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REVIEW ARTICLE

Hepatopancreatoduodenectomy for Locally Advanced Gallbladder Cancer: Is It Worthwhile?

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Abstract

The benefit of hepatopancreatoduodenectomy for locally advanced gallbladder cancer was unclear. An electronic search was conducted in PubMed, Ovid, and the Cochrane Library for the relevant publications reported in the literature between January 1990 and November 2021. Twenty-two studies involving 126 patients met the inclusion criteria. Major and minor hepatectomies were performed in 45.6% and 54.4% patients respectively. R0 (microscopically negative margin) resection was achieved in 74.6% patients. The morbidity and 90-day mortality rates were 60.1% and 8.7% respectively. The median overall survival after surgery was 18 months. Multivariate analysis showed that R0 resection was the only independent prognostic factor for survival (hazard ratio 0.115, 95% confidence intervals 0.030–0.445; $P=0.002$). Hepatopancreatoduodenectomy was suggested in patients with locally advanced gallbladder cancer provided that R0 resection can be achieved.

Keywords Gallbladder Cancer · Resection · Survival · Prognostic Factors

Introduction

Combined hepatectomy and pancreatoduodenectomy (hepatopancreatoduodenectomy, HPD) was proposed as a treatment primarily for advanced hepatobiliary malignancies that otherwise could not be completely resected. Despite the high perioperative risk of the procedure, a favorable post-operative 5-year overall survival (OS) rate of 32.3–49.2% justified its use in patients with cholangiocarcinoma [1–3]. However, the survival benefit of HPD for locally advanced gallbladder cancer (GBC) remained an issue of debate, knowing that some studies reported a poor survival outcome in GBC patients [4, 5], while others demonstrated almost the same survival outcome in cholangiocarcinoma cohorts [1, 2]. But as the sample size in all these studies was relatively small, it was difficult to reach a consensus about the benefit of HPD. The present study aimed to investigate short- and long-term survival outcome of HPD in larger cohorts of GBC patients through pooled analysis of cases previously reported in the literature.

Patients and Methods

The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement [6].

Literature Review

An electronic search was conducted in PubMed, Ovid, and the Cochrane Library for the relevant literature published from January 1990 to November 2021. The search terms used were "hepatopancreatoduodenectomy," "gallbladder cancer," and "combined liver and pancreatic resections." Reference lists from eligible articles were screened manually for additional publications. Case reports and case series assessing surgical outcomes of HPD for adult patients with GBC were considered for inclusion. Publications with any of

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Table 1 Patient characteristics

Parameters	
Sex ($n=105$), no. (%)	
Man	38 (36.5)
Woman	67 (63.5)
Age ($n=105$)	
Median (range), years	64 (27–80)
Portal vein embolization ($n=112$), no. (%)	15 (13.4)
Preoperative biliary drainage ($n=64$), no. (%)	28 (42.8)
T classification ($n=89$), no. (%)	
pT2	13 (14.6)
pT3	30 (33.7)
pT4	46 (51.7)
Lymph node metastasis ($n=110$), no. (%)	
Absent	27 (24.5)
Present	83 (75.5)
American Joint Committee on Cancer stage ($n=112$), no. (%)	
I	1 (0.9)
II	3 (2.7)
III	28 (25)
IV	80 (71.4)
Differentiation grade ($n=28$), no. (%)	
Good	9 (32.1)
Moderate	16 (57.1)
Poor	3 (10.7)
Surgical margin, ($n=126$), no. (%)	
Positive	32 (25.6)
Negative	94 (74.6)
Extents of hepatectomy ($n=126$), no. (%)	
Major hepatectomyy	58 (45.6)
Right trisectionectomy	12
Extended right hepatectomy	35
Right hepatectomy	8
Left hepatectomy	1
S4 + S5 + S6 resection	1
Central bisegmentectomy + S1 resection	1
Minor hepatectomy	68 (54.4)
S4b + S5 resection	23
S4b + S5 + S6 resection	3
S4 + S5 resection	1
S4 + S3 resection	1
S4b + S1 resection	1
Wedge resection of the gallbladder bed	31
Unknow	8
Types of pancreatoduodenectomy ($n=126$), no. (%)	
Whipple pancreaticoduodenectomy	93 (74.4)
Pylorus-preserving pancreaticoduodenectomy	27 (20.8)
Substomach-preserving pancreaticoduodenectomy	6 (4.8)
Portal vein reconstruction ($n=117$), no. (%)	28 (23.9)
Combined colectomy ($n=126$), no. (%)	24 (19.1)
Operating time ($n=21$)	
Median (range), min	595 (405–847)
Blood loss ($n=21$)	

Table 1 (continued)

Parameters	
Median (range), ml	1892 (460–7520)
Morbidity ($n=69$), no. (%)	40 (60.1)
Pancreatic fistula	8 (11.5)
Hepatic failure	7 (10.1)
Mortality ($n=126$), no. (%)	11 (8.7)

the following were excluded: the absence of follow-up data; individual patient data unknown, published in languages other than English, reviews, abstracts, editorials, expert consensus statements, and animal studies. In the case of duplicate publications, the most recent report was selected.

Data collected included patient demographics, preoperative management, surgical procedures, duration of operation, estimated blood loss, pathological findings, postoperative morbidity, 90-day mortality, and survival. Extents of liver resection were classified as major (≥ 3 Couinaud's hepatic segments) and minor (< 3 segments) hepatectomy according to the Brisbane 2000 terminology for liver anatomy and resection [7].

Statistical Analyses

Results were presented as median (range) unless otherwise specified. OS was calculated from the time point of resection until the date of death from any cause or last follow-up. Survival curves were generated using the Kaplan–Meier method and then compared by means of the log rank test. Variables with $P<0.100$ in the univariable analysis were included in a multivariable Cox hazard analysis to identify prognostic factors for survival. $P<0.05$ was indicated significant. All statistical analyses were done using SPSS for Windows 22 software (SPSS, Chicago, IL, USA).

Results

Characteristics of the Study Population

Twenty-two studies involving 126 patients that met inclusion criteria were included in the final analysis (Table 1) [8–29]. Most patients were women (63.5%) with a median age of 64 (range 27–80) years. Preoperatively, 13.4% patients underwent portal venous embolization (PVE) and 42.8% patients underwent biliary drainage. The pathological assessment revealed that R0 (microscopically negative margin) resection was achieved in 74.6% patients. According to the American Joint Committee on Cancer (AJCC) TNM classification, pT3/4 tumor and lymph node metastasis (LNM) were found in 85.4% and 75.5% patients respectively. Consequently, most patients (96.4%) presented stage III/ IV disease.

Operative Outcomes

Major or minor hepatectomy was performed in 45.6% and 54.4% patients respectively. The types of pancreatoduodenectomy (PD) were conventional Whipple's (74.4%), pylorus preserving (20.8%), or substomach-preserving (4.8%) PD. Combined resection of the portal vein and colon was applied in 23.9% and 19.1% patients respectively. The median operative time and estimated blood loss were 595 (range 405–847) min and 1892 (range 460–7520) mL respectively. The overall morbidity was 60.1%, with a hepatic failure and pancreatic fistula incidence of 10.1% and 11.5% respectively. The 90-day mortality rate was 8.7% ($n=11$). Nine deaths (7.1%) were postoperative complications-related including seven due to hepatic failure, one due to liver abscess, and one due to methicillin resistant *Staphylococcus aureus* septicaemia. The remaining two patients (1.6%) died in the hospital from disease progression 60 and 63 days after surgery.

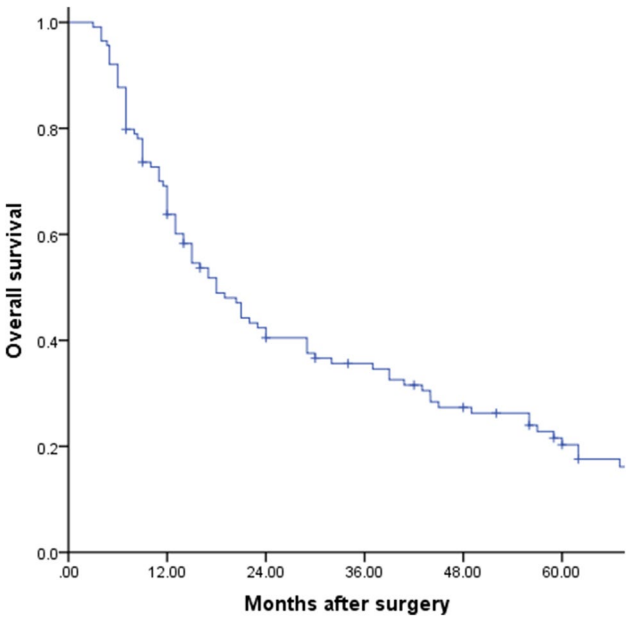

Fig. 1 Cumulative survival curves

Long-term Outcomes

Excluding the 11 postoperative deaths, 82 of the remaining 115 patients died of tumor recurrence, and seven patients died of other causes with no evidence of disease due to senility ($n=1$), perforating peritonitis ($n=1$), pneumonia and cardiac failure ($n=1$), other cancers ($n=2$), hepatic cirrhosis ($n=1$), or unknown reason ($n=1$). The OS rate for the 115 patients was 69.1% at 1 year, 35.5% at 3 years, and 20.3% at 5 years, with median OS of 18 months (Fig. 1). Univariate analysis showed that PVE, preoperative biliary drainage, portal vein reconstruction, pT4 tumor, and R0 resection were significant predictors of survival, and multivariate analysis showed that R0 resection was the only independent significant variable (hazard ratio 0.115, 95% confidence intervals 0.030–0.445; $P=0.002$) (Table 2). The 5-year OS rate was 25.5% with R0 resection *versus* 3.7% without.

Discussion

Gallbladder cancer was a highly lethal disease with a dismal prognosis, and complete tumor resection provided the only chance for cure. GBC was prone to infiltrate adjacent organs

Table 2 Factors associated with overall survival

Characteristics	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex				
Man	1.0 (reference)			
Woman	1.192 (0.735–1.934)	0.476		
Age, years				
> 60	1.0 (reference)			
≤60	0.864 (0.527–1.416)	0.562		
Portal vein embolization				
No	1.0 (reference)		1.0 (reference)	
Yes	2.052 (1.121–3.755)	0.020	2.773 (0.195–39.517)	0.452
Preoperative biliary drainage				
No	1.0 (reference)		1.0 (reference)	
Yes	2.281 (1.179–4.413)	0.014	1.339 (0.572–3.133)	0.501
Extents of hepatectomy				
Major hepatectomyy	1.0 (reference)		1.0 (reference)	
Minor hepatectomy	0.678 (0.445–1.034)	0.071	0.832 (0.267–2.598)	0.752
Types of PD				
Whipple PD	1.0 (reference)			
Pylorus-preserving PD	0.888 (0.505–1.562)	0.681		
Portal vein reconstruction				
No	1.0 (reference)		1.0 (reference)	
Yes	2.388 (1.399–4.076)	0.001	2.246 (0.396–12.759)	0.361
Combined colectomy				
No	1.0 (reference)			
Yes	1.133 (0.640–2.008)	0.667		
Surgical margin				
Positive	1.0 (reference)		1.0 (reference)	
Negative	0.298 (0.187–0.477)	<0.001	0.115 (0.030–0.445)	0.002
T classification				
pT3	1.0 (reference)		1.0 (reference)	
PT4	1.868 (1.069–3.264)	0.028	1.287 (0.421–3.935)	0.658
Lymph node metastasis				
Negative	1.0 (reference)			
Positive	1.159 (0.693–1.939)	0.574		
AJCC stage				
III	1.0 (reference)			
IV	1.291 (0.793–2.101)	0.304		

*H*R Hazard ratio; CI,Confidence interval, *PD* pancreatoduodenectomy, *AJCC* American Joint Committee on Cancer

or vascular structures. When this occurs, an en bloc resection was often required to achieve a negative margin. Generally, selection criteria of HPD for GBC were as follows: (1) lower bile duct involvement, (2) pancreatic infiltration, (3) massive duodenal infiltration, and (4) bulky LNM invading the pancreatic head. Long-term survival was the most objective parameter for assessment of therapeutic strategies for malignant tumors. The present pooled analysis with a relatively large cohort of patients showed that HPD offered a 20.3% 5-year OS rate, which is significantly higher than 0% as reported in subjects receiving non-surgical treatments [30]. Despite the high mortality of 8.7% in the present series of patients, the substantial survival benefit may outweigh such operative risk. Several recent reports from high-volume centers have reported the improved operative outcomes with a mortality rate below 5% [2, 3], highlighting that HPD should be considered in experienced high-volume centers. The main goal of isolating HPD to specific hospital teams is to facilitating surgeons gaining experience with the complex technique required and adapting their care based on this experience.

The present study demonstrated that R0 resection was the only independent predictor of OS, highlighting the basic rules of surgical radicality in oncological surgery for malignancy. Positron emission tomography computed tomography (PET-CT) [31] and laparoscopic staging techniques [32] have proven to be able to avoid unnecessary surgical exploration and resection. On the other hand, effective strategies for increasing the R0 resection rate were undoubtedly important to improve the therapeutic outcome for resection of GBC. The efficacy of neoadjuvant therapy (NT) on surgical radicality was well documented in patients with rectal and pancreatic cancer [33, 34], but was poorly described in GBC. In 2015, a retrospective analysis of neoadjuvant gemcitabine-platinum based regimen given to 37 patients with locally advanced GBC found that 18 (48.6%) of the 37 patients were able to undergo surgical resection with an R0 resection rate in 17 (94.4%) of the 18 patients [35]. Subsequently, another single institution reported their experience with the use of neoadjuvant gemcitabine followed by radiation in 28 patients with locally advanced GBC, and the result was similar. Among these patients, 41.3% (18/28) patients underwent surgical resection and the R0 resection rate was 77.8% (14/18) [36]. These encouraging results may warrant a prospective study to provide stronger evidence on the value of NT in GBC.

Although LNM has been frequently reported as a reliable predictor of the survival outcome in patients with GBC [37], the present study failed to demonstrate this relationship. We found that 11 of the 17 5-year survivors with LNM showed no residual tumor after HPD, and only 1 patient with nodal involvement survived 5 years with the residual tumor. A report from Japan documented that 11 of their 60 patients with LNM survived more than 5 years after resection [38]. Taken together with the results in the previous reports, GBC with LNM was not a contraindication to a curative resection.

The current data demonstrated no differences in OS between patients who underwent major hepatectomy and those who underwent minor hepatectomy, which further supported the notion that choice of the hepatectomy type should be determined by the extent of CBC invasion [39].

This study had some limitations. First, information on parameters was not uniformly presented in the pooled patients due to its retrospective nature; therefore, it was difficult to assess the prognostic impact of serum albuminemia, tumor size, histologic type, histologic grade, lymphatic invasion, perineural invasion, and adjuvant treatment. Second, only case reports and case series were retrieved and studies without individual patient data were excluded, which may introduce selection bias. Lastly, the long study interval (1990–2021) may influence the results by the variations in treatment protocols.

In conclusion, in patients with locally advanced gallbladder cancer, hepatopancreatoduodenectomy was suggested when an R0 resection can be achieved.

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Declarations

Conflicts of Interest None declared.

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