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EDITORIAL – PANCREATIC TUMORS

Survival Benefit of Neoadjuvant Therapy for Extrahepatic Cholangiocarcinoma: Real or Artifact?

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In the absence of prospective clinical trials, the role of neoadjuvant therapy for non-pancreatic periampullary cancers remains poorly defined. Just this past year, the first clinical trial to compare perioperative chemotherapy versus upfront surgery followed by adjuvant chemotherapy in patients with pancreatic adenocarcinoma was activated (Alliance A021806; NCT04340141). However, designing a similar trial for periampullary malignancies has been fraught with challenges, including a relatively low incidence of these malignancies, preoperative diagnostic uncertainty, heterogeneity across tumor types, and limited data supporting the role of adjuvant therapy in this patient population.

In the accompanying article by Adam et al., the authors report a retrospective, propensity-matched analysis designed to compare survival among patients with non-pancreatic periampullary cancers treated with preoperative chemotherapy and surgery versus upfront resection (UR) using a decade of data from the National Cancer Database (NCDB).[1] When stratified by disease type, receipt of neoadjuvant therapy was associated with improved median overall survival (OS) of 38 versus 26 months in the subgroup of patients with extrahepatic cholangiocarcinoma, a finding that persisted on adjusted analysis (hazard ratio 0.69, 95% confidence interval 0.54–0.89). The reported survival benefit in this patient population is intriguing, particularly given the poor 5-year survival rate of 15–25% in patients with locoregional disease.[2] The biologic rationale for preoperative therapy in this setting is compelling, specifically the potential to provide early treatment of occult micrometastatic disease, enhance patient selection, and improve margin-negative resection rates.

In examining 10 years of hospital-based data, the study by Adam et al. identified approximately 2500 patients with extrahepatic cholangiocarcinoma; however, only 157 of these patients received neoadjuvant therapy. Although 3:1 propensity matching was performed, the small cohort limits analytic power and should also raise concerns that this represents a highly select group of patients. The authors acknowledge the limitation that many patients with distal cholangiocarcinoma treated with neoadjuvant therapy were likely presumed to have pancreatic adenocarcinoma at diagnosis and treated with pancreatic cancer chemotherapeutic regimens. The very real challenge of making this diagnostic distinction in the preoperative setting is relevant, both to the interpretation of findings from this retrospective study, as well as to their clinical application. If a definitive diagnosis of extrahepatic cholangiocarcinoma can be made preoperatively, which neoadjuvant regimen would be most appropriate?

Due to the inability to distinguish chemotherapy from radiation-sensitizing chemotherapy within the NCDB, neoadjuvant therapy was defined as receipt of preoperative chemotherapy, regardless of the use of radiation. Therefore, this group of 157 may have been treated with chemotherapy, chemoradiation, or both, and details regarding the specific chemotherapeutic regimen, number of cycles, and radiotherapy type and dosage are lacking. These common limitations of the NCDB must be considered when interpreting the results of a retrospective comparative effectiveness analysis based on these data.

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Perhaps the most important limitation relevant to this study however is the influence of immortal time bias. Immortal time bias is the error resulting from assigning patients to an intervention during which the outcome event cannot occur.[3,4] In the accompanying article, patients assigned to the neoadjuvant therapy cohort by definition could not have died during the intervention period (receipt of preoperative chemotherapy and surgery); thus, they must have lived long enough to complete preoperative chemotherapy and surgery in order to be included. In this study, OS was defined as time from diagnosis to death, rather than time from surgery to death. For the neoadjuvant therapy group, time spent on preoperative therapy is counted towards their survival, leading to immortal time bias.

An alternative approach to mitigate the effect of immortal time bias would be to perform a conditional landmark analysis, in which a fixed, arbitrary time point during follow-up is selected, and only patients alive at the designated time point are included.[3] If a 9-month time point was applied to this study, for example, only patients surviving at least 9 months from the time of diagnosis, in the neoadjuvant or UR group, would be included in the study.

Additionally, patients who received neoadjuvant therapy but did not undergo resection due to disease progression, decline in performance status, or any other reason were excluded from the denominator. Limiting the neoadjuvant therapy cohort to only those patients able to complete therapy without progression results in significant selection bias towards improved survival. Ideally, the neoadjuvant cohort would include all patients deemed resectable at diagnosis and treated with preoperative therapy and intent for surgery, regardless of whether definitive resection occurred. However, resectability status and intended treatment are not captured within the NCDB and can therefore not be assessed.

Not surprisingly, rates of receipt of adjuvant therapy in both the neoadjuvant and UR cohorts were low, likely a result of conflicting evidence to support its use as well as substantial postoperative morbidity following resection for extrahepatic cholangiocarcinoma. However, it is worth pointing out that more than 50% of the UR cohort received *no adjuvant therapy*; in other words, more than half of this comparison cohort represents a cohort of patients treated with surgery alone. In this case, the findings do not represent the specific benefit of preoperative chemotherapy versus adjuvant chemotherapy, but rather the benefit of preoperative chemotherapy versus surgery alone.

Finally, how should we interpret the association of chemotherapy with improved survival in this study when multiple prior phase III randomized trials have failed to demonstrate a benefit of adjuvant chemotherapy in patients with cholangiocarcinoma? By intention-to-treat analysis, the phase III randomized BILCAP trial found no improvement in OS between patients treated with surgery followed by adjuvant capecitabine versus surgery alone.[5] ESPAC-3 also found no OS benefit of adjuvant 5-fluorouracil or gemcitabine chemotherapy on intention-to-treat analysis in patients with resected periampullary cancers, including 96 patients with intrapancreatic cholangiocarcinoma.[6] Similarly, no disease-free survival benefit was observed in a phase III trial of patients randomized to adjuvant chemotherapy with fluorouracil and mitomycin C versus observation.[7] Finally, two phase III trials failed to demonstrate a survival advantage of adjuvant gemcitabine-based chemotherapy compared with surveillance.[8,9] Given the lack of prospective data to support a survival benefit of chemotherapy, retrospective, comparative effectiveness studies should be interpreted with caution as the risk of a spurious result is high.[10]

Acknowledging the limitations of this study, based on the evidence presented and a strong biologic rationale, consideration for neoadjuvant therapy in patients with extrahepatic cholangiocarcinoma is compelling. Ideally, a randomized clinical trial could be designed to answer this question, although it would require overcoming the multitude of challenges preventing completion of multimodality trials in this patient population to date. Until then, we must interpret the findings of this type of real-world study with caution, careful to avoid attributing causality to an intervention previously unsupported by clinical trial data and highly subject to immortal time bias.

DISCLOSURE Rebecca A. Snyder declares no conflicts of interest.

REFERENCES

1. Adam M. Glencer A. AlMasri S. Winters S. Bahary N. Singhi A. et al. Neoadjuvant Therapy Versus Upfront Resection for Non-Pancreatic Periampullary Adenocarcinoma. *Ann Surg Oncol*. 2022. https://doi.org/10.1245/s10434-022-12257-x.
2. SEER*Explorer: An interactive website for SEER cancer statistics. Available at: https://seer.cancer.gov/explorer/. Published 2020. Accessed 28 Feb 2022.
3. Lai T-Y, Hu Y-W. Neoadjuvant therapy in resectable pancreatic cancer: immortal time bias and its correction. *J Clin Oncol*. 2017;35(14):1623.
4. Yadav K, Lewis RJ. Immortal time bias in observational studies. *JAMA*. 2021;325(7):686–7.
5. Bridgewater J, Fletcher P, Palmer DH, et al. Long-term outcomes and exploratory analyses of the randomized phase III BILCAP study. *J Clin Oncol*. 2022;40(18):2048–57.
6. Neoptolemos JP, Moore MJ, Cox TF, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs Observation on Survival in Patients With Resected Periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA*. 2012;308(2):147–56.
7. Takada T, Amano H, Yasuda H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III

multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. *Cancer*. 2002;95(8):1685–95.
8. Edeline J, Benabdelghani M, Bertaut A, et al. Gemcitabine and oxaliplatin chemotherapy or surveillance in resected biliary tract cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): a randomized phase III study. *J Clin Oncol*. 2019;37(8):658–67.
9. Ebata T, Hirano S, Konishi M, et al. Randomized clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer. *Br J Surg*. 2018;105(3):192–202.
10. Karim S, Booth CM. Effectiveness in the absence of efficacy: cautionary tales from real-world evidence. *J Clin Oncol*. 2019;37(13):1047–50.