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Does adjuvant radiation provide any survival benefit after an R1 resections for pancreatic cancer?

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ABSTRACT

Background. The benefit of adding external beam radiation to adjuvant chemotherapy in patients that have undergone a margin positive resection for early stage, pancreatic ductal adenocarcinoma has not been determined definitively.

Methods. The National Cancer Data Base was queried to evaluate the utility of adjuvant radiation in patients with pathologic stage I–II pancreatic ductal adenocarcinoma who underwent upfront pancreatoduodenectomy with a positive margin (margin positive resection) between 2004 and 2013.

Results. In the study, 1,392 patients met inclusion criteria, of whom 263 (18.9%) were lymph node-negative (pathologic stages IA, IB, IIA) and 1,129 (81.1%) were node-positive (pathologic stage IIB); 938 (67.4%) patients received adjuvant radiation and chemotherapy, while 454 (32.6%) received adjuvant chemotherapy alone. Cox modeling stratified by nodal status demonstrated the benefit of radiation to be statistically significant only in node positive patients (hazard ratio 0.81, 95% confidence interval, 0.71–0.93). Node-positive patients receiving adjuvant radiation and chemotherapy had an adjusted median survival of 17.5 months vs 15.2 months for those receiving adjuvant chemotherapy alone ($P = .003$). In patients who had negative nodes, there was no difference in overall survival with radiation (22.5 vs 23.6 months, $P = .511$).

Conclusion. Addition of radiation to adjuvant chemotherapy after a margin positive resection confers a survival benefit albeit limited (about 2 months) in patients with node-positive pancreatic head cancer. (Surgery 2017;160:XXX-XXX.)

Pancreatic ductal adenocarcinoma (PDAC) is diagnosed typically late in the course of the disease. Patients only rarely develop symptoms at early pathologic stages.[1] The diagnosis often is made after patients have developed clinically detectable, locally advanced or metastatic disease. For patients who present at a clinical stage early enough to allow resection, recurrence is the norm. This observation suggests that the vast majority of patients who present "early" harbor subclinical metastases or have systemic disease at the time of diagnosis.[2]

The observation that most patients with PDAC present with disseminated cancer has led practitioners to question the benefit of external beam radiation and other nonsurgical loco-regional treatments that traditionally have been considered important adjuncts to operative resection in patients with aggressive malignancies.[3-6] Literature supporting the use of nonsurgical loco-regional therapies like radiation in pancreatic cancer is sparse.[6] There is only one randomized trial examining adjuvant radiation (XRT) in isolation in patients with resected pancreas cancer (European Study Group for Pancreatic Cancer [ESPAC]-Trial 1). This trial demonstrated decreased overall survival in the cohort treated with chemoradiotherapy compared with the cohort treated with chemotherapy alone.[7] Retrospective evaluations of multi-institutional studies have included

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heterogeneous patient populations with mixed pathologies but have generally shown some benefit to radiation.[3,8-10]

The National Cancer Data Base (NCDB) was used to analyze the outcomes associated with the addition of radiation therapy to adjuvant chemotherapy in a subpopulation of PDAC patients who would seem to have the greatest potential to benefit from improved locoregional control: those with early stage PDAC who undergo upfront operative resection but have microscopic positive margins (R1 resection) on final pathology.

Methods

Data source

The NCDB, a nationwide, facility-based cancer database, is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons (ACS) and the American Cancer Society.[11] The database reports annual data currently that represents 70% of all newly diagnosed cancers in the United States from nearly 1,500 hospitals that maintain CoC-accredited cancer programs.[11] The data provided in the NCDB only represents patients treated at continuously CoC-accredited facilities. Incorporated data are coded and reported to the NCDB following nationally implemented protocols designed by the North American Association of Central Cancer Registries.[12] All data available within the NCDB are compliant with the privacy requirements of the Health Insurance Portability and Accountability Act. Institutional review board approval was not warranted for this investigation, because patient, provider, and hospital information were derived from a deidentified NCDB file, and the analysis itself was retrospective in nature. The American College of Surgeons and CoC have not verified and are not responsible for the analytic or statistical methodology used or the conclusions drawn from these data by the investigators.

Patient selection

Patients diagnosed with pathologic stage I–II PDAC according to the seventh edition of the American Joint Committee on Cancer (AJCC) who had a standard pancreatoduodenectomy/Whipple procedure (PD) or pylorus-preserving pancreatoduodenectomy (PPPD) with microscopic positive margins between 2004 and 2013 were included in this study.[13] The aim of this study was to determine the benefit of adjuvant radiation above and beyond adjuvant chemotherapy treatment alone in patients who had upfront operative resection with microscopic positive margins. The definition of an R1 resection was not standardized (e.g., whether a positive margin was defined as tumor cells at the margin or within 1 mm of the margin). Therefore, all patients in this analysis received adjuvant chemotherapy. Treatment with adjuvant radiation therapy was stratified into 2 mutually exclusive categories: no radiation therapy (chemotherapy alone, ACT) and adjuvant chemoradiation therapy (ACRT). Radiation therapy was administered by external beam. Patients who had previous cancers, macroscopically positive margins, no adjuvant chemotherapy, neoadjuvant chemotherapy, or neoadjuvant radiation, metastatic disease, and missing treatment data were excluded.

Variables studied

Patient characteristics analyzed included age, sex, race, insurance status, comorbidity index, and socioeconomic status (SES). Age was assessed categorically (18–55, 56–65, 66–75, >75). Race grouping was analyzed in accordance with the categorizations of non-Hispanic White, Black, Hispanic, Asian/Pacific Islander, and other according to the US Census.[14] Insurance status was categorized as uninsured, private, Medicaid/Medicare, other, and unknown. Patient comorbidity was evaluated using Deyo's modification of Charlson's comorbidity index (0, 1, 2).[15] ZIP-code data were used as representative measures of average income and education which were utilized collectively to create a SES variable stratified into low, medium, and high categories. Facility characteristics analyzed included facility type and location. Facility type encompassed 5 categories: community, comprehensive community, academic/research, integrated cancer network, and other. The CoC designates facility categories based on facility/organization type, variety of services provided, involvement in resident training, and clinical research.[16] Facility location was derived from the 9 regions of states according to the United States Census.[17] Pathologic staging was assigned to the patients analyzed using the American Joint Committee on Cancer seventh edition TNM classifications; the T categorizations (T1, T2, T3), nodal status, vascular abutment (absent, present), histologic tumor grade (I, II, III/IV), and operative procedure (PD versus PPPD) were analyzed. Nodal status stratified patients into 2 main subgroups: node-negative (pathologic stages IA, IB, and IIA) and node-positive (pathologic stage IIB). Vascular abutment assessed tumor extension to any "major" blood vessel, including the aorta, gastroduodenal, hepatic, pancreatoduodenal, and celiac arteries, and the superior and portal mesenteric veins. Survival was reported as all-cause dead or alive.

Statistical analysis

Patient, facility, and tumor characteristic trends of receiving ACRT versus ACT were analyzed using χ^2 and analysis of variance tests. Multivariable binary logistic regression was utilized to identify independent predictors of ACRT use. Cox proportional hazards regression was used to analyze risk adjusted survival trends. Statistical analyses were conducted using IBM SPSS 22.0 statistical software (IBM Corp., Armonk, NY). All statistical tests were 2-sided. Confidence intervals (CI) are reported at a 95% significance level.

Results

Patient cohort characteristics

In the study, 1,392 patients met the inclusion criteria; 263 (18.9%) were node-negative (pathologic stages IA, IB, or IIA) and 1,129 (81.1%) were node-positive (pathologic stage IIB; Fig 1). In addition, 780 (56.0%) were male and 612 (44.0%) were female. The median age was 64 (range 26–89), most patients were Caucasian (83.5%), had Medicaid or Medicare (49.2%), and were treated at an academic/research facility (53.5%). Fully 1,207 (86.7%) patients had a standard PD, while 185 (13.3%) had a PPPD. Overall, 454 (32.6%) patients received ACT alone, while 938 (67.4%) received adjuvant chemotherapy with radiation (Table 1). The rate of XRT utilization for all patients decreased from 81.0% in 2004 to 58.8% in 2013 ($P < .001$), with a similar trend observed in both node-negative patients (95.0% vs 66.7%, $P = .165$) and node-positive patients (77.5% vs 57.3%, $P = .001$) (Fig 2).

Factors associated with ACRT

χ^2 and multivariable analyses were used to identify factors associated with ACRT utilization (Tables 1 and 2). Multivariable analysis adjusting for age, comorbid disease state, nodal disease, facility type and location, and histologic tumor grade identified that patients

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Table 1
Cohort characteristics.

Characteristic	ACT	ACRT	*P* value
	454 (32.6%)	938 (67.4%)	
Mean age	65	63	.009
Age			.012
18–55	80 (17.6%)	199 (21.2%)	
56–65	151 (33.3%)	330 (35.2%)	
66–75	145 (31.9%)	305 (32.5%)	
>75	78 (17.2%)	104 (11.1%)	
Sex			.764
Male	257 (56.6%)	523 (55.8%)	
Female	197 (43.4%)	415 (44.2%)	
Race			.476
Caucasian	376 (82.8%)	787 (83.9%)	
Black	37 (8.1%)	61 (6.5%)	
Hispanic	28 (6.2%)	49 (5.2%)	
API	10 (2.2%)	32 (3.4%)	
Other	3 (0.7%)	9 (1.0%)	
Insurance status			.067
None	12 (2.6%)	29 (3.1%)	
Private	189 (41.7%)	446 (47.5%)	
Medicaid/Medicare	243 (53.5%)	442 (47.2%)	
Other government	3 (0.7%)	14 (1.5%)	
Unknown	7 (1.5%)	7 (0.7%)	
Socioeconomic status			.991
Low	88 (19.4%)	175 (18.7%)	
Middle	94 (20.7%)	197 (21.0%)	
High	247 (54.4%)	514 (54.8%)	
Unknown	25 (5.5%)	52 (5.5%)	
Comorbidity index			.027
0	275 (60.6%)	634 (67.6%)	
1	145 (31.9%)	254 (27.1%)	
2	34 (7.5%)	50 (5.3%)	
Facility type			.025
Community	12 (2.6%)	50 (5.3%)	
Comprehensive	122 (26.9%)	275 (29.3%)	
Academic	260 (57.3%)	485 (51.7%)	
Integrated Cancer Network	51 (11.2%)	120 (12.8%)	
Other	9 (2.0%)	8 (0.9%)	
Surgery			.262
PD	387 (85.2%)	820 (87.4%)	
PPPD	67 (14.8%)	118 (12.6%)	
Pathologic stage			.024
IA	4 (0.9%)	13 (1.4%)	
IB	6 (1.3%)	23 (2.5%)	
IIA	55 (12.1%)	162 (17.3%)	
IIB	389 (85.7%)	740 (78.8%)	
Pathologic T stage			.728
T1	7 (1.5%)	20 (2.1%)	
T2	47 (10.4%)	101 (10.8%)	
T3	400 (88.1%)	817 (87.1%)	
Tumor grade			.024
I	36 (7.9%)	86 (9.2%)	
II	210 (46.3%)	489 (52.1%)	
III/IV	195 (43.0%)	325 (34.6%)	
Unknown	13 (2.8%)	38 (4.1%)	
Nodal status			.002
Node negative	65 (14.3%)	198 (21.1%)	
Node positive	389 (85.7%)	740 (78.9%)	
Vascular abutment			.358
No	411 (90.5%)	834 (88.9%)	
Yes	43 (9.5%)	104 (11.1%)	

ACT, Adjuvant Chemotherapy; *ACRT*, Adjuvant Chemoradiation; *API*, Asian or Pacific Islander; *PD*, Pancreatoduodenectomy; *PPPD*, Pylorus-Preserving Pancreatoduodenectomy.

18–55 years old (odds ratio [OR] 2.03; 95% confidence interval [CI] 1.34–3.08) and those treated in New England (OR 2.98; 95% CI, 1.48–6.01) were more likely to receive ACRT (Table 2). Those with a higher Charlson-Deyo scores were less likely to be treated with ACRT compared with those with a score of zero (OR 0.70; 95% CI, 0.54–0.91 for 1; OR 0.57; 95% CI, 0.35–0.93 for 2). Patients with node-positive disease (pathologic stage IIB) were less likely to receive ACRT compared with those with node-negative disease (pathologic stages IA, IB, IIA; OR 0.60; 95% CI, 0.44–0.83). Academic/research facilities were less likely to treat patients with ACRT compared with community cancer programs (OR 0.41; 95% CI, 0.21–0.80). Patients with histologic tumor grades III/IV were less likely to receive ACRT compared with those with tumors of grade II (OR 0.73; 95% CI, 0.57–0.94; Table 2).

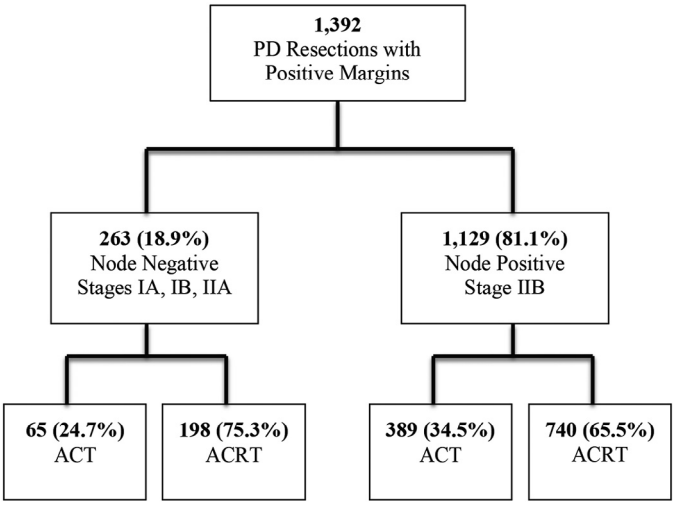

Fig. 1. Treatment modality breakdown. Reported stages are pathologic stages.

Overall survival analysis

Overall survival profiles of patients receiving adjuvant chemotherapy alone and adjuvant chemoradiation were compared using

Table 2
Multivariable logistic regression for independent predictors of adjuvant chemoradiation utilization.

Predictor	OR (95% CI)	*P* value
Age		
>75	1 (Reference)	—
18–55	2.03 (1.34–3.08)	.001
56–65	1.70 (1.18–2.45)	.004
66–75	1.64 (1.14–2.37)	.008
Facility type		
Community	1 (Reference)	—
Comprehensive	0.55 (0.28–1.08)	.083
Academic	0.41 (0.21–0.80)	.009
Integrated Cancer Network	0.58 (0.28–1.22)	.151
Facility location		
East North Central	1 (Reference)	—
New England	2.98 (1.48–6.01)	.002
Middle Atlantic	0.67 (0.45–0.99)	.046
South Atlantic	0.81 (0.55–1.19)	.285
East South Central	0.75 (0.44–1.28)	.288
West North Central	1.16 (0.73–1.85)	.526
West South Central	0.88 (0.52–1.48)	.616
Mountain	0.78 (0.42–1.45)	.427
Pacific	0.49 (0.32–0.75)	.001
Comorbidity index		
0	1 (Reference)	—
1	0.70 (0.54–0.91)	.007
2	0.57 (0.35–0.93)	.023
Nodal status		
Node negative	1 (Reference)	—
Node positive	0.60 (0.44–0.83)	.002
Tumor grade		
II	1 (Reference)	—
I	1.05 (0.67–1.64)	.843
III/IV	0.73 (0.57–0.94)	.015
Unknown	1.20 (0.61–2.35)	.599

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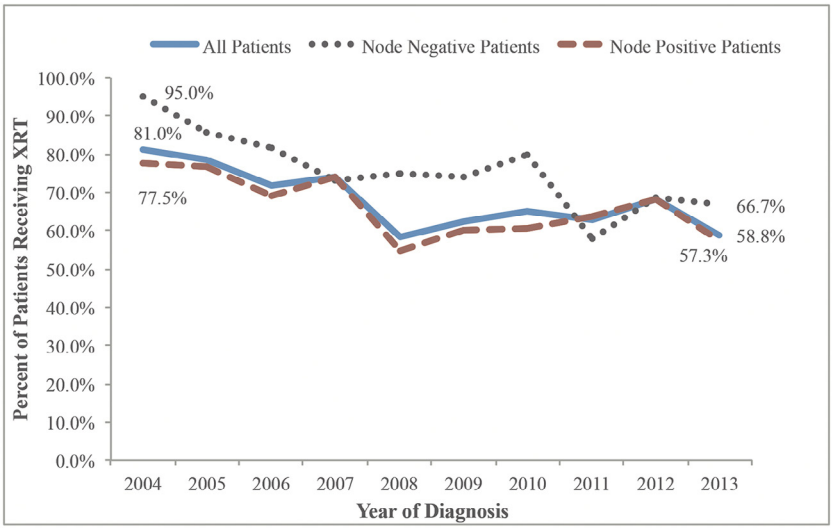

Fig. 2. XRT utilization, 2004 to 2013. Rate of XRT utilization for all patients decreased from 81.0% to 58.8% from 2004 to 2013 ($P < .001$). XRT utilization in node-negative patients decreased from 95.0% to 66.7% ($P = .165$). XRT utilization in node-positive patients declined from 77.5% to 57.3% ($P = .001$).

adjusted Cox proportional hazards regressions. Survival analyses were stratified by nodal status-node-negative (pathologic stages IA, IB, and IIA) and node-positive (pathologic stage IIB) and adjusted for age, sex, race, SES, insurance, surgical procedure (PD versus PPPD), adjuvant radiation therapy, vascular abutment, pathologic T stage, histologic tumor grade, facility type, and comorbid disease state. In patients with node-positive disease, ACRT conferred a statistically significant survival benefit (HR 0.81; 95% CI 0.71–0.93) over ACT alone (Table 3). Other factors associated with survival for node-positive patients included Charlson-Deyo comorbidity index, SES, and race (Table 3). Vascular abutment and histologic tumor grade were not significant independent predictors of mortality for node-positive patients. In node-negative patients, ACRT conferred no overall survival benefit (HR 1.13; 95% CI, 0.79–1.62) compared with ACT. Vascular abutment was independently associated with impaired overall survival in node negative patients (HR 1.99; 95% CI, 1.28–3.11), as was histologic tumor grades III/IV (HR 1.51; 95% CI, 1.08–2.10; Table 3). Treatment at an academic/research facility was associated independently with improved overall survival in node-negative patients (HR 0.49; 95% CI, 0.25–0.96). Age, sex, operative procedure, pathologic T stage, and insurance status were not associated independently with survival for either node-positive or node-negative patient subgroups. The adjusted median overall survival for node-positive patients receiving ACRT was 17.5 months compared with 15.2 months for those receiving ACT ($P = .003$; Fig 3, A). For node-negative patients, adjusted median overall survival was 22.5 months for those receiving ACRT and 23.6 months for those receiving ACT ($P = .511$; Fig 3, *B*). To better clarify the absolute magnitude of the benefit of adding adjuvant radiation to adjuvant chemotherapy, Cox models were re-run to include patients who did not receive any adjuvant treatment at all. In addition, 619 patients who underwent PD but did not receive any adjuvant treatment were identified. Adjusted median survival for patients receiving no adjuvant treatment was compared with those who received adjuvant chemotherapy and to those who received adjuvant chemoradiation therapy. In this analysis, adjusted median overall survival for node-negative patients was found to be 12.2 months for patients receiving no adjuvant therapy, 25.0 months for those receiving adjuvant chemotherapy alone and 22.8 months for patients receiving adjuvant chemoradiotherapy. There was no statistical difference between those receiving chemotherapy and those receiving chemoradiotherapy in this analysis ($P = .252$). For node-positive patients, adjusted median overall survival was 9.3 months for those receiving no adjuvant therapy, 14.9 months for those receiving adjuvant chemotherapy, and 16.9 months for patients receiving adjuvant chemoradiotherapy. There was a statistical difference between all treatment groups in this analysis ($P < .001$).

Discussion

In this retrospective analysis, the NCDB was utilized to identify a large, multi-institutional cohort of patients with early pathologic stage PDAC that had upfront PD with microscopic-positive margins from 2004–2013. This analysis sought to determine the survival benefit associated with adding loco-regional radiation to adjuvant systemic chemotherapy. The analysis was further stratified by nodal status to identify patients more clearly who might benefit from XRT. Patients were subgrouped as either node-negative (pathologic stages IA, IB, IIA) or node-positive (pathologic stage IIB). A trend in decreasing utilization of adjuvant radiation in patients with pathologic stage I or II, margin-positive PDAC was observed from 81% in 2004 to 58.8% in 2013. χ^2 and multivariable analyses demonstrated that younger patients with fewer comorbid conditions and less concern for distant disease (node-negative pathology) were more likely to be treated with radiation therapy. A marginal (~2.5 month) but statistically significant survival benefit for XRT in patients with node-positive disease was identified. In patients with node-negative disease, there was no survival benefit associated with adding XRT to adjuvant chemotherapy.

Evidence to support the use of radiation therapy in PDAC has been limited, and no consensus on the optimal use of radiation in this patient population has been established. The only randomized trial to examine radiation in isolation was the ESPAC-1 trial, which randomized 73 patients with resected PDAC to treatment with chemoradiation alone, 75 to chemotherapy alone, 72 to both chemoradiation and chemotherapy, and 69 to resection alone.[7] This trial demonstrated a significant survival benefit in patients being treated with adjuvant chemotherapy alone and found a deleterious effect to treatment with chemoradiation. This study has been

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Table 3
Adjusted Cox proportional hazards regression.

Characteristic	Node-negative disease		Node-positive disease	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Treatment modality				
ACT	1 (Reference)	—	1 (Reference)	—
ACRT	1.13 (0.79–1.62)	.511	0.81 (0.71–0.93)	.003
Age				
18–55	1 (Reference)	—	1 (Reference)	—
56–65	1.24 (0.81–1.90)	.323	1.13 (0.94–1.36)	.203
66–75	1.38 (0.86–2.23)	.184	1.07 (0.85–1.35)	.574
>75	1.03 (0.58–1.84)	.921	1.18 (0.90–1.55)	.226
Sex				
Male	1 (Reference)	—	1 (Reference)	—
Female	1.17 (0.86–1.59)	.309	1.01 (0.88–1.15)	.936
Race				
Caucasian	1 (Reference)	—	1 (Reference)	—
Black	1.03 (0.59–1.79)	.924	1.14 (0.87–1.48)	.336
Hispanic	1.23 (0.71–2.13)	.457	0.87 (0.64–1.17)	.357
API	0.96 (0.49–1.88)	.894	0.46 (0.28–0.76)	.002
Other	1.07 (0.12–9.50)	.952	1.08 (0.52–2.22)	.841
Insurance				
Uninsured	1 (Reference)	—	1 (Reference)	—
Private	0.80 (0.34–1.88)	.607	0.81 (0.52–1.28)	.370
Medicaid/Medicare	1.09 (0.74–1.59)	.678	1.08 (0.90–1.30)	.402
Other government	—	.945	1.35 (0.75–2.44)	.320
Unknown	0.93 (0.21–4.22)	.930	0.78 (0.38–1.58)	.482
Socioeconomic status				
Low	1 (Reference)	—	1 (Reference)	—
Middle	1.04 (0.66–1.64)	.868	0.84 (0.69–1.04)	.109
High	0.79 (0.52–1.20)	.276	0.73 (0.61–0.88)	.001
Unknown	1.06 (0.53–2.12)	.874	0.82 (0.59–1.14)	.242
Facility type				
Community	1 (Reference)	—	1 (Reference)	—
Comprehensive	0.53 (0.26–1.06)	.073	0.91 (0.66–1.25)	.570
Academic	0.49 (0.25–0.96)	.039	0.78 (0.58–1.07)	.122
Integrated Cancer Network	0.53 (0.25–1.13)	.100	0.82 (0.58–1.17)	.277
Surgery				
PD	1 (Reference)	—	1 (Reference)	—
PPPD	1.17 (0.72–1.89)	.535	0.92 (0.75–1.11)	.366
Comorbidity index				
0	1 (Reference)	—	1 (Reference)	—
1	1.40 (1.00–1.96)	.052	1.23 (1.06–1.42)	.005
2	1.73 (0.95–3.14)	.071	1.33 (1.01–1.74)	.043
Vascular abutment				
No	1 (Reference)	—	1 (Reference)	—
Yes	1.99 (1.28–3.11)	.002	1.13 (0.92–1.39)	.262
Pathologic T stage				
T1	1 (Reference)	—	1 (Reference)	—
T2	1.35 (0.63–2.86)	.440	1.36 (0.64–2.88)	.423
T3	0.95 (0.50–1.82)	.886	1.88 (0.91–3.89)	.088
Tumor grade				
II	1 (Reference)	—	1 (Reference)	—
I	1.17 (0.73–1.87)	.525	0.94 (0.73–1.21)	.621
III/IV	1.51 (1.08–2.10)	.015	1.14 (0.99–1.31)	.060
Unknown	0.53 (0.22–1.25)	.144	1.25 (0.89–1.77)	.203

criticized, because a substantial percentage of patients in this trial received suboptimal radiation therapy.[7] The Gastrointestinal Tumor Study Group (GITSG 9173) was one of the earliest randomized trials to compare surgery alone with surgery followed by chemoradiotherapy.[18] The GITSG analysis was limited to resections with negative margins and had slow accrual with a final sample size of only 43 patients. This study included only patients treated with both adjuvant chemotherapy and radiotherapy.[18] The European Organization for Research and Treatment of Cancer (EORTC 40891) randomized patients to observation or chemoradiotherapy after pancreatic resection.[19] This study found no significant differences in survival between these 2 groups. This analysis consisted of heterogeneous tumor histologies (PDAC and nonpancreatic periampullary adenocarcinomas). Due to the limitations of these randomized trials, it is difficult to determine the optimal use of radiation in resected PDAC, although the results of ESPAC-1 have very likely driven the observed decrease in the use of radiation over time.

Several retrospective, multi-institutional studies have evaluated the impact of adding radiation to adjuvant chemotherapy. Many of these studies have demonstrated a survival benefit of adjuvant chemoradiation over chemotherapy or resection alone.[3,8-10] These studies typically analyze heterogeneous patient cohorts in regard to pathologic stage, resection margin status, type of resection (PD, pancreatectomy), and status of nodal disease. One prior analysis from the NCDB using an older dataset has attempted to examine the role of XRT utilizing a propensity score match to compare survival outcomes associated with ACT versus ACRT. This study identified a benefit with adjuvant chemoradiation therapy compared with ACT in all patients analyzed together (node-positive and node-negative).[3] This study included both distal pancreatectomy and pancreatoduodenectomy patients and did not break out the Cox modeling for the subset of patients who had R1 resections and lymph node-negative disease.[3]

To the best of our knowledge, the present study is the largest, multi-institutional analysis with the most contemporary dataset that evaluates only patients resected with microscopic positive margins. While the overall use of adjuvant radiotherapy was found to be declining over time, there seems to be national trends in the utilization of XRT toward patients with node-negative disease. This is counterintuitive as this group seems less likely to benefit from adjuvant radiation treatment. It must be noted that radiation therapy to the abdominal region has been associated with substantial short- and long-term risks and clinical costs. These include pancreatitis, pancreatic insufficiency, steatorrhea, diabetes mellitus, peptic ulceration, delayed gastric emptying, enteritis, and small bowel obstruction.[20,21] Given the present findings, it is possible to justify XRT in patients with node-positive disease, but considering the costs associated with the treatment, the limited observed survival benefit (~2.5 months), and the potential for radiation-related toxicity, it may be more prudent to withhold radiation and consider adding it later in the sequence of therapy or to use it only in the event that there is clinical evidence of local recurrence.

There are several limitations to the dataset used in this study. The NCDB is a retrospectively accruing dataset and by nature is subject to selection and omitted variable bias. The NCDB lacks data pertaining to disease recurrence and disease-specific survival precluding any analysis from assessing whether adjuvant chemoradiation provides increased loco-regional control over chemotherapy alone. There is heterogeneity within the dataset with regard to the method of delivery of the radiation and the dose received. Additionally, there are no data regarding whether or not a patient completed the course of radiotherapy. Despite these limitations, this study represents a robust survival analysis of the most recent cohort of patients with early stage PDAC resected to microscopic positive margins receiving either adjuvant chemotherapy or adjuvant chemoradiation. In patients undergoing an upfront R1 PD for early stage PDAC, the addition of adjuvant radiation to adjuvant chemotherapy decreased markedly during the years under review, 2004–2013. The subgroup of R1 resected patients with lymph-node positive, pathologic stage IIB disease experienced a small (~2.5 month) but statistically significant survival benefit when radiation was added to adjuvant chemotherapy. Additional randomized controlled trials with health-related quality of life metrics and a cost-benefit analysis are needed to determine if the benefit associated with radiation justifies its use in node-positive pathologic stage IIB disease.

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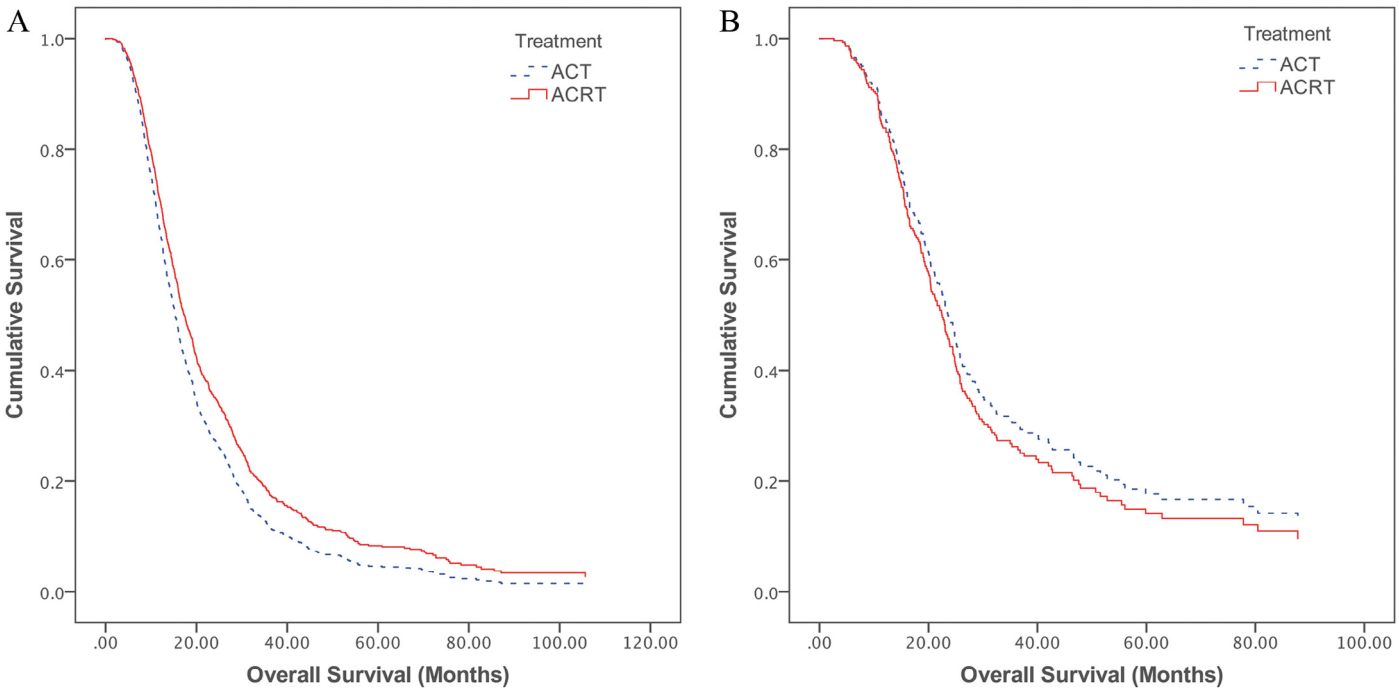

Fig. 3. (*A*) Adjusted overall survival curves for node-positive patients. Adjusted median survival for node-positive patients receiving ACRT was 17.5 months vs 15.2 months for node-positive patients receiving ACT alone ($P = .003$). (*B*) Adjusted overall survival curves for node-negative patients. Adjusted median survival for node-negative patients receiving ACRT was 22.5 months vs 23.6 months for node-negative patients receiving ACT alone ($P = .511$).

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