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Nodal downstaging as a treatment goal for node-positive pancreatic cancer

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ABSTRACT

Background: Nodal metastases portend a poor prognosis in patients with localized pancreatic cancer. Neoadjuvant therapy is associated with pathologic nodal downstaging in up to 38% of patients. However, the optimal type of neoadjuvant therapy for achieving nodal downstaging is unclear.

Methods: We conducted a retrospective cohort study of patients with nonmetastatic, clinically node-positive pancreatic cancer treated with neoadjuvant therapy and surgery identified in the National Cancer Database (2006–2014). Patients were stratified based on the neoadjuvant therapy regimens they received: multiagent chemotherapy; single-agent chemotherapy; multiagent chemotherapy with radiation; and single-agent chemotherapy with radiation. Associations between nodal downstaging and the type of neoadjuvant therapy received and overall risk of death were evaluated using multivariable regression analyses.

Results: Among the 603 pancreatic ductal adenocarcinoma patients treated with neoadjuvant therapy, 400 received multiagent chemotherapy (202 with radiation) and 203 received single agent chemotherapy (151 with radiation). Relative to multiagent chemotherapy, single-agent chemotherapy was associated with a lower likelihood of nodal downstaging (relative risk ratio 0.38 [95% CI 0.17–0.85]). Use of radiation was associated with a significantly greater likelihood of nodal response (single-agent chemotherapy with radiation: relative risk ratio 1.77 [1.36–2.30]; multiagent chemotherapy with radiation: relative risk ratio 1.91 [1.49–2.45]; radiation use overall (versus no radiation): relative risk ratio 2.12 [1.68–2.68]). Compared with patients who remained pathologically node positive after neoadjuvant therapy, node negative status was associated with a significantly lower risk of death (hazard ratio 0.61 [0.49–0.76]) regardless of whether radiation was used (hazard ratio 0.63 [0.48–0.82]) or not (hazard ratio 0.45 [0.29–0.72]).

Conclusion: Nodal downstaging is associated with a survival benefit in patients with node-positive pancreatic ductal adenocarcinoma and is most likely to be achieved with neoadjuvant therapy that includes radiation. Single-agent chemotherapy neoadjuvant therapy was least likely to result in nodal downstaging.

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Introduction

It is estimated that pancreatic ductal adenocarcinoma (PDAC) will be newly diagnosed in 55,440 patients and account for 44,330 cancer deaths in the United States in 2018.[1] Although the mortality of many cancers has dropped over the years, annual pancreatic cancer mortality in the United States during the past two decades has remained relatively unchanged, with an annual rate of 10–11 per 100,000 people.[1] Deaths from PDAC are expected to increase throughout the next 12 years, surpassing prostate and colorectal cancers in men and breast and colorectal cancers in women to become a top 3 leading cause of cancer-related death, despite projections to be tenth in incidence.[2]

Curative management for PDAC patients with localized disease consists of multimodality therapy centered around surgical resection, with other nonoperative treatment modalities administered either preoperatively or postoperatively. Although resection has traditionally been considered the most important aspect of potentially curative treatment, increasingly there is an appreciation that surgery alone is inadequate for PDAC. Even among patients with localized disease, rates of disease recurrence are high and

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long-term survival remains poor.[3] In recognition of the critical role nonsurgical therapies play, guidelines have recently proposed the use of these modalities in the neoadjuvant setting as an acceptable alternative to upfront surgery for the management of patients with potentially resectable disease.[4]

Patients with clinically positive lymph nodes may be a specific subgroup of patients with potentially resectable, localized disease for whom neoadjuvant therapy (NT) might be particularly beneficial. Earlier work has established that regional nodal metastases portend a worse prognosis for PDAC. These patients have been shown to benefit from multimodal therapy, and when nonsurgical treatment is administered in the neoadjuvant setting, conversion of nodal status from positive to negative, or nodal downstaging, may occur in more than one-third of patients.[5–7] However, currently there are little data to inform which types of NT are associated with the greatest likelihood of nodal downstaging. In particular, whether inclusion of radiotherapy as part of NT might confer a benefit remains unclear. Thus, the goals of our study were to ascertain which types of NT best achieve nodal downstaging and to assess the extent to which this response might be associated with improved survival. Our hypothesis was that the use of radiation is associated with higher rates of nodal downstaging.

Materials and Methods

Data

This was a retrospective cohort study using the National Cancer Data Base (NCDB). The NCDB is a prospectively maintained, hospital-based registry that collects data on more than 70% of incident cancers diagnosed annually. NCDB contains data from patients diagnosed with incident cancer at more than 1,500 Commission on Cancer (CoC) accredited centers in the United States. The NCDB is a joint project of the American College of Surgeons CoC and the American Cancer Society. This study was approved by the Institutional Review Board of the Baylor College of Medicine and the Michael E DeBakey VA Medical Center Research & Development Committee, Houston, TX.

Study subjects

Between 2006 and 2014, a total of 207,370 patients between the ages of 18 and 79 years with a diagnosis of PDAC were identified. We applied standard exclusions for using NCDB data (Fig 1), leaving us with a cohort of 603 patients with nonmetastatic, T1-3 clinically node-positive PDAC treated with NT. The exclusion based on treatment at the reporting facility served to optimize the accuracy of treatment ascertainment.

Variables

Patient-level information on demographic, clinical, tumors, and the use of all forms of cancer-directed therapy are provided in the NCDB. Education and income are derived from the 2012 American Community Survey. A Charlson-Deyo index is provided and used to quantify the burden of comorbid conditions. Regarding tumor-related information, there are two data points for disease staging. The first is clinical staging, which is based on the best available staging data before the initiation of the first course of treatment. The second is pathologic staging. Clinical staging data for each patient was used to restrict the cohort to those with clinically node-positive disease. Our group has evaluated the performance of clinical nodal staging for early stage PDAC as reported in the NCDB.[5] Although the NCDB does not offer details regarding which staging modalities were used (cross-sectional imaging, endoscopic ultrasound, possible tissue biopsy erroneously entered as clinical nodal status, or some combination thereof), we found that clinical nodal staging bore a low negative predictive value of 50%, but a very high positive predictive value of 95%.[5] As such, the current study seeking to evaluate the incidence of nodal downstaging among patients with cN+ disease forms a reliable premise. Pathologic staging data were then used to ascertain whether patients had a nodal response (ypN0) or not (ypN+) after NT.

In addition to being stratified by the presence or absence of pathologic nodal response, patients were also categorized by the type of NT received. NCDB does not specify the types of chemotherapy drugs used but does allow for determination of single-agent versus multiagent regimens. Thus, four NT groups were created: (1) multiagent chemotherapy (MAC); (2) single-agent chemotherapy (SAC); (3) MAC and radiation; and (4) SAC and radiation. NCDB does not provide information on whether patients who received radiation were treated with systemic therapy followed by concurrent chemotherapy and radiation or only concurrent chemotherapy and radiation. Therefore, as is routinely done using NCDB data, patients were categorized simply as having received radiation or not.

Analysis

Standard descriptive statistics were used to evaluate categorical and continuous variable distributions. The primary outcome of interest was overall survival (OS). The Kaplan-Meier method and log-rank test were used to compare OS among those who did and did not achieve a pathologic nodal response after NT. Multivariable Poisson regression with robust standard errors was used to evaluate the association between the type of NT administered and a pathologic nodal response. Poisson regression was used because the model outcome (ie, pathologic nodal downstaging) was relatively common and, in these cases, logistic regression may overestimate the strength of the association.[8–10] Model covariates were selected nonparsimoniously and included age, sex, race, insurance type, income, education, comorbidity, rurality, treatment facility type, and tumor site. The association between the presence of a pathologic nodal response and overall risk of death was evaluated using multivariable Cox regression. Similar covariates were used in addition to surgical margin status and the use of adjuvant therapy. In both the Poisson and Cox models, the type of NT was modeled in two ways: first by stratifying treatment into the four established treatment groups, and second based on the receipt of radiation or not. Finally, we performed subset analyses focusing on patients who received negative margin (R0) resection and those treated at academic/research centers.

Our cohort had a low rate of missing data, with only 6.0% of patients with at least one missing covariate data point. To address missing values, modeling was conducted in both a case-complete fashion and using multiple imputation by chained equations. Similar results were obtained and thus imputed results are presented. Statistical comparisons were two-sided and considered significant at $P < .05$. All analyses were performed using SAS v 9.4 (SAS Institute, Cary, NC).

Results

Among the 603 clinically node-positive PDAC patients, 32.8% received neoadjuvant MAC, 8.6% SAC, 33.4% MAC and radiation, and 25.0% SAC and radiation. Demographic, facility, and clinical characteristics stratified by treatment group are presented in Table I. Patients who received MAC (with or without radiation) were more frequently treated at academic hospitals. Patients treated without neoadjuvant radiation more frequently received postoperative

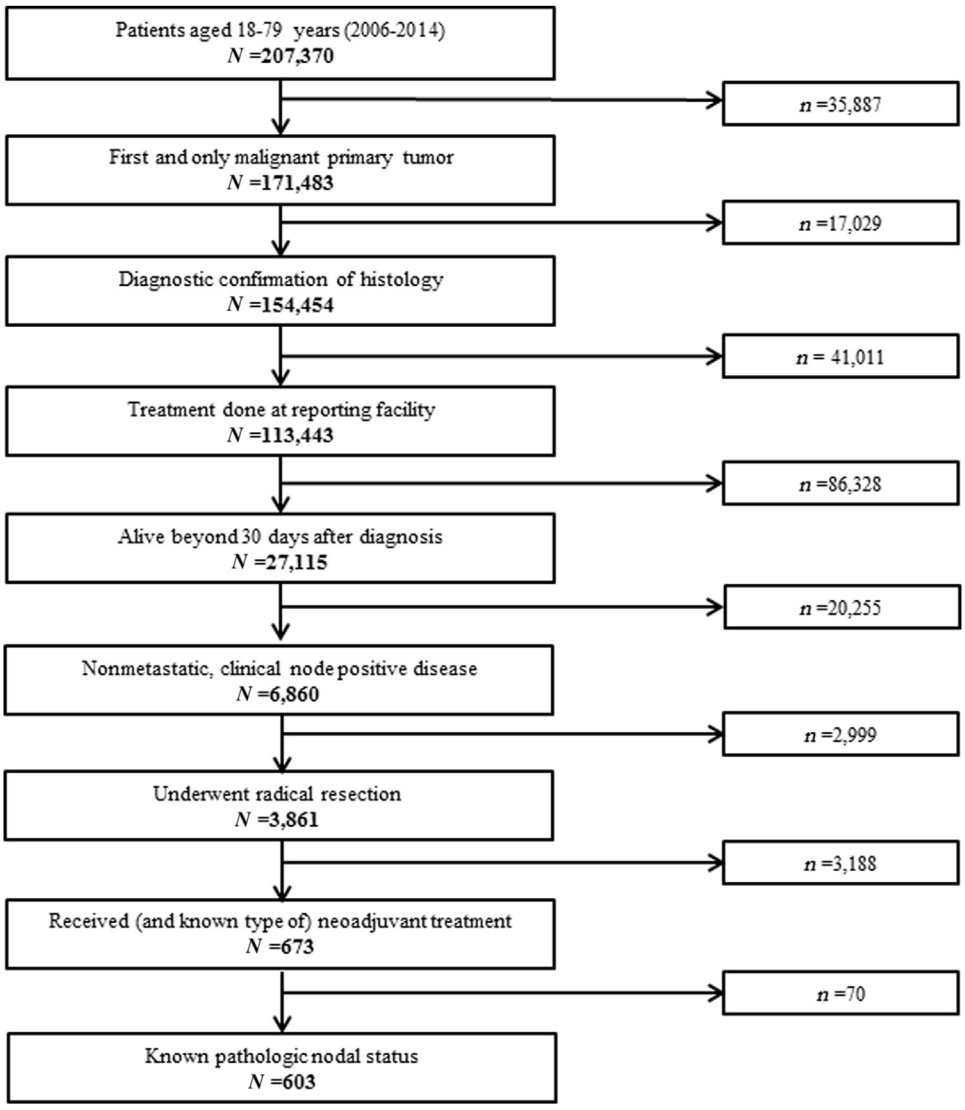

Fig 1. Flow diagram of study cohort definition.

adjuvant therapy (52.0% vs 29.5% for patients treated with radiation, $P < .001$).

Nodal downstaging

Unadjusted rates of nodal downstaging associated with type of NT are presented in Fig 2. NT that included radiation was associated with higher rates of nodal downstaging when compared with NT that did not (53.0% with vs 25.6% without, $P < .001$). When radiation was not used, rates of nodal response in patients treated with MAC were higher compared with those treated with SAC (29.3% vs 11.5%, $P = .009$). When radiation was used, there was no significant difference in nodal response comparing the use of MAC with SAC (54.5% versus 51.0%, $P = .52$).

Figure 3 is a forest plot demonstrating the association between the various NT regimens and the likelihood of achieving a nodal response on multivariate analysis. Relative to patients treated with neoadjuvant MAC without radiation, use of SAC without radiation was associated with a lower likelihood of nodal downstaging (relative risk ratio [RRR] 0.38 [95% CI 0.17–0.85]). By comparison, the addition of radiation to NT was associated with a significantly greater likelihood of nodal response regardless of the type of chemotherapy used (SAC and radiation: RRR 1.77 [1.36–2.30]; MAC and radiation: RRR 1.88 [1.46–2.45]). Overall, the use of radiation was associated with a significantly higher chance of a pathologic nodal response (RRR 2.12 [1.68–2.68]).

Survival

Figure 4 presents the OS stratified by pathologic nodal status. We observed a statistically and clinically significant difference in OS, comparing patients who remained ypN+ with those who became ypN0: median survival 22.5 months ypN+ vs 31.3 months ypN0 (log rank, $P < .001$). Table II displays the risk of death associated with some variables of interest on adjusted analysis. Relative to patients who remained ypN+ after NT, there was a significant ~40% decrease in the risk of overall death among those who became ypN0 (hazard ratio [HR] 0.61 [0.49–0.76]). The benefit associated with achieving nodal downstaging was observed both in patients who received radiation as part of NT (HR 0.63 [0.48–0.82]) and those who did not (HR 0.45

Table I
Demographic and clinical characteristics of the study cohort

	Multiagent chemotherapy and radiation ($n = 202$)	Multiagent chemotherapy ($n = 198$)	Single-agent chemotherapy and radiation ($n = 151$)	Single-agent chemotherapy ($n = 52$)
Demographics				
Age (years), median [IQR]	61.0 [55.0–68.0]	61.0 [53.0–68.0]	61.0 [54.0–67.0]	64.5 [56.5–71.5]
Male sex (%)	52.5	58.6	54.3	50.0
Race (%)				
White	89.6	88.4	83.4	90.4
Black	9.4	9.6	15.2	7.7
Other	1.0	2.0	1.3	1.9
Comorbidity index (%)				
0	64.9	67.7	62.3	59.6
1	28.2	25.8	33.1	36.5
≥ 2	6.9	6.6	4.6	3.9
Facility				
Hospital T=type (%)				
Academic/research	80.2	76.3	67.6	69.2
Comprehensive Cancer center	8.9	15.2	17.9	21.2
Community cancer center	1.5	1.0	1.3	1.9
Other	9.4	6.1	11.9	5.8
Missing	0	1.5	1.3	1.9
Clinical				
Tumor location (%)				
Head	84.2	77.8	88.1	78.9
Body	9.9	10.1	3.3	3.9
Tail	1.5	4.6	2.0	1.9
Not otherwise specified	4.5	7.6	6.6	15.4
Tumor grade (%)				
Well differentiated	5.9	5.1	12.6	5.8
Moderately differentiated	33.2	37.4	38.4	53.9
Poorly differentiated	16.3	27.8	20.5	25.0
Undifferentiated	2.0	0.5	0.7	0
Missing	42.6	29.3	27.8	15.4
Surgical margin (%)				
Positive	13.9	17.2	16.6	21.2
Missing	0.5	1.0	1.3	3.9
Lymph nodes Examined, median [IQR]	16.5 [10.0–24.0]	18.0 [12.0–26.0]	12.0 [6.0–18.0]	19.0 [15.0–26.0]
Adjuvant therapy (%)	31.2	49.5	27.2	61.5

IQR, interquartile range.

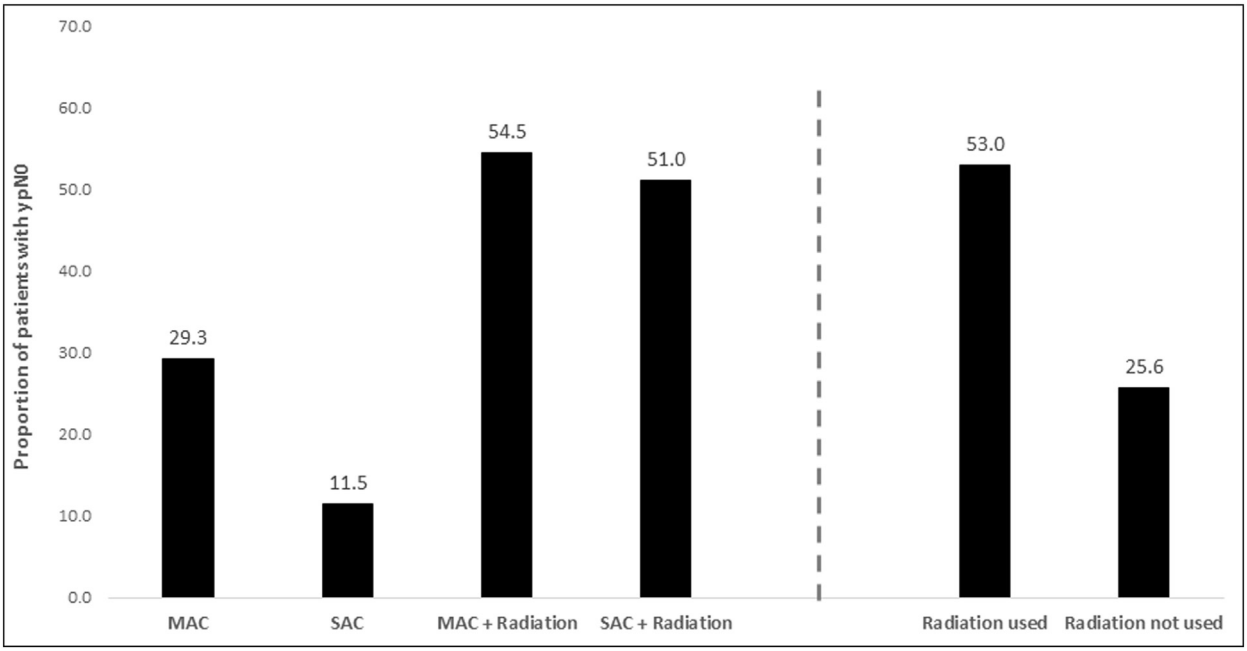

Fig 2. Unadjusted rate of nodal downstaging stratified by type of neoadjuvant treatment. *MAC*, multi-agent chemotherapy; *SAC*, single-agent chemotherapy.

[0.29–0.72]). In fact, inclusion of radiation as part of NT was not itself associated with a survival benefit. In subset analyses of patients with R0 resection and of patients treated at academic/research centers, we confirmed that, regardless of the manner in which this was accomplished, getting to ypN0 conferred a survival benefit (Table II).

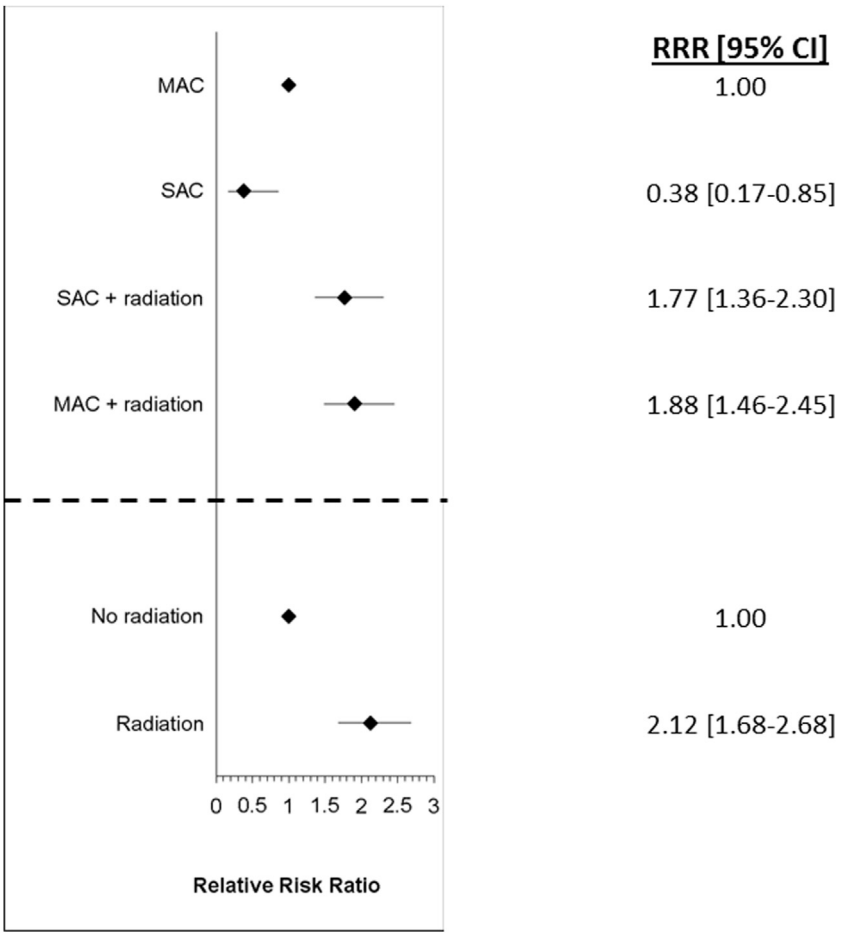

Fig 3. Association between type of neoadjuvant treatment and pathologic nodal downstaging. *MAC*, multi-agent chemotherapy; *SAC*, single-agent chemotherapy.

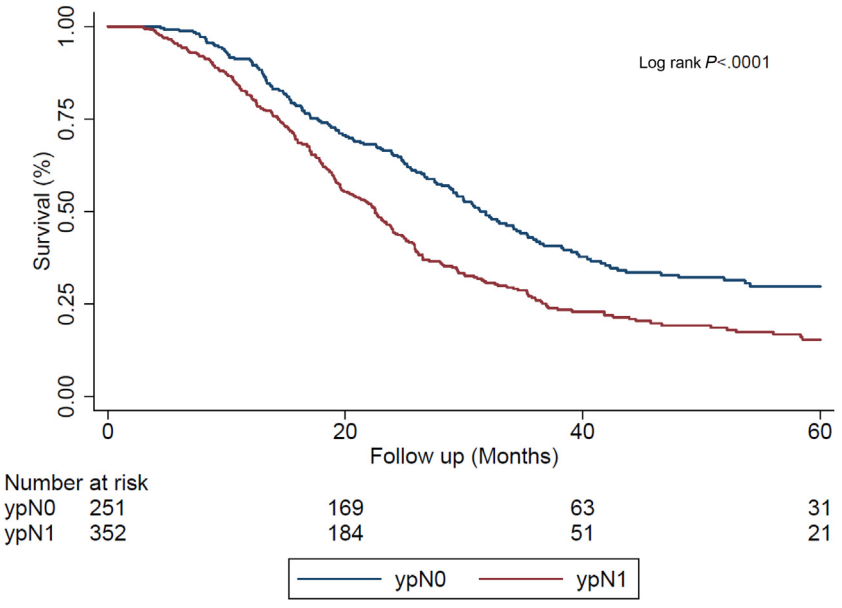

Fig 4. Overall survival stratified by nodal response.

Discussion

Traditionally, the indications for NT in patients with PDAC have been narrow, reserving its application for patients with borderline resectable anatomy. But, in light of a growing body of literature supporting NT, current guidelines from the American Society for Clinical Oncology now suggest that NT can be considered in patients who are otherwise deemed candidates for upfront resection.[4] However, there are no currently available data from prospective randomized trials to inform the optimal NT regimens in patients

Table II
Adjusted analysis for overall survival among all patients (*top*), stratified for patients with R0 resection only (*middle*), and those treated at academic/research centers only (*bottom*)

Variable	All neoadjuvant treatments			Neoadjuvant with XRT			Neoadjuvant without XRT		
	HR	95% CI		HR	95% CI		HR	95% CI	
All patients									
Treating facility type*									
Academic/research program	0.74	0.52	1.06	**0.59**	**0.37**	**0.91**	0.79	0.39	1.60
Community CP	0.75	0.32	1.76	0.61	0.20	1.89	0.69	0.17	2.70
Comprehensive community CP	0.89	0.58	1.37	0.62	0.35	1.08	1.33	0.60	2.92
Positive margin	**1.68**	**1.30**	**2.17**	**1.61**	**1.14**	**2.27**	**1.95**	**1.29**	**2.96**
ypN0 (REF − ypN+)	**0.61**	**0.49**	**0.76**	**0.63**	**0.48**	**0.82**	**0.45**	**0.29**	**0.72**
XRT part of neoadjuvant	1.13	0.90	1.40	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*
Adjuvant therapy	0.96	0.78	1.19	1.04	0.78	1.37	0.89	0.64	1.24
Patients with R0 resection									
Treating facility type*									
Academic/research	**0.63**	**0.41**	**0.98**	0.64	0.37	1.10	**0.43**	**0.19**	**0.98**
Community cancer program	1.79	0.65	4.92	2.31	0.62	8.55	0.78	0.13	4.64
Comprehensive community CP	0.66	0.40	1.10	0.52	0.27	1.00	0.70	0.28	1.73
ypN0 (REF − ypN+)	**0.58**	**0.46**	**0.74**	**0.61**	**0.45**	**0.82**	**0.41**	**0.19**	**0.98**
XRT part of neoadjuvant	1.18	0.93	1.51	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*
Adjuvant therapy	0.99	0.78	1.25	1.09	0.80	1.48	0.90	0.61	1.32
Patients treated at academic/research programs									
Positive margin	1.68	1.23	2.30	1.40	0.91	2.17	**2.42**	**1.47**	**3.99**
ypN0 (REF − ypN+)	**0.57**	**0.44**	**0.73**	**0.57**	**0.42**	**0.79**	**0.42**	**0.24**	**0.72**
XRT part of neoadjuvant	1.22	0.95	1.58	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*
Adjuvant therapy	0.99	0.77	1.26	1.14	0.82	1.58	0.79	0.54	1.15

* *REF*, integrated network CP; *CP*, cancer program; XRT, radiation therapy.

presenting with localized PDAC, including those with clinically node-positive disease. Because node-positive patients are known to have a worse prognosis and because nodal downstaging can be achieved with NT, our study supports two important findings regarding the management of PDAC patients with clinically positive lymph nodes. First, the inclusion of radiation as part of NT is associated a greater likelihood of achieving nodal downstaging than NT consisting solely of chemotherapy. Second, regardless of the manner in which it was achieved, nodal downstaging after NT is associated with a significant survival benefit. This held true in stratified analyses of patients who received negative margin resection and those treated at academic/research centers.

The aggressive nature of PDAC is well recognized and considered largely responsible for its generally poor outcomes. In recent years, certain tumor biologic features have been identified that predict an especially poor prognosis, including elevated serum CA19-9. Bergquist et al[11] found that CA19-9 elevation occurred in two-thirds of patients with stage I-II PDAC and, when present, was associated with a significantly increased risk of death. Of importance, they determined that NT was able to abrogate this increased mortality, supporting the argument that CA19-9 elevation represents biologic (instead of anatomic) borderline resectability and should be an indication for NT.[11] In the same context, nodal involvement has been strongly associated with worse survival for PDAC, and patients with node-positive disease appear to derive benefits from adjunctive, nonsurgical therapies.[5–7,12] On the basis of these factors and the known significant risk of failure to receive adjuvant therapy after pancreatectomy, our group has suggested elsewhere that the presence of nodal metastasis might constitute an indication for NT in patients who otherwise might be considered for surgical resection. In patients with early-stage PDAC, we found that clinically positive lymph node status had an excellent positive predictive value (95%), such that basing treatment planning on this finding was reliable, and further demonstrated a 38% rate of nodal downstaging with the use of NT for these patients.[5] Although this response likely reflects favorable tumor biology, we suspected that it could also be influenced by the type of NT received, thus prompting the current study.

In recent years, novel chemotherapy regimens with efficacy in the metastatic setting have dramatically changed the landscape of NT for borderline or potentially resectable PDAC. Gemcitabine plus albumin-bound paclitaxel and FOLFIRINOX, which are associated with improved survival when compared with to single-agent gemcitabine for patients with metastatic PDAC,[13,14] have become the preferred regimens employed in the neoadjuvant setting.[15] They are currently being compared head-to-head in a phase 2 trial of perioperative therapy for resectable PDAC.[16] Other recent and ongoing trials are exploring the role of preoperative radiation therapy. Katz et al[17] demonstrated that a neoadjuvant regimen that included capecitabine-based radiation therapy after modified FOLFIRINOX for borderline resectable PDAC yields a high rate of margin-negative resection and a 46% rate of significant treatment response, including a 13% rate of complete response. Two prospective randomized multicenter trials are investigating whether standard (NEOPA) or hypofractionated (PREOPANC) neoadjuvant chemoradiation regimens might be associated with a survival benefit relative to the use of upfront surgery.[18,19] Our current data suggest the greatest rates of nodal downstaging are achieved with NT regimens that include radiation therapy. This is consistent with results from a multi-institutional study that found that the benefits of adjuvant chemoradiation were limited to patients with node-positive disease.[20]

Until the results of ongoing clinical trials of NT for potentially resectable PDAC become available, an important management challenge is selecting the appropriate indications and most effective NT regimen for a given patient. Because achieving a nodal response is associated with a clear survival benefit, our findings suggest that in clinically node-positive patients, achieving ypN0 should be a primary goal of NT and may serve as an important prognostic indicator. Because the NCDB does not provide any anatomic information or the reason radiation was used, we elected to avoid directly comparing survival associated with the various NT regimens because of an inability to address the unmeasured biases inherent to such a comparison. Nonetheless, the fact that a nodal response was associated with a significantly decreased risk of death, regardless of whether radiation was used, supports the concept that it is the final pathologic nodal status achieved and not

the specific type of treatment that matters. Still, it is likely that nodal downstaging is not an "all-or-none" phenomenon. Rather, we suspect that, much like primary tumor response, nodal response may be complete (true nodal downstaging), incomplete, or nonexistent. The assessment of the degree of treatment response in each lymph node, however, is not routinely done. With this in mind, perhaps the finding of persistently suspicious lymph nodes after some NT might warrant consideration for delivery of all chemotherapy neoadjuvantly or for administration of consolidative chemoradiation before surgery. Because achieving N0 status may serve as an indicator of tumor biology, a reflection of treatment effect, and a predictor of survival, it may represent a worthwhile treatment goal to aim for in patients with node-positive PDAC.

The results presented in our work should be interpreted in light of several notable limitations. This was a retrospective study and is thus inherently subject to selection bias. The NCDB neither provides information on the specific type of chemotherapy regimen used nor the amount of chemotherapy administered. Given the period covered in our study (2006–2014), it is very possible that the results herein reported do not adequately represent the current landscape of neoadjuvant MAC regimens for PDAC, which mostly include FOLFIRINOX and gemcitabine with nab-paclitaxel. However, in light of the significant risk for grade 3 and 4 toxicity associated with these regimens, and FOLFIRINOX in particular,[14] our data would suggest that, for patients with clinically positive lymph nodes who are able to receive radiation but have poor tolerance to MAC, NT consisting of SAC with radiation could be an effective option and might be preferable to SAC alone. As noted in this report, given the observational nature of these data, treatment intent cannot be ascertained. However, because a primary goal of our study was to ascertain the rate of nodal downstaging associated with various types of NT, omission of patients who dropped out of NT and never received pancreatectomy should not be a major limitation. Data on disease progression during treatment and recovery of performance status are lacking. Clinical information used for surgical planning that may have impacted treatment sequencing, such as surgical anatomy, is unavailable. Similarly, information on the imaging modalities and staging procedures used (eg, endoscopic ultrasound) is not provided, but as our group has previously demonstrated, the positive predictive value of clinical nodal staging is high.[5] Finally, disease-specific mortality and progression-free survival are not available in the NCDB.

In conclusion, for patients with node-positive PDAC, the inclusion of radiation as part of NT is associated with a greater likelihood of nodal downstaging. Our data also suggest that, regardless of the manner in which this response is achieved, nodal downstaging is associated with a significant survival benefit and may be a measurable treatment goal. Ongoing randomized controlled trials evaluating the use of neoadjuvant radiation will likely shed further light on the efficacy of specific NT regimens that may include radiation. Overall, in clinically node-positive PDAC patients, nodal response to NT may be an important data point to consider.

Disclosure

The funding body had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

The views expressed in this report are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs, Baylor College of Medicine, or the American College of Surgeons Commission on Cancer. The data used in this study are derived from a deidentified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusion drawn from these data. No preregistration exists for the study reported in this article.

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