Editorial Commentary

The value of CA19-9 dynamics in decision making for treatment of locally advanced pancreatic cancer

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies with a dismal 5-year overall survival of only 12% across all stages of disease (1). Poor survival is primarily driven by its asymptomatic nature and early propensity of systemic spread of disease (1,2). Even in patients with localized disease who undergo resection, treatment failure occurs in approximately two out of three patients in the form of local or systemic progression of disease (3,4). In combination with improved local and systemic control via multiagent chemotherapy regimens, recent advances in surgical techniques such as improvements in vascular reconstructions and arterial divestment have increased surgical candidacy in patients with locally advanced pancreatic cancer (LAPC) (5-9). The current treatment approach for patients with LAPC now entails induction chemotherapy followed by surgical resection if deemed appropriate (10). However, there remains considerable variability in adherence to these guidelines (11-15). Determining surgical candidacy such that a patient derives maximal benefit from resection remains a challenge (16). This is primarily due to lack of reliable biomarkers to assess treatment response early on during induction therapy to guide treatment decision making.

Carbohydrate antigen 19-9 (CA19-9) is the most frequently used prognostic and monitoring biomarker for assessment of disease in pancreatic cancer. Except in CA19-9 non-producers (approximately 15–20% of the patients), CA19-9 levels at diagnosis and their dynamic changes are often used to inform treatment decisions (17). In this noteworthy nationwide effort, Seelen *et al.* define a minimal (≥40%) and optimal (≥60%) percent decrease in CA19-9 survival cut-off after 2 months of induction therapy (13). The authors demonstrate that these cut-offs are robust predictors of patient prognostication. Moreover, CA19-9 response may serve as a surrogate biomarker for favorable tumor biology and treatment response, hence informing optimal candidacy for surgical selection. Indeed, they demonstrate that in CA19-9 producers, this cut-off was associated with survival, in addition to surgical resection, SBRT, and duration of induction therapy. Similarly, in a study on LAPC after induction treatment with FOLFIRINOX, at the Heidelberg University Hospital, a 60% reduction in CA19-9 was identified as the optimal cut-off and yielded a positive predictive value for resectability of 83% (18). Furthermore, a post-treatment level of <91.8 U/mL was predictive of resectability and survival. Interestingly, patients above the cut-off did not benefit from resection compared to exploration only in terms of overall survival (18).

While a sufficient decrease and low post-induction treatment levels seem convincing in informing treatment decisions, the role of pre-treatment CA19-9 remains controversial. While having an important prognostic value, pretreatment CA19-9 levels do not necessarily predict resectability in LAPC (9,18). Seelen *et al.* address this

important clinical question via a sub-analysis of patients with pre-treatment levels of >500 and <500 U/mL with significantly worse outcomes in inadequate responders with high pre-treatment levels. The optimal decrease of CA19-9 was only independently associated with an improved survival in patients with <500 U/mL pre-treatment levels and therefore questions the applicability of this threshold in patients with higher baseline levels. Further research, such as creating a composite score combining these values, may be necessary to increase applicability to patients with high pretreatment levels. Second, further research is necessary to inform treatment decisions in patients that fail to meet these cut-offs for optimal treatment response. Alva-Ruiz *et al.* have shown promising results for change in regimen in patients with unsuccessful induction treatment (19). However, high-level evidence for the decision on prolonging treatment with the same regimen versus switching the regimen versus surgery, to date, is lacking (20,21). Third, it is unlikely that CA19-9 as a sole biomarker can predict surgical candidacy with high accuracy. Currently, large efforts are being undertaken in employing liquid biopsies to harness ctDNA and circulating tumor cells as biomarkers of systemic disease and treatment response (22). Multianalyte tests could help determine the presence and extent of systemic disease and therefore define optimal surgical candidates for surgery as the most effective local treatment.

To date, evidence suggests that using CA19-9 dynamics with a cut-off of ≥60% reduction is the best data we have for treatment decision making after 2 months of induction chemotherapy in clinical practice. We would like to congratulate the authors on conducting a robust nationwide analysis to address this important question in the management of LAPC. This study adds to the growing evidence that CA19-9 dynamics can add value in patient prognostication and determining surgical candidacy in LAPC and hence improve survival.

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References

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17-48.
2. Springfeld C, Ferrone CR, Katz MHG, et al. Neoadjuvant therapy for pancreatic cancer. Nat Rev Clin Oncol 2023;20:318-37.
3. Rompen IF, Levine J, Habib JR, et al. Progression of Site-Specific Recurrence of Pancreatic Cancer and Implications for Treatment. Ann Surg 2023. [Epub ahead of print]. doi: 10.1097/SLA.0000000000006142.
4. Habib JR, Kinny-Köster B, Bou-Samra P, et al. Surgical Decision-Making in Pancreatic Ductal Adenocarcinoma: Modeling Prognosis Following Pancreatectomy in the Era of Induction and Neoadjuvant Chemotherapy. Ann Surg 2023;277:151-8.
5. Kinny-Köster B, Habib JR, van Oosten F, et al. Conduits in Vascular Pancreatic Surgery: Analysis of Clinical Outcomes, Operative Techniques, and Graft Performance. Ann Surg 2023;278:e94-e104.
6. Schneider M, Hackert T, Strobel O, et al. Technical advances in surgery for pancreatic cancer. Br J Surg 2021;108:777-85.
7. Fietkau R, Grützmann R, Wittel UA, et al. R0 resection following chemo (radio)therapy improves survival of primary inoperable pancreatic cancer patients. Interim results of the German randomized CONKO-007± trial. Strahlenther Onkol 2021;197:8-18.

8. Habib JR, Kinny-Köster B, van Oosten F, et al. Periadventitial dissection of the superior mesenteric artery for locally advanced pancreatic cancer: Surgical planning with the "halo sign" and "string sign". Surgery 2021;169:1026-31.
9. Hartlapp I, Valta-Seufzer D, Siveke JT, et al. Prognostic and predictive value of CA 19-9 in locally advanced pancreatic cancer treated with multiagent induction chemotherapy: results from a prospective, multicenter phase II trial (NEOLAP-AIO-PAK-0113). ESMO Open 2022;7:100552.
10. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021;19:439-57.
11. Hackert T, Sachsenmaier M, Hinz U, et al. Locally Advanced Pancreatic Cancer: Neoadjuvant Therapy With Folfirinox Results in Resectability in 60% of the Patients. Ann Surg 2016;264:457-63.
12. Gemenetzis G, Groot VP, Blair AB, et al. Survival in Locally Advanced Pancreatic Cancer After Neoadjuvant Therapy and Surgical Resection. Ann Surg 2019;270:340-7.
13. Seelen LWF, Doppenberg D, Stoop TF, et al. Minimum and Optimal CA19-9 Response After Two Months Induction Chemotherapy in Patients with Locally Advanced Pancreatic Cancer: A Nationwide Multicenter Study. Ann Surg 2023. [Epub ahead of print]. doi: 10.1097/SLA.0000000000006021.
14. Walma MS, Brada LJ, Patuleia SIS, et al. Treatment strategies and clinical outcomes in consecutive patients with locally advanced pancreatic cancer: A multicenter prospective cohort. Eur J Surg Oncol 2021;47:699-707.
15. Brown ZJ, Heh V, Labiner HE, et al. Surgical resection rates after neoadjuvant therapy for localized pancreatic ductal adenocarcinoma: meta-analysis. Br J Surg 2022;110:34-42.
16. Oba A, Del Chiaro M, Fujii T, et al. "Conversion surgery" for locally advanced pancreatic cancer: A position paper by the study group at the joint meeting of the International Association of Pancreatology (IAP) & Japan Pancreas Society (JPS) 2022. Pancreatology 2023;23:712-20.
17. Kinny-Köster B, Habib JR, Wolfgang CL, et al. Favorable tumor biology in locally advanced pancreatic cancer-beyond CA19-9. J Gastrointest Oncol 2021;12:2484-94.
18. Heger U, Sun H, Hinz U, et al. Induction chemotherapy in pancreatic cancer: CA 19-9 may predict resectability and survival. HPB (Oxford) 2020;22:224-32.
19. Alva-Ruiz R, Yohanathan L, Yonkus JA, et al. Neoadjuvant Chemotherapy Switch in Borderline Resectable/Locally Advanced Pancreatic Cancer. Ann Surg Oncol 2022;29:1579-91.
20. Vreeland TJ, McAllister F, Javadi S, et al. Benefit of Gemcitabine/Nab-Paclitaxel Rescue of Patients With Borderline Resectable or Locally Advanced Pancreatic Adenocarcinoma After Early Failure of FOLFIRINOX. Pancreas 2019;48:837-43.
21. Thalji SZ, Aldakkak M, Christians KK, et al. Neoadjuvant chemotherapy for pancreatic cancer: Quality over quantity. J Surg Oncol 2023;128:41-50.
22. Javed AA, Floortje van Oosten A, Habib JR, et al. A Delay in Adjuvant Therapy Is Associated With Worse Prognosis Only in Patients With Transitional Circulating Tumor Cells After Resection of Pancreatic Ductal Adenocarcinoma. Ann Surg 2023;277:866-72.

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