Editorial Commentary

Intraoperative blood loss in perihilar cholangiocarcinoma: should we aim below a certain cut-off?

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Perihilar cholangiocarcinoma (pCCA) is a rare tumor that arises at the biliary confluence. Curative treatment entails extrahepatic bile duct resection, usually combined with major liver resection to obtain negative margins. These major procedures harbor considerable risks that are the highest among any elective cancer surgery. The 90-day mortality rate after these procedures is 12%, which can be attributed to postoperative liver failure in about 85% of patients (1-3). The risk of postoperative liver failure can be decreased with preoperative management (e.g., biliary drainage and portal vein embolization) and intraoperative management (e.g., minimizing blood loss).

The most frequent symptom of pCCA is jaundice caused by biliary obstruction. This causes coagulopathy and impairs liver regeneration of the future liver remnant. Preoperative biliary drainage aims to mitigate these effects (4,5). Several studies showed that the risks of surgery decrease when the preoperative bilirubin levels fall below 2 mg/dL (4,6). However, biliary drainage is not without disadvantages, and 90-day mortality rates after biliary drainage for malignant hilar obstruction can reach up to 30% (7,8). This is mostly due to cholangitis, which can require multiple drainage procedures and rapid deterioration of the patient's condition. This can delay surgery or even cause patients to become unfit for surgery. When a resection is performed after an episode of cholangitis, the risk of postoperative secondary liver failure and mortality is increased (3,9,10). Therefore, it is essential to select patients who require biliary drainage and to perform biliary drainage in experienced centers after multidisciplinary team discussion (11).

Furthermore, the assessment and optimization of the future remnant liver with either portal or double vein embolization are essential to maximize the future liver remnant and decrease the risk of primary postoperative liver failure (3,5,12). Despite these preoperative steps to minimize the risks of surgery, intra-operative decision making and events can also contribute to the risk of postoperative liver failure and mortality.

In particular, intraoperative blood loss and blood transfusions have been correlated with postoperative liver failure and mortality (13). In a recent article, Kawakatsu *et al.* aimed to identify a "goal value" of intraoperative blood loss. Their team at Nagoya University in Japan has a long history of excellence in surgery for pCCA. In recent years, they have campaigned on minimizing blood loss as a safety improvement. They found that intraoperative blood loss corrected for body weight was associated with the comprehensive complications index (CCI) (14). The authors recommend limiting blood loss to less than 10 mL/kg, because the median CCI was 38 (interquartile range, 31–46) with blood loss below 10 mL/kg as opposed to 42 (interquartile range, 35–51) in those with more

blood loss. The cut-off of 10 mL/kg was based on a restricted cubic spline model that they presented in *Fig. 3*. At visual inspection of the data, the resulting model appeared rather similar to a linear model. The authors did not test the fit and performance of their model compared to a linear model. Moreover, the intercept of a linear model would be rather small, as is also reflected by the small difference in CCI when applying the 10 mL/kg cutoff. We conclude that the authors have been very successful in both limiting blood loss and mitigating the adverse effect of blood loss on the CCI. In their practice, the increase of CCI is small with increasing blood loss.

The main discussion point is to what extent intraoperative blood loss is a modifiable risk factor. Blood loss can be reduced by several strategies that are widely used in liver surgery. These include low central venous pressure, the anterior approach, vascular inflow occlusion, and pharmacological interventions (e.g., sublingual nitroglycerine) (15). In addition, the technique of parenchymal transection is related to blood loss (15). Aside from these strategies, proper surgical skills, awareness, and attitude towards bleeding may further limit blood loss.

However, blood loss is in part a non-modifiable factor depending on the extent of disease and, therefore, the complexity of the resection and (vascular) reconstruction. The authors used corrected analyses that included parameters such as the type of hepatectomy and vascular resection to correct for these factors. Additional unmeasured confounding factors may influence the results. For instance, data on previous surgery, medical history, medication use, and coagulation parameters were not reported.

The below 10 mL/kg setpoint was achieved in only 63 out of the 425 patients (15%), even in the experienced hands of the surgeons at Nagoya University. The extent of surgery and disease stage were higher in the group with more blood loss, despite the corrected analysis. The median difference in CCI between the groups was only 4.5 points, which comes down to about one grade II complication in addition to two IIIa complications. The clinical relevance of this difference is almost negligible.

Nevertheless, it is reasonable to assume that limiting blood loss as much as possible makes liver surgery safer, especially for pCCA. Blood loss is a risk factor for postoperative liver failure, for which patients with pCCA are already predisposed due to the small future liver remnants and considerable risk of preoperative cholangitis. However, blood loss is, to some extent, a reflection of the surgical complexity of the resection. Although the limit of 10 mL/kg blood loss is an interesting concept, it might be more relevant to simply minimize blood loss as much as possible. Future studies should investigate the relation of blood loss and postoperative complications in other multicenter cohorts.

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Footnote

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