

REVIEW ARTICLE

A systematic review of safety and efficacy of hepatopancreatoduodenectomy for biliary and gallbladder cancers

Yanming Zhou, Zuobing Zhang, Lupeng Wu & Bin Li

Department of Hepatobiliary & Pancreatovascular Surgery, First Affiliated Hospital of Xiamen University, 55 Zhenhai Road, Xiamen 361003, China

Abstract

Objectives: To review the evidence on the safety and efficacy of hepatopancreatoduodenectomy for biliary and gallbladder cancers.

Methods: Medline and EMBASE were systematically searched for papers of hepatopancreatoduodenectomy in patients with biliary and gallbladder cancers.

Results: Eighteen studies involving 397 patients were reviewed. Major hepatectomy was undertaken in 81.3% of the 397 patients and the R0 resection rate was 71.3%. The morbidity and mortality rates were 78.9% and 10.3%, respectively. The 5-year overall survival rate ranged from 3% to 50% (median = 31%). The 5-year survival rate in patients who underwent curative resection was 18–68.8% (median = 51.3%), and 0% in patients who received non-curative resection.

Conclusions: Hepatopancreatoduodenectomy is a challenging procedure with high morbidity and mortality rates. However, this procedure can provide a chance of long-term survival in patients in whom curative resection is feasible.

Received 29 May 2015; accepted 29 July 2015

Correspondence

Yanming Zhou, Department of Hepatobiliary & Pancreatovascular Surgery, First Affiliated Hospital of Xiamen University, 55 Zhenhai Road, Xiamen 361003, China. Tel: +86 (0)592 2139708. Fax: +86 (0)592 2137289. E-mail: zhouymsxy@sina.cn

Introduction

Bile duct cancer (BC) and gallbladder cancer (GC) are aggressive diseases with dismal prognosis, for which surgery remains the most effective treatment option in patients with resectable disease.^{1,2} Although hepatopancreatoduodenectomy has been performed for advanced stage disease as an attempt at curative resection over the past three decades, only a few sporadic case reports or small patient series have been published and the surgical outcomes of the procedure have not been adequately analyzed.^{3–10} The purpose of the present study was to perform a systematic review of the literature to evaluate the safety and efficacy of hepatopancreatoduodenectomy for BC and GC.

These authors contributed equally to this work.

Materials and methods

Study selection

A literature search was performed using Medline and EMBASE databases from the date of the earliest report of hepatopancreatoduodenectomy in 1991³ to October 2014. Search terms were “hepatopancreatoduodenectomy,” “cholangiocarcinoma,” “bile duct cancer,” “gallbladder cancer,” and “combined liver and pancreatic resections.” Reference lists from relevant articles were checked manually for additional studies of interest. Only studies with at least five patients who underwent hepatopancreatoduodenectomy and published in English were included. Letters, reviews, abstracts, editorials, expert opinions, non-English language papers and animal studies were excluded. In the case of multiple publications of a given cohort of patients, only the most recent one was used.

Two investigators (JY and YZ) independently reviewed all the retrieved studies that met the inclusion and exclusion criteria. Discrepancies between the two reviewers were resolved by discussion and consensus. The two reviewers extracted data on the following categories: authors, country, study design, study period, number of patients, sex, age, type of disease, type of the surgical procedure, duration of operation, estimated blood loss, proportion of R0 resection (no microscopic residual tumor), morbidity, mortality, and survival. The level of evidence of each study was categorized according to the Evidence-based Medicine Levels of Evidence.¹¹

Statistical analysis

Pooled statistics were presented as total and percentage for categorical variables and as median values and range for continuous variables.

Results

Characteristics of the study population

Eighteen studies involving 397 patients were finally included in the review.^{3,4,7-10,12-23} Fig. 1 demonstrates a flow diagram of the selection process. The characteristics of the included studies are summarized in Table 1. All these studies were observational (level IV evidence). Underlying diagnoses were BC (n = 241, 61%), GC (n = 152, 38%), ampullary tumor (n = 1),

neuroendocrine tumor of the pancreas with coexistent metastases to the liver (n = 1), liver and pancreas metastases from colon cancer (n = 1), and gastrointestinal stromal tumor of the duodenum with liver metastases (n = 1).

Surgical outcomes

The surgical outcomes of the 18 studies are summarized in Table 2. There were 41 reported in-hospital deaths in 397 patients having hepatopancreatoduodenectomy. The causes of death available in 26 patients included hepatic failure (n = 11), tumor progression (n = 3), obstruction of the reconstructed portal vein (n = 2), intraabdominal bleeding (n = 2), multi-organ failure (n = 2), liver abscess (n = 2), suppurative cholangitis (n = 1), pneumonia (n = 1), methicillin resistant staphylococcus aureus septicemia (n = 1), and peritonitis (n = 1).

Regarding the long-term result, the five-year overall survival in patients who underwent R0 resection was 18–68.8% (median = 51.3%), and 0% in those with R1 or R2 resection. The 5-year survival rate in BC patients and GC patients ranged from 0% to 64% (median = 33%) and from 0% to 43% (median = 10.4%), respectively.

Discussion

The overall prognosis for biliary and gallbladder cancers remains dismal, mainly due to the advanced stage of the disease at

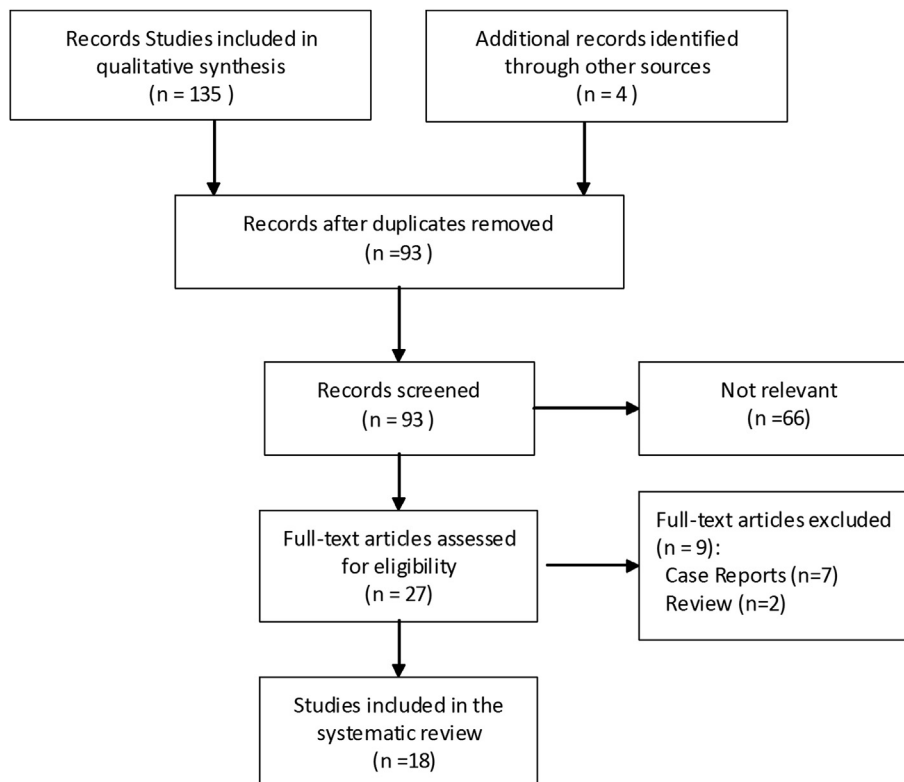


Figure 1 Flow diagram for the selection of eligible studies

Table 1 Literature review of hepatopancreatoduodenectomy for biliary and gallbladder cancers

Reference	Year	Country	Number of patients	Male gender, n	Mean age (years)	BC, n	PVE, n	BD, n
Nimura <i>et al.</i> ³	1991	Japan	24	8	61	10	0	16
Nakamura <i>et al.</i> ⁴	1994	Japan	7	4	58	0	0	4
Shirai <i>et al.</i> ⁷	1997	Japan	17	4	64	0	0	4
Yoshimi <i>et al.</i> ⁸	2001	Japan	13	7	68	13	0	12
Sasaki <i>et al.</i> ⁹	2002	Japan	16	9	61	0	0	3
Hirono <i>et al.</i> ¹⁰	2006	Japan	11	3	63	6	1	8
Kaneoka <i>et al.</i> ¹²	2007	Japan	20	7	64	10	14	–
Miwa <i>et al.</i> ¹³	2007	Japan	26	14	63	17	20	20
Ota <i>et al.</i> ¹⁴	2007	Japan	32	11	57	4	4	22
Urahashi <i>et al.</i> ¹⁵	2007	Japan	12	6	58	12	–	–
Nanashima <i>et al.</i> ¹⁶	2008	Japan	11	6	67	8	5	–
Wakai <i>et al.</i> ¹⁷	2008	Japan	28	18	63	17	0	–
Hemming <i>et al.</i> ¹⁸	2010	USA	22	–	–	9	–	–
Kaneoka <i>et al.</i> ¹⁹	2010	Japan	14	10	62	14	6	–
Ebata <i>et al.</i> ²⁰	2012	Japan	85	61	69	85	67	81
Lim <i>et al.</i> ²¹	2012	Korea	23	14	58	13	1	–
Sakamoto <i>et al.</i> ²²	2013	Japan	19	12	–	14	17	–
Utsumi <i>et al.</i> ²³	2014	Japan	17	10	68	9	1	10
Total/Median or %			397 (7–85)	204 (54.4%)	63 (57–69)	241 (60.7%)	136 (37.5%)	180 (72.6%)

BC, bile duct cancer; PVE, portal venous embolization; BD, biliary drainage.

presentation. Both diseases have the propensity to invade extensively, not only along the bile duct but also into adjacent organs via the lymphatics and perineural spaces. With the support of advances in surgical techniques and perioperative management, hepatopancreatoduodenectomy has been performed to improve the resectability and outcome of patients with biliary and gallbladder cancers. However, this aggressive procedure remains controversial in regard to the balance between the survival benefit and high risk of mortality and morbidity. As demonstrated in the present study, postoperative complications occurred in 78.9% patients, resulting in a perioperative mortality of 10.3%. Hepatic failure was the most reported source of perioperative mortality, mainly related to insufficient liver remnant. Most hepatopancreatoduodenectomies (81.3%) include a major hepatectomy (≥ 3 Couinaud's hepatic segments) that removed large amount of hepatic mass. Preoperative portal vein embolism (PVE) is purposed to improve safety and tolerance of major hepatectomy and increase respectability by inducing homolateral atrophy and contralateral compensatory hypertrophy of the remnant liver. Nimura *et al.*³ performed hepatopancreatoduodenectomy without PVE in 24 patients of whom 6 died. In their recent series of 85 patients, 78.8% patients received preoperative PVE, of whom only 2 died.²⁰ These observations indicate that preoperative PVE is an effective procedure to reduce the risk for postoperative liver failure and associated mortality.

Preoperative hyperbilirubinemia also increases the risk of hepatic failure following hepatopancreatoduodenectomy. It appears that biliary obstruction increases susceptibility to endotoxemia, impairs the function of hepatocyte mitochondria, and reversibly reduces the activity of microsomal mixed function oxidase (MFO).²⁴ Preoperative biliary drainage can promote early bile duct decompression in future remnant lobe(s), improve liver function, and prevent cholangitis.²⁵ A recent meta-analysis of six randomized clinical trials (RCT) failed to show any significant benefit of using preoperative biliary drainage in jaundiced patients planned for surgery.²⁶ However, these studies included mostly bypass surgeries and palliative resections, and there were very few major hepatectomies combination with an obstructed liver. Hyperbilirubinemia is reported to be strongly associated with increased in-hospital mortality after extended hepatectomy.²⁷ Thus, preoperative biliary drainage should be recommended before major hepatectomy combined with pancreatoduodenectomy in jaundiced patients, accepting there is no RCT-based evidence.

Another life-threatening complication of hepatopancreatoduodenectomy is pancreatic anastomotic leakage, which is associated with intraabdominal hemorrhage and abscesses. Sakamoto *et al.*²² reported one patient died who of bleeding from a pancreatic fistula and subsequent hepatic failure after hepatopancreatoduodenectomy. Wrapping an omental flap around the dissected splanchnic vessel in pancreatoduodenectomy has been

Table 2 Surgical outcomes following hepatopancreatoduodenectomy

Reference	Number of patients	MH, n	PVR, n	CPD, n	PPPD, n	OT (min)	BL (ml)	Morbidity, n	HF, n	PF, n	Mortality, n	R0 R, n	MS (months)	5-year OS (%)
Nimura <i>et al.</i> ³	24	17	11	24	0	–	–	19	7	3	6	22	7	6
Nakamura <i>et al.</i> ⁴	7	5	2	7	0	537	1980	5	0	0	0	2	12	–
Shirai <i>et al.</i> ⁷	17	2	0	17	0	–	–	–	0	0	1	10	21	24
Yoshimi <i>et al.</i> ⁸	13	8	3	3	10	686	3700	9	0	6	1	7	–	–
Sasaki <i>et al.</i> ⁹	16	4	–	7	9	650	2014	11	1	1	1	13	29.5	43
Hirono <i>et al.</i> ¹⁰	11	8	3	10	1	716	4116	9	4	4	2	–	8	–
Kaneoka <i>et al.</i> ¹²	20	20	14	5	14	550	1602	10	2	4	3	7	12	32
Miwa <i>et al.</i> ¹³	26	19	4	–	–	–	1588	8	0	2	0	–	–	41
Ota <i>et al.</i> ¹⁴	32	32	14	–	–	561	6505	29	15	7	15	20	–	3
Urahashi <i>et al.</i> ¹⁵	12	10	1	–	–	–	–	–	–	–	0	–	–	33
Nanashima <i>et al.</i> ¹⁶	11	8	–	3	8	703	1778	4	1	2	0	8	13	–
Wakai <i>et al.</i> ¹⁷	28	28	8	11	17	654	1875	23	6	7	6	17	9	11
Hemming <i>et al.</i> ¹⁸	22	–	–	–	–	–	–	–	–	–	0	22	–	22
Kaneoka <i>et al.</i> ¹⁹	14	13	5	3	11	550	1354	8	3	3	0	9	63	50
Ebata <i>et al.</i> ²⁰	85	79	24	6	59	762	2696	84	64	60	2	64	31.2	37
Lim <i>et al.</i> ²¹	23	23	1	10	13	–	–	21	2	–	3	17	–	22.4
Sakamoto <i>et al.</i> ²²	19	19	9	–	–	810	2300	18	14	18	1	14	–	32
Utsumi <i>et al.</i> ²³	17	10	7	15	2	540	1030	15	–	8	0	16	22	30
Total/ Median or %	397	305 (81.3%)	106 (30.5%)	121 (42.3%)	144 (50.3%)	652 (537– 810)	1980 (1030– 6505)	273 (78.9%)	119 (34.4%)	125 (36.7%)	41 (10.3%)	248 (71.3%)	13 (7–63)	31 (3–50)

MH, major hepatectomy (≥ 3 Couinaud's hepatic segments); PVR, portal vein resection; CPD, conventional pancreatoduodenectomy; PPPD, pylorus-preserving pancreatoduodenectomy; OT, operative time; BL, blood loss; HF, hepatic failure; PF, pancreatic fistula; R0 R, R0 resection; MS, median survival; OS, overall survival.

reported to decrease the risk of postoperative intraabdominal bleeding.²⁸ In addition, external drainage of pancreatic juice by inserting a tube into the main pancreatic duct is a technique that has been suggested to prevent a pancreatic fistula, in which pancreatic juice is diverted away from anastomosis.²⁹ Miwa *et al.*¹³ reported no pancreatic leak in a series of 22 patients undergoing complete external drainage of pancreatic juice, followed by second-stage pancreateojejunostomy. Thus accepting the relatively

low levels of evidence on which to base decisions the authors propose the current algorithm (Fig. 2) for patients being considered for combined hepatopancreatoduodenectomy.

In this systematic review, the 5-year survival rate is 3–50% (median = 31%), which is better than that of a reported series of subjects with unresectable tumors,³⁰ suggesting that aggressive resection may be justified in well selected and prepared patients with advanced biliary and gallbladder cancers. In particular,

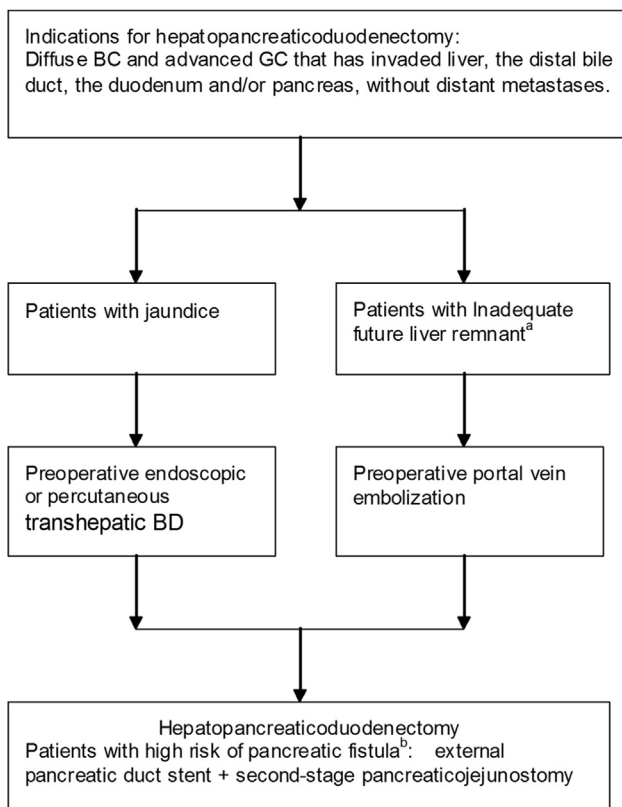


Figure 2 Flow diagram of operative indications and strategies to reduce surgical risk of hepatopancreatoduodenectomy. BC, bile duct cancer; GC, gallbladder cancer; BD, biliary drainage; ^a, $\leq 20\%$ in normal liver, $\leq 30\%$ with significant fibrosis or steatosis, and $\leq 40\%$ in cirrhosis³¹; ^b, soft pancreatic texture and a nondilated pancreatic duct

patients who underwent curative resection had a significantly better prognosis than those with non-curative resection emphasizing the importance of preoperative selection.

Several articles analyzed the impact of the disease type on the prognosis of patients undergoing hepatopancreatoduodenectomy and reported inconsistent results. Nimura, Miwa, Wakai, Hemming, Lim, Utsumi and their colleagues found that the survival rate of BC and GC patients was comparable.^{3,13,17,18,21,23} On the contrary, Sakamoto *et al.*²² reported that the survival rate in GC patients was lower than that in BC patients. However, in their series, the clinical stage was IV in 3/14 BC patients and IV in all 5 GC patients ($P = 0.002$). Biliary infiltration was positive in all 5 GC patients and the radial margin was positive in 4. The worse prognosis for GC may have been due to its more advanced stage and a lower R0 resection rate as compared with BC.

This review was limited by the quality of the evidence reported in the literature, its retrospective nature and the small sample size. The predictive variables for patient selection were not well addressed. Further prospective multi-center studies may help improve identification of patients in whom hepatopancreatoduodenectomy offers benefits.

In conclusion, hepatopancreatoduodenectomy for biliary and gallbladder cancers is a challenging procedure with high morbidity and mortality rates. However, this procedure can provide the chance for long-term survival if curative resection is feasible. Preoperative biliary drainage in jaundiced patients, PVE scheduled for major hepatectomy, and external drainage of pancreatic juice may decrease the risk of surgery.

Competing interests

The authors have declared that no competing interests exist.

Conflicts of interest

None to declare.

References

1. Ishikawa, T., Horimi, T., Shima, Y., Okabayashi, T., Nishioka, Y., Hamada, M., et al. (2003). Evaluation of aggressive surgical treatment for advanced carcinoma of the gallbladder. *J Hepatobiliary Pancreat Surg*, 10, 233–238.
2. Seyama, Y., & Makuuchi, M. (2007). Current surgical treatment for bile duct cancer. *World J Gastroenterol*, 13, 1505–1515.
3. Nimura, Y., Hayakawa, N., Kamiya, J., Maeda, S., Kondo, S., Yasui, A., et al. (1991). Hepatopancreatoduodenectomy for advanced carcinoma of the biliary tract. *Hepatogastroenterology*, 38, 170–175.
4. Nakamura, S., Nishiyama, R., Serizawa, A., Nishiwaki, Y., Konno, H., et al. (1994). Hepatopancreatoduodenectomy for advanced gallbladder carcinoma. *Arch Surg*, 129, 625–629.
5. Tsukada, K., Yoshida, K., Aono, T., Koyama, S., Shirai, Y., Uchida, K., et al. (1994). Major hepatectomy and pancreatoduodenectomy for advanced carcinoma of the biliary tract. *Br J Surg*, 81, 108–110.
6. Miyagawa, S., Makuuchi, M., Kawasaki, S., Hayashi, K., Harada, H., Kitamura, H., et al. (1996). Outcome of major hepatectomy with pancreatoduodenectomy for advanced biliary malignancies. *World J Surg*, 20, 77–80.
7. Shirai, Y., Ohtani, T., Tsukada, K., & Hatakeyama, K. (1997). Combined pancreaticoduodenectomy and hepatectomy for patients with locally advanced gallbladder carcinoma: long term results. *Cancer*, 80, 1904–1909.
8. Yoshimi, F., Asato, Y., Amemiya, R., Shioyama, Y., & Itabashi, M. (2001). Comparison between pancreatoduodenectomy and hepatopancreatoduodenectomy for bile duct cancer. *Hepatogastroenterology*, 48, 994–998.
9. Sasaki, R., Takahashi, M., Funato, O., Nitta, H., Murakami, M., Kawamura, H., et al. (2002). Hepatopancreatoduodenectomy with wide lymph node dissection for locally advanced carcinoma of the gallbladder—long-term results. *Hepatogastroenterology*, 49, 912–915.
10. Hirono, S., Tani, M., Kawai, M., Ina, S., Uchiyama, K., & Yamaue, H. (2006). Indication of hepatopancreatoduodenectomy for biliary tract cancer. *World J Surg*, 30, 567–573.
11. CEBM. (2001). *Oxford Center for Evidence-based Medicine: The Levels of Evidence*. <http://www.cebm.net/index.aspx?o=1025> [accessed 19.07.15].
12. Kaneoka, Y., Yamaguchi, A., & Isogai, M. (2007). Hepatopancreatoduodenectomy: its suitability for bile duct cancer versus gallbladder cancer. *J Hepatobiliary Pancreat Surg*, 14, 142–148.
13. Miwa, S., Kobayashi, A., Akahane, Y., Nakata, T., Mihara, M., Kusama, K., et al. (2007). Is major hepatectomy with

- pancreatoduodenectomy justified for advanced biliary malignancy? *J Hepatobiliary Pancreat Surg*, 14, 136–141.
14. Ota, T., Araida, T., Yamamoto, M., & Takasaki, K. (2007). Operative outcome and problems of right hepatic lobectomy with pancreatoduodenectomy for advanced carcinoma of the biliary tract. *J Hepatobiliary Pancreat Surg*, 14, 155–158.
 15. Urahashi, T., Yamamoto, M., Ohtsubo, T., Katsuragawa, H., Katagiri, S., & Takasaki, K. (2007). Hepatopancreatoduodenectomy could be allowed for patients with advanced intrahepatic cholangiocarcinoma. *Hepatogastroenterology*, 54, 346–349.
 16. Nanashima, A., Nagasaki, T., Sumida, Y., Abo, T., Tobinaga, S., Takeshita, H., et al. (2008). An experience of hepatopancreatoduodenectomy in patients with hepatobiliary malignancies. *Hepatogastroenterology*, 55, 1691–1694.
 17. Wakai, T., Shirai, Y., Tsuchiya, Y., Nomura, T., Akazawa, K., & Hatakeyama, K. (2008). Combined major hepatectomy and pancreatoduodenectomy for locally advanced biliary carcinoma: longterm results. *World J Surg*, 32, 1067–1074.
 18. Hemming, A. W., Magliocca, J. F., Fujita, S., Kayler, L. K., Hochwald, S., Zendejas, I., et al. (2010). Combined resection of the liver and pancreas for malignancy. *J Am Coll Surg*, 210, 808–814.
 19. Kaneoka, Y., Yamaguchi, A., Isogai, M., & Kumada, T. (2010). Survival benefit of hepatopancreatoduodenectomy for cholangiocarcinoma in comparison to hepatectomy or pancreatoduodenectomy. *World J Surg*, 34, 2662–2670.
 20. Ebata, T., Yokoyama, Y., Igami, T., Sugawara, G., Takahashi, Y., Nimura, Y., et al. (2012). Hepatopancreatoduodenectomy for cholangiocarcinoma: a single-center review of 85 consecutive patients. *Ann Surg*, 256, 297–305.
 21. Lim, C. S., Jang, J. Y., Lee, S. E., Kang, M. J., & Kim, S. W. (2012). Reappraisal of hepatopancreatoduodenectomy as a treatment modality for bile duct and gallbladder cancer. *J Gastrointest Surg*, 16, 1012–1018.
 22. Sakamoto, Y., Nara, S., Kishi, Y., Esaki, M., Shimada, K., Kokudo, N., et al. (2013). Is extended hemihepatectomy plus pancreaticoduodenectomy justified for advanced bile duct cancer and gallbladder cancer? *Surgery*, 153, 794–800.
 23. Utsumi, M., Sadamori, H., Shinoura, S., Umeda, Y., Yoshida, R., Nobuoka, D., et al. (2014). Risk factors of morbidity and predictors of long-term survival after hepatopancreatoduodenectomy for biliary cancer. *Hepatogastroenterology*, 61, 2167–2172.
 24. Maguchi, H., Takahashi, K., Katanuma, A., Osanai, M., Nakahara, K., Matuzaki, S., et al. (2007). Preoperative biliary drainage for hilar cholangiocarcinoma. *J Hepatobiliary Pancreat Surg*, 14, 441–446.
 25. Iacono, C., Ruzzenente, A., Campagnaro, T., Bortolasi, L., Valdegamberi, A., & Guglielmi, A. (2013). Role of preoperative biliary drainage in jaundiced patients who are candidates for pancreatoduodenectomy or hepatic resection: highlights and drawbacks. *Ann Surg*, 257, 191–204.
 26. Fang, Y., Gurusamy, K. S., Wang, Q., Davidson, B. R., Lin, H., Xie, X., et al. (2013). Meta-analysis of randomized clinical trials on safety and efficacy of biliary drainage before surgery for obstructive jaundice. *Br J Surg*, 100, 1589–1596.
 27. Vauthey, J. N., Pawlik, T. M., Abdalla, E. K., Arens, J. F., Nemr, R. A., Wei, S. H., et al. (2004). Is extended hepatectomy for hepatobiliary malignancy justified? *Ann Surg*, 239, 722–730.
 28. Maeda, A., Ebata, T., Kanemoto, H., Matsunaga, K., Bando, E., Yamaguchi, S., et al. (2005). Omental flap in pancreaticoduodenectomy for protection of splanchnic vessels. *World J Surg*, 29, 1122–1126.
 29. Zhou, Y., Yang, C., Wang, S., Chen, J., & Li, B. (2011). Does external pancreatic duct stent decrease pancreatic fistula rate after pancreatic resection?: a meta-analysis. *Pancreatology*, 11, 362–370.
 30. Fiteni, F., Jary, M., Monnier, F., Nguyen, T., Beohou, E., Demarchi, M., et al. (2014). Advanced biliary tract carcinomas: a retrospective multi-center analysis of first and second-line chemotherapy. *BMC Gastroenterol*, 14, 143.
 31. Abdalla, E. K., Adam, R., Bilchik, A. J., Jaeck, D., Vauthey, J. N., & Mahvi, D. (2006). Improving resectability of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol*, 13, 1271–1280.