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Comment on "Dynamics of Serum CA19-9 in Patients Undergoing Pancreatic Cancer Resection"

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The recurrence rate of pancreatic ductal adenocarcinoma (PDAC) in the first 2 years after radical resection is about 80%; novel and sensitive biomarkers to detect recurrence are urgently needed in clinical practice.[1] The use of routine post-pancreatectomy tumor biomarker assays may be better suited for early recurrence detection than imaging techniques. We read with interest the recently published article by van Oosten et al.[2] This study supported using CA19-9 as a biomarker to predict PDAC recurrence during follow-up after pancreatectomy. We congratulate this excellent study on its possible potential for clinical application. However, we would like to raise some detailed issues about this study and share our opinions.

First, we were intrigued by parts of the data published in the research. In this study, we noticed that in 2 patients with false-positive results, they had a relative CA19-9 increase of more than 2.6×, but these values remained within normal limits (<37 U/L). Were there additional instances of recurrence in patients exhibiting a 2.6× rise in postoperative CA19-9 levels, yet still below 37 U/L? If not, this could potentially serve as a criterion to exclude recurrence. Based on previous studies,[3] around 13% of PDAC patients lack elevated CA19-9 level, and excluding the Lewis antigen effect, we sought insight into the proportion of patients with preoperative CA19-9 <37 U/L but showing elevated postoperative levels. However, the research lacks information on the number of patients with normal baseline levels; is there a difference in the predictive value of a 2.6× elevation of CA19-9 in patients with different baseline levels of CA19-9? In essence, are other elevated criteria needed for PDAC patients with normal CA19-9 values? In this study, serum CA19-9 levels at diagnosis, postoperative, and postoperative follow-up were analyzed in patients who underwent PDAC resection. However, dynamic changes in CA19-9 were computed solely by dividing the maximum postoperative value by the first postoperative value, potentially overlooking the significance of baseline CA19-9 at diagnosis.

Second, this study omitted the analysis of neoadjuvant and adjuvant therapies' (AT) impact on CA19-9 levels and recurrence risk. In this study, we noticed that a 2.6× elevation of CA19-9 precedes imaging recurrence by an average of 7 to 10 months; the authors did not provide information about whether those patients received AT and their AT options. The exact courses of AT, its starting point, and last day of chemotherapy remain partially unclear. Currently, scarce studies on neoadjuvant therapy for PDAC patients have concentrated on recurrence or CA19-9 dynamics. Postupfront resection, AT has become imperative to forestall early tumor recurrence. AT with gemcitabine and capecitabine in unselected patients doubles the 5-year overall survival rate to about 30% compared with monotherapy with 5-fluorouracil plus folinic acid or gemcitabine. In selected patients, modified AT which included leucovorin, 5-FU, irinotecan and Oxaliplatinresulted in a 5-year survival rate of about 50%.[4] In a study of 80 patients with PDAC by Li et al,[5] 32.5% received chemotherapy before tumor recurrence. By categorizing patients based on imaging results, they found that patients who started treatment before imaging had improved disease-free survival and overall survival Consequently, the study by van Oosten et al holds significance for offering more precise guidance on the early initiation of AT in this patient subgroup.

Third, preoperative CA19-9 levels >100 U/L, elevated postoperative CA19-9 levels, and CA19-9 velocity, defined as >95 U/L changing over 4 weeks, have been associated with recurrence.[6] It prompts an inquiry into whether the timing of postoperative CA19-9 follow-up affects results, potentially offering insights for determining the optimal timing in PDAC patients. Nodal selection of the time of follow-up in postoperative patients with PDAC needs to be further evaluated scientifically. In this study, the authors emphasized the significance of dynamic changes in CA19-9 in guiding recurrence. Therefore, this research bears the potential to contribute as supporting evidence for establishing the ideal timing of follow-up in postoperative PDAC patients.

Finally, it is worth noting that due to Lewis's enzyme defects, CA19-9 levels need to be properly defined in Lewis antigen-negative patients in the PDAC patient population.[6] Approximately 5% to 10% of the PDAC patient population comprises Lewis-negative individuals, known for having minimal or absent CA19-9 secretion.[7] Carcinoembryonic antigen (CEA) and cancer antigen 125 (CA125) are widely used as biomarkers for various types of cancer.[6] And elevated postoperative CA125 is a risk factor for early recurrence for PDAC patients, especially liver recurrence.[8] Moreover, the levels of CEA and CA125 are closely associated with tumor metastasis and response to treatment.[7] And the values of CEA and CA125 were not affected by Lewis enzyme. Luo et al[7] demonstrated that CEA and CA125 exhibit greater sensitivity and high specificity in Lewis-negative PDAC patients, potentially compensating for CA19-9's limited predictive ability in this subset. In this study, the authors did not elaborate on whether patients were tested for serum levels of CEA and CA125. No study has yet discussed whether postoperative CEA and CA125 changes are predictive of recurrence. In addition, van Oosten et al used the value of CA19-9 of ≤5 U/L as a criterion of

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Lewis-negative patients. Only 41.9% of Lewis-negative patients had CA19-9 levels ≤2 U/L, and 52.4% had CA19-9 levels ≤5 U/L.[9] In another cohort study addressing the value of CA19-9 in predicting recurrence,[10] this exclusion criterion was set at 10 U/L. Presently, precise exclusion criteria for CA19-9 serum levels in Lewis-negative PDAC patients are lacking. Sequencing the fucosyltransferase 3 (*FUT3*) gene from genomic DNA to rule out Lewis-negative patients might be a more suitable method. We sincerely expect that this topic will be explored in depth.

We are grateful for the contributions of van Oosten et al and expect the discovery of further interesting findings in this field.

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