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Indications and Outcomes of Hepatopancreatoduodenectomy for Gallbladder Carcinoma and Extrahepatic Cholangiocarcinoma: A Single Center Retrospective Study

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ABSTRACT

Introduction: Hepatopancreatoduodenectomy (HPD) is the only definitive approach to achieve curative resection in locally advanced biliary tract cancers. The study intends to analyze outcomes of this complex surgery in a tertiary care center in Nepal.

Methods: This retrospective study included all patients who underwent HPD for locally advanced biliary tract tumors in Kathmandu Medical College Teaching Hospital from January 1, 2019 to December 31, 2023. Intra-operative findings and post-operative outcomes were analyzed.

Results: Over 5 years, eight patients underwent HPD. Mean age was 60 (45–69) years with a male-to-female ratio of 3:5. Locally advanced carcinoma of the gall bladder (Ca GB) comprised the majority of indications for HPD ($n = 7$), two of which had biliary infiltration. Others had either a conglomerated station 13 lymph node, duodenal infiltration, or both. Segment IV and V of the liver were resected in five patients, and right hemihepatectomy with non-anatomical wedge resection of segment IVb was performed in two patients with right hepatic artery involvement. One patient underwent right hemihepatectomy for Bismuth Type IIIa perihilar tumor with distal biliary infiltration and right hepatic artery involvement. R0 resection was achieved in 62.5% of the patients. All three patients with tumor infiltrating the biliary tract had R1 resection. Mean ICU and hospital stay was 2.75 ± 1.28 days and 7.62 ± 1.41 days, respectively. Clavien-Dindo Grade II or higher morbidity was observed in 5 (62.5%) patients, with one perioperative mortality (12.5%).

Conclusion: R0 resection with acceptable morbidity can be achieved in selected cases of Ca GB with conglomerated station 13 lymph nodes; however, R0 remains challenging in cases of biliary infiltration.

1 | Introduction

Locally advanced biliary tract tumors have been a challenge to hepatobiliary surgeons. In cases of gall bladder cancer with bile duct infiltration and lymph node involvement, as well as cases of bile duct cancer with widespread infiltration, standard techniques such as hepatectomy or pancreatoduodenectomy (PD) alone may not be able to provide a complete curative resection (R0) [1]. Takasaki et al. first described radical surgery with hepatopancreatoduodenectomy (HPD) for locally advanced gall bladder carcinoma (Ca GB) in 1980 [2]. Subsequently, many surgeons have started applying this concept for other locally

advanced biliary tract tumors as well. HPD is a multi-visceral resection that combines a PD and a major liver resection to create an en-block specimen that encircles the whole extra-hepatic biliary system [3]. HPD is the only definitive way to achieve curative resection in locally advanced biliary tract cancers. Historically, HPD was associated with high morbidity and mortality, resulting mainly from pancreatic fistula or liver failure [4]. But with advanced technology and improved perioperative management, the morbidity and mortality seem to be declining [5]. We aim to analyze the results of this complex procedure, looking only for its indications and perioperative outcomes. Long-term survival will be analyzed in another study.

2 | Methods

This retrospective cross-sectional study incorporated all patients who underwent HPD for various biliary tract tumors in the Department of GI and General Surgery of Kathmandu Medical College Teaching Hospital from January 1, 2019, to December 31, 2023. Data were collected from the hospital records, and the following information was evaluated: initial serum bilirubin level, preoperative biliary drainage, preoperative Ca19.9 level, primary tumor characteristics (location, size, lymph node status, distant metastasis), neoadjuvant therapy (NAT), surgery-associated variables (operative blood loss, duration of operation, intraoperative blood transfusion) and postoperative complications. Standard definitions were applied to classify post-hepatectomy liver failure (PHLF), post-operative pancreatic fistula (POPF) and bile leakage.

Routine preoperative investigations included complete blood count, renal function test, liver function panel, and ultrasonography (USG) of the abdomen and pelvis. Tumor staging was done with contrast-enhanced computed tomography (CECT) scan of the abdomen, pelvis, and chest. CECT-based liver volumetry was calculated in all the patients. Patients with Future Liver Remnant (FLR) < 30%; those with distant metastasis or peritoneal dissemination were excluded. Those with vascular involvement were subjected to USG-guided biopsy of the tumor and neoadjuvant therapy (NAT). The combination of Gemcitabine and Cisplatin was used as NAT, and re-evaluation of the tumor with CECT images was done after 3 cycles based on the Response Evaluation Criteria for Solid Tumors (RECIST). The patient underwent surgery after 3–4 months of initiation of NAT. Percutaneous transhepatic biliary drain (PTBD) was employed preoperatively in FLR in jaundiced patients, and major hepatectomy was undertaken after confirmation of a decreasing trend of bilirubin. Whenever suspicious, imprint cytology was taken from the proximal/distal biliary margin to confirm the extent of malignancy.

3 | Results

There were a total of eight patients (three male and five female) who underwent HPD. Mean age was 60 years (45–69 years). Seven patients (87.5%) had locally advanced Ca GB, of which three had conglomerated station 13 lymph node, one had diffuse biliary infiltration, one had duodenal infiltration, one had conglomerated lymph node with duodenal infiltration and one had biliary extension with a conglomerated lymph node. One patient with Bismuth type IIIa perihilar cholangiocarcinoma (pHCC) with distal biliary infiltration underwent HPD in view of positive intraoperative imprint cytology from the distal biliary margin. Three patients (two Ca GB and one pHCC) had jaundice with vascular involvement. They underwent PTBD followed by NAT. Among the five patients with conglomerated station 13 lymph nodes, only one received NAT because of involvement of the right hepatic artery. Of the three patients receiving NAT, one (33%) had a partial response (PR) and two (67%) had stable disease (SD). They underwent surgery after 3–4 months of initiation of NAT. The remaining five patients underwent upfront surgery. The patient particulars are demonstrated in Table 1.

The median operative time was 382 min (280–515 min). While no patients had portal vein involvement, three had right hepatic artery involvement and underwent right hemihepatectomy.

TABLE 1 | Patient particulars.

Case	Age	Sex	Indication for HPD	HA involvement	Initial serum total bilirubin (mg/dL)	PBD	NAT
1	60	F	Ca GB + D2 infiltration	No	1.7	No	No
2	45	F	Ca GB + cong. St. 13 ln	No	1.9	No	No
3	53	M	pHCC (IIIa) with distal biliary infiltration	Yes	9.0	Yes	Yes
4	68	F	Ca GB + cong. St. 13 ln	No	4.3	No	No
5	63	M	Ca GB + D2 infiltration + congl. St. 13 ln	No	3.2	No	No
6	58	F	Ca GB + diffuse biliary infiltration	Yes	28.0	Yes	Yes
7	69	F	Ca GB + biliary extension + cong. St. 13 ln	Yes	12.5	Yes	Yes
8	64	M	Ca GB + congl. St.13 ln	No	1.6	No	No

Abbreviations: Ca GB, carcinoma gall bladder; cong. St. 13. ln, conglomerated station 13 lymph node; D2, second part of duodenum; HA, hepatic artery; HPD, hepatopancreatoduodenectomy; NAT, neoadjuvant therapy; PBD, preoperative biliary drainage; pHCC, perihilar cholangiocarcinoma.

Non-anatomical wedge resection of segment IVb was combined with right hemihepatectomy in two patients with gall bladder carcinoma. A FLR > 30% was always ensured. The patient with Type IIIa pHCC, however, underwent right hemihepatectomy only. Five patients underwent bisegmentectomy of segments IV and V for Ca GB. The intraoperative picture is shown in Figure 1. Three of eight patients (37.5%) had microscopic positive resection margins in the histopathological analysis, all of whom had biliary involvement by tumor, while the rest (62.5%) had uninvolved resection margins. Station 13 lymph nodes were mostly embedded in the specimen and were reported as peripancreatic lymph nodes according to College of American Pathologists (CAP) protocol. All five patients with conglomerated station 13 lymph nodes were reported to have at least one peripancreatic lymph node involved by invasive carcinoma. The operative findings are demonstrated in Table 2.

Post-operatively, the mean number of days of ICU and hospital stay was 2.75 ± 1.28 days and 7.62 ± 1.41 days, respectively. Out of eight patients in this study, 62.5% ($n = 5$) had CD Grade II or higher complications. One patient each developed clinically relevant POPF (ISGPS Grade B), PHLF (ISGLS Grade B), bile leak (ISGLS Grade A) and delayed gastric emptying (ISGPS Grade A). One patient had a reactionary bleed and underwent re-exploration and control of the bleeder from the superior pancreato duodenal vein (SPDV) on the first post-operative day. One patient developed an intra-abdominal abscess and required pigtail catheter drainage. The perioperative mortality rate was 12.5% ($n = 1/8$). (Table 3) The deceased patient had undergone preoperative biliary drainage with PTBD placement and received NAT for locally advanced Ca GB with biliary extension with conglomerated station 13 lymph nodes with right hepatic artery involvement.

4 | Discussion

In our study, HPD was carried out mainly for selected locally advanced Ca GB with duodenal/biliary infiltration or conglomerated station 13 lymph nodes. Overall R0 resection was possible in five (62.5%) patients. Clavien-Dindo Grade II or higher morbidity was noted in five (62.5%) of the patients, and there was a single perioperative mortality (12.5%).

The perioperative mortality rate in our study was 12.5% ($n = 1/8$). The late disease stage at presentation is mainly responsible for the unfavorable overall prognosis for biliary and gallbladder cancers. HPD has been used to enhance the operability and results of patients with these cancers. The mortality rates have been decreasing, with Japanese authors reporting mortality rates as low as 0%—2.4% compared to 60% a few decades back [6, 7]. However, because HPD is rarely performed in North America, it is still associated with a high overall mortality rate upto 26% [4].

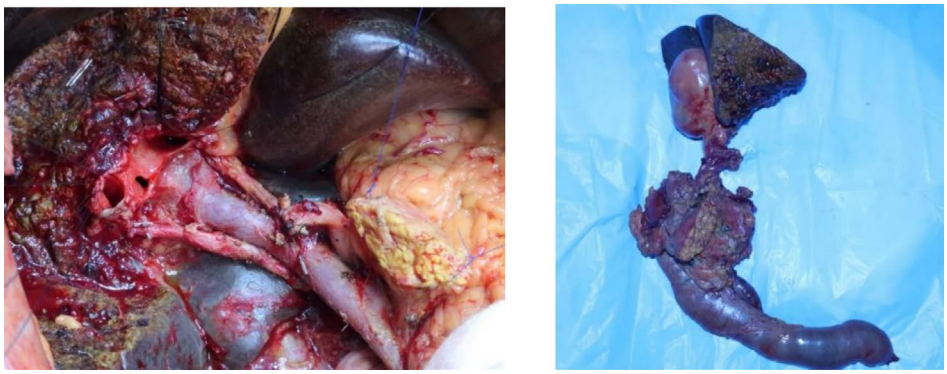

FIGURE 1 | Intraoperative photograph following en block removal of HPD specimen.

TABLE 2 | Operative findings.

Case	Operative time (min)	Type of hepatectomy	Right hepatic artery reconstruction	Resection margin (HPE report)
1	415	Seg IV and V resection	None	R0
2	280	Seg IV and V resection	None	R0
3	440	Rt hemihepatectomy	None	R1 (biliary margin)
4	378	Seg IV and V resection	None	R0
5	515	Seg IV and V resection	None	R0
6	332	Rt hemihepatectomy with seg IVb resection	None	R1 (biliary margin)
7	356	Rt hemihepatectomy with seg IVb resection	None	R1 (biliary margin)
8	340	Seg IV and V resection	None	R0

TABLE 3 | Post-operative outcomes.

Case	PHLF	POPF	Bile leak	Other complications	Post-operative ICU stay	Post-operative hospital stay	Clavien-Dindo classification
1	—	—	Grade A	—	3	8	II
2	—	—	—	Re-exploration for reactionary hemorrhage	5	10	IIIb
3	—	—	—	—	2	6	I
4	—	Grade B	—	DGE	2	7	II
5	—	—	—	Intra-abdominal abscess	4	9	IIIa
6	—	—	—	SSI	1	6	I
7	Grade B	Grade A	—	Pneumonia	3	8	V
8	—	—	—	—	2	7	I

Abbreviations: DGE, delayed gastric emptying; PHLF, post-hepatectomy liver failure; POPF, post-operative pancreatic fistula.

Out of eight patients in our study, 62.5% ($n = 5$) had CD Grade II or higher complications. HPD is associated with a high morbidity rate of over 70% [8, 9], often resulting in ≥ Grade B liver failure (68%) and ≥ Grade B pancreatic fistula (87%) [10]. Ebata et al. found that morbidity rates associated with hepatectomy alone were lower than those associated with HPD. This suggests that PD significantly raises morbidity following hepatic surgery. He explained that, as the majority of patients have thin pancreatic ducts and a soft pancreatic texture, pancreatic fistula and subsequently other infectious complications frequently develop [6].

Five patients in our study underwent upfront surgery, while three patients, who were found to have vascular involvement preoperatively, received NAT. The role of NAT in locally advanced biliary tract cancer is yet to be defined [11]. Some studies [12–14] show no role, while others [15, 16] favor NAT, which allows downstaging the tumor to achieve negative margins and avoid unnecessary surgery in progressive disease. The response rate of biliary tract cancer to chemotherapy is 20%–30% [16]. As there are chances of tumor growth during its performance, NAT, when given to resectable cases, might make them unresectable or may preclude curative resection. In a study by Kato et al., locally advanced biliary tract cancer patients with extensive vascular invasion or inadequate remnant liver volume for major hepatic resection were considered to be unresectable and subjected to NAT. Tumor size reduction followed by surgical resection was possible in 25.6% patients [16].

Three patients with jaundice were subjected to preoperative biliary drainage in our study. The benefits of preoperative biliary drainage include the potential to lower blood loss, enhance the regenerative capacity of the liver, and raise the tolerance of cholestatic liver to ischemia [17]. The threshold serum bilirubin level at which preoperative biliary drainage should be initiated is a topic of debate. To reduce major complications after surgery, some studies recommend preoperative biliary drainage when the bilirubin level is greater than 3 mg/dL, while other studies recommend higher than 5 mg/dL or above 10 mg/dL [17–19]. A study conducted in Japan found that 16% of patients who had a major hepatectomy for biliary tract cancer with obstructive jaundice did not see a preoperative decrease in serum bilirubin level to less than 3 mg/dL, despite undergoing preoperative biliary drainage [20].

No patients in our study were subjected to portal vein embolization because of sufficient FLR volume. Ebata et al. revealed that liver failure rates diminished from 56% to 14% after routine preoperative portal vein embolization as there was a 10% volume gain in the nonembolized liver and a 10% volume loss in the embolized liver without affecting liver function [5]. Efforts to ensure a remnant liver over 40%—50% of the total liver volume are the key to obtaining patient survival [9]. Preoperative portal vein embolization and preoperative biliary drainage in patients with obstructive jaundice address methods for reducing post-operative complications [11].

Some studies have questioned the indication of HPD for carcinoma GB from an oncologic point of view [10, 21], but a survival benefit has been reported with the achievement of R0 resection [11, 22]. R0 resection was achieved in 62.5% ($n = 5$) of patients in our study. Three patients with biliary infiltration, all of whom underwent right hemihepatectomy for suspicion of right hepatic artery involvement, however, had R1 resection. Though the intraoperative imprint cytology was negative for malignancy, the horizontal spread of tumor involving the bile duct could be the reason for the positive proximal resected biliary margin, indicating the advanced nature of the disease. D'Souza et al. reported R0 resection in 74% of cholangiocarcinoma and 87% of gallbladder cancer patients [22]. Only positive resection margins at pathology had a significant impact on overall survival. In a study by Shimizu et al., the 1-, 3-, and 5-year overall survival (OS) rates with R0 resection were 83%, 48%, and 37%, respectively [23].

This study has some limitations. It is a single-center retrospective analysis of just eight patients who underwent HPD in the previous 5 years. A multicenter large-series study would be necessary to validate the results.

5 | Conclusion

The study focused on HPD for locally advanced Ca GB and pHCC. R0 resection with acceptable morbidity can be achieved in selected cases of Ca GB with conglomerated station 13 lymph nodes; however, R0 remains challenging in cases of biliary infiltration.

Conflicts of Interest

The authors declare no conflicts of interest.

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