



Liver transplantation for perihilar cholangiocarcinoma is not a provocative idea

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This is a multicenter benchmarking study on liver transplantation (LT) for perihilar cholangiocarcinoma (PHC) after neoadjuvant chemoradiotherapy (1). The study comprises of 134 patients from 2014 to 2018 among whom the majority had underlying primary sclerosing cholangitis (PSC). Dropout rate was available from 4 out of 17 centers and was 28%, primarily for oncological reasons (tumor progression and lymph node invasion). All patients followed neo-adjuvant chemoradiotherapy according to the Mayo (88%) or Mayo-like protocol. Liver grafts originated from brain-dead donors in 61.3% of cases and from living donors in 29.7% of cases.

Length of stay was 1.4 [1–4] days {median [interquartile range (IQR)]} in intensive care unit (ICU) and overall stay was 7 [6–13] days. Re-intervention rate was 63% and R0-resection was achieved in 94% of cases. One-year overall survival (OS) was 92% and 5-year OS was 55%. Benchmark cut-offs from this study were comparable to cut-offs from another benchmarking study on LT for other indications (2). When comparing with known results of resected PHCs, disease-free survival (DFS) was greater after LT. There was no significant difference in OS. Benefits of LT seemed to lessen after exclusion of PSC cases for whom LT is preferable. There was no significant difference in 90-day mortality. Results of two cohorts were compared to the

“benchmark cohort”: transplanted patients not fulfilling the benchmark criteria (most outcome parameters remained within benchmark values except a higher relaparotomy rate); transplanted patients with no prior neoadjuvant treatment (27 patients presented inferior outcomes, nevertheless staying within benchmark values). Authors concluded that LT is superior to resection for resectable PHC in terms of oncological results.

The Zurich team is well known for its works on surgical morbidity and mortality and, recently, for its benchmarking studies. The present article has been presented and discussed at the European Surgical Association annual meeting in 2022. A smaller sample size than typically found in benchmarking studies has to be noted, although this is likely to be related with the rarity of the disease. Consistent use of a neo-adjuvant protocol in 88% of cases contributes to the robustness of the results.

Outcomes of this retrospective study are equivalent to results of LT in other indications. PHC treated with neo-adjuvant therapy do not seem to lessen the short-term benefits of LT. This benchmarking study provides a baseline against which transplant centers can gauge their performance. Nevertheless, the lack of comparison of survival data beyond one-year post-transplant is regretful.

The authors report having observed a better DFS when

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compared with a cohort of resected Bismuth-Corlette (BC) type IV PHC. There was no information as to the comparability of the groups other than lymph node invasion. This comparison seems hazardous by the arbitrary choice of a subcategory of resected PHCs (BC type IV), by the absence of neo-adjuvant treatment in the latter, and by the inclusion of transplanted patients with underlying PSC. Moreover, the use of the BC classification is questionable as a resectability indicator (3). Comparing resection and transplantation of PHC is notoriously difficult because the treatment and clinical course are rather different: upfront resection or neo-adjuvant treatment with a risk of drop-out that is difficult to identify in an exhaustive manner in a retrospective study. In this article, the dropout rate is estimated at 28% based on data that are reported by only four out of seventeen centers, however, the only related prospective randomized trial (TRANSPHIL, NCT02232932) reported a drop-out rate of 55% in the transplantation arm. In addition, the rarity of PHC slowed the rate of enrollment and led to a premature termination of the trial.

PHC resectability is complex and the various available classifications all have shortcomings. Moreover, heterogeneity in the resection techniques and the lack of a universally accepted standard-of-care make it difficult to assess resection outcomes. To date, in a benchmarking study of resected PHCs, there was only 76% of dorsal sector resection and only 33.4% of extended hepatectomies (H23458 and H45678) (4). Both of the techniques mentioned have been well described by the Nagoya center and have showed a better R0 resection rate but also better long-term oncological outcomes (5-7). The results of the Nagoya center seem to stand out, not only in terms of oncological survival, but also in terms of postoperative morbidity and mortality (1,4,7). Contrary to what has been proposed in the debate following the present article [see response of Pierre-Alain Clavien to Antonio Pinna, p. 853 (1)], rather than trending towards resection in some centers and towards transplantation in others, it is likely that a standardized resection technique should be followed.

In summary, the author's conclusions go far beyond the scope of a benchmarking study. If there are indeed some provocative elements in favor of LT, these are not the first (8). As Pr. Nagino aptly said, "*hepatobiliary surgeons must make an effort to refine their surgical skill to perform difficult hepatobiliary resections, which will lead to an expanded surgical indication and improved survival for patients with this intractable disease. We must take a step forward 'without haste,*

but without rest'." (9).

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References

1. Breuer E, Mueller M, Doyle MB, et al. Liver Transplantation as a New Standard of Care in Patients With Perihilar Cholangiocarcinoma? Results From an International Benchmark Study. *Ann Surg* 2022;276:846-53.
2. Muller X, Marcon F, Sapisochin G, et al. Defining Benchmarks in Liver Transplantation: A Multicenter Outcome Analysis Determining Best Achievable Results. *Ann Surg* 2018;267:419-25.
3. Paul A, Kaiser GM, Molmenti EP, et al. Klatskin tumors and the accuracy of the Bismuth-Corlette classification. *Am Surg* 2011;77:1695-9.
4. 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.
5. Nimura Y, Hayakawa N, Kamiya J, et al. Hepatic segmentectomy with caudate lobe resection for bile duct carcinoma of the hepatic hilus. *World J Surg* 1990;14:535-43; discussion 544.
 6. Nagino M, Kamiya J, Arai T, et al. "Anatomic" right hepatic trisectionectomy (extended right hepatectomy) with caudate lobectomy for hilar cholangiocarcinoma. *Ann Surg* 2006;243:28-32.
 7. Nagino M. Left Hepatic Trisectionectomy With Caudate Lobectomy: Demanding But Essential Routine Surgical Procedure for Perihilar Cholangiocarcinoma. *Ann Surg* 2021;274:e638-40.
 8. Ethun CG, Lopez-Aguilar AG, Anderson DJ, et al. Transplantation Versus Resection for Hilar Cholangiocarcinoma: An Argument for Shifting Treatment Paradigms for Resectable Disease. *Ann Surg* 2018;267:797-805.
 9. Nagino M. Surgical Treatment of Perihilar Cholangiocarcinoma: Resection or Transplant? *Ann Surg*. 2018;267:806-7.

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