

The rise and fall of CA 19-9



Tumour markers abound in the field of gastroenterology. One of the most ubiquitous is carbohydrate antigen 19-9 (CA 19-9), which was first described by Koprowski *et al.* in 1979 as an abnormal glycoprotein, expressed on the surface of colorectal cell lines.^[1] Also referred to as sialyl Lewis-a CA 19-9, it is formed as a result of an aberrant pathway during production of its normal counterpart disialyl Lewis-a.^[2] The latter is a glycoprotein predominantly expressed in non-malignant epithelial cells. The abnormal form can be measured in serum by a specific monoclonal antibody. Ten per cent of the white population lack the Lewis blood group antigen and are unable to produce CA 19-9, even in the presence of malignant disease.^[3,4] High levels of CA 19-9 were subsequently reported in other gastrointestinal malignancies, including pancreas, bile duct, oesophageal and gastric cancer, as well as non-gastrointestinal tumours.^[5] Increased levels have also been observed in non-malignant causes of cholestatic jaundice, particularly chronic pancreatitis and choledocholithiasis. Elevated levels are also seen in hepatitis and cirrhosis, and a number of extra-abdominal non-malignant auto-immune conditions.^[6] CA 19-9 has been extensively investigated as a tumour marker for pancreatic and biliary cancer, as a screening, diagnostic, staging and prognostic modality, and as a measure of response to therapy.

An ideal tumour marker should have a high specificity and sensitivity to avoid false-positive and false-negative results. Using a threshold of 37 kU/l, abnormal levels of CA 19-9 are found in 81.5% of patients with pancreatic cancer and in 85.7% of patients with cholangiocarcinoma.^[5] Data from 22 trials using CA 19-9 for the diagnosis of pancreatic cancer showed that it had a sensitivity of 79% and a specificity of 82% for the diagnosis when a cut-off value of 37 kU/l was used in symptomatic patients.^[7] Raising the cut-off value for CA 19-9 levels increases the specificity. CA 19-9 levels over 1000 kU/ml are reported to have a specificity of 99% for pancreatic malignancy.^[8] The presence of jaundice, a common feature in patients with pancreatic cancer and cholangiocarcinoma, increases the sensitivity, but decreases the specificity, of CA 19-9 for a diagnosis of malignant disease.^[9] Using higher cut-off values in jaundiced patients has been suggested. A value of 300 kU/ml in a jaundiced patient has a specificity of 87%.^[10] In this issue of the SAJS, Rao *et al.* report a diagnostic conundrum posed by extremely elevated CA 19-9 levels leading to a presumptive diagnosis of biliary malignancy which at surgery turned out to be complicated choledocholithiasis. The CA 19-9 levels normalised after appropriate therapy and resolution of the jaundice. This and other similar reports^[11,12] underscore the vulnerability of CA 19-9 as a malignant biliary tract marker, even with the high specificity achieved with a higher cut-off. CA 19-9 levels should therefore always be re-evaluated after effective biliary drainage.

As a diagnostic tool in suspected malignancies, its weaknesses have been highlighted. It fares even worse in the screening arena as, in asymptomatic populations, the positive predictive value (PPV) for pancreatic cancer is 0.5 - 0.9%.^[14,15] These values, in combination with

the low prevalence of pancreatic cancer in the general population, make CA 19-9 unsuitable as a screening method.

CA 19-9 levels are less than perfect in the diagnosis of hepatobiliary cancer; but does it fare better in determining the prognosis and management in those with proven cancers? Pancreatic cancer burden and CA 19-9 serum levels have shown a strong correlation in a number of studies.^[6] Similarly, resectability rates also correlate well with pre-operative CA 19-9 levels. A recent meta-analysis showed that CA 19-9 level <100 kU/l predicted resectability with a PPV of 60 - 80%. Levels >100 kU/l predicted unresectability with an even higher PPV of 90%.^[6] Not surprisingly, CA 19-9 levels are found to be an independent predictor of overall survival. In a study of 1 626 patients who underwent surgery for potentially resectable pancreatic cancer, preoperative CA 19-9 levels >1 000 kU/l were associated with a median postoperative survival of 12.7 months and no 5-year survival.^[15] As patients with high CA 19-9 levels are more likely to have peritoneal and liver metastases, elevated CA 19-9 levels can be used to identify patients who are more likely to benefit from a staging laparoscopy prior to resection.^[16,17] Furthermore, it may not be appropriate to perform complex resections in patients with very high CA 19-9 levels, given the poor long-term survival and marginal benefit-to-risk ratio.^[15]

Post-resection CA 19-9 levels have also been reported to be a predictor of survival. Patients with normal CA 19-9 levels have been shown to have a median survival of 37 months and a 5-year survival of 32%, whereas patients with increasing CA 19-9 levels post resection have a median survival of 11 months, with no 5-year survivors.^[15] In patients receiving chemotherapy, CA 19-9 levels have also been shown to be a reliable marker of response. Those who have stable or decreased CA 19-9 levels 6 - 8 weeks into chemotherapy have a better overall survival than patients whose CA 19-9 levels increase. Increasing levels during chemotherapy indicate early treatment failure, requiring a change in the chemotherapeutic regimen.^[18]

In conclusion, CA 19-9's use as an independent diagnostic marker of hepatobiliary malignancy in symptomatic patients is hampered by its expression in various benign conditions, particularly those causing jaundice. It may have more clinical relevance in estimating prognosis, response to therapy and survival. In terms of clinical decision making, it is imperative that elevations of this tumour marker are interpreted in the context of other diagnostic and prognostic markers available to the multidisciplinary team.

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S Afr J Surg 2013;51(4):114. DOI:10.7196/SAJS.1973

References appear with the editorial online at <http://www.sajs.org.za>, which is accessible by scanning the QR code above.