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# Diagnosis and Staging of Pancreatic Cancer: Role of Ca 19-9 in Diagnosis/Staging and Management

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Since its discovery in 1979, carbohydrate antigen 19-9 (CA 19-9) has become the most widespread tumor biomarker used in the diagnosis and management of patients with pancreatic cancer. Despite the various potential pancreatic tumor biomarkers available, none has been more extensively studied and validated than CA 19-9. In this section we will discuss the role of CA 19-9 in diagnosis, staging, and management of pancreatic adenocarcinoma.

Normal range of CA 19-9 levels is between 0 and 37 U/mL. The usefulness of this tumor-associated antigen greatly depends on the situation. As a screening tool in asymptomatic patients, CA 19-9 levels have been shown to have poor predictive value and routine measurement is not recommended in clinical practice. For patients with symptoms suspicious of pancreatic cancer, elevated CA 19-9 has also been shown to be a poor predictor with a predictive value of 0.5–0.9% [1]. Similarly, in patients with small tumors or with early stages of the disease, CA 19-9 cannot be recommended as a screening tool due to its low sensitivity (~80%) and specificity (~80%) [2].

However, in patients who present with a pancreatic mass, elevated CA 19-9 has a much higher predictive value. As demonstrated by Tessler et al in a study of 150 patients, when elevated CA 19-9 levels >37 U/mL are combined with unintentional weight loss of >20 lbs and total bilirubin ≥3 mg/dL in patients presenting with a pancreatic mass, specificity of CA 19-9 increases to nearly 100% for pancreatic cancer regardless of the extent of imaging abnormalities [1]. Overall, elevated CA 19-9 has a sensitivity and specificity of 79–81% and 80–82%, respectively, in diagnosing pancreatic adenocarcinoma in symptomatic patients.

A caveat in which elevated CA 19-9 must be carefully interpreted is in the presence of obstructive jaundice. Several retrospective reviews and meta-analyses have revealed that in cases of hyperbilirubinemia secondary to obstructive jaundice, CA 19-9 is unreliable in distinguishing between benign and malignant pancreaticobiliary diseases. The mechanisms by which CA 19-9 is falsely elevated in obstructive jaundice are not well understood but it is theorized that increased production of the tumor-associated antigen by cholangiocytes is primarily responsible. In biliary obstruction, increases in biliary ductal pressure are thought to "irritate" cholangiocytes, thereby resulting in increased secretion of CA 19-9. This irritation results in inflamma-

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tory proliferation of CA 19-9, which when combined with decreased clearance of CA 19-9 due to the obstruction causes leakage of CA 19-9 into systemic circulation and ultimately, false elevations in CA 19-9. Therefore, elevations of CA 19-9 in cases of biliary obstruction should be interpreted with caution.

For patients presenting with a pancreatic mass without biliary obstruction, it is well established that elevated CA 19-9 levels not only confer a high predictive value for diagnosing pancreatic carcinoma but significantly affect clinical decisions regarding treatment. CA 19-9 provides a rough estimate of tumor biology and aggressiveness and in recent years has become part of the broader definition for determining resectability. Preoperative CA 19-9 levels have been studied as potential surrogate markers for tumor resectability. Although an optimal cutoff is not well established, preoperative CA 19-9 levels >150 U/mL carry an 88% positive predictive value for determining unresectability, and levels <150 U/mL carry a negative predictive value of 64% [1]. Other studies have shown that a median CA 19-9 level < 100 U/mL correlates with a 41–80% chance of resectability, while levels >100 U/mL suggest advanced or metastatic disease [1]. Unsurprisingly, 96% of tumors with CA 19-9 levels >1000 U/mL are found to be unresectable [3].

The International Association of Pancreatology utilizes CA 19-9 in their definition of borderline resectability—locally resectable tumors are categorized as borderline resectable once CA 19-9 levels are greater than 500 U/mL or regional lymph node metastases are found [4]. Accordingly, these elevated CA 19-9 levels play a pivotal role as completion of adjuvant therapy following major pancreatic surgery is unlikely [4]. As such, in the presence of high CA 19-9 levels, treatment of choice for borderline resectable pancreatic adenocarcinoma becomes neoadjuvant therapy [4].

In one of the largest retrospective cohort studies, Mirkin et al. further evaluated the relationship of pre-treatment CA 19-9 levels taken at diagnosis with overall survival [5]. Data of 4701 patients with stage I-III disease from the National Cancer Database were reviewed [5]. The primary outcome assessed was survival. Among the 4701 patients, 592 patients received neoadjuvant therapy, 1286 patients underwent surgically resection, and 2823 patients received surgical resection and adjuvant chemotherapy [5]. Results revealed no association between pre-treatment CA 19-9 levels ≤ 800 U/mL and survival at any stage for patients who underwent surgical resection with or without adjuvant therapy [5]. However CA 19-9 levels >800 U/mL did correlate with worse survival among all clinical stages [5]. Similarly, for patients who received neoadjuvant therapy with surgery, no association of CA 19-9 levels ≤800 U/mL was seen in stage I or II disease [5]. Pre-treatment CA 19-9 levels >800 U/mL were significantly associated with worse survival in stage I but not stage II or III disease, demonstrating a survival benefit in these patients who receive neoadjuvant therapy [5]. This study overall demonstrated that pre-treatment CA 19-9 levels >800 U/mL are associated with advanced stage of disease and worse survival in all clinical stages [5].

Perhaps the most established and greatest clinical value of CA 19-9 is when used as a means to prognosticate survival and recurrence following surgical resection. Multiple studies have confirmed that following surgical resection, patients who normalize their CA 19-9 levels postoperatively have longer survival than those who do not [3]. Given the half-life of 14 h, it is recommended that CA 19-9 levels be obtained 4–6 weeks following surgery. As a general consensus, CA 19-9 levels <37 U/mL or low preoperative CA 19-9 levels <100 U/mL correlate with early stage of disease and independently predict overall survival [1]. CA 19-9 levels which fail to normalize are attributed to residual disease or occult metastasis and portend a poor overall survival [1]. Additionally, alterations in CA 19-9 levels may be useful in identifying micrometastatic lesions following surgical resection [6].

Several trials have demonstrated survival benefit for patients who receive neoadjuvant therapy and particularly in those who receive neoadjuvant chemotherapy, CA 19-9 has been found to correlate with recurrence and survivability. Similar to those who are surgically resected,

patients who normalize their CA 19-9 levels following neoadjuvant therapy hold a more favorable prognosis and lower incidence of hepatic recurrence [6]. Furthermore, for patients who exhibit a favorable response to neoadjuvant chemotherapy but whose CA 19-9 levels remain above normal, several additional cycles of neoadjuvant therapy may be administered until CA 19-9 normalization, thereby resulting in increased survivability and lower recurrence rates following surgical resection [6].

Measurement of CA 19-9 levels after induction chemotherapy also appears to be of use in determining which patients would benefit from exploratory surgery. Induction chemotherapy with FOLFIRINOX in patients with locally advanced pancreatic cancer may lead to downstaging and in 20–25% of cases result in surgically resectable disease [7]. Determining which tumors meet resectability criteria, however, may not always be clear. Following induction chemotherapy, treatment response and resectability are typically assessed with CT-imaging using the Response Evaluation Criteria in Solid Tumors (RECIST1.1) [7]. In patients who meet RECIST-stable disease, defined as having lack of tumor progression or regression, one of the challenges of CT-imaging is inability to distinguish between fibrotic versus viable tumor tissue [7]. As a result, patients with RECIST-stable disease do not undergo surgical exploration since negative surgical explorations in pancreatic cancer are associated with poorer outcomes [7].

In a small study of 54 patients who underwent induction chemotherapy, Van Veldhuisen and colleagues demonstrated that when combined with criteria meeting RECIST-regression, a decrease of ≥30% in CA 19-9 levels improved the sensitivity, positive predictive value, and negative predictive value for determining resectability [7]. Based on these results, they postulate that measurement of post-induction chemotherapy CA 19-9 levels may be beneficial in determining resectability in patients with RECIST-stable disease. Further studies with a larger patient population, however, are still needed.

CA 19-9 continues to be used as a surrogate marker of overall response and survival to new experimental therapies. A new strategy in approaching patients with locally advanced or initially unresectable pancreatic cancer, termed "adjuvant surgery," has gained momentum in recent years due to studies reporting improved overall survival for highly selective patient populations who respond favorably to multimodal treatments [6]. Patients who qualify for adjuvant surgery do so after receiving nonsurgical anticancer treatments for more than 240 days, maintain CA 19-9 levels within a relatively low range, and do not show progression or development of occult distant metastasis following various treatment modalities or surgical exploration [6]. Another novel treatment, irreversible electroporation (IRE), a nonthermal ablative technique, has emerged as a potential treatment option for patients with locally advanced pancreatic cancer and measurement of CA 19-9 levels is used to monitor treatment response. In a small multicenter, prospective study of 40 patients with locally advanced pancreatic cancer and 10 isolated local recurrence following surgical resection subsequently treated with IRE, elevated CA 19-9 levels corresponded to poorer survival [8]. CA 19-9 levels >2000 U/mL before IRE and ≤50% reduction in CA 19-9 levels 3 months following IRE were associated with worse overall survival [8].

It is important to remember that pancreatic adenocarcinoma is not the only malignancy with elevated levels of CA 19-9 in the serum. Other cancers that can increase this marker in the serum include cholangiocarcinoma, gall bladder cancer, ampullary carcinoma, hepatocellular carcinoma, gastric cancer, ovarian cancer, colorectal cancer, lung cancer, breast cancer, endometrial cancer, and thyroid cancer.

Furthermore, there are many benign conditions associated with increased CA 19-9 including but not limited to benign biliary stricture, acute cholangitis, Mirrizzi's syndrome, choledocholithiasis, gall stones, acute cholecystitis, acute pancreatitis, primary biliary cirrhosis, hepatic cysts, acute and chronic hepatitis, bronchiectasis, interstitial lung disease, cystic fibrosis, endometriosis, and uncontrolled diabetes mellitus. Furthermore, CA 19-9 is cleared through the

kidney and levels can be elevated with chronic kidney disease and reduced glomerular filtration rate. There are also some individuals with elevated CA 19-9 where there is no apparent cause. Thus, it is important to check and interpret serum CA 19-9 level in the right clinical context.

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