Utility of Tumor Markers in Determining Resectability of Pancreatic Cancer

Michael G. Schlieman, MD; Hung S. Ho, MD; Richard J. Bold, MD

Hypothesis: Despite advances in preoperative radiologic imaging, a significant fraction of potentially resectable pancreatic cancers are found to be unresectable at laparotomy. We tested the hypothesis that preoperative serum levels of CA19-9 (cancer antigen) and carcinoembryonic antigen will identify patients with unresectable pancreatic cancer despite radiologic staging demonstrating resectable disease.

Design and Setting: Academic tertiary care referral center.

Patients: From March 1, 1996, to July 31, 2002, 125 patients were identified who underwent surgical exploration for potentially resectable pancreatic cancer based on a preoperative computed tomographic scan; in 89 of them a preoperative tumor marker had been measured.

Main Outcome Measures: Preoperative tumor markers (CA19-9 and carcinoembryonic antigen) were correlated with extent of disease at exploration. As CA19-9 is excreted in the biliary system, CA19-9 adjusted for the degree of hyperbilirubinemia was determined and analyzed.

Results: Of the 89 patients, 40 (45%) had localized disease and underwent resection, 25 (28%) had locally advanced (unresectable) disease, and 24 (27%) had metastatic disease. The mean adjusted CA19-9 level was significantly lower in those with localized disease than those with locally advanced (63 vs 592; \( P = .003 \)) or metastatic (63 vs 1387; \( P < .001 \)) disease. When a threshold adjusted CA19-9 level of 150 was used, the positive predictive value for determination of unresectable disease was 88%. Carcinoembryonic antigen level was not correlated with extent of disease.

Conclusions: Among the patients with resectable pancreatic cancer based on preoperative imaging studies, those with abnormally high serum levels of CA19-9 may have unresectable disease. These patients may benefit from additional staging modalities such as diagnostic laparoscopy to avoid unnecessary laparotomy.

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Pancreatic cancer is a lethal disease for which the death rate approaches the incidence. For the minority of patients who present with localized disease, surgical resection offers the only chance of cure. Unfortunately, determining which patients have localized disease is not straightforward, and often occult metastases are discovered during laparotomy. Current staging with the use of bolus-contrast, triple-phase helical computed tomography (CT) is only 75% to 80% accurate at determining resectability, and further radiologic and endoscopic staging procedures have not significantly improved the accuracy.\(^1\)\(^2\)\(^3\)

Therefore, approximately one quarter of patients will have unresectable tumors discovered at the time of operation and may have endured an unnecessary laparotomy.\(^1\)\(^2\)\(^3\) This issue is important because recovery from the unnecessary laparotomy further delays palliative systemic therapy. Various screening modalities have been promoted, such as laparoscopy, though the yield of such studies remains less than 15%\(^2\)\(^4\)\(^5\).

The 2 most studied tumor markers that have been evaluated in the diagnosis and prognosis of patients with pancreatic cancer are carcinoembryonic antigen (CEA) and CA19-9 (cancer antigen). Carcinoembryonic antigen is an acid glycoprotein in the periphery of the tumor cell membrane, where it is released into surrounding body fluids. Its level is elevated in cancers from several organs, including colon, breast, lung, ovary, and pancreas, where the level is elevated in 50% of patients. CA19-9 is a monosialoganglioside/glycolipid that can be detected in low levels in healthy individuals (<40 U/mL), and the level is elevated in several types of can-
cancer, including pancreatic, hepatocellular, gastric, colorectal, and ovarian. Elevated CA19-9 levels can also be seen in benign conditions of extrahepatic biliary obstruction such as pancreatitis and cholelithiasis. This has limited the diagnostic utility of CA19-9 in patients who present with biliary obstruction of unclear cause. Several studies have shown that high levels of CA19-9 (>300 U/mL) correlate with advanced disease. However, most of these studies included patients with known metastatic disease. Only Forsmark et al examined CA19-9 levels in patients with potentially resectable disease by preoperative imaging, but the sample size was too small to offer meaningful analysis. To date, to our knowledge, has specifically correlated preoperative CEA or CA19-9 levels with the extent of disease in patients whose disease was deemed potentially resectable by preoperative radiographic studies. Therefore, we tested the hypothesis that preoperative serum levels of CA19-9 and CEA are significantly elevated in patients with unresectable pancreatic cancer despite radiologic staging demonstrating resectable disease.

**METHODS**

This was a retrospective study of 125 consecutive patients seen at an academic tertiary care referral center from March 1, 1996, to July 31, 2002, with potentially resectable adenocarcinoma of the pancreas. Pancreatic adenocarcinoma was histologically confirmed by pathologic examination of the resected specimen or, if unresected, by intraoperative biopsies; all other histologic variants were excluded from the analysis. Patients with primary duodenal cancer, ampullary cancer, or tumors of the distal bile duct were also excluded. All patients' tumors were determined to be potentially resectable by the operating physician with the use of at least a preoperative bolus-contrast, triple-phase, helical CT scan. Resectability was defined as a tumor limited to the pancreas (no extension to the superior mesenteric or portal vein or superior mesenteric artery) without evidence of celiac nodal, peripancreatic, or hepatic metastasis. All patients were then operatively staged by laparotomy (86 patients) or diagnostic laparoscopy (3 patients). Patients with resectable disease underwent either pancreaticoduodenectomy (36 patients) or distal pancreatectomy (4 patients) on the basis of tumor location (Table 1). Tumors were considered unresectable if the patient was found to have metastases (liver, peritoneum, or celiac lymph nodes) or local invasion defined as involvement of the primary tumor with the superior mesenteric artery, superior mesenteric vein, or portal vein. All patients who underwent resection of any part of the portal vein or superior mesenteric vein with or without venous bypass were excluded.

Laboratory results were reviewed for preoperative CA19-9, CEA, and total bilirubin levels drawn simultaneously and within 2 weeks before surgery. Of the 125 patients, 89 had preoperative CA19-9 and total bilirubin levels drawn; 65 of these had preoperative CEA levels. As both CA19-9 and CEA undergo some degree of biliary excretion, levels may be artificially elevated because of the biliary obstruction caused by the tumor and therefore may not accurately reflect tumor volume. To adjust for the effect of biliary obstruction on serum levels of CA19-9 and CEA, we developed an adjusted CA19-9 or CEA to account for the degree of biliary obstruction. A threshold of serum bilirubin level of 2.0 mg/dL (34.2 µmol/L) for adjusting the tumor markers was based on the reference range of bilirubin levels reported by our clinical laboratory (0.3-1.3 mg/dL [5.1-22.2 µmol/L]) and reported alteration in the pharmacokinetics of various medications and their metabolites in the setting of hyperbilirubinemia caused by biliary obstruction.

Of the 89 patients, 24 (27%) were found to have metastatic disease at the time of operative exploration despite preoperative radiologic imaging demonstrating only localized disease (Table 1). An additional 25 patients (28%) were found to have locally advanced, unresectable disease, and the remaining 40 patients (45%) had localized disease and underwent resection of the primary tumors (Table 1). Immediately before exploration, 35 (39%) of the 89 patients had total bilirubin levels of 2 mg/dL or more. Most patients had normal bilirubin levels because of the liberal use of preoperative biliary drainage, and therefore CA19-9 and CEA levels were not obtained until the time of evaluation by a surgeon, at which time the jaundice had resolved because of the biliary drainage. The median CA19-9 level for all patients was 182 U/mL, with a mean of 1037 U/mL. For the patients with localized disease who underwent surgical resection, the median preoperative CA19-9 level was 73.5 U/mL, with a mean level of 386 U/mL. Of the patients with unresectable disease had a 5-fold higher preoperative serum level of CA19-9, with a median of 374 U/mL and mean of 1568 U/mL (P<.001). When patients with unresectable tumors were divided according to locally advanced or metastatic disease, the mean CA19-9 values seemed to correlate with extent of disease; the mean

**RESULTS**

![Table 1](http://archsurg.jamanetwork.com/pdfaccess.ashx?url=/data/journals/surg/9547/)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Finding</th>
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<tbody>
<tr>
<td>Total No. of patients</td>
<td>89</td>
</tr>
<tr>
<td>Sex, No. M/F</td>
<td>41/48</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>63 ± 13</td>
</tr>
<tr>
<td>Disease state, No. (%)</td>
<td>40 (45)</td>
</tr>
<tr>
<td>Localized</td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td></td>
</tr>
<tr>
<td>Location of resected tumors (surgical procedure), No. (%)</td>
<td>36 (88)</td>
</tr>
<tr>
<td>Head (pancreatoduodenectomy)</td>
<td></td>
</tr>
<tr>
<td>Body (distal pancreatectomy)</td>
<td></td>
</tr>
<tr>
<td>Tail (distal pancreatectomy)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin ≥2 mg/dL (≥34.2 µmol/L), No. (%)</td>
<td>35 (39)</td>
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level of patients found to have locally advanced disease was 1090 U/mL, while the mean CA19-9 was 2066 U/mL for patients with metastatic disease (Table 2).

Of the 40 patients with localized disease, 18 (45%) were found to have preoperative bilirubin levels of 2 mg/dL or more; the mean preoperative CA19-9 level in these patients was 775 U/mL compared with 69 U/mL in patients without preoperative hyperbilirubinemia (P = .08). When the CA19-9 level was adjusted for hyperbilirubinemia, the mean adjusted CA19-9 level for patients who underwent resection was 63. The mean adjusted CA19-9 level for all patients with unresectable disease was 981, which was 15-fold higher than that of patients with localized disease (P < .001) (Table 2). The magnitude of the elevation of adjusted CA19-9 also correlated with the extent of disease, as patients who did not undergo resection because of local invasion had a mean value of 592, while patients who did not undergo resection because of metastases had a mean value of 1387 (Table 2). The relationship between the elevation of the adjusted CA19-9 level and resectability had a greater degree of discrimination than that of simple serum levels of CA19-9 (Figure 1). Of the 40 patients who had localized disease and underwent resection, 15 (38%) had preoperative CA19-9 levels greater than 150 U/mL; only 4 (10%) had preoperative adjusted CA19-9 levels greater than 150.

If a value of CA19-9 of 150 U/mL is used as a threshold for predicting unresectability, then this preoperative tumor marker has a sensitivity of 71% and specificity of 68%. When the same threshold value is applied to the adjusted CA19-9, then the specificity improves to 90%, although the sensitivity decreases to 59%. Figure 2 demonstrates how preoperative levels of adjusted CA19-9 are associated with the operative finding of resectability in our cohort of 89 patients. Of the 33 patients with an adjusted CA19-9 level greater than 150, 29 had unresectable disease; the positive predictive value of elevated adjusted CA19-9 level with the operative finding of unresectable pancreatic cancer was 88%. Furthermore, of these 33 patients with an elevated adjusted CA19-9 level, 16 (48%) were found to harbor metastatic disease. Therefore, this group may warrant additional staging mo-

<table>
<thead>
<tr>
<th>Variable</th>
<th>CA19-9, U/mL</th>
<th>Adjusted CA19-9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Resected (n = 40)</td>
<td>73.5</td>
<td>386 ± 1169</td>
</tr>
<tr>
<td>Unresected (n = 49)</td>
<td>374</td>
<td>1568 ± 2979 (P &lt; .001)</td>
</tr>
<tr>
<td>Locally advanced (n = 25)</td>
<td>336</td>
<td>1090 ± 1541 (P = .003)</td>
</tr>
<tr>
<td>Metastatic (n = 24)</td>
<td>431</td>
<td>2066 ± 3942 (P &lt; .001)</td>
</tr>
</tbody>
</table>

*P values are shown for comparison with the resected group.

Figure 1. Distribution of preoperative serum CA19-9 (cancer antigen) levels (A) and preoperative adjusted CA19-9 levels (B) in patients who underwent exploration for potentially resectable pancreatic cancer. One patient in the resected group and 7 in the unresected group had CA19-9 levels greater than 3000 U/mL; none in the resected group and 3 in the unresected group had adjusted CA19-9 levels greater than 3000.

Figure 2. Operative findings in the 89 patients who underwent exploration for potentially resectable pancreatic cancer separated by the presence or absence of elevated preoperative adjusted CA19-9 (cancer antigen) levels. PPV indicates positive predictive value; NPV, negative predictive value.
dalties, such as diagnostic laparoscopy, to avoid an unnecessary laparotomy.

The CEA level was elevated in 32 (49%) of the 65 patients with pancreatic adenocarcinoma in whom it was measured. The mean CEA level for resectable tumors (33 patients) was 5.8 ng/mL compared with 18.1 ng/mL for unresectable tumors (P = .06). The mean CEA level was 5.3 ng/mL for patients found to have metastatic disease (15 patients), and 29.4 ng/mL for patients with locally advanced, unresectable disease (17 patients). Although studies have suggested that hyperbilirubinemia can increase CEA level, we saw no difference when we determined the adjusted CEA level and correlated this with extent of disease.

**COMMENT**

The current evaluation of resectability for patients with pancreatic adenocarcinoma involves at least a helical, contrast-enhanced CT scan. Although technology for this imaging modality has tremendously improved during the last 2 decades, it still misses occult peritoneal or liver metastatic disease (<1 cm) in 4% to 15% and occult vascular involvement in 4% to 19% of the cases. Other modalities of preoperative staging, such as positron emission tomographic scanning and laparoscopy, are being evaluated to improve the detection of unresectable disease. Even when state-of-the-art imaging is available, a substantial number of patients are still found to have occult metastatic disease at the time of surgical exploration. Therefore, we hypothesized that excessively elevated preoperative serum levels of the tumor markers CA19-9 and CEA can be used as an adjunct indicator of unresectable pancreatic adenocarcinoma for the patients deemed to have localized disease on the basis of preoperative CT scan.

Since the first means of antibody detection for CA19-9 was described in 1979, it has been found to be the most useful tumor marker in the diagnosis, prognostic prediction, and evaluation of recurrent disease of pancreatic adenocarcinoma. In one of the first studies evaluating CA19-9 as a prognostic indicator, Steinberg et al. studied 37 patients with any stage of pancreatic adenocarcinoma and found that patients with metastatic disease had a higher mean CA19-9 level (1656 U/mL) than those with resectable disease (423.8 U/mL). During the next 10 years, studies by Tian et al., van den Bosch et al., and Safi et al. demonstrated similar results. However, these studies included patients with radiologic evidence of metastatic disease and did not specifically analyze the group of patients with potentially resectable pancreatic cancer on the basis of preoperative imaging studies. Other studies followed, attempting to determine a cutoff value to determine unresectability, and demonstrated the threshold of CA19-9 level that is associated with metastatic disease to be as low as 37 U/mL and as high as 1000 U/mL. The only report that attempted to determine the threshold CA19-9 level associated with potentially resectable disease examined a subset of 25 patients who appeared to have resectable tumors by radiographic criteria but were found to have unresectable disease on exploration. In these 25 patients, 18 (72%) had a CA19-9 level greater than 300 U/mL. This study involved only a small subset of patients and did not compare them with patients found to have resectable disease at exploration.

Elevated CA19-9 level is not consistently observed for patients with metastatic disease for several reasons. First, patients who are negative for Lewis antigen (a-, b- do not synthesize CA19-9, and this constitutes 4% to 15% of the population. We did not test for Lewis antigen status in our study. Second, hyperbilirubinemia either of benign cause or from malignant obstruction of the common bile duct elevates CA19-9 level. This is believed to be due to hepatic insufficiency to degrade and secrete CA19-9. Several studies have shown that the association of elevated levels of CA19-9 with the diagnosis of pancreatic cancer is significantly obscured in the face of obstructive jaundice, and the cutoff value should be adjusted for hyperbilirubinemia. We have attempted to adjust for this in our study, and this has not been done by any study to date, to our knowledge, evaluating the prognostic value of CA19-9. Third, some patients who are positive for Lewis antigen do not excrete significant levels of CA19-9 despite advanced disease. Whether this is due to CA19-9 not being formed or not being secreted, or antibodies binding to CA19-9 and making it undetectable, is unknown.

The use of diagnostic laparoscopy has been proposed to diagnose occult metastases to decrease the number of unnecessary laparotomies. Although some studies showed the yield of diagnostic laparoscopy to be high, more recent studies have shown that it would only spare 4% to 13% of patients, assuming laparoscopy to be 100% accurate. As a result, this has spurred a considerable debate, but there is a consensus that better patient selection is necessary to improve the yield of diagnostic laparoscopy. The data in our study suggest that an elevated CA19-9 level may be used as a possible selection criterion for diagnostic laparoscopy.

If diagnostic laparoscopy had been performed on the 33 patients with preoperative adjusted CA19-9 levels greater than 150, metastatic disease may have been identified that altered surgical therapy. Sixteen of these 33 patients were found to harbor metastatic disease, with 14 of these found to have either peritoneal or hepatic metastases that could have easily been identified during laparoscopy. This preoperative stratification improves the yield of staging laparoscopy to as high as 42%, sparing almost half of the patients an unnecessary laparotomy. The yield may have been further increased if any of the patients with locally advanced, unresectable disease could have been identified, by means of such maneuvers as laparoscopic ultrasound with an overall positive predictive value of 88%. The role of palliative biliary and/or enteral bypass in patients with unresectable pancreatic cancer is still an area of controversy. Our opinion is that the goal of preoperative evaluation should be the initiation of appropriate therapy, whether surgery for localized disease or chemotherapy for unresectable disease. Patients who are found to harbor metastatic disease at laparoscopy can undergo palliation via endoscopic techniques and rarely require additional surgical therapy. Therefore, CA19-9, but not CEA, is a useful adjunct to other preoperative...
studies in determining which patients with potentially resectable pancreatic adenocarcinoma by preoperative CT scan may actually have advanced disease. Accounting for the degree of hyperbilirubinemia also increases the yield of preoperative serum CA19-9 level as a selection criterion for additional preoperative staging.

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REFERENCES


DISCUSSION

L. William Traverso, MD, Seattle, Wash: The authors have provided a much-needed guideline to allow these patients to begin the correct treatment for their stage of disease. There are 3 stages of pancreatic cancer that a surgeon must know to plan treatment—local tumor that can be resected; locally advanced tumor that cannot be resected but can be treated with chemoradiation therapy; and distant disease from the primary, usually in the liver, that is treated with dual-drug chemotherapy, which is surprisingly effective. No matter what stage of tumor is finally discovered in patients with pancreatic cancer, we have a treatment and all of these treatments are proving to be increasingly effective. My goal for these patients is to not delay them from starting on the correct treatment, particularly the delay by unnecessary open surgery within the group of patients with tumors that are not resectable. This is where this UC Davis study is particularly important.

The authors have provided a solution to that unnecessary delay dilemma. Patients with biliary lesions that are resectable by CT have about a 10% chance of having liver metastases. I would like to discover these hepatic metastases with laparoscopy and get them onto dual-drug therapy without delay. To laparoscopes everyone who is resectable by CT is not indicated, since 90% would not benefit. However, if they have liver metastases and obstructive jaundice, these patients are ideally decompressed with an endoscopically placed stent and then treated with dual-drug therapy. Today’s study shows that the level of serum CA19-9, no matter if adjusted or unadjusted for bilirubin, was significantly higher in the unresectable cases as compared with the much lower level of CA 19-9 in resected cases. Furthermore, if the levels were adjusted for bilirubin elevation, then this tightened the variation of CA19-9 levels among the resected cases. If a patient had a CA19-9 of greater than 150 U/mL, then the PPV was 88%. This means that about 90% of the cases with this elevation of CA19-9 will probably be in the unresected group. In this study 48% had liver metastases. This is the group that would benefit from laparoscopy because half of them would have metastatic disease that may be seen by laparoscopy. These people would not have treatment delayed by open surgery and could be immediately started on the new regimens of dual-drug chemotherapy.

Now some questions. Why choose an adjusted level of 150 when the median adjusted level was 199? Are there some calculations not in the manuscript?
Second, the operating surgeon had to believe the patient was resectable using modern CT scanning. A major variable here is the surgeon's opinion of “resectability” after reading the CT. Therefore, how many surgeons performed these 89 operations? Was the radiologist part of the decision to deem the patient resectable by CT?

Do you have a standardized methodology for the CT of the pancreas? This is important, as the usual abdominal CT scan with oral and IV contrast is insufficient to observe pancreatic tumors.

A modern CT scan of the pancreas has methodology set to yield 3-mm cuts through the area of concern. The arterial phase has to be done at the earliest arterial peak of intravenous contrast, while the portal venous phase must follow at the time when there is early renal cortical filling. This allows the surgeon to actually see the tumor in the early arterial phase and, once located, the radiologist and the surgeon can look for loss of planes in the tumor areas on the portal venous phase. None of these phases is good to see liver involvement, as the liver must be thin-cut sectioned through its entire parenchyma in the arterial phase to see hepatic metastases. This latter weakness will be rectified with newer-generation CT scanners that have more sensors—say around 50 rather than just a few. When you get home, ask your radiologist how many sensors your scanner has.

Sherry Wren, MD, Palo Alto, Calif: Have you done an analysis of CA19-9 in pancreatic head lesions which turn out to be benign, such as chronic pancreatitis or other cystic neoplasms, especially those that have either pancreatic or biliary ductal obstructions?

Lygia Stewart, MD, San Francisco, Calif: Did you have any patients who had preoperative stenting and did you look at the CA19-9 before and after resolution of hyperbilirubinemia?

Carlos A. Pellegrini, MD, Seattle: I believe this paper advances the concept that President Russell discussed yesterday, namely, increasing the quality of the services we deliver for our patients. Saving unnecessary laparoscopies and being able to select those patients who will benefit from another test via a simple blood test is ideal. Congratulations.

Dr Ho: Members and guests of the Association. Dr Traverso wondered about the adjusted CA19-9 level of 150 vs 200. We did various analyses of different values to see which would give the best predictive value, and chose 150.

How many surgeons were involved in all of these cases? Two of us did the majority of the cases. Back in the last century, by that I mean before the year 2000, a few surgeons did one case or so. Since then, only Dr Bold and I were involved, and we agree on almost everything.

Do we involve the radiologist? Yes, we do if the CT scan was done at our institution. Typically, if the outside CT scan shows obvious unresectability, then we don’t get further CT scans. If we have a question, then we prefer our standardized CT scan protocol at UC Davis, which includes both IV and oral contrast with thin cuts through the pancreas.

It is not practical to do the same thing, ie, thin cuts, on the liver, but conceivably if you can work it out with the radiologist using this set of data, it may be worthwhile to do that in a selected group of patients.

Dr Wren, we specifically wanted to concentrate on pancreatic adenocarcinoma, so I don’t have the answer to your question.

Dr Stewart, we did not perform subgroup analysis on those with biliary stent. With regard to Dr Pellegrini’s kind comment, I, too, think that if we involve the radiologists, they are very receptive. In any kind of practice, if you come back and discuss with your colleagues what you think is benefiting the patient and then come up with a protocol, my experience is that the radiologist is quite open to that, as the end result is the overall improvement in the care of the patients.