Editorial

Perihilar-cholangiocarcinoma: what really matters?

Fabrizio Di Benedetto, Paolo Magistri, Stefano Di Sandro

Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, University Hospital of Modena "Policlinico", University of Modena and Reggio Emilia, Modena, Italy

Correspondence to: Prof. Fabrizio Di Benedetto, MD, PhD, FACS. Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, University Hospital of Modena "Policlinico", University of Modena and Reggio Emilia, 41124 Modena, Italy. Email: fabrizio.dibenedetto@unimore.it.

Comment on: Franken LC, Olthof PB, Erdmann JI, *et al.* Short- and long-term outcomes after hemihepatectomy for perihilar cholangiocarcinoma: does left or right side matter? Hepatobiliary Surg Nutr 2021;10:154-62.

Submitted Jun 03, 2022. Accepted for publication Jul 08, 2022.
doi: 10.21037/hbsn-22-225
View this article at: https://dx.doi.org/10.21037/hbsn-22-225

Treatment of peri-hilar cholangiocarcinoma (PHC) is one of the most critical challenges in the modern era of liver surgery (1). In addition to the highly demanding technique and insidious diagnostic work-up, the procedure is often complicated by potentially life-threatening post-operative sequelae. Therefore, accuracy in the pre-operative indication and planning is paramount to mitigate this risk and to improve the outcomes. The decision to either perform a right or left hepatectomy should be based on several factors, including tumor extension, presence of vascular infiltration, study of the future liver remnant (FLR) and center experience. Franken and colleagues reported their valuable experience with patients affected by PHC (2), comparing 76 left sided liver resections (LH) *vs.* 102 right sided liver resections (RH) for PHC, to highlight potential advantages of one approach over the other. Authors showed that no statistically significant differences could be found in both short- and long-term outcomes between the two groups. Interestingly, post-hepatectomy liver failure (PHLF) was more frequently observed after RH (22%) compared to LH (11%), almost reaching a significant threshold (P=0.052). Of note, incidence of PHLF seems to be influenced more by the combination of liver and portal vein resection (P=0.005), rather than by the side of the hepatectomy. Despite the efforts to obtain a radical treatment and the risk of severe morbidity, a R0 resection was obtained in only 39% of the cases, without differences between left- and right-sided hepatectomies (40% and 39%, respectively, P=0.849), having considered any margin <1 mm as R1 including all planes.

These results are consistent with previously published data collected in a recent meta-analysis including 1,031 patients, confirming that LH and RH have comparable survival benefits and R0 resection rates, while short-terms outcomes, morbidity and incidence of PHLF are significantly lower in patients treated with LH (3). It should be mentioned that, even in expert hands, the overall post-operative morbidity rate is considerably high, with an overall incidence of 58% of Clavien-Dindo grade >3 complications and 90-day mortality of 14%, that reached 16% rate in the right-sided resection group compared to 11% in the left-sided resection group in the series by Franken. A systematic review and meta-analysis published in 2019 by the same group and including 4,634 cases of patients that underwent major liver resection for PHC confirmed the high risk of severe post-operative complications. In detail, 30- and 90-day mortality were as high as 5% (95% CI: 3–6%) and 9% (95% CI: 6–12%), respectively, while overall morbidity and severe morbidity were 57% (95% CI: 50–64%) and 40% (95% CI: 34–47%), respectively. When comparing Asian to Western studies, the latter showed significantly higher 30- and 90-day mortality, and overall morbidity [2% *vs.* 8% (P<0.001), 3% *vs.* 12% (P<0.001), and 54% *vs.* 63% (P=0.048), respectively], even when corrected for hospital volume (4).

Recently, benchmark values for surgical and oncological outcomes in patients affected by PHC have been identified after analyzing 1,829 cases treated across three continents (5). Twenty-one benchmark parameters were defined regarding intra-operative outcomes, post-operative morbidity and mortality, and survival. Interestingly, the reported

benchmark for morbidity ≥ Clavien 3a was ≤70%, in-hospital and 90-day mortality rates were 8% and 13%, while the benchmark for overall survival (OS) rates at 1-, 3-, and 5-year was 77.5%, 48.4%, and 39.7%, respectively. Again, this important study reported more favorable outcomes for patients treated in Asian centers, namely significantly better OS [hazard ratio (HR) =1.64; 95% CI: 1.26–2.13; P<0.001] and reduced incidence of PHLF (1.7% *vs.* 7.7%, P=0.018). Moreover, when comparing outcomes after LH and RH, authors highlighted that patients undergoing left sided resections are favored in terms of longer OS (median 61 *vs.* 45 months; HR =1.49; 95% CI: 1.16–1.91; P=0.002), lower in-hospital mortality rate (7.3% *vs.* 1.8%, P<0.001), and lower incidence of PHLF grade B and C (24.2% *vs.* 11.2%, P<0.001) (5). As mentioned by the authors, the choice of the type of liver resection is often influenced by tumor location and extension, nevertheless LH is associated with better outcomes and given the considerably lower mortality rate and equivalence in R0 resection rates, it may be preferred when applicable over RH. In fact, in this study LH remains superior to RH even after adjusting on potential confounding factors like pre-operative portal vein embolization or portal vein resection.

Besides the importance of achieving negative resection margins, it should be mentioned that lymphadenectomy represents an important prognostic factor to predict patients' survival. In a large series of Bismuth-Corlette IV cases, authors identified lymph-node metastasis (N1; HR =1.62), positive margins (R1; HR =1.36), perineural invasion (HR =1.53), and poor grade of differentiation (HR =1.25) as predictors of survival (all P≤0.004) (6). Nevertheless, it was recently reported from a international multicenter database that N+ staging can significantly reduce median OS regardless of the R-status (7). Therefore, besides the benchmark of ≥4 nodes to be retrieved during liver surgery for PHC, it is crucial to perform an adequate regional lymphadenectomy for an optimal staging to increase the quality of surgical treatment.

As brilliantly reported by Nagino in his recent editorial on left hepatic trisectionectomy with caudate lobectomy, surgeons adopting this technique should be aware of the associated technical difficulties (8). In particular, (I) the complicated spatial relationship of bilio-vascular system of the right posterior Glisson, (II) the lack of anatomical landmarks on the liver surface, (III) the position of the right hepatic vein that does not always run along the right intersectional plane (right portal scissura), and (IV) the uneven and curved surface of the right intersectional plane, all together are considered responsible of an "anatomical trap" that makes intraoperative orientation difficult, potentially leading to wrong resection planes and, therefore, increasing the risk of morbidity (e.g., multiple bile ducts to reconstruct, ischemic surface). Therefore, a deep understanding of patients-specific liver anatomy and accurate pre-operative planning, rather than an aimlessly aggressive strategy (9), are needed to achieve benchmark outcomes and to reduce the risk of post-operative morbidity and mortality for our patients.

Under this perspective, we should aim to develop strategies that mitigate these complications without affecting oncological outcomes. A possible resource may be identified in minimally invasive approach for liver resection (MILS), which demonstrated safety and feasibility in all the fields of liver surgery and several advantages over standard open approach, with progressive spread in the last decade (10). Recently a meta-analysis comparing MILS to open approach for PHC was published, including nine studies, 2 robotic and 7 laparoscopic, for a total of 382 patients involved. The study showed that the two groups had comparable blood transfusion rate, R0 resection rate, lymph nodes retrieved, overall and severe morbidity, (Clavien-Dindo classification ≥3), bile leakage rate, wound infection rate, intra-abdominal infection rate, days until oral feeding, 1- and 2-year overall survival and postoperative mortality (11). MILS was significantly associated with longer operative time, faster discontinuation of post-operative analgesia and shorter in-hospital stay. Therefore, the potential advantages coming from MILS still seem dismal compared to the difficulty of the procedure, although not inferior to the standard open in terms of radicality and survival. Moreover, it should be highlighted that minimally invasive PHC requires advanced skills in both resection and reconstruction phases, therefore the learning curve for this kind of procedure is indeed longer compared to standard MILS. As a matter of fact, previous experience in open liver surgery for PHC is required before considering to move to minimally invasive approaches. Notably, some concerns have been raised on the theorical risk of peritoneal tumor dissemination and peritoneal seeding (12). There are wide margins of improvement for MILS approaches, in particular regarding the incidence of abdominal and wound infections, and in the incidence of bile leak. Robotic approach may represent a good implementation in the reconstructive phase, and also demonstrated feasibility in advanced procedures like Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS) (13,14). Currently, minimally

invasive approach to PHC should be reserved to high volume centers to reduce the risks of suboptimal oncological radicality and severe post-operative complications.

In conclusion, data published so far demonstrate that both right- and left-sided liver resections for PHC can achieve benchmark outcomes, although left and extended left trisectionectomies with *en-bloc* caudatectomy [H1234 and H123458, according to the New World terminology (15)] are significantly associated with reduced incidence of PHLF, lower risk of mortality and higher OS rates. Therefore, when factors forcing the choice of the resection side are not present, a left sided resection should be considered to mitigate the risk of life-threatening complications, without indulging into classical "a priori" decisions. Finally, a step-wise adoption of minimally invasive strategies may ultimately contribute to reduce some of the peri-operative sequelae for PHC. Lastly, the necessary seek for oncological radicality should be carefully balanced with the high risk of in-hospital and 90-day mortality in light of a benchmark R0 rate ≥56.7%, and patients' safety and quality of life should remain on top of the priorities in the treatment of PHC.

Acknowledgments

Authors want to thank Modena ARTS (Academy for Robotic and Transplant Surgery) Foundation for the support to clinical research.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-225/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Balci D, McCormack L. Perihilar cholangiocarcinoma: A difficult surgery in a difficult patient where experience matters most. Surgery 2021;170:644-5.
2. Franken LC, Olthof PB, Erdmann JI, et al. Short- and long-term outcomes after hemihepatectomy for perihilar cholangiocarcinoma: does left or right side matter? Hepatobiliary Surg Nutr 2021;10:154-62.
3. Wu W, Cheng Q, Chen J, et al. Left-side vs. right-side hepatectomy for hilar cholangiocarcinoma: a meta-analysis. World J Surg Oncol 2021;19:107.
4. Franken LC, Schreuder AM, Roos E, et al. Morbidity and mortality after major liver resection in patients with perihilar cholangiocarcinoma: A systematic review and meta-analysis. Surgery 2019;165:918-28.
5. Mueller M, Breuer E, Mizuno T, et al. Perihilar Cholangiocarcinoma - Novel Benchmark Values for Surgical and Oncological Outcomes From 24 Expert Centers. Ann Surg 2021;274:780-8.
6. Ruzzenente A, Bagante F, Olthof PB, et al. Surgery for Bismuth-Corlette Type 4 Perihilar Cholangiocarcinoma: Results from a Western Multicenter Collaborative Group. Ann Surg Oncol 2021;28:7719-29.
7. Nooijen LE, Banales JM, de Boer MT, et al. Impact of Positive Lymph Nodes and Resection Margin Status on the Overall Survival of Patients with Resected Perihilar Cholangiocarcinoma: The ENSCCA Registry. Cancers (Basel) 2022;14:2389.
8. Nagino M. Left Hepatic Trisectionectomy With Caudate Lobectomy: Demanding But Essential Routine Surgical Procedure for Perihilar Cholangiocarcinoma. Ann Surg 2021;274:e638-40.
9. Nagino M, Clavien PA. Demise of "Hilar En Bloc Resection by No-touch Technique" as Surgery for Perihilar Cholangiocarcinoma: Dissociation Between Theory and Practice. Ann Surg 2021;274:e385-7.
10. Abu Hilal M, Aldrighetti L, Dagher I, et al. The Southampton Consensus Guidelines for Laparoscopic Liver Surgery: From Indication to Implementation. Ann Surg 2018;268:11-8.

11. Tang W, Qiu JG, Deng X, et al. Minimally invasive versus open radical resection surgery for hilar cholangiocarcinoma: Comparable outcomes associated with advantages of minimal invasiveness. PLoS One 2021;16:e0248534.
12. Liu QD, Chen JZ, Xu XY, et al. Incidence of port-site metastasis after undergoing robotic surgery for biliary malignancies. World J Gastroenterol 2012;18:5695-701.
13. Di Benedetto F, Magistri P, Guerrini GP, et al. Robotic liver partition and portal vein embolization for staged hepatectomy for perihilar cholangiocarcinoma. Updates Surg 2022;74:773-7.
14. Balci D, Sakamoto Y, Li J, et al. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) procedure for cholangiocarcinoma. Int J Surg 2020;82S:97-102.
15. Nagino M, DeMatteo R, Lang H, et al. Proposal of a New Comprehensive Notation for Hepatectomy: The "New World" Terminology. Ann Surg 2021;274:1-3.

Cite this article as: Di Benedetto F, Magistri P, Di Sandro S. Perihilar-cholangiocarcinoma: what really matters? HepatoBiliary Surg Nutr 2022;11(4):616-619. doi: 10.21037/hbsn-22-225