ORIGINAL ARTICLE

Serum carbohydrate antigen 19-9 represents a marker of response to neoadjuvant therapy in patients with borderline resectable pancreatic cancer

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Abstract

Objectives: The purpose of this study was to determine the relationship between carbohydrate antigen (CA) 19-9 levels and outcome in patients with borderline resectable pancreatic cancer treated with neoadjuvant therapy (NT).

Methods: This study included all patients with borderline resectable pancreatic cancer, a serum CA 19-9 level of ≥40 U/ml and bilirubin of ≤2 mg/dl, in whom NT was initiated at one institution between 2001 and 2010. The study evaluated the associations between pre- and post-NT CA 19-9, resection and overall survival.

Results: Among 141 eligible patients, CA 19-9 declined during NT in 116. Following NT, 84 of 141 (60%) patients underwent resection. For post-NT resection, the positive predictive value of a decline and the negative predictive value of an increase in CA 19-9 were 70% and 88%, respectively. The normalization of CA 19-9 (post-NT <40 U/ml) was associated with longer median overall survival among both non-resected (15 months versus 11 months; $P = 0.022$) and resected (38 months versus 26 months; $P = 0.020$) patients. Factors independently associated with shorter overall survival were no resection [hazard ratio (HR) 3.86, $P < 0.001$] and failure to normalize CA 19-9 (HR 2.13, $P = 0.001$).

Conclusions: The serum CA 19-9 level represents a dynamic preoperative marker of tumour biology and response to NT, and provides prognostic information in both non-resected and resected patients with borderline resectable pancreatic cancer.

Received 2 April 2013; accepted 31 May 2013

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Introduction

Serum carbohydrate antigen (CA) 19-9 is the most common tumour marker used in the clinical management of patients with pancreatic ductal adenocarcinoma (PDAC).[1–5] Among patients with radiographically resectable PDAC, CA 19-9 has been used as an indicator of clinically occult metastatic disease,[5] as a criterion for the use of diagnostic laparoscopy prior to surgery,[3,4] as a prognostic marker following resection with or without adjuvant therapy[6,7] and as a director of therapy following postoperative recurrence.[8] Among patients with unresectable, locally advanced or metastatic disease, CA 19-9 has been used as a prognostic marker for survival, as well as an indicator of response to palliative therapies.[1,7,9]

Borderline resectable PDAC, irrespective of the radiographic criteria used to define it, represents a challenging subset of cancer manifestations with local tumour anatomy that lies between the

Funding sources: Khalifa Bin Zayed Al Nahyan Foundation and the Various Donor Pancreatic Research Fund at MD Anderson Cancer Center. MHGK is supported in part by the 2012 Alliance for Clinical Trials in Oncology Clinical Scholar Award.

This manuscript was presented at the annual AHPBA meeting, Miami, 20–24 February 2013.

clearly resectable and unresectable.[10–12] Because patients with borderline resectable cancers are at high risk for margin-positive resection and early disease progression following surgery, patients with this stage of disease are routinely administered neoadjuvant therapy (NT) prior to planned resection.[10,12–15] The goals of this treatment strategy include the achievement of local control of the primary tumour, sterilization of lymphadenopathy and surgical margins, early treatment of presumed micro-metastatic disease, and the evaluation of tumour biology prior to a potentially morbid abdominal operation.[12,14]

Although there is consensus that the use of chemotherapy and/or chemoradiation prior to surgical resection is rational in patients with borderline resectable PDAC, few data exist to guide the details of such management.[10,14] The relative importance of chemotherapy and chemoradiation, the ideal sequence and duration of their administration, and the precise cytotoxic agents to be used in the individual patient are all unclear. In this regard, one of the primary obstacles to the assessment and optimization of multimodal treatment strategies is the absence of a well-defined clinical indicator of response to preoperative therapy. An inexpensive, reproducible and easily measured response metric would be clinically useful to evaluate the efficacy of different preoperative regimens, to determine the optimal duration of each component of multimodal therapy and to estimate prognosis following treatment.

The current authors previously demonstrated that the response of PDAC to NT can be estimated by histopathologic examination of the resected primary tumour. Fibrosis and a marked reduction in the residual viable cancer cells following the administration of NT were associated with a favourable prognosis and may reflect clinically significant cytotoxic activity.[16] However, because a histologic evaluation of tumour response requires an examination of tumour cells and tissue architecture, this dynamic measure of tumour response is unavailable in the preoperative setting. Furthermore, although the change in tumour size as determined radiographically and as classified using RECIST (*r*esponse *e*valuation *c*riteria *i*n *s*olid *t*umours) parameters can be used to estimate response to therapy in patients with many types of cancer, the current authors have previously demonstrated that radiographic 'response' is rare among patients with borderline resectable PDAC treated with NT and, further, when observed, it is not associated with a favourable outcome among patients who undergo subsequent resection.[17]

Using data from two clinical trials of neoadjuvant chemoradiation, the current authors previously demonstrated that serum CA 19-9 levels can provide some clinically relevant prognostic information in patients with potentially resectable PDAC treated with NT.[2,18–20] On this basis, the present study was conducted to verify the hypothesis that a change in CA 19-9 during NT can be used as a surrogate marker of tumour biology and response to therapy in patients with borderline resectable PDAC. The first objective of this analysis was to evaluate the change in serum CA 19-9 from baseline following NT in patients treated for borderline resectable PDAC. The primary aim was to evaluate the association between CA 19-9 levels and survival in this important group of patients.

Materials and methods

Patient selection and definitions

This study was approved by the institutional review board of the University of Texas MD Anderson Cancer Center (MDACC). The institution's prospectively maintained pancreatic translational database[21] was queried for all patients with PDAC who were treated with neoadjuvant chemotherapy and/or chemoradiation and subsequently underwent restaging and consideration for surgery during the period 2001–2010. Strict anatomic staging criteria were assessed by multi-detector, contrast-enhanced computed tomography (CT).[12,17] Included in this study were all patients who presented with primary tumour anatomy that met either MDACC criteria[11,12] or those of the Americas Hepato-Pancreato-Biliary Association (AHPBA), the Society of Surgical Oncology (SSO) and the Society for Surgery of the Alimentary Tract (SSAT)[10] for borderline resectable PDAC (Table 1), in whom serum CA 19-9 was assayed both prior and subsequent to the delivery of NT, and in whom an abnormal CA 19-9 level (defined as $\geq$40 U/ml) prior to treatment was established. Patients with baseline CA 19-9 levels obtained in association with a total bilirubin level of >2 mg/dl were excluded as biliary obstruction can lead to an artificial increase in serum CA 19-9 (Fig. 1).[22]

Neoadjuvant therapy and treatment schema

The current authors routinely treated patients with potentially or borderline resectable PDAC with chemoradiation prior to surgical resection. Systemic chemotherapy was delivered selectively prior to chemoradiation, most commonly to patients meeting MDACC anatomic or clinical criteria for borderline resectable disease.[11,12,18,20] Biliary decompression was generally accomplished with a metal endobiliary stent prior to the initiation of therapy.

The patients reported in this study received chemoradiation based on gemcitabine or 5-fluorouracil with or without induction gemcitabine-based systemic chemotherapy in the neoadjuvant setting.[19,20,23] Prior to ('pre-NT') and following ('post-NT') the administration of NT, patients underwent a comprehensive staging evaluation that routinely included a measurement of serum CA 19-9. Serum samples acquired prior to 6 October 2004 were assayed for CA 19-9 by Quest Diagnostics, Inc. (Madison, NJ, USA). Subsequent samples were assayed using a similar method at MDACC.

Criteria for surgical resection following completion of NT included: (i) a performance status sufficient for major abdominal surgery; (ii) the adequate optimizing of comorbidities, and (iii) no radiographic or intraoperative detection of tumour progression.[18] Serum CA 19-9 was not used as a primary criterion for surgery.

Follow-up

Following resection, patients were evaluated in an intensive surveillance programme every 3–4 months, with an institutional bias