

## Serum CA 19-9 in pancreatic adenocarcinoma: a mini-review for surgeons.

**Running head:** Serum CA19-9 in pancreatic cancer

### Authors:

Su Kah Goh<sup>1, 2, #</sup> MBBS, BMedSc

Grace Gold<sup>1, 2, #</sup> BBiomed, MD

Christopher Christophi<sup>1, 2</sup> FRACS, MD

Vijayaragavan Muralidharan<sup>1, 2</sup> FRACS, PhD

### Affiliations:

<sup>1</sup> Hepato-pancreato-biliary & Transplant Unit, Austin Hospital, Melbourne, Australia

<sup>2</sup> The University of Melbourne Department of Surgery, Austin Hospital, Melbourne, Australia

# co-authors

### Corresponding Author:

Vijayaragavan Muralidharan

Department of Surgery, University of Melbourne,

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Austin Health, Level 8 Lance Townsend Building,  
Studley Rd, Heidelberg, Melbourne, Victoria 3084, Australia  
Phone: +61 (3) 94965000, Fax: +61 (3) 9458 1650  
Email: [muv@unimelb.edu.au](mailto:muv@unimelb.edu.au)

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## Abstract

The optimal management of oncological conditions is reflected by the careful interpretation of investigations for screening, diagnosis, staging, prognostication and surveillance. Serum tumour markers are examples of commonly requested tests in conjunction with other imaging and endoscopic tests that are used to help clinicians to stratify therapeutic decisions.

Serum CA19-9 is a key biomarker for pancreatic cancers. Although this biomarker is considered clinically useful and informative, clinicians are often challenged by the accurate interpretation of elevated serum CA19-9 levels. Recognising the pitfalls of normal and abnormal serum CA19-9 concentrations will facilitate its appropriate use.

In this review, we appraised the biomarker, serum CA19-9, and highlighted the clinical utility and limitations of serum CA19-9 in the investigation and management of pancreatic cancers.

## Introduction

Monoclonal antibodies against the epitope of a sialic acid closely related to the Lewis blood group antigen system were isolated over thirty years ago when murine splenocytes were immunised with human cancer cell lines [1-3]. This sialic acid is known as the Sialyl Lewis A antigen or carbohydrate antigen 19-9 (CA19-9).

CA19-9 is normally embedded on cell surfaces as gangliosides and mucins on epithelial cells of the biliary tract, pancreatic ducts, stomach and prostate [4, 5]. It is also present in low concentrations in the serum, glycosylated on mucins, kininogen and apolipoproteins [6-8]. Extensive research on the biological functions of sialic acids have shown that CA19-9 is involved in cell growth and differentiation [9], signal transduction [10], apoptosis [11], spermatogenesis [12] and immunomodulation [13]. Specifically, CA19-9 has been reported to propagate leukocyte recruitment by mediating adhesion and migration of leukocytes to an inflammatory focus [14].

In a pathological state, abnormal sialic acid glycosylation of mucins can alter the molecular microenvironment and promote proliferation, invasion and metastasis [13]. CA19-9 is suspected to play a vital role in malignant cell adhesion to endothelial cells, transmigration and development of metastases. This is supported by in-vivo observations of patients with pancreatic cancer [15], colorectal cancer [16] and breast cancer [17], whereby elevated CA19-9 is associated with disease progression and inferior outcomes.

Pancreatic cancer accounts for the seventh highest rate of death from cancer worldwide. In 2012, there were an estimated 338,000 new diagnoses and 330,000 deaths internationally from pancreatic cancer and this is projected to rise annually [18]. Due to the late presentations of patients with pancreatic cancer, only 10-20% will undergo potentially curative surgery supplemented by adjuvant chemotherapy. Contributing factors to poor prognosis include the tendency for pancreatic cancer to metastasise early, difficulties in differentiating benign and malignant pancreatic lesions, and the limited effectiveness of systemic therapies. Despite advancement in surgical techniques, peri-operative care as well as therapeutic options, improvement in 5-year survival rates is marginal [19].

The diagnosis and staging of pancreatic lesions is dependent upon multiple imaging modalities including ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), positron emission topography (PET), endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP). Serum CA19-9 is often requested by clinicians in conjunction with these investigations.

The interpretation of CA19-9 levels is often challenging and the utility of this biomarker in the screening, diagnosis, assessment of resectability and prognostication of pancreatic cancer is often unclear. In this review, we present an appraisal of serum CA19-9 (referred to as CA19-9) and its clinical utility.

## Methods

A literature review was performed to identify articles that addressed the significance and interpretation of CA19-9. PubMed search was restricted to articles published in English between January 1979 and December 2016. Relevant publications were identified using the search strategy containing keywords including 'CA19-9', 'carbohydrate antigen 19-9', 'ca199' and 'pancreatic cancer'. Papers were eligible for consideration in this review if the study evaluated i) CA19-9 in pancreatic cancer or ii) the prognostic and/or clinicopathologic value of CA19-9.

### Screening of pancreatic cancer using CA19-9

CA19-9 is ineffective for the screening of pancreatic based on the findings of two large population-scale studies. Kim et al. [20] screened 70,940 asymptomatic patients using CA19-9. Although 1.5% of the screened individuals demonstrated elevated CA19-9, only four patients had pancreatic cancer and two were operable. Despite a sensitivity (SN) of 100% and specificity of 98.5%, the positive predictive value (PPV) was only 0.9% [21]. In the second study 12,840 asymptomatic individuals in Japan underwent screening and 18 were found to have elevated CA19-9. Among them only four had pancreatic cancer [22].

The utility of this biomarker, however, may be useful in the screening of a subset of the population that is at higher risks of developing pancreatic cancers (i.e. patients with a family history of pancreatic cancer, hereditary pancreatitis, and Peutz-Jeghers syndrome) [23-26]. Zubarik et al. showed in their protocol that screening high-risk individuals with that the use of CA19-9 and EUS

was feasible [25]. Among the 546 subjects that were screened in this study, 27 patients demonstrated elevated CA19-9 of whom five neoplastic lesions were detected. These findings are promising for clinical implementation but require further validation and cost-effectiveness studies.

## **Diagnosis of pancreatic cancer using CA19-9**

CA19-9 is satisfactory as a diagnostic biomarker of pancreatic cancer. Steinberg et al examined 1040 patients from 24 case series and reported a median SN and SP of 81% and 90%, respectively [27]. Goonetilleke and Siriwardena examined 22 studies and demonstrated a median SN is 79% and a SP of 82% [28]. Similarly, Huang and Lui examined 2316 individuals from 11 studies and found a median SN of 80% and SP of 80% [29]. However, a separate study of 483 patients by Singh et al. demonstrated that CA19-9 was unreliable [30]. In addition to the low SN of 64% and SP of 69% at a cut-off value of 40 U/mL, CA19-9 did not alter the making of clinical decisions and patient management.

The assessment of multiple serum proteins may improve the diagnostic accuracy of pancreatic cancer. Although the combination of common tumour markers like CA19-9, CEA and CA 125 did not confer an advantage over CA19-9 alone as a diagnostic marker [31-33], the combination of CA19-9, intercellular Adhesion Molecule 1 (ICAM-1) and osteoprotegerin (OPG) differentiated patients with pancreatic cancer from healthy controls [34]. However, these findings still require further confirmation.

Cholestasis in patients with pancreatic cancer who present with obstructive jaundice can confound CA19-9 levels [35, 36]. In these cases, monitoring the kinetics of CA19-9 may have a role in guiding the diagnosis of pancreatic cancer in patients who present with obstructive jaundice [37]. The persistent elevation of CA19-9 of greater than 90 U/mL at least one-week post endoscopic management of biliary obstruction is highly suggestive of an underlying malignancy.

Numerous aetiologies can falsely elevate CA19-9. These include pancreatitis [38], hepatic cysts [39], pancreatic cysts [40], and complications within cysts such as haemorrhage [41] and infection [42]. As such, the interpretation of an elevated CA19-9 in the diagnosis of pancreatic cancer must take in to consideration the relevant clinical findings and investigations.

### **Determining resectability using CA19-9**

The use of pre-operative CA19-9 has been proposed to influence the decision for surgical resection in pancreatic cancer [43, 44]. Hartwig et al [45] shown that CA19-9 was a valuable determinant of resectability, whereby 80% of patients with normal or low levels (<250U/mL) were resectable. Furthermore, they found that the rate of resectability decreased with an increase in serum levels of CA19-9. In a separate study, Alexakis et al demonstrated that the use of CA19-9 cut-off value of >215 U/mL predicted unresectability, secondary to vascular involvement or liver and peritoneal metastases, in a cohort of patients who were initially determined resectable by conventional imaging [46].

Despite the studies demonstrating the accuracy of CA19-9 in predicting resectability, clinical decisions are rarely made based on a single serum biomarker. Although CA19-9 may yield useful clinical information pertaining to tumour burden and tumour biology, it offers little anatomical value (i.e. the relation of the tumour to surrounding vascular structures) that often determines the safety and feasibility of surgical resection. The use of CA19-9 in conjunction with modern imaging techniques may improve the (i) characterisation of resectability, (ii) categorisation of “borderline-resectable” tumours and (iii) selection of patients for neoadjuvant systemic therapy.

### **Prognostic value of peri-operative CA19-9**

Pre-operative CA19-9 level appears to have role in predicting survivability in patients with resectable pancreatic cancer. Hallemeier et al [47] noted that patients with high pre-operative CA19-9 (>180 U/mL) was associated with adverse pathologic features (T3-T4 disease, positive lymph nodes and high histological grade) and decreased survival. Ferrone et al [48] found that pre-operative CA19-9 was an important prognostic marker in patients with resectable pancreatic adenocarcinoma in a retrospective analysis of 424 patients. In this particular study, patients with a preoperative CA19-9 <1000 U/mL had significantly longer median survivals (2.3 years versus 1 year).

The utility of post-operative CA19-9 to predict prognosis was similarly observed by Berger et al. [49]. In this phase III trial, the prospective analysis of this biomarker confirmed its prognostic importance in patients following curative resection using a cut-off value of 180 U/mL. Patients with post-operative CA19-9  $\geq 180$  U/mL had significantly worse survival and were 3.5 times more likely to die

from recurrence than those patients with CA19-9 <180 U/mL.

These findings were also supported by Hartwig et al, who recently demonstrated in a cohort of 1071 patients that pre-operative CA19-9 was an important independent negative prognostic factor [50]. Patients with CA19-9 > 400 U/mL were shown to have significantly worse 5-year survival (HR 1.5). In a separate report, Hartwig et al also showed that an early increase of post-operative CA19-9 was associated with significantly worse 5-year survival (2.8% compared to 31.8%) [45].

The dynamics of peri-operative CA19-9 confer important prognostic value. The normalisation of post-operative CA19-9 was indicative of superior prognosis in a study of 260 patients [51]. This was subsequently confirmed by a key study comprising 1446 patients with pancreatic cancer undergoing resection [52]. The failure of CA19-9 to normalise post-operatively also has a negative impact on survival [48]. Consistently, Abdel-mish et al identified that patients who underwent resection and failed to normalise their CA19-9 within 6 months were associated with worsened survival [53]. The patients with elevated CA19-9 were also 2.2 times more likely to die of pancreatic cancer compared to those who did not demonstrate a rise.

Altogether, these studies support the notion that a raised preoperative and/or persistent elevation of post-operative CA19-9 is associated with worse prognosis. Although CA19-9 may be useful role in estimating prognosis in patients with pancreatic surgery after resection, the utility of CA19-9 in the stratification of adjuvant therapeutic pathways for patients with poor prognoses remains elusive.

## Prognostic value of CA19-9 response to chemotherapy

Most patients with pancreatic cancer undergo chemotherapy treatment. The evidence in the use of CA19-9 to predict response after chemotherapy is uncertain. Although the decrease in CA19-9 following chemotherapy is associated with a longer survival [54-58], two key studies did not demonstrate this relationship. First, Hammad et al did not find a significant association between any magnitude of CA19-9 decline and survival using data derived from a pooled analysis of three phase II trials [59]. Second, Hess et al [60] also concluded that decrease of CA19-9 >50% did not correspond with lengthened survival. Furthermore, they found that the concordance between imaging response and tumour-marker response was not a reliable prognostic indicator. It was observed in their study that almost half of the patients who progressed on CT conversely showed a 50% or greater decrease in CA19-9 concentration. These studies strongly dispute the associations of survival and CA19-9 response after chemotherapy.

Heterogeneity in study design, variation in evaluating chemotherapeutic response and the use of different chemotherapy regimens may account for the discussed discrepancies. Nevertheless, the validity of CA19-9 response to chemotherapy as a predictor of survival remains largely debatable.

## Post-operative surveillance using CA19-9

Of the small proportion of patients diagnosed with pancreatic cancer who are able to undergo

resection with curative intent, post-operative prognosis remains poor and chance of disease recurrence from 66-92% at 2 years [61].

Elevation of CA19-9 post-operatively is suggestive of disease recurrence. However, benign biliary complications such as cholangitis, cholestasis due to anastomotic strictures and liver abscesses can also falsely elevate CA19-9 [62]. The mechanism of benign CA19-9 elevation is likely attributed to (i) increased CA19-9 production by bile duct cells exposed to increased biliary pressure, (ii) inflammatory proliferation of epithelial cells producing CA19-9, (iii) accumulation of CA19-9 in the lumen due to biliary obstruction and decreased clearance of biliary mucins due to cholestasis and (iv) increased permeability between bile and blood with resultant reflux into circulation. It is often difficult to differentiate between the benign causes of CA19-9 elevation and disease recurrence.

Monitoring post-operative CA19-9 levels may have a role in facilitating the early detection of recurrence up to six months prior to clinical or imaging evidence of recurrence deeming the serum levels a valuable tool in surveillance [63, 64]. Attributed to the inherent characteristics of CA19-9, the clinical utility of CA19-9 for post-operative surveillance is still not clearly defined. The American National Comprehensive Cancer Network surveillance guidelines recommend 3-6 monthly CA19-9 levels post curative resection in conjunction with CT imaging for the first 24 months then subsequent yearly intervals thereafter [21]. Whereas the European Society of Medical Oncology 2015 guidelines recommend individualised surveillance and do not recommend routine surveillance post resection as there is no evidence of improved outcomes. Furthermore, they stated that

resources and emphasis should instead be focussed on patients' nutrition, symptoms and psychological wellbeing [65]. These international guidelines are based on retrospective studies and expert opinions, reflecting the deficit of prospective data to guide practice [66, 67].

## Conclusions

CA19-9 has been extensively studied in pancreatic cancers since its discovery over the last three decades. As a tumour marker, CA19-9 continues to be routinely requested by clinicians during the management of pancreatic cancer. Although the test is widely accessible, it is pertinent to recognise the potential pitfalls to ensure appropriate utility and accurate interpretation of any abnormalities.

There are a number of factors that can confound the interpretation of CA19-9. First, up to 20 percent of the population has an inherited deficiency of fucosyltransferase and they do not express CA19-9 [53, 68]. Second, CA19-9 is not exclusively specific to pancreatic cancer and numerous benign aetiologies can falsely elevate CA19-9.

Overall, CA19-9 can be used in clinical setting with caution and as an adjunct to other investigations (**Table 1**). CA19-9 in the screening of pancreatic cancer is unsuitable. However, the utility of CA19-9 with other imaging modalities may confer detection advantages in the subset of population with high-risk factors.

At present, a raised pre-operative CA19-9 should prompt the clinician to re-evaluate resectability. Given the limited specificity of CA19-9, additional imaging with MRI and EUS can better delineate the vasculature, anatomy and extent of disease with a view to guide resectability and reduce the burden of unnecessary laparotomies.

Despite these insufficiencies, there is a role of CA19-9 in prognostication. Studies have shown that reduction in the post-operative levels are associated with longer survival. A raised pre-operative CA19-9 level is associated with poor pathologic findings such as positive lymph nodes and high histologic grade disease and significantly reduced survival. Similarly, a failure of CA19-9 normalisation within 3-6 months of surgery is associated with poorer outcomes. However, the evidence for CA19-9 response to chemotherapy as a marker of prognosis in pancreatic cancer remains debatable.

There is an urgent need for clinical tools that will enable early detection of pancreatic cancer, prognostication after therapy and monitoring of therapy in patients with pancreatic cancer. Despite extensive clinical use of CA19-9 over the last 30 years, its value in influencing therapeutic directions remains limited and needs to be integrated with clinical and radiological assessments.

**Table 1:** Clinical Value of CA19-9 in the Management of Pancreatic Cancer

Stage in Management	Value	Role
Screening	+/-	<ul style="list-style-type: none"><li>• Unsuitable for general population screening</li><li>• May have a role in high risk groups</li></ul>
Diagnosis	++	<ul style="list-style-type: none"><li>• To be used as an adjunct to other investigations</li></ul>
Determining resectability	+	<ul style="list-style-type: none"><li>• Valuable indicator of tumour burden</li><li>• The tumour marker alone is unable to determine anatomical margins</li></ul>
Peri-operative Prognostic Value	+++	<ul style="list-style-type: none"><li>• High pre-operative levels correlate with poor prognosis post resection</li><li>• Failure of post-operative levels to normalise is associated with poorer outcomes</li></ul>
Prognostic value of CA19-9 response to chemotherapy	+	<ul style="list-style-type: none"><li>• Heterogeneity in therapeutic regimes limit the ability for accurate prediction of response</li><li>• Some evidence that decrease in levels with chemotherapy is an indicator of increased survival</li></ul>
Post-operative surveillance	++	<ul style="list-style-type: none"><li>• Rise may occur 6 months prior to radiological recurrence</li><li>• Institution dependent and may have a role in surveillance</li><li>• 3-6 monthly levels for first year, then annual levels</li></ul>

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