ORIGINAL ARTICLE

Downstaging Chemotherapy and Alteration in the Classic Computed Tomography/Magnetic Resonance Imaging Signs of Vascular Involvement in Patients With Pancreaticobiliary Malignant Tumors

Influence on Patient Selection for Surgery

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Objectives: To determine whether computed tomography (CT)/magnetic resonance imaging (MRI) signs of vascular involvement are accurate after downstaging chemotherapy (DCTx) and to highlight factors associated with survival in patients who have undergone resection.

Design: Retrospective cohort study; prospective database.

Setting: University pancreatic disease center.

Patients: Patients with unresectable pancreaticobiliary cancer who underwent curative intent surgery after completing DCTx.

Interventions: Use of CT/MRI scan, pancreatic resection, and palliative bypass.

Main Outcome Measures: Resectability after DCTx and disease-specific survival.

Results: We operated on 41 patients (1992-2009) with locally advanced periampullary malignant tumors after a median of 8.5 months of DCTx. Before DCTx, most patients (38 [93%]) were unresectable because of evidence of vascular contact on CT/MRI scan or operative exploration. Criteria for exploration after DCTx were CT/MRI evidence of tumor shrinkage and/or change in signs of vascular involvement, cancer antigen 19-9 decrease, and good functional status. None had progressive disease. At operation, we resected tumors in 34 of 41 patients (83%), and 6 had persistent vascular involvement. Surprisingly, CT/MRI scan was only 71% sensitive and 58% specific to detect vascular involvement *after* DCTx. "Involvement" on imaging was often from tumor fibrosis rather than viable cancer. Radiographic decrease in tumor size also did not predict resectability ($P=.10$). Patients with tumors that were resected had a median 87% decrease in cancer antigen 19-9 ($P=.04$) during DCTx. The median follow-up (all survivors) was 31 months, and disease-specific survival was 52 months for patients with resected tumors.

Conclusions: In patients with initially unresectable periampullary malignant tumors, original CT/MRI signs of vascular involvement may persist after successful DCTx. Patients should be chosen for surgery on the basis of lack of disease progression, good functional status, and decrease in cancer antigen 19-9.

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PANCREATIC DUCTAL ADENOCARCINOMA (PDAC) is the fourth most common cause of cancer-related deaths in the United States, with an overall 5-year survival of less than 4%.[1] Cholangiocarcinoma, often indistinguishable preoperatively from PDAC occurring in the head of the pancreas, is much less common than PDAC, but the average 5-year survival is equally poor (5%-10%).[2] Cure of either requires surgical resection, although 80% to 85% of patients with these tumors present with either distant metastatic or locally advanced disease and are not candidates for tumor removal.[3,4] Locally advanced disease usually precludes resection because the tumor involves the major abdominal vasculature. In tumors in the head of the pancreas, these vessels include the portal and superior mesenteric veins and the celiac and/or superior mesenteric and hepatic arteries. In the body of the pancreas, the celiac and/or superior mesenteric and hepatic arteries and the splenoportal venous confluence are more commonly involved. The issue usually is not whether involved segments of vessels can be resected safely, along with the adherent tumor. Usually they can be. Instead, it is the empirical observation that none of these

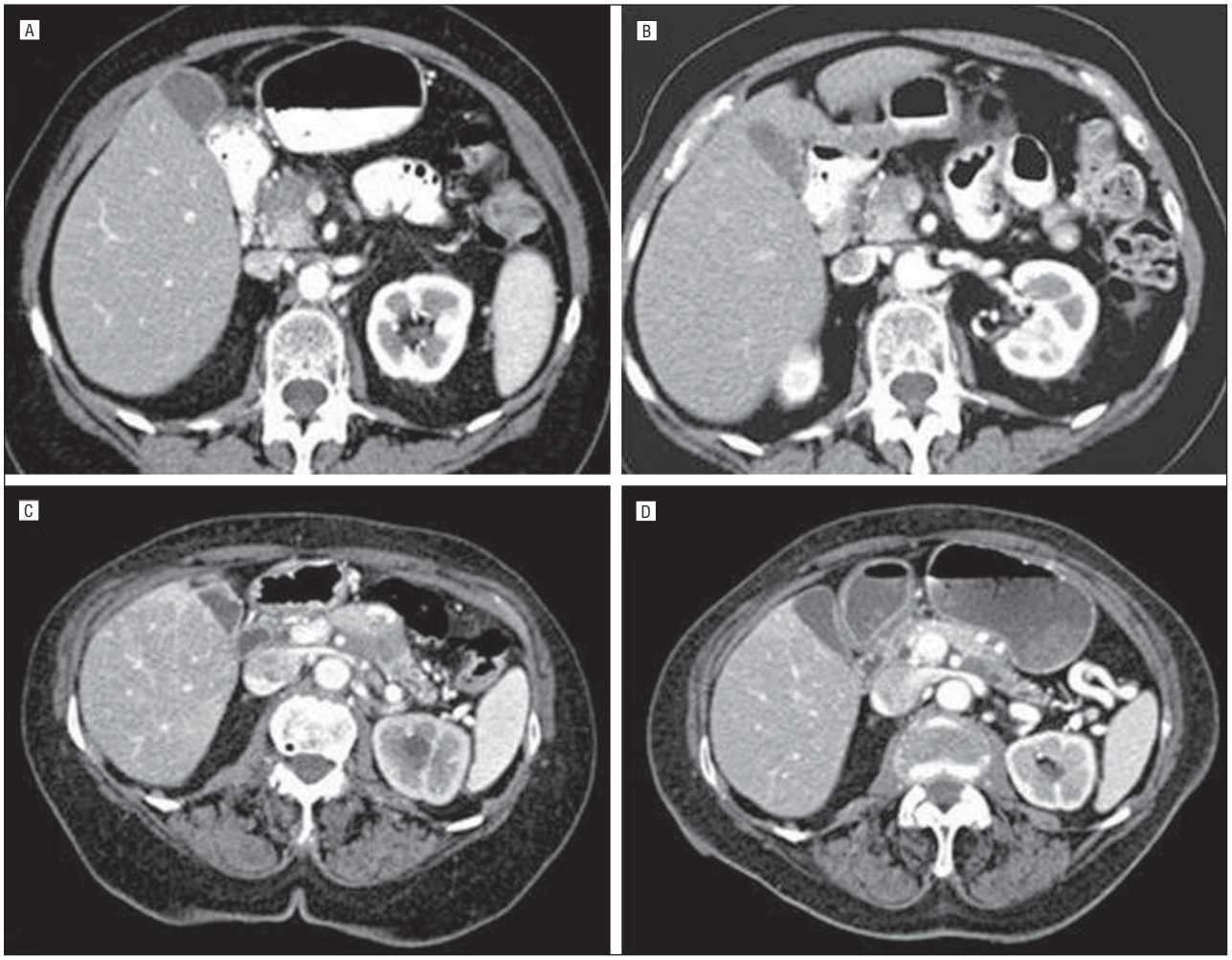

Figure 1. Pretreatment and posttreatment high-resolution computed tomography (CT) scans. A and B, A patient with a borderline resectable pancreatic cancer in the head of the pancreas that abuts the superior mesenteric vein. A, The pretreatment CT scan shows 50% superior mesenteric vein impingement with vessel deformity. B, The posttreatment CT scan (5 months later) shows persistent haziness around the superior mesenteric vein. C and D, A patient with a borderline resectable pancreatic cancer in the body/tail of the pancreas. C, The pretreatment CT scan shows abutment of the superior mesenteric vein. D, The posttreatment CT scan (9 months later) shows persistent haziness around the superior mesenteric vein. Both patients underwent an R0 resection after treatment without vascular resection.

patients appear to be cured by such resections, and the cancer invariably recurs.

For that reason, many surgeons prefer to treat patients with such locally advanced disease with a regimen of chemotherapy, in some cases combined with radiation, in an effort to downstage the disease before reconsidering exploration[5-7] (**Figure 1**). In this highly selected group of patients, resection of these pancreaticobiliary malignant tumors, occasionally with vascular resection, is being performed with increasing frequency.[8-11] Although the benefit of this approach is still unknown, there are single-institution reports of long-term survivors and possible cures.[5] Since 1992, as our own experience with this approach has evolved, and with increasing numbers of patients inquiring as to their suitability for exploration, we thought that it would be useful to review our current indications for exploration in this group and the success of our strategy.

Therefore, the objectives of this study were (1) to review our experience with 41 patients with pancreaticobiliary malignant tumors that were initially unresectable who underwent a course of treatment and then were surgically explored, (2) to determine the accuracy of high-resolution computed tomography (CT)/magnetic resonance imaging (MRI) in predicting vascular involvement and resectability after treatment, (3) to identify other predictors of resectability, and (4) to highlight the factors that are associated with survival in downstaged patients whose tumors were resected.

METHODS

Using a prospectively collected database, we performed a review of all patients from 1992 to 2009 who underwent surgery after a course of treatment with chemotherapy with or without radiation therapy for pancreaticobiliary malignant tumors that were initially diagnosed as being locally advanced. Clinical, radiographic, treatment, histopathologic, and survival variables were recorded for all patients. All information was acquired from the UCLA (University of California, Los Angeles) patients' medical records. Approval from the UCLA Institutional Review Board was obtained before starting the study.

Clinical variables analyzed included age at the time of diagnosis (continuous), sex, and serum cancer antigen (CA) 19-9 levels at the time of initial diagnosis and after completing a course of treatment. Postoperative follow-up included physical examination, measurement of serum CA19-9 levels, and CT of the abdomen and pelvis at 6-month intervals for 5 years after surgery and then yearly thereafter.

All patients underwent a CT or MRI scan of the abdomen before and after completing treatment. Radiographic (CT/MRI) variables analyzed included location of the tumor (head, uncinate, body, or tail), size of the tumor (continuous), vascular contact with tumor (yes or no), and degree of vascular contact with tumor (percentage of vessel circumference). Tumor size was defined as maximum tumor diameter on cross-sectional imaging.

Treatment variables analyzed included whether the patient underwent an initial operation before downstaging (yes or no); the chemotherapy regimen administered; the duration of treatment (continuous); the addition of radiation therapy in addition to chemotherapy (yes or no); initial and downstaged operative findings, including vascular involvement, transverse mesocolon involvement, or distant peritoneal metastases; the operative procedure performed for patients with resectable tumors (a pylorus-preserving Whipple or a standard Whipple); the operative procedure performed for patients with unresectable tumors (an exploratory laparotomy, an enteric bypass, or a biliary bypass); and the estimated blood loss (continuous).

The histopathologic variables scored included the tumor type (pancreatic adenocarcinoma or cholangiocarcinoma), the microscopic surgical margins (positive or negative), lymphovascular invasion (present or absent), perineural invasion (present or absent), lymph node metastases (present or absent), microscopic evidence of residual tumor after treatment (present or absent), tumor size (continuous), and the grade of the tumor (low, intermediate, or high).

All patients had a histopathologically confirmed diagnosis. Most patients underwent a pretreatment endoscopic ultrasound–guided fine needle aspirate or core needle biopsy. An intraoperative core needle biopsy or incisional biopsy was performed for those patients who underwent an initial operation before starting treatment but who did not yet have a confirmed histopathologic diagnosis. All distant metastatic nodules were also biopsied and histopathologically confirmed for cancer. Specialized gastrointestinal pathologists prospectively evaluated specimens in a standard fashion. Each specimen was bisected along its greatest diameter, and the perimeter of the tumor was grossly defined. The entire bisected tumor was partitioned into blocks of tissue *en face* and processed for histologic examination. Tumor grade was classified as high, intermediate, or low on the basis of established criteria, including degree of differentiation, nuclear pleomorphism, and number of mitoses per high-power field.[12] For each tumor specimen, microscopic margins were also recorded. A positive microscopic margin was defined as microscopic tumor cells present at the surgical margin.

End points for evaluation included date of death due to disease and date of last follow-up. The date of death was determined from the medical records or the Social Security Death Index (http://ssdi.rootsweb.ancestry.com/cgi-bin/ssdi.cgi). Survival was measured from the date of diagnosis to the date of last follow-up or death due to disease. The date of recurrence was determined from the medical records and was based on clear evidence of recurrent local or metastatic disease on high-resolution CT/MRI. Biopsies were not routinely performed to confirm recurrence.

Disease-specific survival (DSS) was estimated using the Kaplan-Meier method and compared using the log-rank test. Comparisons between various patient characteristics were performed using the χ^2 test for dichotomous variables, the *t* test for continuous variables, and the Mann-Whitney test for ranked categorical variables.

RESULTS

CLINICAL, RADIOGRAPHIC, AND HISTOPATHOLOGIC CHARACTERISTICS OF ALL PATIENTS

From January 1, 1992, through December 31, 2009, 41 patients with locally advanced pancreaticobiliary malignant tumors underwent surgical exploration after completing a course of treatment (chemotherapy with or without radiation). Thirty-four patients (83%) had tumors that were resected ("resectable patients"), whereas 7 (17%) had tumors that were unable to be resected ("unresectable patients") because of persistent vascular (n=6) or peritoneal (n=1) involvement. The distribution of the clinical, radiographic, treatment, and pathologic survival characteristics for all 41 patients, the 34 resectable patients, and the 7 unresectable patients are illustrated in **Table 1**.

The median (range) age of the patients was 59 (44-81) years. Fifteen patients (37%) were men and 26 (63%) were women. On CT/MRI, 38 patients (93%) had lesions within the head of the pancreas and 3 (7%) had body or tail lesions. Twenty-five patients (61%) underwent an initial operation before chemotherapy, whereas 16 (39%) were deemed unresectable on the basis of CT/MRI findings of vascular contact with the tumor. At the time of the initial operation, 22 tumors were not resected because of vascular involvement and 3 tumors were not resected because of local extension into the transverse mesocolon. There were no patients with metastatic disease.

With improved high-resolution CT/MRI scans, most patients with unresectable tumors are now diagnosed on the basis of imaging results. In our series, 19 of 21 patients (90%) whose condition was diagnosed before 2005 underwent initial exploration. In contrast, 14 of 20 patients (70%) whose condition was diagnosed in 2005 or later were deemed unresectable on the basis of CT/MRI findings alone ($P<.001$). However, having an initial operation to determine that the tumor was unresectable was not associated with a greater chance of resectability after downstaging chemotherapy ($P=.09$).

Before treatment, all patients had a histopathologically confirmed diagnosis via a biopsy at the time of surgery or an endoscopic ultrasound–guided fine needle aspirate or core needle biopsy. There were 39 patients (95%) with pancreatic cancer and 2 (5%) with cholangiocarcinoma. After surgery, all patients received adjuvant treatment. All patients had a significant decrease in their serum CA19-9 levels ($P=.01$). Resected patients who had an elevated CA19-9 level before treatment had a median (range) decrease in CA19-9 level of 87% (62%-99%) ($P<.01$) during downstaging chemotherapy. We were able to obtain the CA19-9 levels for only 2 of the patients who were not resected, thus limiting the analysis for this cohort.

After completing treatment, most resected patients underwent a pylorus-preserving Whipple resection (26 [76%]). Two resected patients had persistent vascular in-

Table 1. Clinical, Radiographic, Treatment, Pathologic, and Survival Characteristics[a]

Characteristic	Patients		
	All (N=41)	Resectable (n=34)	Unresectable (n=7)
Clinical			
Age, median, y	59 (44-81)	60 (44-81)	55 (47-69)
Sex			
Male	15/41 (37)	12/34 (35)	3/7 (43)
Female	26/41 (63)	22/34 (65)	4/7 (57)
Cancer antigen 19-9 level, median (range), U/mL			
Initial	90 (5-6784)	85 (5-1456)	697 (28-6784)
Downstaged	15 (15-46)	14 (3-46)	33 (15-46)
% Change	90 (62-99)[b]	87 (62-99)	97 (95-99)[c]
Radiographic			
Location			
Head	38/41 (93)	32/34 (94)	6/7 (86)
Body/tail	3/41 (7)	2/34 (6)	1/7 (14)
Downstaged computed tomography findings			
No. of patients with such findings	32	25	7
Size, cm	1.8 (0-3.1)	1.8 (0-3.1)	1.9 (0-2.0)
% Change in size, median (range)	47.0 (0-100)	44.7 (0-100)	59.6 (50-100)
Patients with vascular involvement	16/32 (50)	12/25 (48)	4/7 (57)
Treatment			
Underwent initial operation	25/41 (61)	22/34 (65)	3/7 (43)
Chemotherapy regimen			
Gemcitabine based	20/28 (71)	17/25 (68)	3/3 (100)
Fluorouracil based	8/28 (29)	8/25 (32)	0/3
Radiation	11/41 (27)	9/34 (26)	2/7 (29)
Duration of treatment, median, mo	8.5 (4.0-29.8)	8.5 (5.4-29.8)	9.0 (4.0-14.3)
Initial operative findings			
Vascular involvement	22/25 (88)	20/22 (91)	2/3 (66)
Transverse mesocolon involvement	3/25 (12)	2/22 (9)	1/3 (33)
Time from diagnosis to operation, median, mo	9.0 (4.0-29.8)	9.0 (6.8-29.8)	10.8 (4.0-15.4)
Downstaged operative findings			
Vascular involvement	7 (17)	2 (6)	5 (71)
Peritoneal involvement	2 (5)	0	2 (28)
Procedure			
Pylorus-preserving Whipple	NA	26 (76)	NA
Whipple	NA	6 (18)	NA
Distal pancreatectomy and splenectomy	NA	2 (6)	NA
Ex-laparotomy only, with or without biopsy	NA	NA	4 (57)
Enteric bypass	NA	NA	1 (14)
Biliary bypass	NA	NA	2 (29)
Tumor type			
Pancreatic adenocarcinoma	39/41 (95)	32/34 (94)	7/7 (100)
Cholangiocarcinoma	2/41 (5)	2/34 (6)	0/7
Survival, median, mo			
Fluorouracil survivors	31 (10-200)	32 (10-200)	15 (12-45)
Disease-specific survival, %	42	52	24

Abbreviation: NA, not applicable.
[a] Data are given as number (percentage) of patients unless otherwise indicated.
[b] $P < .05$.
[c] n=2.

volvement with viable tumor on histopathologic frozen-section analysis. Thus, these patients underwent a partial venous resection. In contrast, 6 patients were unresectable because of persistent and more extensive vascular involvement, whereas 1 was unresectable because of persistent transverse mesocolon extension.

ACCURACY OF CT/MRI AFTER DOWNSTAGING CHEMOTHERAPY

An increasing number of patients with pancreaticobiliary malignant tumors are receiving a diagnosis of locally advanced *unresectable* disease using high-resolution CT/MRI scans, which eliminates the need for initial surgical exploration. However, after treatment, viable tumor may be replaced by scar tissue, and the ability of CT/MRI to differentiate living tumor from scar tissue is unknown. Thus, we examined the accuracy of CT/MRI to predict persistent vascular involvement *by viable tumor* (**Table 2**). In our series of 41 patients, there was a subset of 32 patients who had clear documentation of both CT/MRI and intraoperative findings after completing downstaging treatment. The sensitivity and specificity of CT/MRI after downstaging treatment to detect vi-

Table 2. Downstaged CT/MRI Findings

Appearance of Vascular Involvement by CT/MRI	Presence of Downstaged Operative Vascular Involvement	
	Yes	No
Yes	5	11
No	2	15

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

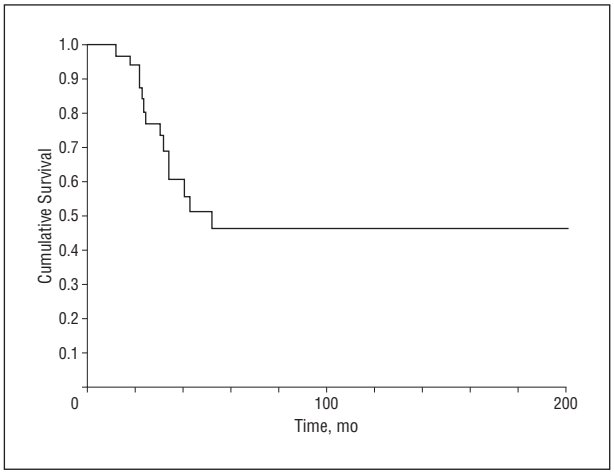

Figure 2. Kaplan-Meier plot of disease-specific survival for all 39 patients with pancreatic ductal adenocarcinoma.

able tumor were 71% and 58%, respectively. Furthermore, the positive and negative predictive values were 31% and 88%, respectively.

SURVIVAL ANALYSIS

We performed a detailed survival analysis on the subgroup of 39 patients with PDAC. The 2 patients with cholangiocarcinoma were excluded. Survival was measured from the time of original diagnosis. There were 15 patients who died of progression of disease, 1 who died from a trauma after 85 months, and 23 who were alive at the time of last follow-up. The median follow-up for surviving patients was 31 months. **Figure 2** illustrates the Kaplan-Meier DSS curve for the entire PDAC cohort (n=39). The median DSS for all patients was 42 months (Figure 2) and for resectable patients was 52 months (**Figure 3**). Only 2 of the 6 unresectable patients (median [range] DSS, 24 [12-45] months) died of disease during the study period, thus limiting survival analysis of this cohort.

The clinical and histopathologic factors that are associated with poor prognosis were evaluated for association with survival for the resectable patient cohort and are listed in **Table 3**. The only prognostic factor that was significant was the presence of lymphovascular invasion ($P=.05$). However, we observed that the survival curve for the resectable patients reached a plateau after 5 years from the time of diagnosis (Figure 3). This plateau represents 9 actual 5-year survivors, which is equivalent to a minimum 5-year survival of 28% (9 of 32). The

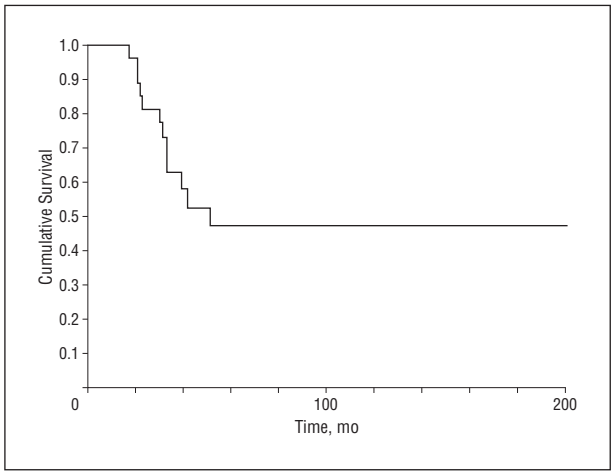

Figure 3. Kaplan-Meier plot of disease-specific survival for the 32 patients who underwent resection.

median (range) follow-up for these 9 patients was 85 (62-200) months. If one considers the 8 resectable patients with less than 5 years of follow-up from the time of diagnosis who have no evidence of disease, then the maximum 5-year survival could be as high as 53% (17 of 32). No disease-related deaths occurred among the 9 patients who survived more than 5 years from the time of diagnosis.

We next compared the poor prognostic characteristics on survival of the cohort of 9 patients who survived at least 5 years with the 12 patients who experienced a PDAC-related death within 5 years (**Table 4**). There were no significant differences. However, the presence of cancer within the lymph nodes trended toward significance ($P=.10$). All 9 patients who survived longer than 5 years did not have any evidence of lymph node metastases in the resected specimen. The median (range) number of lymph nodes sampled was 18 (4-36). Of the patients with positive lymph nodes, the median (range) number of positive lymph nodes was 1 (1-3). In fact, the absence of cancer within the lymph nodes may be a better predictor of survival and possible cure than the presence of residual tumor after treatment. Two of the 12 patients who died of disease within 5 years of diagnosis had no residual tumor after treatment. Furthermore, 5 of the 9 patients who survived at least 5 years after diagnosis had evidence of residual tumor on pathologic examination.

COMMENT

A high-resolution CT/MRI is obtained as part of the evaluation in all patients with pancreaticobiliary malignant tumors. The CT/MRI not only detects the presence of the tumor in most cases but also shows the tumor's relation to the nearby blood vessels when intravenous contrast is administered and arterial and venous phases are captured.[13-21] The radiologist often indicates that there is a "fat plane" between the tumor and blood vessel, which suggests that the 2 can be separated at operation to complete an R0 resection. Tumors without evidence of distant spread or vascular involvement are considered resectable, and these patients are generally explored.

Table 3. Univariate Analysis of Poor Prognostic Variables on Survival for 32 Resectable Patients[a]

Variable	Value	*P* Value
Age, median (range), y	59 (44-81)	.54
Sex		
Female	20/32 (63)	.20
Male	12/32 (37)	
Neo chemo type		
Gemcitabine based	15/23 (65)	.90
Fluorouracil based	8/23 (35)	
Estimated blood loss, median (range), mL	300 (60-800)	.20
Tumor location		
Head	31/32 (97)	b
Body/tail	1/32 (3)	
Margins		
Positive	4/24 (17)	.26
Negative	20/24 (83)	
Lymphovascular invasion		
Present	5/16 (31)	.05
Absent	11/16 (69)	
Perineural invasion		
Present	16/18 (89)	b
Absent	2/18 (11)	
Lymph node analysis		
Positive	6/32 (19)	.12
Negative	26/32 (81)	
Residual tumor		
No	8/32 (25)	.20
Yes	24/32 (75)	
Pathologic tumor size/residual tumor, median (range), cm	1.8 (0.1-4.5)	.30
Grade		
Low	4/18 (22)	.40
Intermediate	11/18 (61)	
High	3/18 (17)	

[a] Data are given as number (percentage) of patients unless otherwise indicated.
[b] One of the groups has a small number of patients.

Table 4. Comparison of Prognostic Factors Among Survival Cohorts[a]

Factor	<5-Year Survival (n=12)	≥5-Year Survival (n=9)	*P* Value
Age, median (range), y	67 (44-77)	59 (51-81)	.30
Sex			
Female	9 (75)	4 (44)	.20
Male	3 (25)	5 (56)	
Neo chemo type			
Gemcitabine based	5 (50)	1 (25)	.40
Fluorouracil based	5 (50)	3 (75)	
Estimated blood loss, median (range), mL	300 (75-800)	350 (300-800)	.30
Tumor location			
Head	11 (92)	9 (100)	b
Body/tail	1 (8)	0	
Margins			
Positive	1 (10)	0	.40
Negative	9 (90)	6 (100)	
Lymphovascular invasion			
Present	2 (50)	0	.10
Absent	2 (50)	4 (100)	
Perineural invasion			
Present	6 (100)	3 (75)	.15
Absent	0	1 (25)	
Lymph node analysis			
Present	2 (17)	0	.10
Absent	10 (83)	9 (100)	
Residual tumor			
Present	10 (83)	5 (56)	.16
Absent	2 (17)	4 (44)	
Pathologic tumor size/ residual tumor, median (range), cm	1.0 (0.1-3.0)	2.0 (0.1-4.5)	.50
Grade			
Low	2 (25)	0	
Intermediate	5 (63)	2 (67)	.40
High	1 (13)	3 (33)	.40

[a] Data are given as number (percentage) of patients unless otherwise indicated.
[b] One of the groups has a small number of patients.

Appropriate management for the group of patients who have locally advanced or borderline resectable disease is less clear. The classification scheme to define patients with such tumors that was developed by the National Comprehensive Cancer Network has been useful.[22] Tumors are classified as borderline resectable if 1 of the following conditions is met: (1) tumor abutment of the superior mesenteric artery, (2) severe unilateral superior mesenteric vein or portal vein impingement, (3) gastroduodenal artery encasement to its origin, or (4) invasion of the transverse mesocolon. Patients with more advanced involvement of surrounding structures are classified as having locally advanced disease. Data suggest a high likelihood of an R1 or R2 resection in patients with locally advanced or borderline resectable disease.[23] Because there is no survival benefit, we and most other physicians believe that resections should not be performed in these cases.

Since 1992, it has been our practice to recommend a minimum 6-month course of treatment in patients with locally advanced or borderline resectable tumors, in an effort to downstage the tumor. The treatment usually consists of a gemcitabine- or fluorouracil-based multidrug regimen, sometimes with the addition of radiation.[23] A number of primarily single-institution trials have examined the success rates of this approach in such patients.[5] The percentage of total patients who were eventually resected ranges from 13% to 54%. In our own experience, from 15% to 20% of patients have been downstaged to the point at which an attempt at resection seemed justified, and we report here that the median DSS of the 32 patients with PDAC who underwent resection was 52 months. There were no operative deaths. There were 9 patients with at least 5 years of survival (median follow-up, 85 months), 1 of whom died of another cause and 8 of whom are alive without evidence of disease, yielding a minimum 5-year survival of 28% (9 of 32). Furthermore, if one considers the 8 patients with less than 5 years of survival who had no evidence of disease at last follow-up, then the maximum possible 5-year survival is 53% (17 of 32). Although these data are encouraging, we recognize that they are anecdotal in nature and pertain to a small number of highly selected patients.

The question of how to choose patients for exploration who appear to have been downstaged is the principal one that stimulated the current study. In the early

years of our own experience, most of our patients were operated on and the determination that they were "unresectable because of vascular invasion or locally extensive disease" was made at the time of surgery. Usually this involved operative efforts to peel the tumor off of a major blood vessel and biopsy of the adherent tissue to confirm its nature. Many of these patients may have had less advanced disease than our more recent ones, because the vascular involvement often was not seen preoperatively or was only hinted at on the imaging studies. More recently, with technical improvements in imaging and increasing clinical experience, more patients are declared unresectable on the basis of imaging evaluation alone.[14,19,20] They are not explored. In the former group without even initial visual (CT/MRI) evidence of vascular involvement, clinical decisions about the success of downstaging therapy and whether patients should be reexplored for an attempt at resection were and still are more straightforward. They are centered primarily on performance status, the response to treatment of the CA19-9 level, and a decrease in tumor size.

In the latter group of patients, who were not explored initially because the CT/MRI imaging showed vascular involvement, decisions about the success of downstaging therapy have been more difficult. We had naively expected that the original imaging signs of vessel involvement by tumor (eg, vessel distortion, flattening, teardrop effect, or haziness adjacent to the vessel) would have disappeared completely. Our experience has shown this to be wrong. Instead, many of these signs persist, although sometimes there is some improvement noted. Indeed, we found that imaging information from CT/MRI scans was only 71% sensitive and 58% specific to detect vascular involvement *after* downstaging chemotherapy. The positive and negative predictive values were 31% and 88%, respectively. Instead, apparent persistent "involvement" on imaging was often from tumor fibrosis proven at the time of surgical resection rather than from viable cancer.

Occasionally, we have used fine-needle aspirate at the time of endoscopic ultrasound to sample the tissue adjacent to the vessels to determine whether viable cancer cells are present. If they are, we have not operated on the patient. Of course, the inability to find cancer cells does not guarantee that they are not there. Intraoperatively, it is always unclear whether the dense tissue surrounding the vessels represents scar or viable cancer, and we biopsy representative areas before committing to the resection. On occasion, when there is persistent adherence of the tissue to a major vein but we cannot prove the presence of residual cancer, we will resect the adherent portion of the vein. We will not resect the celiac or superior mesenteric artery.

Although the CA19-9 level has limited usefulness as a screening tumor marker, it is often used to measure the degree of response to treatment.[24-26] Indeed, the degree of elevation of the CA19-9 level has been shown to be associated with long-term prognosis,[27] and in patients undergoing chemotherapy, a rising serum concentration of CA19-9 often precedes the radiographic appearance of previously occult metastatic disease.[28] At the time of initial presentation, the median (range) CA19-9 level for all of our patients was 90 (5-6784) U/mL (normal range, 0-37 U/mL), and all patients had a significant decrease in their serum CA19-9 level ($P = .01$) with treatment. Resected patients who had an elevated CA19-9 level before treatment had a median (range) decrease of 87% (62%-99%) in CA19-9 level ($P < .05$) during downstaging chemotherapy. Unfortunately, we were able to obtain the CA19-9 levels for only 2 of the patients who were not resected, thus limiting the analysis for this cohort.

In conclusion, we believe that patients with local vascular involvement and initially unresectable pancreaticobiliary malignant tumors who complete a course of treatment should be chosen for surgery on the basis of lack of disease progression, good functional status, and decrease in CA19-9 level rather than of evidence that vessel involvement has disappeared on CT/MRI. In our experience, this management strategy led to a high rate of resectability and an excellent DSS of patients who underwent resection.

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