

Editorial

Tumor Markers for Pancreatic Cancer: What Happens When Preoperative CA 19–9 is Undetectable?

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Currently, CA 19–9 is the most clinically useful serologic marker for pancreatic cancer; it has become the gold standard to which newly discovered markers are compared. First described in 1979,¹ the CA 19–9 antigen was originally defined by a monoclonal antibody produced by hybridomas obtained from a mouse inoculated with the human colon cancer cell line SW 1116. The epitope of this antibody was subsequently identified as a sialylated lacto-*N*-fucopentaose II related to the Lewis^a blood group antigen. In tissue samples, CA 19–9 has been found to be associated with normal tissues of the pancreas, stomach, and biliary tract; bronchial and salivary glands; and pancreatic secretions. In serum, the antigen is associated with circulating mucins and is detectable at basal levels in healthy patients using a radioimmunoassay.

The greatest potential for CA 19–9 lies in the evaluation of patients with pancreatic cancer.² Over the past two decades, an extensive world experience with CA 19–9 has demonstrated it to have a sensitivity up to 90% and a specificity up to 98% in the diagnosis of this malignancy.^{3–5} As with many other tumor markers, however, CA 19–9 is not perfect and false-positive or false-negative findings can occur. For instance, the marker can be elevated in patients with other gastrointestinal malignancies and also in patients with benign disease, particularly when associated with obstructive jaundice or cirrhosis. Likewise, false-negative findings can occur. Patients who are genotypically Lewis^{a-b-} are unable to synthesize CA 19–9 because of a deficiency in a fucosyltransferase specified by the *Le* gene that is involved in its synthesis.⁶

Serum levels of those patients with pancreatic cancer among the 5% to 15% of the general population with the Lewis^{a-b-} genotype, therefore, will be falsely low even in the presence of a large, disseminated pancreatic tumor. For this reason, the maximal sensitivity of this marker falls short of 100%.

In this issue of *Annals of Surgical Oncology*, Berger et al.⁷ from the Fox Chase Cancer Center describe the prognostic value of preoperative CA 19–9 levels in patients with pancreatic cancer in a retrospective review. Their database included 128 patients with pancreatic cancer who had preoperative CA 19–9 levels followed by resection with curative intent. Their data were analyzed according to four distinct preoperative serum CA 19–9 levels: undetectable, normal (<37 U/mL), 38–200 U/mL, and >200 U/mL. On univariate and multivariate analysis, the only factors that were significant for overall survival were lymph node positivity and CA 19–9 grouping.

These findings, which are not surprising, are in accordance with previously published series.^{3–5} This apparent correlation between CA 19–9 serum concentration and tumor load has led many other authors to investigate the potential of this marker to assess prognosis and, therefore, to assist in patient management and therapeutic decision-making. Both Lundin et al.³ and Safi et al.⁴ have shown that among patients with resectable tumors, median survival following surgical resection was significantly longer in those patients with low preoperative CA 19–9 values, although the reference cut-offs (210 U/mL and 400 U/mL) used in their analyses differed. In both series, an elevated CA 19–9 level was associated with postoperative survival of 13 months or less, despite attempted curative resection. In contrast, median survival of patients with lower CA 19–9 levels was upward of 18 months. In the Lundin et al.³ series, a similar discrepancy in survival was found in patients with unresectable dis-

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ease who had palliation. Interestingly, the overall survival rate of patients with a high preoperative CA 19–9 who had attempted curative resection was similar to that of patients with unresectable disease treated palliatively.

Perhaps the most interesting and unexpected finding from the Berger et al.⁷ study in this issue of *Annals of Surgical Oncology* was what happened to patients with pancreatic cancer who had undetectable preoperative CA 19–9 levels. They noted that patients with undetectable preoperative CA19–9 levels had improved survival in resectable pancreatic adenocarcinoma compared with those with elevated CA 19–9 levels. In fact, the seven patients with undetectable CA 19–9 levels (who are presumably Lewis-negative phenotype) had a median overall survival of 32 months. The findings that these patients do better is especially interesting because six of the seven patients in the nonsecretor group had positive lymph nodes, which was the most important predictive factor of poor survival in the multivariate analysis carried out in this study.

Although it is difficult to make any conclusions about such a small group of seven patients, one must wonder why these patients do better than most patients with pancreatic cancer. In fact, one would hypothesize that these patients may do worse because clinicians lose the ability to monitor their CA 19–9 levels and, thus, predict response to therapy and disease progression or recur-

rence. It is unclear why patients with undetectable CA 19–9 levels had a better prognosis despite their lymph node positivity. It may be that *Le* gene negativity is a marker for decreased metastatic potential or aggressiveness; however, as the authors point out, these speculations will have to be borne out in larger studies before any conclusions can be drawn.

REFERENCES

1. Koprowski H, Steplewski Z, Mitchell K, Herlyn M, Herlyn D, Fuhrer P. Colorectal carcinoma antigens detected by hybridoma antibodies. *Somatic Cell Genet* 1979;5:957–71.
2. Katz MH, Moossa AR, Bouvet M. Serologic diagnosis of pancreatic cancer. In: Von Hoff DD, Evans DB, Hruban RH, eds. *Pancreatic Cancer*. Boston: Jones and Bartlett Publishers (in press).
3. Lundin J, Roberts PJ, Kuusela P, Haglund C. Prognostic significance of serum CA 242 in pancreatic cancer. A comparison with CA 19–9. *Anticancer Res* 1995;15:2181–6.
4. Safi F, Schlosser W, Falkenreck S, Beger HG. Prognostic value of CA 19–9 serum course in pancreatic cancer. *Hepatogastroenterology* 1998;45:253–9.
5. Schlieman MG, Ho HS, Bold RJ. Utility of tumor markers in determining resectability of pancreatic cancer. *Arch Surg* 2003; 138:951–5; discussion 955–6.
6. Tempero MA, Uchida E, Takasaki H, Burnett DA, Steplewski Z, Pour PM. Relationship of carbohydrate antigen 19–9 and Lewis antigens in pancreatic cancer. *Cancer Res* 1987;47:5501–3.
7. Berger A, Messzoely I, Ross E, Watson JC, Hoffman JP. Undetectable preoperative levels of serum CA 19–9 correlate with improved survival in patients with resectable pancreatic adenocarcinoma. *Ann Surg Oncol* 2004;11:644–9.