French Editorial Commentary from the ACHBPT

Can we talk about "futile surgery" for the upfront treatment of the perihilar cholangiocarcinoma?

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In this work (1), Ratti *et al.* tries to identify a subgroup of patients with perihilar cholangiocarcinoma (PHC) for whom the benefit of surgery could be compromised by morbidity, mortality and the risk of early tumor recurrence. Data for this study come from a multi-institutional database that includes consecutive patients undergoing elective surgery for PHC in 27 Western centers (with experience of more than 15 major liver resections per year) starting in January 2000. Data from 2,271 patients were analyzed retrospectively. As there is neither international consensus on preoperative management nor standardization of surgical technique, the indications for resection were validated at a local multidisciplinary consultation meeting. Preoperative optimization was standardized with endoscopic or percutaneous biliary drainage to treat jaundice and the performance of portal embolization was proposed in the event of insufficient volume of the future remaining liver. The resection consisted of a standard or extended major hepatectomy combined with a resection of segment 1, associated with a resection of the biliary confluence and lymph node dissection of the hepatic pedicle and the proper hepatic artery (stations 8 and 12). The group considered "futile surgery" was defined based on a composite criterion combining the rate of serious postoperative complications [defined as grade 3 or more according to the Clavien-Dindo classification system (2,3)], and tumor recurrence early onset (defined as relapse on imaging within 12 months of surgery). Among the 2,271 patients selected, 309 (13.6%) constituted the "futile surgery" group. The overall 90-day mortality rate was 12.5%, while the overall serious morbidity rate and early recurrence rate were 30.3% and 22.7%, respectively. In multivariate analysis, American Society of Anesthesiologists (ASA) score ≥3 (P=0.005), carbohydrate antigen 19-9 (CA19-9) ≥100 U/mL (P=0.013), bilirubin at diagnosis ≥50 mmol/L (P=0.025), preoperative cholangitis (P=0.002), portal vein involvement (P=0.02), tumor diameter ≥3 cm (P=0.001), and left-sided resection, i.e., standard or extended left hepatectomy (P<0.001) were all independent risk factors for futility. The authors developed a nomogram to predict the risk of "futile" surgery with an analytical machine learning model, including all independent risk factors. The total points obtained, ranging from 0 to 8, stratified the risk into three categories: low risk (less than 30%; score range, 0–2), intermediate risk (30% to 60%; score range, 3–5), and high risk (greater than 60%; score range, 6–8). The "futile surgery" group had a higher rate of R1 resection margin (57.3% *vs.* 25.7%, P<0.001), a higher T stage (P<0.001), a higher "N+" lymph node status.

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high (63.4% *vs.* 36.5%, P<0.001), and a higher rate of perineural invasion (77.0% *vs.* 62.7%, P<0.001) compared to their counterparts considered "non-futile surgeries". Furthermore, the authors showed that the median overall survival for patients in the "futile group" was statistically lower than that of the "non-futile group" {10 [interquartile range (IQR), 6–14] *vs.* 26 (IQR, 22–31) months, P<0.001}. Similarly, median disease-free survival was also statistically lower [6 (IQR, 3–10) *vs.* 18 (IQR, 15–28) months, P<0.001].

Comments on the article

This is the first score that simultaneously takes into consideration the oncological risk and the risk of post-operative morbidity in the analysis of patients operated on for a PHC. Indeed, liver resection with R0 resection margins remains the only curative option for PHC (4), even if it is accepted that surgery is associated with a high risk of morbidity and mortality, varying from 26% to 68% and 1.4% to 18% (5,6), respectively. The evaluation of this preoperative score represents an important tool in identifying the group of patients for whom serious postoperative complications associated with early recurrence could worsen the expected benefits of surgical resection. The goal of a predictive risk score is to be able to influence modifiable variables/characteristics to optimize surgical outcomes or, when this is not possible, to consider alternative therapeutic strategies. The key question for the analysis of this work concerned the concept of "futile surgery". Ratti *et al.* defined the association of major complications and early recurrence as a "futile group", while several other previous studies only considered early recurrence as an indicator to improve patient selection and avoid hepatectomy considered futile (7-9). Given the high incidence of major complications (10), it seems questionable not to offer surgery with curative intent on the basis of the risk of presenting this type of complication (such as for example radiological drainage which represents a major complication of grade 3 according to the Clavien-Dindo classification system) from an ethical point of view. Indeed, post-operative death alone would have been a more relevant criterion than all major complications. Given that the composite endpoint was not met for patients who died prematurely (and by definition without early recurrence), it is impossible to know in this study whether the authors considered these patients to be part of the "futile" group or not. The authors also hypothesized that post-operative complications (biliary fistula, hemorrhage, septic complications, post-hepatectomy liver failure) would naturally delay access to adjuvant chemotherapy, which would theoretically have an impact on the control of the disease. However, there was no difference in the time to administration of adjuvant chemotherapy between the "futile surgery" and "non-futile surgery" patient groups. The discussion regarding delayed access to adjuvant chemotherapy is more relevant for patients with liver metastases than for those with PHC. Indeed, the real benefit of adjuvant chemotherapy in biliary cancers is not obvious in terms of long-term survival (11). However, it should be noted that targeted therapies based on specific molecular subtyping will soon be a game changer in disease control (12). The strength of the risk score proposed by Ratti *et al.* lies in the detection of preoperative risk factors predictive of strategy failure which intrinsically represent the main challenges in the treatment of this pathology. As is often the case, certain preoperative variables such as the ASA score cannot be optimized before surgery. Furthermore, it is very likely that the emergence of new targeted therapies for the treatment of PHC will allow better selection of patients for surgery. In other words, it is possible in the future that the evolution of CA19-9 after neoadjuvant treatment rather than CA19-9 at the time of diagnosis will determine tumor aggressiveness. The presence of a biliary infection at the time of surgery is known to promote postoperative infectious complications that can lead to the death of the patient. Biliary infections are mainly related to suboptimal endoscopic or percutaneous biliary drainage. In all cases, the preoperative biliary drainage strategy must be discussed between the surgical, radiological and endoscopic teams, given the morbidity and mortality linked to preoperative drainage, especially for left hepatectomies (13,14). From a methodological point of view, the authors used a validated method [Framingham Heart Study methodology (15)] to assess the risk of futility. They used a machine learning model to create an 8-point risk score, but unfortunately, although a significant number of centers participated [27 Western tertiary hepato-pancreato-biliary (HPB) centers], internal-external cross-validation would have been desirable to test the robustness of their results. A final weak point is represented by the study period dating back to the early 2000s. Advances in diagnosis and preoperative optimization have made it possible to evolve the concept of curative surgical resection of the PHC over the last 20 years. In conclusion, the study by Ratti *et al.* highlights the complexity of the management of patients with PHC. The intention to develop this predictive score allowed them to perform precise analysis of multi-institutional data, enabling optimal preoperative selection of candidates with PHC who would benefit most from curative surgery. However, speaking of "futile surgery", as defined by the authors, for a complex pathology in the absence of real therapeutic alternatives to surgical resection to date raises ethical questions.

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Footnote

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