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EDITORIAL – PANCREATIC TUMORS

# Dynamic Behavior of Ca 19-9 and Pancreatic Cancer Recurrence: Enough Data to Drive Salvage Therapy?

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Up to 80% of patients undergoing pancreatectomy for pancreatic ductal adenocarcinoma (PDAC) followed by adjuvant therapy will recur within 2 years, with median recurrence-free survival (RFS) of only 1 year.[1] Historically, the attitude towards postresection follow-up has been mixed: while some authors recommended that surveillance should be only focused on symptoms, others advocated active, recurrence-focused follow-up to assess for early, asymptomatic disease. This latter concept has been fostered by the emerging effectiveness of newly introduced chemotherapy regimens and radiation therapy techniques, which are potentially applicable to recurrent PDAC. Active surveillance involves computed tomography (CT) or positron emission tomography (PET/CT), in combination with measurement of serum carbohydrate antigen (Ca) 19-9 every 3–6 months at least for the first 2 years postoperatively. However, the accuracy of cross-sectional imaging to detect recurrence in the earliest stages is poor, especially in the resection bed, where perivascular soft tissue around major arteries creates diagnostic problems in distinguishing postoperative changes from recurrent disease.[2] Conversely, failure of serum Ca 19-9 normalization or sudden elevation postoperatively could hint at occult recurrence in advance of radiologic and clinical changes. Only a few studies have been performed on the diagnostic accuracy of longitudinal serum Ca 19-9 testing during postpancreatectomy follow-up, with a recent systematic review showing pooled sensitivity of 0.73 and pooled specificity of 0.83 for detecting recurrence.[3] Nonetheless, the temporal relationship between biochemical and radiologic changes remains unclear. This issue of *Annals of Surgical Oncology* reports a study by Dr. Rieser and colleagues on 525 patients undergoing pancreatectomy for PDAC, with the aim of defining the dynamic behavior of Ca 19-9 beyond the 6-month postoperative period and the chronological relationship between Ca 19-9 elevation and radiographic recurrence.[4] Although 55% of the study cohort underwent neoadjuvant chemotherapy, the analysis focused on follow-up from first postoperative value, and did not specifically assess Ca 19-9 values pre- and post-neoadjuvant treatment. This might constitute a limitation of the study design, because recent evidence has shown that Ca 19-9 reduction $> 50\%$ following neoadjuvant therapy is significantly associated with oncologic outcomes postpancreatectomy.[5] The authors tried to overcome this aspect by controlling for neoadjuvant treatment in multivariate analysis, and were able to identify different patterns of Ca 19-9 behavior postresection, with distinct implications for RFS and overall survival (OS). Some 18.5% of patients had normal Ca 19-9 from PDAC diagnosis through postoperative surveillance, representing the category of reference for subsequent analyses. Patients with elevated Ca 19-9 levels from diagnosis through follow-up (34.3%) were at the highest risk of disease recurrence and death. In the postresection normalization group, three surveillance patterns were identified: one with persistent normalization (18.7% of patients), which was associated with the lowest risk; one with a period of normalization followed by persistent elevation (4.9% of patients), which was associated with increased risk of recurrence and death; and one with waxing and waning elevation during follow-up (23.6% of patients). This last pattern did not have worse RFS and OS compared with the reference. In the authors' view, the recognition of a specific pattern of Ca 19-9 behavior during surveillance might be of help to consider salvage therapy,



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especially in the absence of radiographic findings suggestive of tumor recurrence. In this respect, Dr. Rieser and colleagues assessed whether an elevation of Ca 19-9 was a predictor of radiographic recurrence throughout follow-up. During 6-month intervals, the positive predictive value (PPV) of Ca 19-9 elevations was poor (average 35%), but normal Ca 19-9 levels had high negative predictive value (NPV) for detection of recurrence on CT at that time point (average 92%). Next, the predictive value of Ca 19-9 was compared with CT imaging at the next 6-month follow-up, yielding similar results (average PPV = 35%, average NPV = 90%). These data indicate that normal Ca 19-9 is strongly associated with absence of recurrence on imaging, but high Ca 19-9 is unfortunately frequently discordant with imaging findings at a given timepoint or at the next 6-month period. Therefore, conditional analysis was performed based on when Ca19-9 was first elevated to when radiographic recurrence was first identified. Conditional RFS was longer for patients with normal Ca 19-9 than for patients with elevated Ca 19-9. Additionally, the median time from Ca 19-9 elevation to radiographic recurrence ranged from 6 to 18 months during 6-month intervals. At each time point studied, postresection Ca 19-9 elevation predicted markedly worse RFS, and the impact of Ca 19-9 status on RFS increased at each additional time point. The same concept applied for OS.

Taken together, these results show that elevated Ca 19-9 on surveillance has prognostic significance at all time points and precedes radiographic recurrence by more than 6 months. Furthermore, Ca 19-9 offers an opportunity to assess conditional survival to counsel patients. The question, however, remains: should salvage treatment be established based only on Ca 19-9 elevation in otherwise asymptomatic patients, without proven radiographic evidence of recurrence? Should we intensify Ca 19-9 measurements to recognize a specific pattern? Or should we just wait for radiographic evidence of disease or symptoms? Dr. Rieser and colleagues do not have a specific answer to these questions, and—honestly—I do not either. This is and will remain a heavily debated issue between surgeons and oncologists at multidisciplinary tumor boards: "why should we start chemotherapy based only on Ca 19-9 elevation if the patient is doing well and CT scan is negative?" Surely, patient age, performance status, and time elapsed from pancreatectomy also play a role in this highly individualized decision process.

Although the study by Dr. Rieser is limited by its retrospective nature and heterogeneity of patient and treatment factors, it adds relevant information on Ca 19-9 surveillance pattern and the temporal relationship between tumor marker elevation and radiologic recurrence. I could not agree with the authors more: a better understanding of these relationships can be used to search for the most appropriate follow-up approach and to plan future Ca 19-9-driven prospective clinical trials on time to initiate salvage therapy for recurrent PDAC.

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