



Better Defining the Role of Total Neoadjuvant Radiation: Changing Paradigms in Locally Advanced Pancreatic Cancer

Roberto J. Vidri, MD^{1,2}, Anne O. Vogt, MS¹, Dougald C. Macgillivray, MD, FACS¹, Ian J. Bristol, MD¹, and Timothy L. Fitzgerald, MD, FACS^{1,3}

¹Division of Surgical Oncology, Tufts University School of Medicine-Maine Medical Center, Portland, ME; ²Division of Surgery, St. Mary's Regional Medical Center, Lewiston, ME; ³Maine Medical Center Cancer Institute, Scarborough, ME

ABSTRACT

Background. This study was designed to better define the role of radiation (Neo-Rad) in addition to neoadjuvant multiagent chemotherapy (NAT) for the treatment of locally advanced pancreatic cancer.

Methods. Retrospective cohort study using the NCDB. Individuals with AJCC clinical T3/T4 pancreatic carcinoma who underwent resection and multiagent chemotherapy were included. Kaplan–Meier, logistic-regression, and Cox proportional-hazard models were used for analysis.

Results. A total of 2703 patients were included; 2039 had T3 and 664 had T4 tumors, and 1092 (40.4%) received Neo-Rad. Median follow-up was 22.5 months. During the study period, there was increased use of NAT and a decline in the use of Neo-Rad. Addition of Neo-Rad did not affect 30-day (2.51% vs. 3.24%, $p = 0.272$) or 90-day mortality (5.23% vs. 6.38%, $p = 0.216$). Neo-Rad was not associated with improved overall survival on univariable (25.95 vs. 24.7 months, $p = 0.202$), or multivariable analyses (hazard ratio [HR] 0.94; 95% confidence interval [CI] 0.85–1.05). Time from diagnosis to definitive surgery was increased by Neo-Rad (204 vs. 115 days, $p < 0.001$). Neo-Rad was associated with increased pathologic downstaging in T3 (32.8% vs. 14.4%) (odds ratio [OR] 2.90; 95% CI

2.30–3.66) and T4 tumors (88.9% vs. 77.8%) (OR 2.29; 95% CI 1.44–3.67); complete pathologic response (5.3% vs. 1.6%) (OR 2.89; 95% CI 1.73–4.83), and increased R0 resection rates (85.7% vs. 76.8%) (OR 1.79; 95% CI 1.44–2.23).

Conclusions. The use of neoadjuvant therapy is increasing for the treatment of locally advanced pancreatic cancer. The addition of radiation to neoadjuvant chemotherapy is associated with improved antineoplastic effectiveness (downstaging, complete pathologic response), surgical resection (R0 rates), but has no effect on overall survival.

The use of neoadjuvant systemic therapy for pancreatic cancer has increased over the past decade.^{1,2} Potential advantages for the use of neoadjuvant therapy for locally advanced pancreatic cancer include timely treatment of occult micrometastatic disease, tumor downstaging, improved patient selection, and increased R0 resection rates.^{3–6}

Treatment regimens for pancreatic cancer have evolved significantly over the past several years. Multiagent chemotherapy regimens, such as FOLFIRINOX and nab-paclitaxel plus gemcitabine, have improved survival for patients with metastatic disease. Patients treated with nab-paclitaxel plus gemcitabine have response rates of 23% with up to 35% 1-year survival rates compared with 22% 1-year survival rates in those receiving gemcitabine alone. Patients treated with FOLFIRINOX have response rates as high as 32% and have demonstrated improved survival compared with patients treated with gemcitabine (11.1 vs. 6.8 months).^{7,8}

Surgical resection remains the only effective and potentially curative treatment for pancreatic cancer. However, most patients are not candidates for resection due to

Presented at the New England Surgical Society 99th Annual Meeting, Portland, ME, September 21, 2018.

© Society of Surgical Oncology 2019

First Received: 13 February 2019;
Published Online: 8 July 2019

T. L. Fitzgerald, MD, FACS
e-mail: tlfitzgera@mmc.org

the presence of advanced disease upon presentation. Given their effectiveness in the metastatic setting, neoadjuvant multiagent chemotherapy regimens have become the standard of care for locally advanced and borderline resectable pancreatic tumors. Currently, the NCCN guidelines and The American Society of Clinical Oncology recommend neoadjuvant multiagent chemotherapy followed by restaging and definitive resection.^{9,10}

Several authors have defined benefits associated with the administration of neoadjuvant therapy for advanced pancreatic malignancies. A retrospective review of the NCDB, including more than 15,000 subjects, concluded that patients receiving neoadjuvant therapy had improved overall survival compared with upfront surgery.⁵ Despite higher attrition rates, patients receiving neoadjuvant therapy still had a significant survival benefit.³

A few prospective trials have offered to contradict data regarding the effects on outcomes of adjuvant radiation when administered in patients treated with curative intent.^{11,12} In an era of more effective chemotherapy, the role of radiation as a part of multimodality treatment regimens remains poorly defined. Recent publications evaluating the use of neoadjuvant radiation in addition to multiagent chemotherapy regimens have failed to demonstrate a clear benefit in survival; however, most suggest increased rates of tumor downstaging and R0 resections rates.^{13–17} A phase 2 randomized trial is currently underway comparing the use of neoadjuvant chemotherapy and chemoradiation in borderline resectable pancreatic ductal adenocarcinomas.¹⁸

To better define the role of radiation in addition to neoadjuvant multiagent chemotherapy for locally advanced pancreatic cancer, we performed a retrospective cohort study utilizing a large national dataset. Overall survival was used as the primary outcome measure. Secondary endpoints included tumor downstaging, complete pathologic response (CPR), and rate of R0 resections. We hypothesize that administration of preoperative radiotherapy as part of a multimodality treatment regimen will lead to increased overall survival, as well as pathologic response.

PATIENTS AND METHODS

National Cancer Database

The National Cancer Data Base (NCDB) was started in 1989 as a joint program of the Commission on Cancer (CoC) of the American College of Surgeons (ACS) and the American Cancer Society. It is the largest cancer database in the world, containing approximately 34 million cancer records from more than 1500 CoC-accredited hospitals in the United States. These data encompass approximately

70% of all cancer diagnosis.¹⁹ The CoC requires that all cancer occurrences be reported to the NCDB annually. NCDB is a deidentified database that falls under the Institutional Review Board exemption category.

Eligibility

Surgical patients with American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) T3 and T4 tumors, comprising stage IIA, IIB, and III pancreatic cancer diagnosed between 2006 and 2014 were identified. Histology codes 8010 (Carcinoma, NOS), 8140 (Adenocarcinoma), and 8500 (Ductal Carcinoma) were included. The inclusion of T3 and T4 tumors combined was utilized to define locally advanced pancreatic cancer. Only subjects who received “multiagent chemotherapy” and “beam radiation” were included. All subjects in this study received neoadjuvant multiagent chemotherapy; the difference between groups is based on the addition of radiation therapy. Those receiving “radiation before surgery” and “radiation therapy before and after surgery” were classified as having received neoadjuvant radiation (Neo-Rad) as part of their treatment. Subjects missing survival data were excluded.

Statistical Analysis

Complete-case analysis was performed. Continuous data are presented as means and standard deviations (SDs) or median and interquartile range (IQR). Categorical variables are presented as frequencies and percentages. Statistical significance for categorical values was determined using the Pearson’s Chi squared test. Means for continuous variables were compared using a two-sample *t* test.

The Kaplan–Meier method was used to determine survival probabilities. The log-rank test was used to compare survival distributions among groups. Univariable and multivariable Cox proportional hazards models were used for survival analysis. Results are reported as hazard ratio (HR), confidence interval (CI), and *p* value. Multivariable regression models were adjusted for age, sex, race, ethnicity, insurance type, geographic location, income, Charlson–Deyo Score, facility type, surgery performed, TNM node and tumor classifications, and surgical margin status. A clear change in treatment regimens is noted in the year 2011; therefore, a dichotomized year variable was introduced for all models to control for potential confounding. Given the potential for immortal time bias secondary to longer time to definitive surgery in patients who received radiation therapy, survival analysis were performed utilizing the beginning of treatment as initial exposure, instead of diagnosis time. For the Neo-Rad group, subjects became at risk with initial administration of

TABLE 1 Patient characteristics

Variable	Radiation	No radiation	<i>p</i>
Number	1092	1611	
Age (mean, SD)	61.7 (9.3)	63.9 (10.3)	< 0.001
Sex			0.28
Female	552 (50.5%)	780 (48.4%)	
Male	540 (49.5%)	831 (51.6%)	
Race			0.47
White	933 (85.4%)	1372 (85.2%)	
Black	80 (7.3%)	101 (6.3%)	
Hispanic	41 (3.8%)	73 (4.5%)	
Other	38 (3.5%)	65 (4.0%)	
Type of insurance			0.010
Medicaid	45 (4.1%)	69 (4.3%)	
Medicare	413 (37.8%)	693 (43.0%)	
Not insured	21 (1.9%)	20 (1.2%)	
Other (government)	20 (1.8%)	17 (1.1%)	
Private insurance	579 (53.0%)	777 (48.2%)	
Unknown	14 (1.3%)	35 (2.2%)	
Region			< 0.001
Unknown	13 (1.2%)	17 (1.1%)	
Midwest	334 (30.6%)	391 (24.3%)	
Northeast	279 (25.5%)	413 (25.6%)	
South	354 (32.4%)	509 (31.6%)	
West	112 (10.3%)	281 (17.4%)	
Income			0.14
< \$30,000	93 (8.5%)	187 (11.6%)	
\$30,000–34,999	179 (16.4%)	259 (16.1%)	
\$35,000–\$45,999	284 (26.0%)	402 (25.0%)	
\$46,000+	493 (45.1%)	697 (43.3%)	
Not available	43 (3.9%)	66 (4.1%)	
Metro			0.23
Metropolitan	862 (78.9%)	1228 (76.2%)	
Rural	21 (1.9%)	32 (2.0%)	
Unknown	34 (3.1%)	72 (4.5%)	
Urban	175 (16.0%)	279 (17.3%)	
Facility type			< 0.001
Academic/research program	775 (71.0%)	1029 (63.9%)	
Community cancer program	21 (1.9%)	45 (2.8%)	
Comprehensive community cancer program	187 (17.1%)	375 (23.3%)	
Integrated network cancer program	96 (8.8%)	145 (9.0%)	
Unknown	13 (1.2%)	17 (1.1%)	
Charlson–Deyo Disability score			0.28
0	754 (69.0%)	1138 (70.6%)	
1	271 (24.8%)	393 (24.4%)	
2	50 (4.6%)	67 (4.2%)	
3	17 (1.6%)	13 (0.8%)	

TABLE 1 continued

Variable	Radiation	No radiation	<i>p</i>
AJCC Clinical T			< 0.001
T3	743 (68.0%)	1296 (80.4%)	
T4	349 (32.0%)	315 (19.6%)	
AJCC Clinical N			0.003
N0	701 (64.2%)	926 (57.5%)	
N1	370 (33.9%)	647 (40.2%)	
Unknown/missing	21 (1.9%)	37 (2.4%)	
Surgery type			0.76
Pancreatectomy	62 (5.7%)	81 (5.0%)	
Whipple	881 (80.7%)	1309 (81.3%)	
Other	149 (13.6%)	221 (13.7%)	
Surgical margins			< 0.001
R0	901 (82.5%)	1168 (72.5%)	
R1	86 (7.9%)	199 (12.4%)	
R2	65 (6.0%)	154 (9.6%)	
Unknown/missing	40 (3.7%)	90 (5.6%)	
Time to definitive surgical resection in days (mean, SD)	203.96 (80.77)	115.21 (86.5)	< 0.001

TABLE 2 Odds ratios (OR) and 95% confidence intervals (CI) for pathologic response: R0 resection, complete pathologic response, and tumor downstaging

	Univariable OR (CI)	<i>p</i>	Multivariable OR (CI)	<i>p</i>
Complete pathologic response ^a				
T3	3.18 (1.73–5.83)	< 0.001	2.58 (1.38–4.82)	0.003
T4	3.66 (1.47–9.12)	0.005	4.02 (1.54–10.46)	0.004
Combined (T3/T4)	3.58 (2.18–5.89)	< 0.001	2.89 (1.73–4.83)	< 0.001
R0 resection ^b				
T3	1.52 (1.19–1.95)	0.001	1.45 (1.13–1.88)	0.004
T4	3.17 (2.11–4.75)	< 0.001	3.37 (2.17–5.24)	< 0.001
Combined (T3/T4)	1.80 (1.46–2.22)	< 0.001	1.79 (1.44–2.23)	< 0.001
Tumor downstaging ^a				
T3	2.90 (2.30–3.66)	< 0.001	2.77 (2.17–3.53)	< 0.001
T4	2.29 (1.44–3.67)	0.001	2.15 (1.28–3.62)	0.004
Combined (T3/T4)	2.89 (2.43–3.45)	< 0.001	2.79 (2.32–3.35)	< 0.001

^aMultivariable model controlling for: age, sex, race, ethnicity, insurance type, geographic location, income, Charlson–Deyo Score, facility type, TNM node, year, and tumor classifications

^bIncludes control for type of surgery performed

radiation. Subjects in the NAT group became at risk at initiation of systemic therapy. The proportional hazards assumption, assessed using the Schoenfeld residuals, was not violated in our models.

Logistic regression models were used for analysis of tumor downstaging, R0 resection, and CPR. For analysis of tumor downstaging, data were dichotomized into initial, image determined clinical T stage, and final pathological examination results. Data on race and ethnicity was

categorized into white, black, Hispanic, and other. Geographic location was categorized as: South, West, Northeast, Midwest, and unknown. Surgical procedures were classified as “Whipple procedure,” “Pancreatectomy,” and “Other” (Includes partial pancreatectomies and unspecified operations). Statistical significance was defined as a $p < 0.05$. STATA statistical software (StataCorp. 2015. Release 14. College Station, TX) was used for analysis.

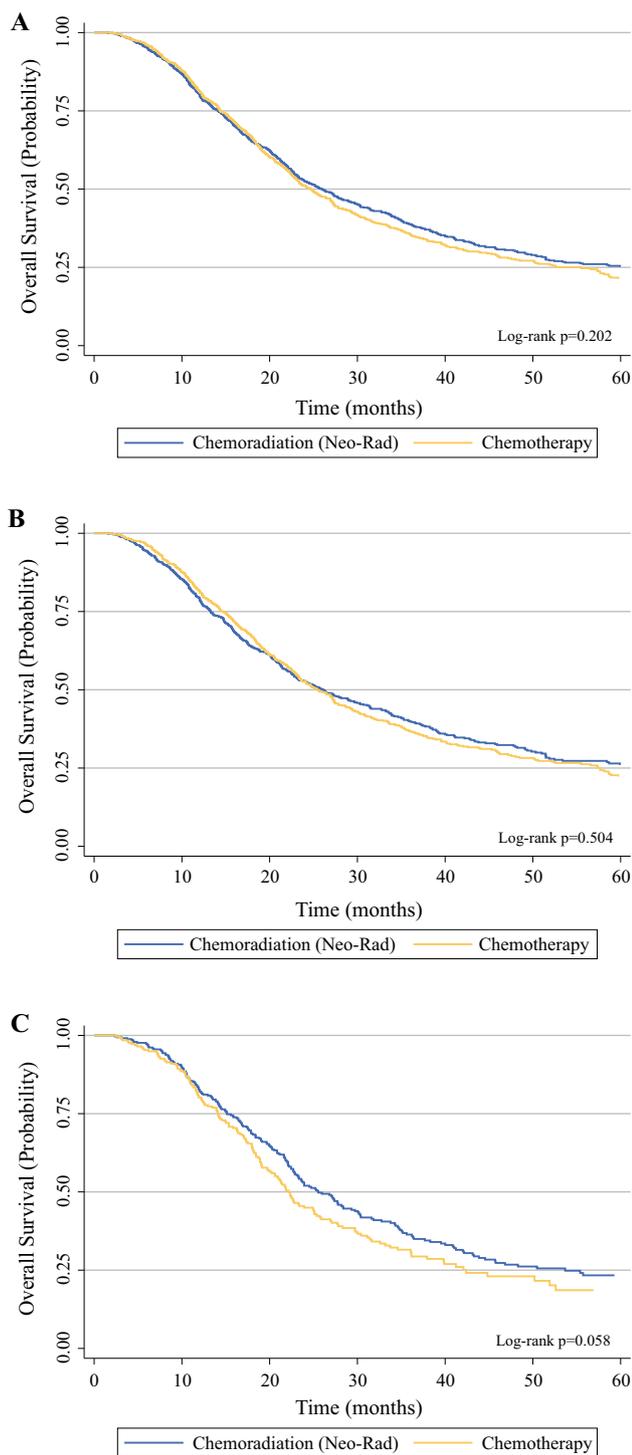


FIG. 1 Overall survival by treatment regimen for combined T3 and T4 tumors (a), T3 tumors (b) and T4 tumors (c). Plot is truncated at 60 months

RESULTS

A total of 2703 patients were included. Median age was 64 years (interquartile range [IQR] 14), 50.7% of patients were male, 85.3% were white, and 70% had a Charlson–

Deyo Score < 1. Neoadjuvant radiation was administered to 40.4% of patients; these were younger (61.7 vs. 63.9 years) and more likely to be treated at an academic or research facility (71% vs. 63.9%; Table 1). Median follow-up was 22.5 months (IQR 25.9). Time to definitive surgical treatment from diagnosis was increased by the administration of Neo-RAD (204 vs. 115.2 days, $p < 0.001$).

Pathologic Effects

Administration of Neo-RAD was associated with higher CPR rates (5.33% vs. 1.55%, $p < 0.001$), R0 resection rates (85.65% vs. 76.79%, $p < 0.001$), and tumor downstaging (50.27% vs. 25.88%, $p < 0.001$). Stratified analysis demonstrated similar effects in T4 tumors for CPR (7.49% vs. 2.17%, $p = 0.003$) and R0 resections (86.93% vs. 67.72%, $p < 0.001$). Neo-RAD also led to increased pathological downstaging in T4 tumors (88.93% vs. 77.78%, $p < 0.001$). T3 tumors demonstrated a similar effect for CPR (4.34% vs. 1.41%, $p < 0.001$), R0 resection rates (85.06% vs. 78.88%, $p = 0.001$), and tumor downstaging (32.81% vs. 14.41%, $p < 0.001$; Table 2). Forty-two (1.6%) patients with clinical T3 tumors were upstaged to T4 tumors on final pathologic evaluation.

Stratified analyses of all the models by year (2011) resulted in slight variations in the point estimates; however, a strong correlation persisted between the use of radiation therapy and pathologic response across strata.

Survival Analysis

The addition of radiation to the treatment regimen was not associated with increased overall survival; median 26.95 versus 24.7 months (HR 0.94; 95% CI 0.85–1.05; Fig. 1). No survival advantage was encountered when the analyses were stratified by TNM “T” classification (Table 3). Patients with T3 tumors who received Neo-RAD had a median survival of 26.2 months compared with 25.5 months in those who received only chemotherapy. Median survival for patients with T4 tumors who received Neo-RAD also was similar (25.6 vs. 22.2 months). Neo-RAD did not increase 30-day (2.51% vs. 3.24%, $p = 0.272$) or 90-day mortality (5.23% vs. 6.38%, $p = 0.216$). Initiation of systemic therapy happened on average 34.6 days from diagnosis for all patients (Neo-Rad: 31.8 vs. NAT: 37 days). Subjects who received Neo-RAD waited approximately 105.6 days from diagnosis to administration of radiation. Mean duration of radiation therapy was 33.7 days. Five-year survival was 25.2% for the Neo-Rad group and 21.4% for the NAT group.

TABLE 3 Hazard ratio (HR) and 95% confidence intervals (CI) for overall survival: neoadjuvant chemoradiation and neoadjuvant chemotherapy alone

Tumor stage	Univariable HR (CI)	<i>p</i>	Multivariable ^a HR (CI)	<i>p</i>
T3	0.96 (0.85–1.09)	0.504	0.98 (0.86–1.11)	0.701
T4	0.82 (0.67–1.01)	0.059	0.83 (0.67–1.04)	0.106
Combined (T3/T4)	0.93 (0.84–1.04)	0.202	0.94 (0.85–1.05)	0.301

^aAdjusted for: age, sex, race, ethnicity, insurance type, geographic location, income, Charlson–Deyo Score, facility type, type of surgery performed, TNM node and tumor classifications, and surgical margin status, year

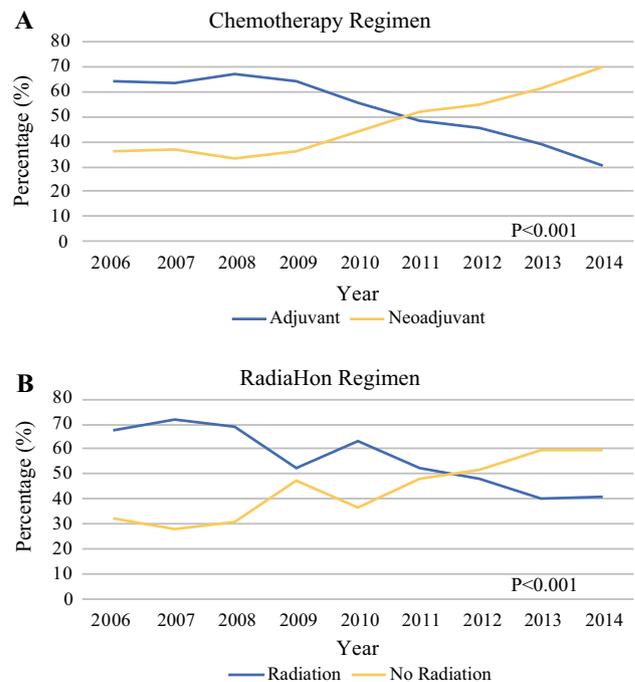
Treatment Trends

Over the study period, there was an overall increase in the use of neoadjuvant chemotherapy for the treatment of pancreatic tumors. In 2006, 35.8% of patients with stage II and III pancreatic cancer received neoadjuvant chemotherapy; this increased to 69.7% by 2014. A clear shift in treatment paradigms is appreciated after the year 2011. Conversely, the addition of radiation to neoadjuvant treatment regimens appears to decrease over the same time period. In 2006, Neo-Rad was used in 67.9% of subjects compared with 40.7% in 2014 (Fig. 2).

DISCUSSION

In an era of increasingly effective chemotherapeutic regimens, the use of neoadjuvant therapy for patients with locally advanced pancreatic tumors is becoming more commonplace. Despite this, no high-quality data exist to guide clinicians regarding the role of radiotherapy for locally advanced and borderline resectable pancreatic cancer. The data presented in this manuscript suggest that the addition of radiotherapy *t-o* neoadjuvant multiagent chemotherapy regimens for locally advanced pancreatic cancer is associated with increased tumor downstaging, complete pathologic response rates, R0 resection, but not improved overall survival. This dataset also demonstrates that the use of neoadjuvant chemotherapy, for those receiving multiagent chemotherapy, has increased over the past decade. However, the use of radiation therapy has decreased.

The addition of radiotherapy to neoadjuvant chemotherapy is the subject of the ongoing ALLIANCE trial (A021501). In this trial, subjects with borderline resectable pancreatic cancer are being randomized to receive either eight cycles of modified FOLFIRINOX or seven cycles of modified FOLFIRINOX followed by stereotactic body radiation therapy. Those who complete this regimen will proceed to pancreatectomy.¹⁸ In contrast,

**FIG. 2** Use of neoadjuvant chemotherapy (a) and use of neoadjuvant radiation over study period (b)

our data represent a retrospective review of patients with both borderline resectable and locally advanced pancreatic cancer as the NCDB data does not allow for the distinction between these two groups.

Achieving a complete resection confers the only possibility of a cure for patients with pancreatic cancer. Small prospective trials have suggested that as many as 84–100% of patients who receive preoperative chemoradiation and subsequently undergo surgical resection achieve complete resections (R0).^{14,15,17} A retrospective review of the NCDB found that 82% of individuals treated with neoadjuvant radiation achieved R0 resections compared with 72% for those treated with chemotherapy alone.¹⁶ Our results reinforce this association. For the chemoradiation group, R0 resections were achieved in 85.65% of subjects

compared with 76.79% in the chemotherapy group. This effect was similar when subjects with T3 and T4 tumors were analyzed independently.

Patients who received Neo-Rad were more likely to achieve CPR (5.3% vs. 1.6%). CPR has been associated with improved survival and serves as a marker for treatment effectiveness in local and systemic disease control. For the chemotherapy-only group, our results are similar to those previously reported.³ Although difficult to measure given the lack of individualized data, our analysis also suggest the existence of an effect of radiation therapy on tumor downstaging. This effect was stronger for patients with T3 tumors but also was significant for those with T4 tumors.

The addition of radiation therapy to neoadjuvant multiagent chemotherapy appears to be associated with improved survival for pancreatic cancer. In a single institution trial, patients treated with preoperative gemcitabine, oxaliplatin, radiation and surgical resection had a reported median survival of 27.1 months; for those with borderline resectable tumors, median survival was 25.4 months.¹⁷ A review by Stessin et al.¹³ of patients with pancreatic cancer in the SEER database also suggests a survival advantage. In our study, subjects who received neoadjuvant chemoradiation had a median survival of 26.95 months compared with 24.7 months for those who received only chemotherapy. This difference was not statistically significant. However, these results have to be interpreted in the context of the study design and NCDB data. Our study included only patients who completed neoadjuvant therapy and surgery; thus a selection bias exists. We are unable to analyze subjects who did not proceed to surgery in either group, because NCDB does not provide data on treatment intention or “dropout” rates. The literature suggests that in patients who received neoadjuvant chemotherapy only 60–70% proceed to surgical resection.^{20,21} For those who received chemoradiation, this number may be as low as 50%.¹⁵ Also, subjects in the Neo-Rad group had increased time from diagnosis to definitive surgery, which is expected. It is likely that neoadjuvant chemoradiation aids in selecting patients who have achieved disease control and will survive longer. It should be noted that not all the increased time to definitive surgery in the NeoRad group could be directly attributed to delivery of radiotherapy. It is possible that some subjects in this group were treated with additional cycles of chemotherapy.

A trend toward the increased use of neoadjuvant chemotherapy for the treatment of locally advanced pancreatic cancer has been observed in the past decade. The introduction of FOLFIRINOX in 2011 is clearly reflected in our data and marked a transition toward the use of neoadjuvant regimens. The use of radiation, however, started to decrease at around the same time period. In this

data, we found that only 36% of patients with T3 tumors received radiation as part of a multimodality regimen. However, the majority (52.6%) of those with T4 tumors are treated with chemoradiation. The most likely explanation for this is lack of definitive evidence demonstrating the beneficial effects of radiation and no increase in morbidity.

The NCDB does not collect information on therapeutic decision making or resectability criteria. This represents an unavoidable limitation. For analysis purposes, the combination of T3 and T4 tumors reasonably encompasses the categories of borderline and locally advanced unresectable pancreatic tumors. The NCDB provides a large number of cases for analysis, with inherent limitations. Data are abstracted from medical records within CoC accredited hospitals only, which could affect the generalization of results and include errors in data input. Recurrence information, an important measure of therapeutic success for patients with pancreatic cancer, is not collected. Furthermore, no data explain patient selection toward the administration of radiotherapy. Multivariable models accounting for known predictors of survival in pancreatic cancer were utilized in an attempt to reduce confounding.

CONCLUSIONS

The use of radiation as part of a neoadjuvant multimodality treatment regimen for locally advanced pancreatic cancer is associated with improved outcomes, such as tumor downstaging, increased rate of R0 resection, and complete pathologic response. For those who complete treatment, chemoradiation does not appear to confer a survival benefit. Increased use of neoadjuvant chemotherapy was noted. However, the use of neoadjuvant chemoradiation remains low in the treatment of locally advanced pancreatic cancer. Pending data from larger, prospective trials, and based on these data and that of other investigators, the use of radiation therapy as part of neoadjuvant multimodality regimens for the treatment of patients with locally advanced pancreatic cancer should be considered.

REFERENCES

1. Mirkin KA, Hollenbeak CS, Gusani NJ, Wong J. Trends in utilization of neoadjuvant therapy and short-term outcomes in resected pancreatic cancer. *Am J Surg.* 2017;214(1):80–8.
2. Parmar AD, Vargas GM, Tamirisa NP, Sheffield KM, Riall TS. Trajectory of care and use of multimodality therapy in older patients with pancreatic adenocarcinoma. *Surgery.* 2014;156(2):280–9.
3. Shubert CR, Bergquist JR, Groeschl RT, et al. Overall survival is increased among stage III pancreatic adenocarcinoma patients receiving neoadjuvant chemotherapy compared to surgery first

- and adjuvant chemotherapy: an intention-to-treat analysis of the National Cancer Database. *Surgery*. 2016;160(4):1080–96.
4. Mirkin KA, Hollenbeak CS, Wong J. Survival impact of neoadjuvant therapy in resected pancreatic cancer: a prospective cohort study involving 18,332 patients from the National Cancer Data Base. *Int J Surg*. 2016;34:96–102.
 5. Mokdad AA, Minter RM, Zhu H, et al. Neoadjuvant therapy followed by resection versus upfront resection for resectable pancreatic cancer: a propensity score matched analysis. *J Clin Oncol*. 2017;35(5):515–22.
 6. Marsh RDW, Baker M, Catenacci DV, et al. Peri-operative modified FOLFIRINOX (mFOLFIRINOX) in resectable pancreatic cancer (PDAC): a pilot study. Alexandria: American Society of Clinical Oncology; 2016.
 7. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817–25.
 8. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369(18):1691–703.
 9. NCCN (NCCN). Pancreatic adenocarcinoma. 2017; Version 3.2017. https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 15 July 2018.
 10. Balaban EP, Mangu PB, Khorana AA, et al. Locally advanced, unresectable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2016;34(22):2654–68.
 11. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004;350(12):1200–10.
 12. Moghanaki D. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Gastrointestinal Tumor Study Group. *Cancer*. 1987;59:2006–10.
 13. Stessin AM, Meyer JE, Sherr DL. Neoadjuvant radiation is associated with improved survival in patients with resectable pancreatic cancer: an analysis of data from the surveillance, epidemiology, and end results (SEER) registry. *Int J Radiat Oncol Biol Phys*. 2008;72(4):1128–33.
 14. Talamonti MS, Small W, Mulcahy MF, et al. A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. *Ann Surg Oncol*. 2006;13(2):150–8.
 15. Turrini O, Ychou M, Moureau-Zabotto L, et al. Neoadjuvant docetaxel-based chemoradiation for resectable adenocarcinoma of the pancreas: new neoadjuvant regimen was safe and provided an interesting pathologic response. *Eur J Surg Oncol*. 2010;36(10):987–92.
 16. Colbert LE, Hall WA, Nickleach D, et al. Chemoradiation therapy sequencing for resected pancreatic adenocarcinoma in the National Cancer Data Base. *Cancer*. 2014;120(4):499–506.
 17. Kim EJ, Ben-Josef E, Herman JM, et al. A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. *Cancer*. 2013;119(15):2692–700.
 18. Katz MH, Ou F-S, Herman JM, et al. Alliance for clinical trials in oncology (ALLIANCE) trial A021501: preoperative extended chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas. *BMC Cancer*. 2017;17(1):505.
 19. Bilimoria KY, Bentrem DJ, Stewart AK, Winchester DP, Ko CY. Comparison of commission on cancer-approved and -nonapproved hospitals in the United States: implications for studies that use the National Cancer Data Base. *J Clin Oncol*. 2009;27(25):4177–4181.
 20. O'Reilly EM, Perelshteyn A, Jarnagin WR, et al. A single-arm, nonrandomized phase II trial of neoadjuvant gemcitabine and oxaliplatin in patients with resectable pancreas adenocarcinoma. *Ann Surg*. 2014;260(1):142–8.
 21. Rose JB, Rocha FG, Alseidi A, et al. Extended neoadjuvant chemotherapy for borderline resectable pancreatic cancer demonstrates promising postoperative outcomes and survival. *Ann Surg Oncol*. 2014;21(5):1530–7.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.