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Response to: Comment on "Dynamics of Serum CA 19-9 in Patients Undergoing Pancreatic Cancer Resection"

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We thank Gao and colleagues for their interest in our study.[1] The authors propose interesting suggestions for further analysis that can be conducted within our patient cohort. Carbohydrate antigen (CA) 19-9 remains the only biomarker with sufficient accuracy that is currently used in the diagnostic workup and posttreatment monitoring of patients with pancreatic cancer.[2] Our study showed that during follow-up after pancreatic cancer resection, a 2.6-fold increase in CA 19-9 can precede imaging diagnosis of disease recurrence by 7 to 10 months.[1] Early detection of pancreatic cancer recurrence might increase the number of patients eligible for recurrence-focused treatment, which is associated with subsequent survival benefits.[3] We agree with the authors that further exploration of this cohort might provide a deeper understanding about the use of CA 19-9 as a biomarker during follow-up after pancreatic cancer resection.

First, the authors question whether a 2.6× rise in postoperative CA 19-9 levels, while remaining within normal limits (<37 U/mL), could serve as a criterion to exclude disease recurrence. This suggestion was raised because we reported that 2 patients had false-positive results (eg, a >2.6× relative CA 19-9 increase without confirmation of recurrence), with maximum CA 19-9 levels below 37 U/mL.[1] Further investigation of our cohort resulted in 7 other patients with a 2.6-fold CA 19-9 increase and levels within normal limits, in whom disease recurrence was present. Based on these findings, we would not suggest that a 2.6× increase in CA 19-9 that remains within normal limits should serve as an exclusion criterion for recurrence.

In our cohort, 32 patients had preoperative CA 19-9 levels below 37 U/mL. In this small subgroup of patients, the 2.6 threshold for relative change was associated with a sensitivity of 0.45 and a specificity of 1. This means that all patients without disease recurrence were correctly classified as such (no false positives). As emphasized in our article, it is particularly important to correctly classify patients who do not have recurrence, to minimize the chance of being subjected to unnecessary chemotherapy.[1] Therefore, we would recommend to use a 2.6× elevation in all patients, irrespective of the preoperative CA 19-9 values.

Second, the impact of neoadjuvant and adjuvant therapies on CA 19-9 levels and recurrence risk was highlighted by the commenters. In our study, 173 patients (64%) received neoadjuvant therapy, which consisted of fluorouracil, leucovorin, irinotecan, and oxaliplatin chemotherapy in the majority of patients (n = 65; 37%).[1] Adjuvant chemotherapy was administered in 222 patients (83%), of which 121 patients (45%) received fluorouracil, leucovorin, irinotecan, and oxaliplatin and 66 patients (24%) received a gemcitabine-based regimen.[1] In Table 1, we show stratified results with regard to CA 19-9 values, disease recurrence, and survival in patients who received no (neo)adjuvant treatment (n = 9), neoadjuvant therapy only (n = 38), neoadjuvant and adjuvant treatments (n = 135), and adjuvant therapy only (n = 87). Despite apparently higher baseline CA 19-9 levels in patients who received neoadjuvant treatment (either with or without adjuvant therapy), the difference was not statistically significant between the 4 groups. This reflects current clinical care, in which baseline CA 19-9 values are increasingly incorporated in the decision-making process regarding upfront surgery or (neo)adjuvant treatment strategies.[4–6] In patients with neoadjuvant treatment, CA 19-9 levels dropped substantially after treatment. Postsurgery, CA 19-9 levels did not show clear differences between the 4 groups. At time of recurrence diagnosis, the levels in the neoadjuvant-only or adjuvant-only groups were somewhat higher. Higher CA 19-9 levels at baseline and at recurrence diagnosis might reflect a more aggressive tumor biology.[7] Nevertheless, the proportion of patients that developed recurrence during follow-up and the disease-free interval after resection did not differ between the patient groups. Consequently, despite the clear impact of neoadjuvant therapy and tumor resection on CA 19-9 levels, the applied treatment strategy does not seem to affect CA 19-9 levels at recurrence and recurrence risk. This implies again that the 2.6× elevation in CA 19-9 values is applicable to all patients, irrespective of the treatment strategy they receive. Patients in our study did not receive recurrence-focused treatment before imaging confirmation. Hence, the impact of initiation of treatment based on CA 19-9 elevation as proposed by Li et al[8] could not be assessed in our cohort and requires further investigation.

Third, the authors mentioned the importance of investigating the optimal timing of postoperative CA 19-9 follow-up. To be able to detect a relative increase in CA 19-9 during follow-up, it is essential to measure CA 19-9 in the first few weeks after resection. This is often refrained from in current clinical practice. In our cohort, the median time until a 2.6× CA 19-9 increase in patients with disease recurrence was 6.8 months (range: 0.9–37.2 months). Receiver operating characteristic curve analysis showed that the optimal timing to detect a 2.6-fold elevation of CA 19-9 is at 11.7 months, with a sensitivity of 72% and a specificity of 63%. The average concordance indices for a

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TABLE 1.

Outcomes Regarding CA 19-9 Values, Disease Recurrence, and Survival After Stratification for Treatment Regimen

Total Cohort (n = 271)	No (N)AT (n = 9; 3%)	NAT Only (n = 38; 14%)	NAT + AT (n = 135; 50%)	AT Only (n = 87; 32%)	*P*
Baseline CA 19-9 levels, median (IQR)	32.1 (19.3–80.2)	263.4 (103.2–918.0)	288.6 (93.5–724.7)	118.8 (57.0–242.4)	0.52
Post-NAT CA 19-9 levels, median (IQR)	NA	82.6 (33.0–220.2)		NA	
Postoperative CA 19-9 levels, median (IQR)	19.5 (17.5–51.8)	32.8 (17.1–52.8)	28.7 (15.7–53.2)	26.0 (15.1–51.7)	0.74
Recurrence, n (%)	7 (78%)	29 (76%)	108 (80%)	63 (72%)	0.55
CA 19-9 levels at recurrence diagnosis, median (IQR)	30.6 (19.7–123.5)	162.7 (52.1–322.2)	88.1 (27.6–305.0)	136.7 (39.4–269.5)	0.48
Time from surgery until 2.6× CA 19-9 elevation, median (IQR)	5.15 (3.5–11.6)	5.3 (2.5–11.4)	7.8 (4.8–12.3)	8.6 (5.1–13.7)	0.68
Time from surgery until imaging recurrence diagnosis, median (IQR)	9.5 (8.4–16.8)	9.5 (3.6–18.4)	11.6 (8.2–15.4)	15.3 (11.6–19.6)	0.45
Disease-free interval, median (95% CI)	15.4 (9.0–NR)	16.1 (7.6–28.4)	13.1 (12.2–15.2)	18.7 (15.6–27.3)	0.11
Recurrence treatment, n (%)	4 (57%)	12 (41%)	70 (65%)	39 (62%)	0.04
Overall survival, median (95% CI)	20.7 (15.8–NR)	42.3 (26.5–NR)	27.5 (26.0–32.8)	36.5 (28.1–NR)	0.10

Univariate analysis was performed to compare the 4 groups. A χ^2 or Fisher exact test was used to compare categorical outcomes; Kruskal-Wallis tests was performed to compare nonnormally distributed continuous outcomes; time-to-event outcomes were compared using Kaplan-Meier curve analysis. Disease-free interval was calculated from the date of surgery until the date of recurrence or last follow-up; overall survival was calculated from the date of surgery until the date of death or last follow-up.

AT indicates adjuvant therapy; CA 19-9, carbohydrate antigen 19-9; CI, confidence interval; IQR, interquartile range; NA, not applicable; NAT, neoadjuvant therapy; NR, not reached.

3-monthly, 4-monthly, or 6-monthly follow-up strategy during the first 2 years after surgery were found to be 0.62, 0.61, and 0.57, respectively. Consequently, a 3-monthly strategy appears to have the highest predictive accuracy to detect disease recurrence after pancreatic resection. However, considering that a follow-up strategy with a 3-monthly interval was most frequently applied in this retrospective observational cohort study, these results may be subjected to bias.

Finally, the authors raise a valid point concerning Lewis antigen-negative patients within the pancreatic cancer patient population. As mentioned by the authors, several smaller studies show associations between carcinoembryonic antigen (CEA) and CA 125 and risk of (early) recurrence.[9,10] When reviewing the role of serum tumor markers specifically for the detection of pancreatic cancer recurrence during follow-up, only one article reported on CEA, showing a sensitivity of only 50% and specificity of 65%.[2] As such, unlike CA 19-9, CEA and CA 125 are not routinely assessed. Nevertheless, we do agree with the authors that Lewis antigen-negative patients constitute an appropriate subgroup in whom the use of CEA and CA 125 for recurrence detection during follow-up could be studied further. In the future, we believe routine assessment of liquid biopsies could provide better sensitivity and specificity for both Lewis antigen-negative and antigen-positive pancreatic cancer patients compared to currently known serum markers. In a study testing a clinical circulating tumor DNA assay with *KRAS*, we showed that circulating tumor detected during follow-up predicted clinical recurrence (sensitivity: 90%, specificity: 88) with a median lead time of 3 months.[11] Although enthusiasm is high and the field is evolving rapidly, liquid biopsy testing is still mainly performed in study settings or in commercial institutions.[12] Further prospective studies will need to firmly establish clinical and cost benefit before liquid biopsies are routinely used in the standard care of pancreatic cancer patients.

As rightfully commented by Gao and colleagues, discovery of interesting findings in this field can be expected in ongoing and future studies. To establish the true value of recurrence-focused follow-up with routine serum CA 19-9 testing and follow-up imaging, and determine optimal follow-up intervals, prospective randomized studies are needed. The Recurrence Disease Detection after Resection of Pancreatic Adenocarcinoma using a Standardized Surveillance Strategy (RADAR-PANC) trial (NCT04875325) is anticipated to provide the first prospective evidence regarding the impact of a 3-monthly recurrence-focused CA 19-9 and imaging follow-up after pancreatic cancer resection on survival and patient quality of life, and results are eagerly awaited.

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