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Neoadjuvant Therapy is Associated with a Reduced Lymph Node Ratio in Patients with Potentially Resectable Pancreatic Cancer

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Abstract

Background—The use of neoadjuvant therapy (NAC) for the treatment of potentially resectable pancreatic cancer remains controversial. In this study we sought to evaluate cancer-specific end-points in patients undergoing a NAC vs. a surgery-first (SF) approach with specific emphasis on lymph node metastases.

Methods—Two hundred twenty two patients who underwent NAC and eighty-five patients who underwent SF were identified from 1990–2008 and compared for cancer-related end-points. Peripancreatic lymph nodes from one hundred thirty five neoadjuvant therapy patients were evaluated for histologic tumor regression.

Results—Patients who underwent NAC followed by surgery had improved overall survival and time to local recurrence compared to SF approach. NAC patients were less likely to have lymph node metastases ($p=0.001$), lymphovascular invasion (LVI) and had smaller tumors. On multivariate analysis, lymph node positivity was associated with SF, tumor size and the presence of LVI. NAC patient with N0 disease had equivalent outcomes to patients with a low-LNR (.01–0.15), while patients with a LNR >0.15 had reduced survival, and time to local and distant

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recurrence. 10/135 (7.4%) of NAC patients had evidence of tumor regression in at least 1 lymph node.

Discussion—Patients with potentially resectable PDAC selected to undergo NAC had improved survival and longer time to recurrence. Although some of these differences may be related to improvements in multimodality therapy completion rates, tumor regression in lymph node metastases exists and may demonstrate a biologic benefit of NAC compared to a SF approach.

INTRODUCTION

Although surgical resection remains the mainstay of therapy for patients with potentially resectable pancreatic cancer (PDAC), multimodality therapy, including chemotherapy and radiation, is associated with improved oncologic outcomes^{1–5}. Despite significant improvements in operative technique, little progress has been made in the overall survival (OS) for patients with PDAC in the last 40 years. The majority of patients develop distant metastatic disease, but up to 80% of patients will develop locally recurrent disease as well⁶, with the majority of recurrences occurring within 1–3 cm from the resection margin⁷. For patients with potentially resectable PDAC, current recommendations include a surgery first (SF) approach followed by adjuvant chemotherapy/chemoradiation⁸. However, adjuvant therapy completion rates for patients treated with a SF approach remain low, ranging from 47–60%^{1,3,9,10}. Given the disappointing results with adjuvant therapy, the use of neoadjuvant therapy has emerged as a promising alternative for the treatment of PDAC. Theoretical benefits of neoadjuvant therapy include early treatment of micrometastatic disease, selection of patients likely to manifest metastatic disease during treatment who can be spared the morbidity associated with surgical resection and potential tumor downstaging. Administration of neoadjuvant chemoradiation (NAC) is included in the NCCN guidelines for patients with borderline resectable PDAC. However, data regarding the use of NAC for patients with potentially resectable PDAC is limited. Although the feasibility and safety of NAC has been demonstrated, a potential biologic benefit of NAC remains controversial.

Recently, the lymph node ratio (LNR), defined as the number of nodes with metastatic disease among the total number of retrieved lymph nodes, has been evaluated in patients with PDAC. Although the data are conflicting, the majority of studies show that a LNR <0.2 is associated with improved prognosis compared to patients with a LNR >0.2^{11–15} and that the LNR is a stronger prognostic indicator than traditional N0/N1 stratification. However, these studies have all evaluated the LNR after a SF approach. To date, there are no data regarding the LNR as a prognostic indicator following NAC.

The presence of metastatic tumor in the peripancreatic lymph nodes is one of the strongest prognostic indicators for patients who undergo resection for PDAC⁴. Studies in the use of NAC for the treatment of breast and rectal cancer have demonstrated tumor regression in the lymph nodes following neoadjuvant treatment^{16,17}. Although this phenomenon has not been demonstrated in patients with PDAC, data regarding the importance of pathologic stage following NAC and tumor response support the concept of tumor downstaging or response as an important factor when determining overall prognosis^{18,19}.

The goal of our study was to evaluate cancer-specific end-points in patients undergoing a NAC vs. SF approach at a single-institution. In addition, we sought to evaluate the histologic effect of NAC on peripancreatic lymph nodes and the prognostic utility of the LNR on outcomes.

METHODS

This study was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center. We retrieved clinical data on all patients who underwent surgical resection for PDAC between 1990–2008 from our prospectively maintained, institutional pancreatic tumor database²⁰. In addition, all patients treated with NAC from 2002–2007 who did not undergo resection were identified and included in OS analyses. We excluded from analysis patients with a final diagnosis of invasive adenocarcinoma arising in an intraductal papillary mucinous neoplasm, mucinous cystadenocarcinoma, or any other nonpancreatic periampullary adenocarcinoma (n=12), patients that had chemotherapy or radiation prior to presentation at our institution (n=35), patients classified with borderline-resectable or locally-advanced disease (n=49) and patients that received intra-operative radiation (IORT, n=109)

Treatment Sequencing and Therapy

Most patients with potentially resectable PDAC underwent NAC prior to surgery. Patients received external-beam radiation (30 or 50.4 Gy) with concurrent gemcitabine, 5-FU or capecitabine. Gemcitabine-based, systemic chemotherapy was delivered prior to chemoradiation in selected cases. All patients underwent restaging evaluation after completion of NAC. Patients who underwent initial surgery were most often those who chose this treatment sequence but also were those in whom a cytologic diagnosis of malignancy could not be confirmed preoperatively or those in whom NAC could not be delivered effectively. The decision to administer adjuvant therapy was influenced by the prevalence of high-risk factors, the perceived benefit of adjuvant therapy, the bias of the surgeon, and the referral pattern. PD was performed using standardized technique^{21,22}. Patients were staged according to the AJCC Cancer Staging guidelines²³.

Follow-up

Following resection, patients were evaluated every 3–4 months using physical examination; chest radiography and abdominal CT and extended Intervals were to 6 months after 2 years. The development of a new low-density mass or abdominal lymphadenopathy in the region of the resected pancreas or mesenteric root was considered locoregional recurrence. A low-density mass in the liver or lungs or new-onset ascites was considered a distant recurrence. Only the first site(s) of recurrent disease was documented for this study. Time to recurrence (TTR) is defined as from the time of surgery to the time of first locoregional or distant recurrence or to the time of last contact. OS was defined as from the time of diagnosis to the time of death or to the time of last contact.

Histologic Analysis of Lymph Node Metastasis

Archival hematoxylin & eosin stained slides of lymph node sections from surgical specimens of 132 patients who underwent neoadjuvant therapy were examined. The lymph node architecture was studied carefully in all cases. A node was called positive when metastatic deposit of any size was detected by a light microscopic examination with hematoxylin & eosin stain only. For negative nodes in the group which received neoadjuvant CXRT, any node containing a geographic area of complete fibrosis (without any other associated lymph nodal pathology, like granulomas) was presumed to have a metastatic deposit originally, which had a complete response with neoadjuvant CXRT and thus was labelled as a node turning negative from presumed positive.

Statistical Analysis

Categorical variables were compared using χ^2 or Fisher's exact test; Wilcoxon's rank sum test (t-test) and the Kruskal-Wallis test (ANOVA) were used to compare the distributions of continuous variable among different groups. A logistic regression model was obtained by first including an initial set of candidate predictor variables with a p-value < 0.10 in the univariate analysis. A stepwise elimination is then performed using 0.05 for the significance level of the Wald chi-square for an effect to stay in the model. The distributions of TTR and OS were estimated by the Kaplan-Meier method and compared using the log-rank test. All tests are two sided. P-values less than 0.05 are considered statistically significant. All analyses are conducted using SAS (version 9.1, Cary, NC) software and S-Plus (Insightful Corp., Seattle, WA).

RESULTS

Demographic and Treatment Characteristics

The clinicopathologic and treatment characteristics of the 307 patients included in the study who underwent surgical resection for pancreatic PDAC are reported in Table 1. Approximately 25% of patients were treated before 2000, and this did not differ amongst the groups. All patients were classified as having potentially resectable disease based on preoperative imaging^{24,25}. Two hundred twenty-two (73%) of patients received neoadjuvant chemoradiation (NAC) and eighty-five patients (27%) had a surgery first approach (SF). Of the 222 patients receiving NAC, 94 (42%) received both preoperative systemic therapy and chemoradiation, 124 (56%) received chemoradiation alone, and four (2%) received preoperative chemotherapy alone. 25 (11%) of NAC patients received additional post-operative adjuvant therapy compared to 68% of SF (p<0.001). The demographic characteristics of patients who received NAC were similar to those who did not (p>0.05).

Pathologic Characteristics and Lymph Node Metastasis

The median tumor size was 2.8 cm (range 0–8 cm) in the NAC group compared to 3 cm in the SF group (p=0.036; Table 1). The majority of carcinomas were either moderately or poorly differentiated, which did not differ between the groups. However, patients receiving NAC were less likely to have N1 disease compared to patients who underwent SF (50% vs. 74%; p<0.001). Although there was no difference in the median number of lymph nodes

harvested between the two groups ($p=0.23$), patients undergoing SF had a greater median number of involved lymph nodes than patients who underwent NAC (1 vs. 3; $p<0.001$). In addition, patients who underwent NAC were less likely to have lymphovascular ($p<0.001$) or perineural invasion ($p<0.001$) on final pathologic analysis. The median lymph node ratio for all patients and patients with lymph node-positive disease receiving NAC was significantly lower than for patients who underwent SF (Table 1). Multivariate logistic regression was performed to evaluate for factors associated with LN positive disease (Table 2). There was a significantly lower odds of LN positive disease at resection in the NAC group ($p=0.05$), in patients without evidence of LVI ($p<0.001$), in those with smaller tumors ($p=0.004$).

Time to Cancer Progression and Survival in Relation to Neoadjuvant Therapy and Lymph Node Status

Median follow-up for all patients was 26 months (90 months for survivors). Patients treated with NAC but did not have surgical resection of their tumor had reduced survival compared to NAC + resection or SF (Fig. 1A). For patients that underwent surgical resection, the administration of NAC was associated with prolonged median OS and time to local recurrence (LR) (Fig. 1). There was no difference in time to distant recurrence (DR) for patients who underwent a SF vs. NAC-resection (Fig 1C). 2- and 5-year OS, LR and DR rates are listed in Fig. 1D.

As shown in Table 1, the median LNR was 0.03 for all patients and 0.14 for patient with lymph-node positive disease for patients undergoing NAC. As there are no data regarding the optimal cutoff point for LNR for patients who received neoadjuvant therapy, we chose the following cutoff points as they reflected the median LNR for patients with N+ disease: 0, 0.01–0.14, 0.15. A LNR 0.15 was associated with a shorter median OS and time to distant recurrence compared to patients with node-negative disease or a low-LNR (Fig. 2). Interestingly, following NAC, there was no difference in cancer-related end points for patients with N0 disease and a low-LNR (Fig. 2). For patients who underwent SF, although there was a difference in time to distant recurrence based on lymph node status, we were not able to identify any differences in OS or time to LR (data not shown). Therefore, we did not stratify these patients by LNR.

Additional factors related to local recurrence were assessed. Patients who underwent vascular resection had a trend toward reduced LR ($p=0.054$) compared with patients who did not require vascular resection (data not shown).

Lymph Node Fibrosis/Tumor Regression following Neoadjuvant Therapy

In an effort to explain decreased LN+ rate for patients who underwent NAC, we evaluated resected lymph nodes for evidence of tumor regression/fibrosis (Fig. 3). 10/135 (7.4%) of patients had evidence of intranodal fibrosis, which is consistent with regression of previous metastatic tumor.

DISCUSSION

In this study, patients with potentially resectable PDAC selected to receive NAC that underwent resection had improved OS and TTLR compared to patients treated with a SF

approach. In addition, NAC was associated with a lower incidence of LN+ disease. For patients treated with NAC who had N0 disease or a low-LNR (0.01–0.14), there was no difference in OS, TTLR or TTDR. Patients with a high-LNR (≥ 0.15) had reduced OS, TTLR and TTDR. Finally, we found evidence of lymph node fibrosis among some patients who had received NAC, indicating tumor regression. These data demonstrate a potential biologic benefit of NAC for patients with resectable PDAC.

In the treatment of patients with PDAC, the administration of multimodality therapy leads to improved OS relative to surgery alone^{1,3,5,26–28}. NAC has several potential advantages including identification of patients who are likely to benefit from surgical resection, improved multimodality completion rates and possible tumor down-staging. Previous studies have demonstrated improved multimodality therapy completion rates following NAC compared to a SF approach, which may account for some of the survival differences seen when comparing NAC and SF approaches¹. However, whether or not a potential biologic advantage to NAC exists has been debated. In this study, we found that the use of NAC with surgical resection was associated with improved LR rates compared to patients that underwent a SF approach. Although most patients with PDAC will succumb to distant disease, as many as 80% of patients will recur locally as well, highlighting the importance of local control⁶.

Lymph node status is one of the most prognostic indicators for survival for patients with resected pancreatic cancer⁴. Using a SF approach, as many as 75% of patients have evidence of lymph node involvement at the time of surgical resection^{14,15,29}. We found that NAC was associated with a reduced likelihood of LN+ disease. Other factors associated with LN+ disease included tumor size and LVI. Patients treated with NAC were significantly less likely to have LVI and had smaller tumors. This is similar to other studies that have demonstrated lower LN+ rates for patients following NAC³⁰.

The use of the LNR as a prognostic marker for patients with PDAC has had mixed results^{11–15,29,30}, but the majority of studies have shown it to be a better predictor of survival than N0/N1 status alone^{11–15,29,30}. LNR ranges used to stratify patients have varied, but usually center around a LNR of 0.2^{12,14,29}. However, to date, there are no studies that evaluate the use of the LNR following NAC. Based on the mean LNR, we chose to set a cut-off point of 0.15. Patients with N0 disease or a low-LNR (0.01–0.14) had similar outcomes in regards to OS, TTLR or TTDR. These data suggest that the LNR may serve as a better prognostic parameter following NAC than standard N0 or N1 annotation.

Tumor regression in axillary and mesorectal lymph nodes has been previously demonstrated following neoadjuvant therapy of breast and rectal cancer, respectively^{16,17}. Evidence of tumor regression or response to neoadjuvant therapy is associated with nodal fibrosis, and is distinguishable from reactive lymph nodes, which show pericapsular and subcapsular fibrosis. We found that 7.4% of patients treated with NAC had evidence of tumor regression in at least 1 lymph node. Although the number of patients that had evidence of lymph node regression is relatively low, this preliminary study is the first to demonstrate this phenomenon in patients with PDAC following NAC. Further study with a more rigorous

evaluation of the lymph nodes following NAC may yield higher percentages of patients with lymph node regression.

This study has several limitations including the retrospective nature (including non-randomization of the treatment groups), the relatively long treatment period and the variability in the use of chemotherapy. However, we feel that these limitations did not greatly affect the results of this study as most of the factors that influence the decision to offer NAC should introduce bias in favor of the SF group.

In summary, our study demonstrates in patients with potentially resectable PDAC, completion of NAC and surgical resection is associated with improved survival and time to recurrence. Although some of these differences may be related to improvements in adjuvant therapy completion rates and patient selection, tumor regression in lymph node metastases exists and may demonstrate a biologic benefit of NAC compared to a SF approach.

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Synopsis

The use of neoadjuvant therapy in patients with potentially resectable pancreatic cancer is associated with improved survival, time to local recurrence and reduced lymph node involvement.

Figure 1.

Kaplan-Meier estimate of (A) overall survival for all patients who underwent neoadjuvant therapy (NAC, all), NAC +/- resection vs. surgery first. (B, C) Kaplan-Meier estimate of time to local recurrence (B) and time to distant recurrence (C) for patients who underwent neoadjuvant therapy and resection (NAC, resected) vs. surgery first. (D) 2 & 5-year overall Survival, local and distant recurrence rates for patients who underwent NAC + resection vs. surgery first.

Figure 2.

Kaplan-Meier estimate of (A) overall survival (B) time to local recurrence and (C) time to distant recurrence for patients who underwent neoadjuvant chemoradiation stratified by LNR.

Figure 3. Hematoxylin & Eosin 40x section of lymph nodes. (A) Untreated: negative for metastasis; (B) Untreated: positive for metastasis; (C) Neoadjuvant CXRT: negative for metastasis; (D) Neoadjuvant CXRT: geographic area of fibrosis within lymph node, suggestive of treatment effect on a metastatic deposit.

Table 1

Clinicopathologic characteristics of patients with resected pancreatic adenocarcinoma by neoadjuvant chemoradiation status.

Clinical factor	Total	Neoadjuvant Chemoradiation	Surgery First	p-value*
N	307	222	85	
Gender, n (%)				0.460
Male	167 (55)	126 (56)	43 (50)	
Female	138 (45)	96 (44)	42 (40)	
Age, median (range), y	64 (35–86)	64 (35–86)	64 (40–85)	0.664
Year of Diagnosis				0.99
1990–1999		56 (25)	21 (24)	
2000–2008		166 (75)	64 (76)	
Preoperative Therapy, n (% positive)				
Chemoradiation, n (% positive)	218 (98)	218 (98)	N/A	-
Chemotherapy, n (% positive)	94 (42)	94 (42)	N/A	-
Postoperative Therapy, n (% positive)	83 (27)	25 (11)	58 (68)	<0.001
Chemoradiation, n (% positive)	40 (13)	0	39 (46)	<0.001
Chemotherapy, n (% positive)	59 (20)	23 (10)	36 (42)	<0.001
Type of resection, n (%)				0.400
Pancreaticoduodenectomy	278 (91)	204 (92)	74 (87)	
Distal pancreatectomy	27 (9)	17 (7)	10 (12)	
Total pancreatectomy	2 (1)	1 (1)	1 (1)	
Operative blood loss, median (range), mL	700 (75–18000)	700 (75–18000)	800 (100–7000)	0.362
Re-operative, n (%)	33 (11)	30 (14)	3 (4)	0.011
Pre-referral exploration	12 (4)	12 (5)	0	0.029
Pre-referral bypass	21 (7)	18 (9)	3 (4)	0.155
Vascular Resection, n (%)	92 (30)	69 (31)	23 (27)	0.491
CA 19–9, n (%)				0.131
<1000	221 (72)	165 (74)	56 (66)	
>1000	35 (11)	26 (12)	9 (11)	
Unavailable	51 (17)	31 (14)	20 (24)	
Tumor size, median (range), cm	2.8 (0–8)	2.8 (0–8)	3 (0.8–7.5)	0.036
Lymph node status, n (%)				<0.001
N0	132 (43)	112 (50)	22 (26)	
N1	175 (57)	111 (50)	63 (74)	
Margin status, n (%)				0.084
R0	275 (90)	203 (92)	72 (85)	
R1	32 (10)	19 (9)	13 (15)	
Lymphovascular invasion, n (%)				<0.001
Negative	142 (46)	118 (53)	24 (29)	

Clinical factor	Total	Neoadjuvant Chemoradiation	Surgery First	p-value*
Positive	118 (38)	68 (31)	50 (58)	
Unavailable	47 (16)	36 (16)	11 (13)	
Perineural invasion, n (%)				0.003
Negative	44 (14)	40 (18)	4 (5)	
Positive	231 (75)	156 (70)	75 (88)	
Unavailable	32 (11)	26 (12)	6 (7)	
Tumor Grade, n (%)				0.076
Well-differentiated	21 (7)	11 (5)	10 (12)	
Moderately-differentiated	187 (61)	136 (61)	51 (61)	
Poorly-differentiated	87 (28)	63 (29)	24 (27)	
Unavailable	12(4)	12 (5)	0	
Number of Positive Lymph Nodes, median (range)	1 (0–25)	1 (0–20)	3 (0–25)	<0.001
Median number of lymph nodes examined, n (range)	19 (1–55)	18 (2–55)	20 (1–48)	0.213
Lymph Node Ratio, All median (range)	0.05 (0–0.08)	0.03 (0–0.54)	0.11 (0–0.8)	<0.001
Lymph Node Ratio, N1 median (range)	0.14 (0.02–0.8)	0.13 (0.03–0.54)	0.2 (0.02–0.8)	<0.001

Table 2

Univariate & Multivariate Logistic Regression of Factors Associated with Lymph Node Positivity

		Univariate	Multivariate	
Parameter		p-value	Hazard Ratio (95% CI)	p-value
Therapy Sequence	SF	<0.001	Ref.	0.05
	NAC		0.48 (0.25–0.99)	
Post-operative chemotherapy	Neg.	0.08	Ref.	0.03
	Pos.		0.38 (0.16–0.88)	
Tumor Size	Per 20mm	0.005	2.02 (1.25–3.27)	0.004
LVI	Neg.	<0.001	Ref.	<0.001
	Pos.		6.48 (3.31–12.7)	