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EDITORIAL – HEPATOBILIARY TUMORS

Major Hepatectomy for Perihilar Cholangiocarcinoma: Taking Sides

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Perihilar cholangiocarcinoma represents a particular challenge to surgeons and patients alike. The challenges to lesions or biliary strictures in the liver hilum occur for several reasons and involve a number of aspects, from establishing a diagnosis, to preoperative management, surgical technical solutions, and the overall multimodal and multidisciplinary approach to disease management.

Resection is the only curative option for perihilar cholangiocarcinoma but it can be technically challenging and with associated risks, particularly for postoperative liver failure after major hepatectomy.[1] Liver surgery performed for other indications, typically colorectal liver metastasis, is now being performed, with morality rates of around 1–3%,[2] but hepatectomies for primary liver malignancies are still fraught with much higher rates of morbidity and mortality. Indeed, for perihilar cholangiocarcinoma, postoperative morbidity is reported to occur in up to three-quarters of all patients, with postoperative mortality reported in up to 30% of high-risk patients.[3] A considerable part of the very high 90-day mortality is related to postoperative liver failure caused by an insufficient future liver remnant after major liver resection. The problem of postoperative liver failure remains a considerable challenge despite several ways of both estimating future liver volume and several attempts at modifying volume prior to major resection.[1] Ideally, due to the often-present cholestasis and cholangitis in the liver prior to surgery, the recommended future liver remnant volume should preferably be ≥40% to reduce the risk of insufficient function and subsequent liver failure after hepatectomy for perihilar cholangiocarcinoma. Indeed, reducing perioperative morbidity and mortality is an overarching goal in complex liver surgery, and is a particular concern in major liver surgery for perihilar cholangiocarcinoma.[3]

The surgical intention and oncological goal of a resection for perihilar cholangiocarcinoma should be to achieve a complete resection of the tumor-bearing liver segments with microscopically free margins (i.e. R0 resection), including the extrahepatic bile ducts and an appropriate lymphadenectomy. Sometimes parts of the portal vein, or even, more rarely, affected hepatic arteries, are resected and reconstructed to achieve an *en bloc* resection with an attempt at free margins.[4] The planned liver resection is usually dictated by the extent of tumor involving either the right- or left-sided biliary duct (and by involvement of the first- and second-order bile ducts) as designated by the Bismuth–Corlette classification (Fig. 1). The type of liver resection (i.e. sidedness of hepatectomy) is determined by the predominant side of the bile ducts involved in the liver, with either right- or left-dominant lesions. In order to follow surgical oncological principles, a hemihepatectomy should be inclusive of segment 4 and with the caudate lobe (Segment 1)[5,6] in addition to the extrahepatic bile duct and locoregional lymphadenectomy. For a left-sided resection, segment 4 is part of the left liver, hence a left-sided hepatectomy includes S4 and leaves a comparable larger future liver remnant as the volume of the right liver is larger than the left. For right-sided resections, this results in an 'extended right hemihepatectomy'(Segments S5, S6, S7, S8 + S4 + S1), with higher associated risks for a smaller (and insufficient) future liver remnant and

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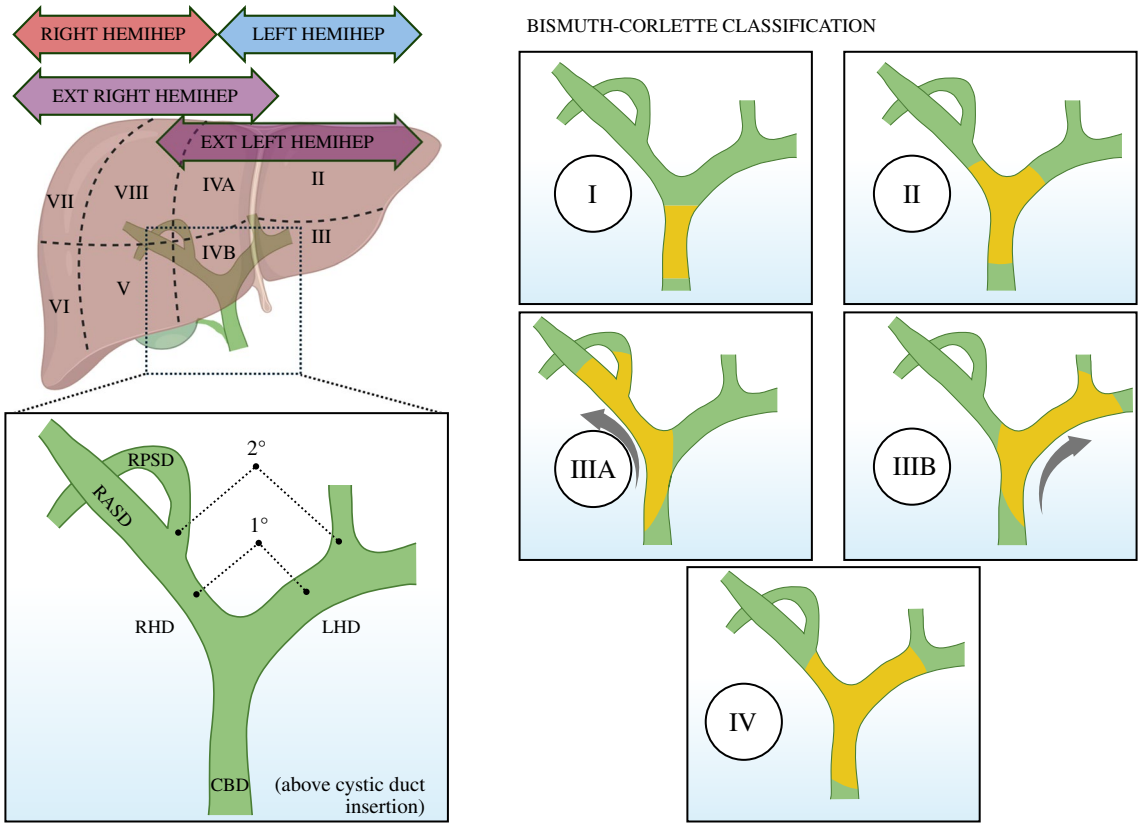

FIG. 1 Perihilar cholangiocarcinoma and Bismuth–Corlette classification. First- and second-order bile ducts are indicated by 1° and 2°. *CBD* common bile duct, *RHD* right hepatic duct, *LHD* left hepatic duct, *RPSD* right posterior sectorial duct, *RASD* right anterior sectorial duct, *hemihep* hemihepatectomy. Made in part using www.Biorender.com

the need for preoperative volume modification by any of the available techniques, such as portal vein embolization (PVE), with or without hepatic vein embolization (i.e. double vein embolization) or associated liver partitioning and portal vein ligation for staged hepatectomy (ALPPS). However, the volume hypertrophy may not translate into functional liver tissue, which may explain the increased risk of complications in the setting of right-sided liver resection. Indeed, several studies have pointed to better outcomes for left-sided liver resection in perihilar cholangiocarcinoma.[7] Despite this, there are arguably several other advantages with extended right-sided hepatectomy related to vascular anatomy (easier left portal vein reconstruction on the left side, and left hepatic artery more often free of tumor involvement), biliary ductal anatomy (usually longer on the left side for better margin-free resection and easier biliary reconstruction), and hepatic dissection that favors the right-sided (extended) surgical strategy.[8] However, there seems to be no oncological difference between either a left- or right-sided approach to resection for perihilar cholangiocarcinoma,[9] even if there are particular surgical difficulties and postoperative challenges with complications and the postoperative course to either side.

However, 'what is right' and 'what should be left', is still a much-debated question when it comes to taking sides for resection of perihilar cholangiocarcinoma. Of note, a recent systematic review found no clear differences between left- and right-sided resections, based on data from 14 cohort studies including 1072 patients.[9] Of note, two-thirds of the studies were reported from Asian centers, with data from only four Western centers.[9] Hence, in this issue of *Annals of Surgical Oncology*, it is interesting to see the study by Olthof et al.[10] and the *Perihilar Cholangiocarcinoma Collaboration Group*, who present a large series spanning 23 years, covering 25 Western centers and including >1700 patients who underwent major liver surgery for confirmed perihilar cholangiocarcinoma (excluding those with benign diagnosis on pathology). What stands out among the several findings in that study is the much higher 90-day mortality rate after any right-sided hepatectomy (90-day mortality at 18%) compared with any left-sided hepatectomy (90-day mortality at 9%), notably twice as high. Furthermore, the 90-day mortality rate was lowest for left-sided hemihepatectomy (at 8%) and highest for extended right-hepatectomy (19%), with a clear statistical significance for the difference. Associated risk factors for 90-day mortality were higher

age, higher American Society of Anesthesiologists (ASA) score, and presence of preoperative cholangitis. Patients undergoing a right-sided liver resection had significantly higher postoperative morbidity and higher prevalence of liver failure (16% for the whole group, and 19% and 23% for the right and extended right groups, respectively). The findings have led the group to propose that whenever feasible, a left-sided resection should be performed for perihilar cholangiocarcinoma.[10] Similar findings have been reported by others,[7] but in smaller studies.

The retrospective design and the considerable time span during which patients were treated are recognized as limitations by the authors, as well as the lack of information regarding the institution's policy or the individual surgeons' decision to do a left- or right-sided resection. The variation in resectability criteria in perihilar cholangiocarcinoma is a challenge in and of itself, with considerable variation between institutions, between continents, and over time.[11,12] No information is provided regarding the extent of biliary duct tumor involvement or involvement of vessels on either side (i.e. that would have precluded a choice between left- or right-sided resection). Data on an estimated future liver remnant (± PVE) is not provided, nor is actual remnant liver function for those who had a resection. While the available adjuvant (or neoadjuvant) chemotherapy may not be very effective, the idea that those with a larger liver volume after surgery were more likely to receive multimodal chemotherapy could be entertained. Several changes to liver surgery occurred during the study inclusion period. Hence, the authors proposal, based on the study results, that a left-sided hepatectomy should be attempted whenever feasible may have value to it, if not only for hypothesis-generating purposes; however, there may be several assumptions and considerations to make before jumping to firm conclusions.

The rhetoric question remains whether tumor location is the sole dictator of type of resection. From the point of considering lower associated risk of postoperative liver failure (yet slightly higher but non-significant risk in the incidence of bile leak), a left-sided resection may be preferred; however, this may not be technically feasible for several reasons. The 'standard' anatomy of the bile ducts (Fig. 1) found in about two-thirds of patients[13,14] is not universal and several subtypes of variant anatomy and distribution may prevent or complicate the given technical solutions for resection and reconstruction. Indeed, the anomalies and variants are several-fold and include all the structures in the hilar complex, with a greater appreciation of this over time and with enhanced imaging opportunities and experience in complex hepatobiliary surgery.[15] Indeed, novel software and imaging-guided tools can enhance preoperative planning by structured mapping of the biliary tree, detail the lesions at hand, and delineate the proposed resection plane at a more detailed level than in the past.[16,17] This may guide surgeons in not only better preoperative planning of resection (and surgical safety) but also the chance to achieve a possible R0 resection, for optimal oncological outcomes. Of note, in the study by Olthof et al.,[10] there was no difference in rates of surgical oncological outcomes between types of resection, i.e. rates of lymph node metastases, distant metastasis, R0 resection or poor differentiation or perineural invasion in tumors.

The survival difference observed in the cohort with left-sided resection compared with right-sided then begs the question whether the tumor biology is dictated by simple sidedness or by differences in molecular profiles of the lesions. Is it the liver resection itself or failure to receive multimodal therapy, including chemotherapy, that drives prognosis related to side of resection? This cannot be answered by the data at hand but would be a much-needed question to address for future studies, to potentially disclose the differences in survival reported despite similarity in surgical oncological outcomes from resection. There are several reasonable and common arguments for proposing a preferred approach for right-sided resection for perihilar cholangocarcinoma.[8] The current study points to certain advantages of a left-sided surgical approach[10] that may be considered in cases deemed suitable for either a left- or right-sided resection. The data at hand may be too premature for taking sides to sidedness in liver surgery for perihilar cholangiocarcinoma, but it certainly provides room for reflection and food for thought.

DISCLOSURES Kjetil Soreide is currently employed part-time at Karolinska University Hospital, but has no affiliation or connection to the work related to the Perihilar Cholangiocarcinoma Collaboration Group.

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