Editorial

Ca19-9 and pancreatic cancer: Is it really that good?

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In the current issue of *Journal of Gastrointestinal Oncology*, Ballehaninna and Chamberlain (1) provide a comprehensive appraisal of the utility of Ca19-9 in pancreatic cancer. The authors suggest a number of roles for Ca19-9 including: (I) As a diagnostic and screening tool in symptomatic patients; (II) In the assessment of tumour stage and respectability; (III) As a biomarker of prognosis following resection; (IV) In the assessment of response to chemotherapy; (V)As a predictor of post-operative recurrence.

Indeed, the only area where Ca19-9 would not appear to be useful is in population screening. However, in analyzing each of these areas in turn, it is clear that there is a major limitation to the use of Ca19-9 as the universal biomarker in pancreatic cancer, namely what is the optimal cut off level for assessment? Each of the areas evaluated demonstrated marked variation in median levels of Ca19-9 for the variable assessed, and likewise the cut-off levels utilized for determining outcome measures. This leaves the clinician with the quandary as to what levels to use for basing their clinical decisions. Certainly a tumour marker whose diagnostic threshold varies would not be optimal, and would lead to a great deal of confusion. Indeed, as a result of the diagnostic overlap, the American Society of Clinical Oncology does not currently advocate its use for screening, evaluation of resectability or disease follow-up (2).

There are a number of reasons to account for the variations in the Ca19-9 levels reported in the individual studies. The authors highlight the fact that between 1 in 10 and 1 in 20 patients with pancreatic cancer will not express Ca19-9 at all. There are also racial and gender variations in expression of Ca19-9 with highest levels observed in Caucasians (3). Ca19-9 is well known to be elevated in benign conditions (4), as acknowledged in the review, and these must be taken into consideration in relation to the diagnosis of malignancy.

The confusion caused by obstructive jaundice in interpreting Ca19-9 levels is also well documented. It is well known that benign pancreato-biliary disease may cause a rise in Ca19-9, usually related to biliary obstruction. In interpreting Ca19-9 levels in an individual believed to have pancreatic cancer it is important for the clinician to be aware whether a stent was inserted and if so was the Ca19-9 level taken pre-or post-stenting. Marrelli and colleagues (5) reported that bilirubin levels fall in patients with benign disease following stenting but remain elevated in those with malignant disease. Furthermore it has been shown that for benign disease the Ca19-9 levels correlate with bilirubin but for malignant disease these to variables are independent of each other (6).

A further factor in the confusion is the term that is often interchangeably used for pancreatic cancer. Traditionally, series of pancreatic resections have indicated a predominance of pancreatic carcinoma but with more accurate pathological evaluation (7) the prevalence of pancreatic adenocarcinoma is lower and that of distal common bile duct cholangiocarcinoma higher, with similar prevalence for ampullary lesions (8). The Ca19-9 levels of these tumours, when assessed separately are significantly different, and so failure to accurately characterize the nature of the periampullary lesion will certainly affect the assessment of Ca19-9 (6). Likewise, histopathological assessment of the lesions according to the format popularised by Verbeke (7) will radically alter assessment of tumour resection status and of stage that in turn may account for the variation in data in relation Ca19-9 and disease stage.

Despite the questions raised regarding Ca19-9, it is

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certainly the most useful clinical biomarker we have for pancreatic cancer. However, it is clear that currently, at least, there is not one level that can be agreed upon to determine good and poor prognosis tumours. It is imperative therefore that biomarkers such as Ca19-9 are interpreted in a multi-disciplinary team setting where the patient's status, such as the relationship of the Ca19-9 to pre-operative stenting and concurrent disease processes, is clear when clinical decisions are being made. In such a setting it is likely to be a much more powerful tool.

Finally, given the vogue for consensus statements, it would be appropriate timing for such a conference to evaluate Ca19-9 and its role in pancreatic cancer and to set cut of values for Ca19-9 against which future studies can be compared. Such a process for carcinoembryonic antigen levels in pancreatic cystic lesions lead to the Sendai guidelines (9) adopting a CEA level of ≥192 ng/mL as that for determining if a cyst deemed positive for CEA or not. Such a process for Ca19-9 would, within a short period of time, through audit processes, allow confirmation that such guideline values were correct and would aid all clinicians managing pancreatic cancer.

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