Original Article

The Use of Tumor Markers to Assess Pancreatic Cancer Resectability

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ABSTRACT

Introduction: *Pancreatic cancer has the poorest stage-specific survival rate compared to all other solid tumors and is currently the eighth leading cause of cancer-related deaths worldwide. Thus, approximately one-quarter of patients have unresectable tumors found at surgery, potentially resulting in unnecessary laparotomy. The majority of patients have unresectable locally advanced or metastatic disease, and therefore treatment measures are purely palliative in nature.* ***Methods & Materials:*** *This comparative study was conducted from July to December 2022 at the Department of Hepatobiliary Surgery, Enam Medical College and Hospital, Savar, Bangladesh. Fifty patients were identified who underwent surgical evaluation for resectable pancreatic cancer based on preoperative computed tomography examination measuring preoperative tumor markers.* ***Results:*** *Of the 50 patients, 23 (46%) had localized disease and underwent resection, 14 (28%) had locally advanced (unresectable) disease, and 13 (26%) had metastatic disease. Mean adjusted CA19-9 levels were significantly lower in patients with localized disease than in patients with locally advanced (63 vs. 592; P = .003) or metastatic disease (63 vs. 1387; P = .003). When a threshold adjusted CA19-9 level of 150 was used, the positive predictive value for determination of un- resectable disease was 60%. Carcinoembryonic antigen level was not correlated with extent of disease.* ***Conclusion:*** *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*

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staging modalities such as diagnostic laparoscopy to avoid unnecessary laparotomy.

Keywords: *Tumor Markers, Pancreatic Cancer, Resectability.*

INTRODUCTION

Pancreatic cancer has the poorest stage-specific survival rates compared to other solid tumors and is currently the eighth leading cause of cancer-related deaths worldwide[1]. In 2014, an estimated 46,420 new cases of pancreatic cancer will be diagnosed in the United States, resulting in approximately 39,590 deaths from pancreatic cancer. This will make pancreatic cancer the fourth leading cause of cancer-related deaths in the United States[2]. Current staging using bolus contrast and triple-phase spiral computed tomography (CT) is only 75-80% accurate in determining resectability, and other radiological and endoscopic staging techniques have not significantly improved accuracy[3-5]. Approximately one-quarter of patients have unresectable tumors discovered at surgery, potentially resulting in unnecessary laparotomy[4]. This aspect is important because unnecessary laparotomy recovery further delays palliative systemic therapy. Although various screening methods such as laparoscopy are being promoted, the yield of such studies is less than 15%[4,6,7]. The majority of patients suffer from unresectable locally advanced or metastatic disease, and therefore treatment measures are purely palliative in nature. Until the past decade, gemcitabine monotherapy was the standard of care for patients with locally advanced or metastatic pancreatic cancer, due to its demonstrated improvement in overall survival (OS) compared with fluorouracil[8]. Despite the improvement in OS, the objective responses observed with gemcitabine monotherapy were undermined by the significant increased cost of combination therapy, both in terms of economic costs and impact on quality of life due to the increased side effect profile of the combination therapy. Carcinoembryonic antigen is an acidic glycoprotein located in the periphery of tumor cell membranes, from where it is secreted into the surrounding body fluids. Its levels are elevated in cancers of multiple organs, including colon, breast, lung, ovarian, and pancreatic cancer, with 50% of patients having elevated levels. CA19-9 is a monosialoganglioside/glycolipid that can be detected at low concentrations (300 U/ml) in healthy individuals and correlates with advanced disease[9-10,11]. To date, to our knowledge, there are no studies that have specifically correlated preoperative CEA or CA19-9 levels with the extent of disease in patients whose disease was deemed potentially resectable based on preoperative radiographic findings.

METHODS & MATERIALS

This was a retrospective study conducted from July to December 2022 at the Department of Hepatobiliary Surgery, Enam Medical College Hospital, Savar, Bangladesh. Fifty (50) patients who underwent surgical evaluation for resectable pancreatic cancer were identified based on preoperative computed tomography examination measuring preoperative tumor markers. Pancreatic adenocarcinoma was histologically confirmed by pathological examination of the resected specimen or by intraoperative biopsy if not resected. All other histological variants were excluded

from the analysis. Patients with primary duodenal cancer, papillary carcinoma, or distal bile duct tumors were also excluded. In all patients, the tumor was deemed potentially resectable by the surgeon using at least one preoperative triple-phase spiral CT scan with bolus contrast. Resectability was defined as tumor confined to the pancreas (no spread to the superior mesenteric vein, portal vein, or superior mesenteric artery) and no evidence of metastasis to the celiac lymph nodes, peritoneum, or liver. Tumors were considered unresectable if patients were found to have metastases (liver, peritoneum, or celiac lymph nodes) or local invasion (defined as invasion of the superior mesenteric artery, superior mesenteric vein, or portal vein by the primary tumor). All patients in whom any portion of the portal vein or superior mesenteric vein had been resected with or without a venous bypass were excluded.

Laboratory results were reviewed for preoperative CA19-9, CEA, and total bilirubin levels measured simultaneously within 2 weeks before surgery. CA19-9 and total bilirubin levels were measured preoperatively in 40 of 50 patients. Thirty-two of these patients had preoperative CEA values. Because both CA19-9 and CEA are excreted to some extent via bile, bile duct obstruction by tumors may artificially elevate levels and therefore may not accurately reflect tumor volume. Various reports have shown that bilirubin levels are a reasonable marker of altered bile excretion, with significant changes occurring at levels above 1.5 times the upper limit of normal or approximately 2.0mg/dL. Therefore, adjusted tumor marker levels (CA19-9 or CEA) in patients with bilirubin levels ≥2mg/dL (i.e., considered to have altered bile excretion) were determined by dividing serum tumor marker levels by bilirubin levels. In patients with normal biliary excretion (ie, bilirubin level <2.0 mg/dL), the actual serum tumor marker level was used. Positive predictive values and negative predictive values for determining resectability were determined with threshold values of 150 U/mL for CA19-9 and 2.5 ng/mL for CEA. Statistical analysis was initially performed by means of analysis of variance for all 3 sample groups, and subsequent Wilcoxon 2-sample test, given the possibility of a nonnormal sample distribution. Statistical significance was assumed for $P<0.05$.

RESULTS

Of the 50 patients, 13 (26%) were found to have meta- static disease at the time of operative exploration de- spite preoperative radiologic imaging demonstrating only localized disease **[Table I]**. An additional 14 patients (28%) were found to have locally advanced, unresectable disease, and the remaining 23 patients (46%) had localized disease and underwent resection of the primary tumors **[Table I]**.

Table I: Characteristics of Patients with Preoperative CA19-9 (Cancer Antigen) And Total Bilirubin Determination (*n*=50)

Characteristic	Finding
Total No. of patients	50
Sex, No. M/F	24/26
Age, y, mean ± SD	63 ± 13
Disease state, No. (%)	
Localized	23 (46)
Locally advanced	14 (28)
Metastatic	13 (26)
Location of resected tumors (surgical procedure), No. (%)	

Head (pancreaticoduodenectomy)	30 (60)
Body (distal pancreatectomy)	2 (4)
Tail (distal pancreatectomy)	1 (2)
Bilirubin ≥2 mg/dL (≥34.2 μmol/L), No. (%)	29 (58)

Immediately before exploration, 29 (58%) of the 50 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 re- section, the median preoperative CA19-9 level was 73.5 U/mL, with a mean level of 386 U/mL **[Table II]**. 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 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 II]**. Of the 23 patients with localized disease, 10 (43.4%) 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 II]**. The magnitude of the elevation of adjusted CA19-9 also correlated with the ex- tent 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 II]**. Furthermore, of these 32 patients with an elevated adjusted CA19-9 level, 18 (36%) were found to harbor metastatic disease. Therefore, this group may warrant additional staging modalities, such as diagnostic laparoscopy, to avoid an unnecessary laparotomy. The CEA level was elevated in 25 (50%) of the 50 patients with pancreatic adenocarcinoma in whom it was measured. The mean CEA level for resectable tumors (32 patients) was 5.8 ng/mL compared with 18.1 ng/mL for unresectable tumors (*P* =.66). The mean CEA level was 5.3 ng/mL for patients found to have metastatic disease (8 patients), and 29.4 ng/mL for patients with locally advanced, unresectable disease (10 patients). Although studies have suggested that hyperbilirubinemia can in- crease CEA level, we saw no difference when we deter- mined the adjusted CEA level and correlated this with extent of disease.

Table II: Preoperative CA19-9 (Cancer Antigen) and Adjusted CA19-9 Levels in Patients with Resected and Unresected Pancreatic Adenocarcinoma

Variable	CA19-9, U/mL		Adjusted CA19-9	
	Median	Mean ± SD	Median	Mean ± SD
Resected (n = 40)	73.5	386 ± 1169	25.5	63 ± 98
Unresected (n = 49)	374	1568 ± 2979 (P<.001)	199	981 ± 2340 (P<.001)
Locally advanced (n = 25)	336	1090 ± 1541 (P = .003)	156	592 ± 1157 (P = .003)
Metastatic (n = 24)	431	2066 ± 3942 (P<.001)	243	1387 ± 3114 (P<.001)

DISCUSSION

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[10,12-14]. Other methods of preoperative staging, such as positron emission tomography and laparoscopy, are currently being evaluated to improve the detection of unresectable disease. Even with the availability of state-of-the-art imaging techniques, a significant number of patients are still found to have occult metastases at the time of surgical exploration. Therefore, we hypothesized that highly elevated preoperative serum levels of the tumor markers CA19-9 and CEA could be used as additional indicators of unresectable pancreatic adenocarcinoma in patients with suspected localized disease based on preoperative CT examinations. Over the next decade, studies by Tian et al.[11], van den Bosch et al.[15]. and Safi et al.[16]. found similar results. However, these studies included patients with radiological evidence of metastases and did not specifically analyze the population of patients with potentially respectable pancreatic cancer based on preoperative imaging studies. There are three stages of pancreatic cancer that surgeons need to know about in order to plan treatment: locally advanced tumors that cannot be removed but can be treated with chemotherapy and radiation therapy; and tumor removal from the primary tumor, usually in the liver, and treatment with incredibly effective two-drug chemotherapy. No matter what stage of tumor is ultimately found in a pancreatic cancer patient, there are treatments, and all of these treatments are proving increasingly effective. My goal with these patients is to discourage appropriate treatment, especially unnecessary open surgery for the group of patients with unresectable tumors. This study from UC Davis is particularly important in this regard. It is believed that this is because the liver cannot break down and secrete CA19-9[17]. Some studies have shown that the association between elevated CA19-9 levels and the diagnosis of pancreatic cancer is significantly unclear in obstructive jaundice and that the cutoff value needs to be adjusted in hyperbilirubinemia[18]. We have tried to take this into account in our study, but to our knowledge, this has not been done in studies evaluating the prognostic value of CA19-9. Third, some patients who are

Lewis antigen positive do not excrete significant levels of CA19-9, even as the disease progresses. It is unclear whether this is because CA19-9 is not produced or secreted, or because antibodies bind to CA19-9 and make it undetectable[17]. To reduce the number of unnecessary laparotomies, the use of diagnostic laparoscopy to diagnose occult metastases has been proposed. Although some studies have shown that diagnostic laparoscopy is highly beneficial[19-21]. recent studies have shown that, assuming a 100% survival rate with laparoscopy, it only saves 4-13% of patients[4,13]. This has generated considerable debate, but there is consensus that better patient selection is necessary to improve the diagnostic yield of laparoscopy. Data from our study suggest that elevated CA19-9 levels can be used as a selection criterion for laparoscopy. This preoperative stratification would increase the yield of staged laparoscopy by up to 42%, saving almost half of the patients from unnecessary laparotomy. The yield could have been further increased if a proportion of patients with locally advanced unresectable disease had been identified using measures such as laparoscopic ultrasound[22], with an overall positive predictive value of 88%. The role of palliative biliary and/or enteric bypass in patients with unresectable pancreatic cancer remains controversial. In our opinion, the goal of preoperative evaluation should be to initiate appropriate treatment, whether surgery for localized disease or chemotherapy for unresectable disease. Patients with metastases detected during laparoscopy can be treated palliatively using endoscopic techniques and rarely require additional surgical treatment[23]. Therefore, CA19-9 (but not CEA) is a useful addition to other preoperative tests to determine which patients with pancreatic adenocarcinoma resectable by preoperative CT examination actually have advanced disease. Taking into account the degree of hyperbilirubinemia also increases the yield of preoperative serum CA19-9 levels as a selection criterion for additional preoperative staging. Moreover, adjusting for the value of bilirubin level reduced the variability of CA19-9 levels between resected cases. If the patient had a CA19-9 level above 150 U/mL, the PPV was 88%. This means that about 90% of cases with elevated CA19-9 belong to the probably non-resected group. In this study, 48% had liver metastases. Half of this group has metastatic disease that can be visualized by laparoscopy, so this group would benefit from laparoscopy. For these people, open surgery would not delay treatment and the new doublet chemotherapy could be started immediately.

Conclusion:

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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