Comment on “Perihilar cholangiocarcinoma—novel benchmark values for surgical and oncological outcomes from 24 expert centers”

Yasunari Kawabata, Yoshitsugu Tajima

Department of Digestive and General Surgery, Shimane University Faculty of Medicine, Izumo, Shimane, Japan

Correspondence to: Yasunari Kawabata, MD, PhD. Department of Digestive and General Surgery, Shimane University Faculty of Medicine, 89-1 Enyacho, Izumo, Shimane 693-8501, Japan. Email: batayan5@med.shimane-u.ac.jp.


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Perihilar cholangiocarcinoma (PHC) is an aggressive malignancy of the biliary tracts with a dismal outcome. Although the primary goal of surgery for PHC is complete tumor removal with negative resection margins and regional lymphadenectomy, surgery for PHC with curative intent remains a challenge for surgeons because it involves complex surgical procedures such as bile duct resection, major hepatectomy, and/or vascular resection. These intensive procedures are often associated with postoperative complications, including severe morbidity and 30-day mortality with incidences of 40% and 5%, respectively (1). From the perspective of surgical and oncological safety, the standardization of aggressive surgical approaches and the establishment of standardized benchmark values that secure the best achievable outcomes are warranted in the treatment of patients with PHC.

Recently, clinical data analyses based on multicenter, large-scale studies to establish a standard point for clarifying intended goals and subjects, i.e., benchmarking studies, have been applied to several complex surgical procedures, including major liver resection and transplantation (2-4), pancreatectomy (5,6), and esophagectomy (7). These established benchmark methodologies have been helpful in identifying the best achievable results and defining optimal clinically relevant endpoints, so-called “benchmark values” (8). However, a standardized strategy for the best achievable outcomes remains unclear in the surgical management of PHC. Therefore, robust and standardized outcome references are desired to improve the quality management of PHC surgery. Mueller et al. attempted to identify novel benchmark values for PHC surgery based on an established benchmark methodology and published the results in a study titled “Perihilar cholangiocarcinoma—novel benchmark values for surgical and oncological outcomes from 24 expert centers” (9). Their methodology consisted of a multinational web-based Delphi survey from 24 high-volume expert centers on 3 continents over the 5-year study period.

In their study, 21 outcome indicators after liver resection for PHC were identified as novel benchmark values reflecting overall morbidity, mortality, and oncological outcomes, which included 4 operative factors, 11 postoperative complications (such as morbidity at 3 months and in-hospital or 3-month mortality), and 6 oncological outcomes, through retrospectively collected data on 708 low-risk (benchmark) cases of 1,829 consecutive patients who underwent PHC surgery with major liver resection. Benchmark (low-risk) cases were restricted to those without major comorbidities based on American Society of Anesthesiologists (ASA) class ≥3; obesity [body mass index (BMI) ≥35 kg/m²]; and chronic cardiovascular, pulmonary, renal, or metabolic diseases (9). Cases requiring liver transplantation, central resections, pancreatecoduodenectomy, or vascular reconstruction due to tumor extension were also excluded. In the authors’ analysis, benchmark cutoffs were derived from the 75th percentile (for indicators of a worse outcome) or the 25th percentile (for indicators of a good outcome) of the median value of
each participating center (8,10). Basically, benchmarking analyses should present statistical ranges, above which comparative results are significantly poorer and below which the results are better. Therefore, the benchmark cutoff setting is important and affects the interpretation of outcomes, because in a patient population associated with high morbidity, only the lower threshold of the range is valuable to serve as a marker for acceptable versus lower complication rates in analyzing other populations (2-4). Further evaluation of whether the setting of these benchmark cutoffs is reproducible, objective, and universal will be needed to reach worldwide consensus.

In a subgroup analysis for testing patient age as a risk factor, there were no differences in the comprehensive complication index (CCI), clinically relevant liver failure, re-laparotomy rate, or in-hospital mortality between elderly (>75 years of age) and younger (<50 years of age) patients. Additionally, BMI and tumor stage were not associated with surgical or oncological results. These results also showed the utility of these newly identified benchmark values beyond ethnic and regional differences.

From the point of view of surgical techniques and oncological outcomes, the current study demonstrated that a left-sided hepatectomy showed a significantly more favorable overall survival (OS) as compared to a right-sided hepatectomy [61 vs. 45 months, hazard ratio (HR) 1.49, 95% confidence interval (CI): 1.16–1.91, P=0.002] despite the fact that there was no difference in R1/2 resection rates between the groups (left 29.5% vs. right 28.1%, P=0.69). This result conflicts with the universally believed concept that an extended right-sided hepatectomy is more favorable and increases the chance of R0 resection on the left hepatic duct. Moreover, increased in-hospital mortality was observed in right-sided hepatectomies as compared to left-sided hepatectomies (7.3% vs. 1.8%, P<0.001), as well as a significantly higher rate of clinically relevant liver failure (International Study Group of Liver Surgery grade B/C) (24.2% vs. 11.2%, P<0.001). In addition, patients who underwent right-sided hepatectomy with a routine portal vein (PV) resection, i.e., a non-touch approach, were significantly associated with higher morbidity, higher 3-month mortality, and worse OS and disease-free survival compared to those without PV resection. This result provided us with innovative and valuable information, and we need to remodel surgical strategies for PHC to achieve the best outcomes from this novel benchmark study.

On the other hand, Asian centers showed better outcomes, including prolonged OS (HR 1.64, 95% CI: 1.26–2.13, P<0.001) with a lower severe liver failure rate (1.7% vs. 7.7%, P=0.018). A tendency toward lower in-hospital mortality (2.0% vs. 5.9%, P=0.06) was also observed when compared with non-Asian centers in this homogeneous benchmark cohort. The preoperative routine liver function tests [e.g., the indocyanine green (ICG) test] and modulation of a future liver remnant before right-sided hepatectomy through PV embolization in Asian centers may contribute to the lower rate of clinically relevant post-hepatectomy liver failure and better outcomes. Meanwhile, this benchmark study demonstrated that being a non-Asian center was not an independent risk factor for either mortality or morbidity in a multivariable analysis. These results revealed that the benchmarking approaches are useful for identifying properly validated worldwide reference values excluding most confounding factors related to individual patients, tumor behavior, or institutional characteristics (8,10), and the novel benchmark values presented in this study can be utilized as a quality-improvement tool in PHC surgery.

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