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Original Research

Extended liver surgery for gallbladder cancer revisited: Is there a role for hepatopancreatoduodenectomy?

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ABSTRACT

Gallbladder cancer (GBCA) is a rare and fatal disease and the majority of patients presents with advanced stage. Surgical resection associated with lymphadenectomy is the only chance for cure. For patients in stages III and IV, extended resection is the only treatment to achieve R0 margins. For GBCA invading the hepatoduodenal ligament and pancreatoduodenal region, the resection of extrahepatic bile duct and pancreas is necessary. Hepatopancreatoduodenectomy (HPD) represents the most complex and challenging procedure in the hepatopancreatobiliary region. Kuno at the Cancer Institute Hospital Tokyo performed the first HPD in Japan in 1974 and in 1980 Takasaki presented five cases and the 30-day mortality was 60%. After that, other countries started to perform the procedure including United States and Brazil. The main complications are liver failure and pancreatic fistula. Advancements in perioperative care, surgical technique, medical instruments and post-operative at intensive care unit have resulted in reduction in morbidity and mortality. The use of portal vein embolization is indicated to increase the liver volume in patients with insufficient remnant. Preoperative biliary drainage can prevent cholangitis and improve hepatic function. This procedure should be recommended before extended HPD in jaundiced patients. Operative results with mortality rates below 5% at high volume centers suggest that HPD should be performed at centers with expertise in hepatopancreatobiliary surgery.

1. Introduction

Gallbladder cancer (GBCA) is a rare disease but is the most common tumor of the biliary tract, representing 80–95% of all tumors. It is a fatal disease with poor prognosis with over one-third of patients presenting with distant metastasis at time of diagnosis and a median overall survival of six months and a 5-year survival rates ranges from 5% to 15%. Chile, Japan and Northern India are areas of high incidence and source of significant mortality. Unfortunately, the majority of patients presents with advanced disease due to the late onset of the symptoms [1–3].

For patients with advanced gallbladder cancer liver resection including the gallbladder bed and clearance of regional lymph node has been used widely to obtain curative resection and provide the chance for cure. The gallbladder has an anatomical proximity to liver,

hepatoduodenal ligament, duodenum and colon. Due to patterns of tumor cell spread, extensive surgical resection is necessary to achieve R0 margins in patients with locally advanced GBCA. Unfortunately only 10% of these patients are considered candidates for resection.

Hepatopancreatoduodenectomy (HPD) as a standard operation is the only opportunity to achieve the R0 resection in selected patients with advanced GBCA at experienced hepatobiliary institutions. With the improvement in surgical technique, anesthesia and perioperative care the mortality rate has fallen below 5%, with no mortality in some centers [1–3]. A considerable experience in hepatopancreatobiliary resections and specific surgical skill, including vascular resection, is necessary to perform this aggressive surgery safely [1,2,4,5]. In this review we revisit the still debated role of hepatopancreatoduodenectomy in locally advanced GBCA.

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Fig. 1. Hepatopancreatoduodenectomy. 1a) Resection including hemihepatectomy and pancreatoduodenectomy; 1b) Reconstruction; 1c) Specimen.

1.1. Definitions

Hepatopancreatoduodenectomy is defined as en bloc resection of the liver, gallbladder, extrahepatic bile duct and the pancreatoduodenum (Fig. 1). In Nagoya, the HPD must include the entire extrahepatic bile duct with adjacent liver and the pancreatoduodenum. The authors emphasize that if the hilar bile duct remains in situ, this procedure should not be defined as HPD. This is different from the definition of HPD in West, which is consisted of heterogeneous procedures of liver resection and pancreatoduodenectomy [1,6,7].

Patients with gallbladder cancer and involvement of only regional lymph node could be operated on by minor hepatic resection plus pancreatoduodenectomy. Major HPD is the resection of three or more Couinaud's liver segments associated with pancreato-duodenectomy. Extended right hepatectomy associated with pancreato-duodenectomy are a very complex operation with high morbidity and mortality mainly in patients with some degrees of cholestasis [1,6,7].

1.2. History

HPD represents the most difficult and challenging procedure in the hepatobiliary region. Dr. Kuno performed the first case of HPD on June 12, 1974 at the Cancer Institute Hospital Tokyo, for an advanced GBCA with involvement of the duodenum [6–8]. In 1980 Takasaki et al. presented five cases of HPD for locally advanced GBCA invading the duodenum and pancreatic head. The 30-day mortality was 60%. The remaining two patients were alive for 5 and 16 months. Since then several hepatopancreatobiliary surgeons, mainly in Japan, have used this complex approach to treat a small number of patients with GBCA or cholangiocarcinoma (Table 1) [3–5,7,9–33].

1.3. Indications

The most important issue regarding HPD for patients with advanced GBCA invading the hepatoduodenal ligament, pancreatoduodenal region and peripancreatic tissue is whether this operation could achieve R0 resection and could achieve long-term survival. It is necessary to identify which types of disease and for what extent of the invasion the procedure may have surgical and oncological benefits. HPD should be selected for patients in whom cancer-free margins of the hepatic ducts and the dissected plane could be reached [1,6–8,14]. GBCA patients with distal bile duct involvement, pancreatic infiltration, massive duodenal infiltration, bulky lymph node metastasis around the pancreatic head are candidates for pancreatoduodenectomy. Macroscopic non-curative resections should be avoided. The outcome of R2 resections is dismal. Distant metastasis, paraaortic lymph node metastases, peritoneal seeding, chronic liver disease and severe comorbidities are also considered contraindications for HPD [1,6–8,14] (Table 2).

Table 1

Reports on HPD for advanced gallbladder or other biliary tract cancer.

Year	Author	Country	Disease	Number of cases	Mortality	5-year survival
1976	Kasumi ⁸	Japan	GBC	1	0	NA
1980	Takasaki ⁹	Japan	GBC	5	3 (60%)	NA
1983	Nakamura ¹⁰	Japan	GBC	2	0	NA
1987	Sugiura ¹¹	Japan	GBC	16	6 (38%)	NA
1987	Nimura ¹²	Japan	GBC	10	2 (20%)	NA
1988	Hanyu ¹³	Japan	GBC	3	1 (33%)	NA
1991	Nimura ¹⁴	Japan	GBC/BDC	14	25%	4.1%
1994	Nakamura ¹⁵	Japan	GBC	7	0	0
1994	Tsukada ¹⁶	Japan	GBC/BDC	2	28.6%	0
1996	Miyagawa ¹⁷	Japan	GBC/BDC	3	0	NA
1997	Shirai ¹⁸	Japan	GBC	17	5.9%	29%
2001	Yoshimi ¹⁹	Japan	GBC	13	1 (7.7%)	12%
2004	D'Angelica ²⁰	USA	Multiple	1	0	NA
2007	Miwa ²¹	Japan	GBC/BDC	9	0	25%
2007	Kaneoka ²²	Japan	GBC/BDC	10	3 (15%) ^a	0
2007	Ota ²³	Japan	GBC/BDC	28	47%	3%
2008	Nanashima ²⁴	Japan	GBC/BDC	3	0	0
2008	Wakai ²⁵	Japan	GBC/BDC	11	6 (21%) ^a	9%
2010	Hemming ²⁶	USA	GBC/BDC	9	0	24%
2012	Lim ²	South Korea	GBC/BDC	10	3 (13%) ^a	10%
2013	Sakamoto ⁴	Japan	GBC/BDC	5	1 (5%) ^a	0
2014	Utsumi ²⁷	Japan	GBC/BDC	5	0	30%
2015	Yamamoto ²⁸	Japan	GBC	21	0	39.8%
2015	Tran ⁵	USA	Multiple	15	NA	NA
2016	Fukami ²⁹	Japan	GBC/BDC	14	5 (13%) ^a	18%
2016	Fernandes ³⁰	Brazil	GBC/BDC	18	10 (34%) ^a	NA
2018	Aoki ³¹	Japan	GBC/BDC	13	1 (2%) ^a	33%
2019	Mizuno ³²	Japan	GBC/BDC	38	7 (18%) ^a	11%
2019	D'Souza ³³	Europe	GBC/BDC	31	10 (15%) ^a	25% ^b

BDC – Bile duct cancer; GBCA – Gallbladder cancer; HPD – hepatopancreatoduodenectomy; NA – Not available.

^a Included GBCA and BDC.

^b Included GBCA and BDC.

Preoperative tumor staging could include computed tomography, magnetic resonance image and PET-CT. Computed tomography is important to assess the tumor extent, especially for the hepatic artery and the portal vein [1,6,27,34,35]. ECOG performance status and comorbidities of patients are among the important factors for preoperative decision making. The final decision for HPD is an intraoperative judgment since the reliability of preoperative imaging is still quite limited.

The data on neoadjuvant chemotherapy for advanced GBCA is lacking. For adjuvant therapy the capecitabine-based chemotherapy is indicated based on the BILCAP trial. The role of adjuvant chemoradiation with gemcitabine plus capecitabine followed by chemoradiotherapy for gallbladder carcinoma remains undefined [36].

Table 2
Indications and contraindications for HPD in gallbladder cancer.

Indications
Locally advanced disease: Tumors originating from the fundus or body (“Liver-bed” type) Tumors involving the hepatic hilus (“Hepatichilus” type) Tumors forming a bulky mass (“Liver-bed and hepatichilus” type) Tumors with extensive local lymph nodes metastases (“Lymph-nodal” type)
Ebata T et al. J Hepatobiliary Pancreat Surg (2007)
Contraindications
Macroscopic noncurative resections Distant metastasis Para-aortic lymph node metastases Peritoneal seeding Chronic liver disease Severe comorbidities

1.4. Surgical technique

HPD has several variations. The common HPD procedure includes right hepatectomy (or variations as extended right hepatectomy; left hepatectomy; extended left hepatectomy; central hepatectomy including segment 4,5 and 8; segmentectomy 4b/5) with pancreatoduodenectomy (Fig. 1a, b, c, d). The procedure starts with pancreatoduodenectomy followed by hepatectomy with or without vascular resection. Complete standardized lymph node dissection is necessary in all cases. The extent of node dissection include lymph nodes 5, 6, 8a, 12a, 12b1, 12b2, 12c, 12h, 13a, 13b, 14a, 14b, 17a, 17b. The specimen can be removed en bloc. This is followed by biliary, gastrointestinal and pancreatic reconstructions [1,6,7,27].

1.5. Vascular resection

To achieve R0 resection, careful inspection of the portal vein and hepatic arteries of the future liver remnant is crucial. Vascular resection/reconstruction would be necessary in the cases of patients with vascular invasion, particularly at the portal vein. Reconstruction can be made with saphenous vein, jugular vein, renal vein or other vascular graft. Resection of hepatic artery during HPD for advanced GBCA is a more challenging procedure and the clinical significance is unclear because of the high mortality as well as the poor survival benefit [6,20,27,34]. The saphenous vein is most common graft for the arterial reconstruction. Major HPD with vascular resection should be performed in specialized hepatopancreatobiliary centers [6,7,20,27,34].

1.6. Complications

Hepatopancreatoduodenectomy remains controversial in regard to the balance between the high rate of postoperative complication and the survival benefit. After HPD, the morbidity range from 35% to 100% and the mortality range from 0% to 47%, related mainly to post-hepatectomy liver failure (PHLF) and pancreatic fistula (Table 3). High-volume centers have presented improving operative results with mortality rates below 5% suggesting that HPD should be performed [10,12,17,22,25,32,35,37].

Post-hepatectomy liver failure (PHLF) is the most severe complication and close-related to perioperative mortality, mainly after extended hepatectomy (three or more Couinaud's liver segments) with small liver remnant [20,22,26,38]. Complete preoperative evaluation of the future liver remnant using volumetric analyses and the consequently use of portal vein embolization (PVE) to increase the remnant liver volume in

Table 3
Complications related to HPD.

Post-operative liver failure (PHLF)
Pancreatic fistula Bile leakage Infections complications Intra-abdominal abscess Hepatic abscess Wound infection Intra-abdominal bleeding Ascites Renal failure Pulmonary complications Chyle leak

patients with insufficient remnant volume is desirable. PVE improved the safety of major hepatectomy and increase resectability. In patients with GBCA, PVE is indicated if the future liver remnant is inferior to 50%, which include patients undergoing right hepatectomy, right trisectionectomy, and a left trisectionectomy combined with pancreatoduodenectomy [14,20,22,23,26,34,35].

Post-hepatectomy liver failure has been often observed in patients with previous biliary obstruction and preoperative hyperbilirubinemia, which increase the risk of in-hospital mortality after extended hepatopancreatoduodenectomy. Biliary drainage preoperatively can prevent cholangitis and improve hepatic function and the regeneration of the future liver remnant. This procedure is recommended before extended HPD in jaundiced patients (Fig. 2) [1,6,20,22].

The second common life-threatening postoperative complication is pancreatic fistula (POPF) and is commonly associated with intra-abdominal bleeding and abscess. The pancreatic fistula hampers the recovery of the patient, causing in-hospital mortality. Most patients with gallbladder cancer have soft pancreatic texture of the gland and small pancreatic duct, increasing the risk of pancreatic fistula. The incidence of pancreatic fistula is higher after HPD compared with that observed in patients who underwent pancreatoduodenectomy for adenocarcinoma of the pancreatic head. Procedures have been described to minimize pancreatic fistula including 2-stage pancreatojejunostomy, external pancreatic juice drainage, wrapping omental flap and completion pancreatectomy [20,22,39]. Torres et al. described a safe technique of pancreatic anastomosis, which could reduce the incidence of pancreatic fistula [40]. Total pancreatectomy with or without spleen preserving could be the ultimate option in patients with high risk POPF.

1.7. Prognosis

The overall prognosis for resected GBCA is determined by the stage of the disease at presentation and the possibility of curative resection. Patients who underwent curative resection has significantly better prognosis than those with non-curative resection and patients with unresectable tumors. A five-year survival rate has been reported 30% in median (range, 3%–50%). The presence of bile duct infiltration has a dismal consequences and the disease free survival and 1-year survival rate is very low. The survival rates reported at 1-,2-, and 5-year were 39.7%, 20.4%, and 6.8% respectively with a postoperative mortality between 12.5 and 34.2% [3,15,26,30,35]. The main cause of death after surgery is post-hepatectomy liver failure. It could be avoided by selecting the patient by careful evaluation of the future liver remnant, portal vein embolization and biliary decompression when indicated. This aggressive surgical treatment is only justified in selected patients [9,10,16–19,21,24,25,32]. Our experience including 18 patients with GBCA undergoing HPD showed a high mortality, but improving along the time [12].

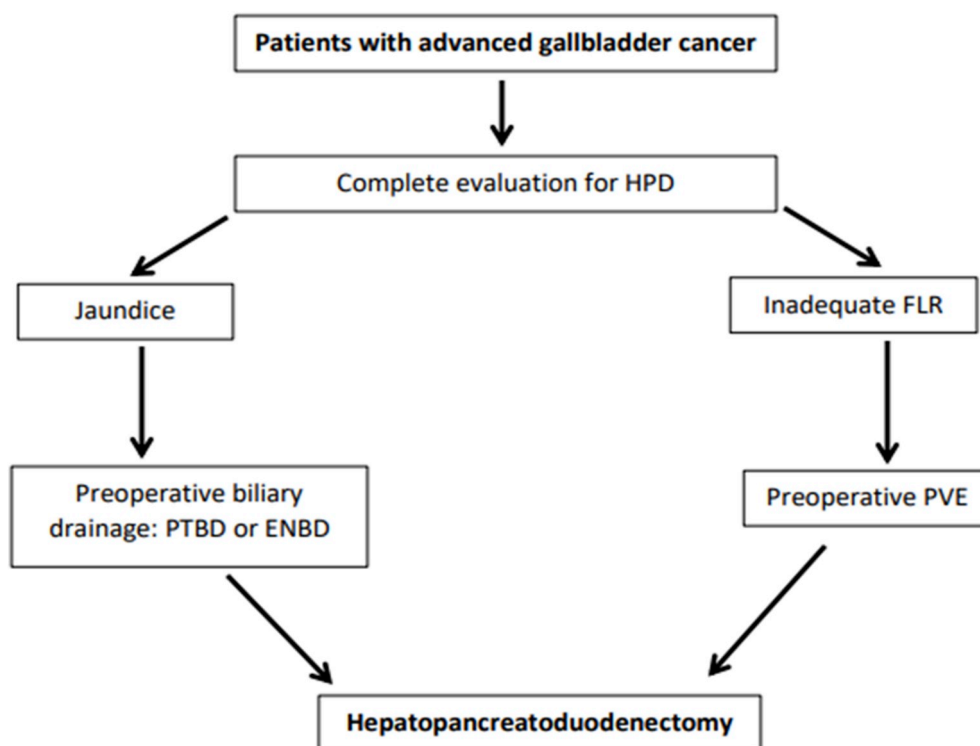


Fig. 2. Management of patients with advanced gallbladder carcinoma.

2. Conclusions

Hepatopancreatoduodenectomy can provide the chance for long-term survival for gallbladder cancers if R0 resection is achieved. However it is a complex procedure with high postoperative morbidity and mortality. A dedicated preoperative work-up, including preoperative biliary drainage in jaundiced patients, portal vein embolization for major liver resection, together with a safe pancreatic anastomosis, may improve the surgical outcome. HPD should be performed at high volume centers with expertise in hepatopancreatobiliary surgery.

Provenance and peer review

Commissioned, externally peer-reviewed

Data statement (author)

1. Surgical aspects of gallbladder carcinoma.
2. Modality of treatment including Hepatopancreatoduodenectomy is suggested.
3. How to minimize morbidity and mortality are discussed.
4. Value of portal vein embolization are presented
5. Selection of patients for HPD are discussed

Declaration of competing interest

No conflict of interest.

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