



Hepatopancreaticoduodenectomy for biliary cancer: operative strategies determine near-zero operative mortality, but tumor biology determines an acceptable long-term outcome

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We would like to congratulate Aoki *et al.* on their promising surgical and oncological outcomes of performing the complicated multi-organ curative resection for biliary cancer, so-called hepatopancreaticoduodenectomy (HPD) (1). HPD depicts one of the most challenging surgical procedures aiming to resect neoplasm occupying the zone around hepatoduodenal ligament in the en bloc fashion. The essence of HPD, when being applied to bile duct cancer, is to completely remove the extrahepatic bile ducts to the level of hepatic hilum (2). For locally advanced gallbladder neoplasm, HPD should also be a rational resection to the extent which could include either longitudinally to liver bed/duodenum, or laterally to hepatic hilum/extrahepatic bile duct. In 1990's, HPD was mainly applied to patients with locally advanced gallbladder cancers (3,4). Similar to the early period of our 30-year experience (unpublished data), we performed HPD as a curative resection for patients with gallbladder cancer invasion to both the liver and the duodenum but the outcome and prognosis were unsatisfactory, when compared with those with bile duct cancer.

It is believed that the aggressive tumor behavior and relatively delayed diagnosis of gallbladder cancer might lead to the dismal prognosis; however, a radical resection did improve survival in selected cases. A 12-year retrospective review (1990-2002) reported by Dixon *et al.* (5) had found out that adopting this radical resection approach in patients with gallbladder cancer had led to an improved survival in the last 6 years, where R0 resection was performed more

frequent than the early 6 years (5-year survival: 35% *vs.* 5%, respectively, $P < 0.03$).

In addition to the aggressive tumor behavior and the delay of diagnosis, advanced stage and lower R0 resection rate for gallbladder cancer might also result in unfavorable outcome (6). In 2007, Kaneoka *et al.* (7) reported that conducting HPD in patients with gallbladder cancer had yielded a dismal 5-year survival, when comparing to patients with bile duct cancer (0% *vs.* 64%, respectively, $P < 0.001$). A recent meta-analysis (6) on HPD for biliary cancer also disclosed that using HPD to treat patients with gallbladder cancer failed to show better survival than those with bile duct cancer (5-year survival: 10.4% *vs.* 33%, respectively).

One-fourth of the current cohort proposed by Aoki *et al.* was gallbladder cancer; six of them received combined colon resection and R0 resection. The surgical result was inspiring, but the 5-year survival of the gallbladder cancer patients was inferior to that of bile duct cancer (although no statistical significance was reached). Owing to improvements in perioperative preparation and surgical skills, HPD has been proposed as a feasible and safe procedure for bile duct cancer and gallbladder cancer in high-volume centers. From viewpoints of the oncologic outcome, we would rather be conservative when facing locally advanced but potentially resectable gallbladder cancer that requires HPD or other aggressive surgeries.

Since favorable survival might not be achievable by the similarly radical operations for gallbladder cancers due to its aggressive tumor behavior. Neoadjuvant chemo-

radiation therapy followed by surgery probably offers a superior oncologic outcome than the surgery itself (8). Ebata *et al.* conducted HPD on 85 patients with perihilar cholangiocarcinoma and achieved a promising long-term outcome (9). The fact is that HPD might be not a promisingly radical treatment for advanced gallbladder cancer.

The major technical obstacles for HPD were potentially insufficient liver remnant (LR) and leakage of pancreaticojejunostomy (PJ)/pancreatic fistula (PF). Owing to the potentially insufficient LR, the refinement of preoperative portal vein embolization and biliary drainage has remarkably decreased the surgical morbidity and mortality (1,10). However, the PF rate remained unsatisfactorily high among different series of procedures (11,12). The risk factors contributing to PF include the diameter of the pancreatic duct, the texture of pancreas, patient characteristics, and technique of anastomosis (13,14).

In our opinion, the method of anastomosis depends on surgeon's preference, because using PJ or pancreaticogastrostomy had controversy in reducing postoperative pancreatic leakage. There is no universal consensus about the optimal anastomosis technique. We had performed 931 pancreaticoduodenectomies (PD) between 2001 and 2015 for various etiologies. PJ remained the main anastomosis method chosen in our center. However, Pessaux *et al.* (15) suggested an external pancreatic duct stent reduce the rate of PF and overall morbidity in high-risk patients with soft pancreas and non-dilated pancreatic duct according to a prospective multicenter randomized trial.

The current report of Aoki *et al.* emphasized the utilization of two-stage PJ, which is to perform PJ in average 3 months after the first resection and partial reconstruction according to the risk grading of the pancreas. The median interval between the two operations is 112 days (84–258 days). The two-stage PJ, or two-stage gastrointestinal reconstruction, is regarded as a “damage control” procedure in emergent surgery other than an elective surgical procedure. However, Hasegawa *et al.* has reported the largest cohort using two-stage PJ for PD (16), the rate of PF was still 16% after the second stage reconstruction. It is not overwhelmingly convincing for us to follow the same strategy in the concerns of patients' compliance and care for PD. For PD itself, in the past decade, we only performed a delayed PJ for one case who suffering from uncontrolled duodenal ulcer bleeding with hypovolemic shock. The patient received reconstruction 3 days after the first PD. Two-stage PJ, especially for HPD, might still be considered as a good therapeutic strategy to

overcome PJ insufficiency inducing leakage and subsequent liver failure of LR. However, for a well-experienced surgeon with high hospital volume, one-stage PJ can still be done safely (9).

In conclusion, Aoki's excellent work supported that HPD has demonstrated acceptable safety and favorable long-term survival with aggressive application of preoperative portal vein embolization and biliary drainage. To reduce the rate and sequelae of PF, the strategy of two-stage reconstruction is suggested, especially for centers and surgeons without much experience.

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