer death (29)
4	None	33	Liver, lung	Cancer death (32)
5	None	41	Liver	Cancer death (35)
6	None	41	Local recurrence	Cancer death (9)
7	None	58	Peritoneum	Cancer death (13)
8	None	47	Liver	Cancer death (11)
9	None	56	None	Survive (15)
10	Delayed gastric empty	58	None	Survive (12)
11	Abscess, Liver failure	69	None	Survive (12)