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ORIGINAL ARTICLE

Neoadjuvant stereotactic body radiation therapy for nonmetastatic pancreatic adenocarcinoma

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ABSTRACT

Background: Neoadjuvant therapy is a strategy for resectable and borderline resectable pancreatic cancer, but a consensus approach regarding optimal management is undetermined. Neoadjuvant options include chemotherapy with/without radiotherapy. Stereotactic body radiation therapy (SBRT) is a novel radiation technique that may provide benefit over conventionally fractionated radiation therapy (CFRT) in the neoadjuvant setting. The purpose of the present study is to determine neoadjuvant treatment with SBRT to other neoadjuvant treatment options for patients with resectable pancreatic cancer.

Material and methods: The National Cancer Database was queried (2004–2015) for patients with nonmetastatic pancreatic adenocarcinoma receiving neoadjuvant therapy followed by pancreatectomy. Patients were categorized based on the type of neoadjuvant treatment administered. Statistics included temporal trend assessment by annual percent change (APC), predictors for SBRT by multivariable logistic regression, Kaplan–Meier overall survival (OS) analysis without and with propensity matching, and Cox proportional hazards modeling for univariable OS analysis.

Results: Of 5828 patients, 332 (5.7%), 3234 (55.5%) and 2262 (38.8%) received neoadjuvant chemo-SBRT, chemotherapy, and chemo-CFRT, respectively. SBRT utilization increased from 0% in 2004 to 9.5% in 2015, with a greater APC after 2010 ($p < .001$). SBRT was more likely to be utilized in patients with T3–4 and node-positive disease ($p < .05$ for all). The chemo-SBRT cohort was associated with a higher OS rate before and after propensity matching ($p < .05$ for both). The rate of R0 resection was higher in radiotherapy groups than the chemotherapy cohort ($p < .001$).

Conclusions: Utilization of neoadjuvant SBRT for pancreatic cancer is increasing. In the neoadjuvant setting, chemo-SBRT may improve R0 resection and OS over chemotherapy and chemo-CFRT, although confirmatory prospective studies are needed for confirmation.

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Introduction

Pancreatic cancer is an aggressive malignancy and is projected to rise from the third to the second leading cause of cancer death in the US by 2030 [1]. The prognosis of pancreatic cancer is poor, with a 5-year survival of about 7%, with the only opportunity for long-term survival coming from selected patients undergoing complete surgical resection [2,3]. Neoadjuvant therapy is a promising strategy that is currently recommended for patients with borderline resectable and high-risk resectable diseases due to the increased likelihood of R0 resection, possibly turning patients who were previously inoperable into surgical candidates, and by selecting patients most likely to benefit from surgery [4–12].

However, there is currently a lack of consensus regarding the optimal neoadjuvant approach. Multi-agent chemotherapy has demonstrated both improved radiographic response and overall survival (OS) compared to single-agent chemotherapy [13]. Radiation therapy (RT) has been demonstrated to improve margin-negative resection rates and local control, though has not been associated with improved OS [6,14–16]. Stereotactic body radiation therapy (SBRT), an advanced radiotherapy technique delivering ablative doses of radiation in a few fractions, could, due to the tight margins used during treatment delivery, potentially minimize the toxicity of normal surrounding tissues. Also, due to the small number of treatments used when delivering SBRT, its use would minimize interruptions in chemotherapy delivery [17], and data supports its use in select cases for patients with unresectable pancreatic cancer [18,19]. While several single institution studies have reported that SBRT is an attractive neoadjuvant option with margin negative resection rates above 90% and improved survival with mild radiation toxicities [20], there is currently insufficient data to recommend it as a standard treatment regimen.

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Supplemental data for this article can be accessed here.

Table 1. Baseline socioeconomic, clinical and treatment characteristics of all patients by cohorts.

Characteristic	All ($n = 5828$)	Chemotherapy $n = 3234$ (%)	Chemo-CFRT $n = 2262$ (%)	Chemo-SBRT $n = 332$(%)	p Value
Socioeconomic characteristics					
Age					.122
<50	571 (9.8%)	308 (9.5%)	240 (10.6%)	23 (6.9%)	
51–69	3579 (61.4%)	1967 (60.8%)	1398 (61.8%)	214 (64.5%)	
≥70	1678 (28.8%)	959 (29.7%)	624 (27.6%)	95 (28.6%)	
Gender					.441
Male	3014 (51.7%)	1696 (52.4%)	1152 (50.9%)	166 (50.0%)	
Female	2814 (48.3%)	1538 (47.6%)	1110 (49.1%)	166 (50.0%)	
Race					<.001
White	5089 (87.3%)	2852 (88.2%)	1936 (85.6%)	301 (90.7%)	
African American	521 (8.9%)	253 (7.8%)	249 (11.0%)	19 (5.7%)	
Other/not recorded	218 (3.7%)	129 (4.0%)	77 (3.4%)	12 (3.6%)	
Charlson Deyo score					.133
0	3965 (68.0%)	2240 (69.3%)	1495 (66.1%)	230 (69.3%)	
1	1488 (25.5%)	804 (24.9%)	601 (26.6%)	83 (25.0%)	
2	281 (4.8%)	142 (4.4%)	127 (5.6%)	12 (3.6%)	
3	94 (1.6%)	48 (1.5%)	39 (1.7%)	7 (2.1%)	
Facility type					<.001
Nonacademic	2114 (36.3%)	1207 (37.3%)	870 (38.5%)	37 (11.1%)	
Academic	3654 (62.7%)	1992 (61.6%)	1367 (60.4%)	295 (88.9%)	
Not recorded	60 (1.0%)	35 (1.1%)	25 (1.1%)	0 (0.0%)	
Insurance					.002
Private	2705 (46.4%)	1487 (46.0%)	1057 (46.7%)	161 (48.5%)	
Medicaid	277 (4.8%)	151 (4.7%)	116 (5.1%)	10 (3.0%)	
Medicare	2589 (44.4%)	1475 (45.6%)	960 (42.4%)	154 (46.4%)	
Not insured	93 (1.6%)	45 (1.4%)	48 (2.1%)	0 (0.0%)	
Other/not recorded	164 (2.8%)	76 (2.4%)	81 (3.6%)	7 (2.1%)	
Income					<.001
<$63000	3775 (64.8%)	2039 (63.0%)	1532 (67.7%)	204 (61.4%)	
≥$63000	1995 (34.2%)	1170 (36.2%)	697 (30.8%)	128 (38.6%)	
Not recorded	58 (1.0%)	25 (0.8%)	33 (1.5%)	0 (0.0%)	
% without high school degree					.001
<14.0	2329 (4.0%)	1317 (40.7%)	864 (38.2%)	148 (44.6%)	
14.0–19.9	1402 (24.1%)	770 (23.8%)	538 (23.8%)	94 (28.3%)	
20.0–28.9	1205 (2.7%)	637 (19.7%)	511 (22.6%)	57 (17.2%)	
≥29.0	691 (11.9%)	404 (12.5%)	266 (11.8%)	21 (6.3%)	
Unknown	201 (3.4%)	106 (3.3%)	83 (3.7%)	12 (3.6%)	
Distance from facility					<.001
<20 miles	2922 (5.1%)	1630 (50.4%)	1192 (52.7%)	100 (30.1%)	
≥20 miles	2853 (49.0%)	1582 (48,9%)	1039 (45.9%)	232 (69.9%)	
Not recorded	53 (.9%)	22 (0.7%)	31 (1.4%)	0 (0.0%)	
Year of diagnosis					<.001
2004–2009	1114 (19.1%)	484 (15.0%)	614 (27.1%)	16 (4.8%)	
2010–2015	4714 (80.9%)	2750 (85.0%)	1648 (72.9%)	316 (95.2%)	
Disease characteristics					
Clinical T stage					<.001
T1	311 (5.3%)	182 (5.6%)	119 (5.3%)	10 (3.0%)	
T2	1445 (24.8%)	885 (27.4%)	516 (22.8%)	44 (13.3%)	
T3	2827 (48.5%)	1529 (47.3%)	1098 (48.5%)	200 (60.2%)	
T4	861 (14.8%)	366 (11.3%)	422 (18.7%)	73 (22.0%)	
Tx	384 (6.6%)	272 (8.4%)	107 (4.7%)	5 (1.5%)	
Tumor size (cm)					.967
Median	3.2	3.2	3.3	3.2	
<3	2191 (37.6%)	1235 (38.2%)	830 (36.7%)	126 (38.0%)	
3–4.9	2665 (45.7%)	1465 (45.3%)	1049 (46.4%)	151 (45.5%)	
≥5	731 (12.5%)	400 (12.4%)	290 (12.8%)	41 (12.3%)	
Unknown	241 (4.1%)	134 (4.1%)	93 (4.1%)	14 (4.2%)	
Clinical N stage					<.001
N0	3708 (63.6%)	2026 (62.8%)	1475 (65.2%)	207 (62.7%)	
N1	1710 (29.3%)	930 (28.8%)	664 (29.4%)	116 (35.2%)	
Nx	410 (7.0%)	271 (8.4%)	122 (5.4%)	7 (2.1%)	
Primary location					.004
Head	4423 (75.9%)	2463 (76.2%)	1721 (76.1%)	239 (72.0%)	
Body	481 (8.3%)	235 (7.3%)	207 (9.2%)	39 (11.7%)	
Tail	311 (5.3%)	196 (6.1%)	98 (4.3%)	17 (5.1%)	
Other/NOS	613 (10.5%)	340 (10.5%)	236 (10.4%)	37 (11.1%)	
Treatment characteristics					
Chemotherapy agent					<.001
Single-agent	1616 (27.7%)	526 (16.3%)	1061 (46.9%)	29 (8.7%)	
Multiagent	3997 (68.6%)	2543 (78.6%)	1152 (50.9%)	302 (91.0%)	
Chemotherapy, NOS	215 (3.7%)	165 (5.1%)	49 (2.2%)	1 (0.3%)	
Surgical margin					<.001
Negative	4621 (79.3%)	2456 (75.9%)	1883 (83.2%)	282 (84.9%)	
Microscopic	625 (10.7%)	398 (12.3%)	202 (8.9%)	25 (7.5%)	

(*continued*)

Table 1. Continued.

Characteristic	All ($n = 5828$)	Chemotherapy $n = 3234$ (%)	Chemo-CFRT $n = 2262$ (%)	Chemo-SBRT $n = 332$(%)	p Value
Macroscopic	60 (1.0%)	39 (1.2%)	20 (0.9%)	1 (0.3%)	
Residual, NOS	379 (6.5%)	252 (7.8%)	109 (4.8%)	18 (5.4%)	
Unknown	143 (2.5%)	89 (2.8%)	48 (2.1%)	6 (1.8%)	

chemo-SBRT: chemotherapy combined with stereotactic body radiotherapy; chemo-CFRT: chemotherapy combined with conventionally fractionated radiotherapy; NOS: Not Otherwise Specified.

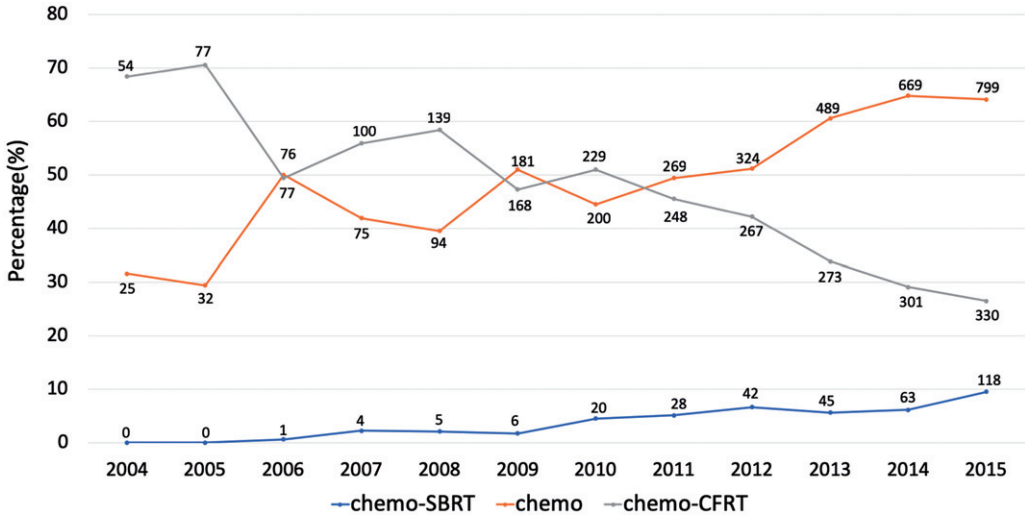

Figure 1. The trends of utilization of three neoadjuvant modalities for pancreatic adenocarcinoma from 2004 to 2015. chemo-SBRT: chemotherapy combined with stereotactic body radiotherapy; chemo: chemotherapy; chemo-CFRT: chemotherapy combined with conventionally fractionated radiotherapy.

The purpose of this study was to use the national cancer database (NCDB) to identify the utilization of SBRT in the neoadjuvant setting for pancreatic adenocarcinoma, and to compare clinical outcomes for patients treated with each regimen of neoadjuvant therapy.

Material and methods

Data source and study population

This retrospective analysis was conducted using the National Cancer Data Base (NCDB), a joint project of the commission on cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB contains de-identified information from approximately 70% of newly diagnosed cancers in the US. The data used in the study were derived from a de-identified NCDB file (2004–2015). The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data by the investigators. As all patient information in the NCDB database is de-identified, this study was exempt from institutional review board evaluation.

The present study included patients with newly-diagnosed pancreatic adenocarcinoma coded by the International Classification of Disease (ICD-O-3 codes: 8140, 8141, 8143, 8144, 8147, 8154, 8163, 8210, 8221, 8255, 8260, 8262, 8290, 8310, 8440, 8441, 8470, 8471, 8480, 8481, 8490, 8500, and 8550) with clinical stage T1-4N0-1M0 disease undergoing pancreaticoduodenectomy and receiving neoadjuvant treatment. Information including demographic, clinical, and treatment data were collected on each patient. Patients with unknown radiation modality and dose or those treated with radioactive implants or brachytherapy were excluded.

Patients were grouped into three cohorts based on the preoperative modality delivered: patients who received chemotherapy as well as "stereotactic radiosurgery, NOS (not otherwise specified)," "LINAC radiosurgery," or external beam RT with a daily fraction dose $\geq$6 Gy in no more than 10 fractions were defined as the chemo-SBRT cohort; patients receiving chemotherapy and non-SBRT radiation were defined as being in the chemotherapy-conventionally fractionation radiation therapy (CFRT) cohort; and patients receiving neoadjuvant systemic chemotherapy alone were categorized as being in the chemotherapy (chemo) cohort.

Statistical analyses

Demographic, clinical, and treatment characteristics were compared among these three cohorts using chi-square tests or Fischer exact test. Variables were tested for collinearity and interaction. Univariate and multivariable logistic regression were performed including variables with calculating variance inflation factors (VIF) < 10 to determine characteristics predictive for SBRT administration over CFRT [21]. Temporal trends of different modalities were evaluated with graphical assessment, and estimated by annual percent change (APC) [22].

Survival analysis was conducted using the Kaplan–Meier method after excluding patients without documented follow-up, and the log-rank test was used for cohort comparisons. Survival was defined as the interval between the date of diagnosis and the date of death or last follow-up. Univariate

Table 2. Assessment of resectability and staging response after neoadjuvant therapy.

Characteristic	Chemotherapy $n = 3234$ (%)	Chemo-CFRT $n = 2262$ (%)	Chemo-SBRT $n = 332$(%)	p Value
Surgical margin				<.001
Negative	2456 (75.9%)	1883 (83.2%)	282 (84.9%)	
Microscopic	398 (12.3%)	202 (8.9%)	25 (7.5%)	
Macroscopic	39 (1.2%)	20 (.9%)	1 (.3%)	
Residual, NOS	252 (7.8%)	109 (4.8%)	18 (5.4%)	
Unknown	89 (2.8%)	48 (2.1%)	6 (1.8%)	
Changes of T stage				<.001
Upstaging	747 (23.1%)	360 (15.9%)	34 (1.2%)	
Downstaging	511 (17.0%)	631 (27.9%)	117 (35.2%)	
Changes of N stage				<.001
Upstaging	1000 (3.9%)	355 (15.7%)	79 (23.8%)	
Downstaging	214 (6.6%)	333 (14.7%)	51 (15.4%)	
Changes of analytic stage				<.001
Upstaging	1082 (33.5%)	463 (2.5%)	85 (25.6%)	
Downstaging	592 (18.3%)	699 (3.9%)	113 (34.0%)	
Postoperative LOS (days, mean ± SD)	9.5 ± 7.3	1.3 ± 6.3	1.6 ± 8.6	
30-day readmission	210 (6.5%)	201 (8.9%)	21 (6.3%)	.014
30-day mortality	49 (2.0%)	39 (2.0%)	4 (1.9%)	.994
90-day mortality	97 (4.0%)	120 (6.2%)	8 (3.7%)	.014

chemo-SBRT: chemotherapy combined with stereotactic body radiotherapy; chemo-CFRT: chemotherapy combined with conventionally fractionated radiotherapy; NOS: Not Otherwise Specified; LOS: length of stay; SD: standard deviation.

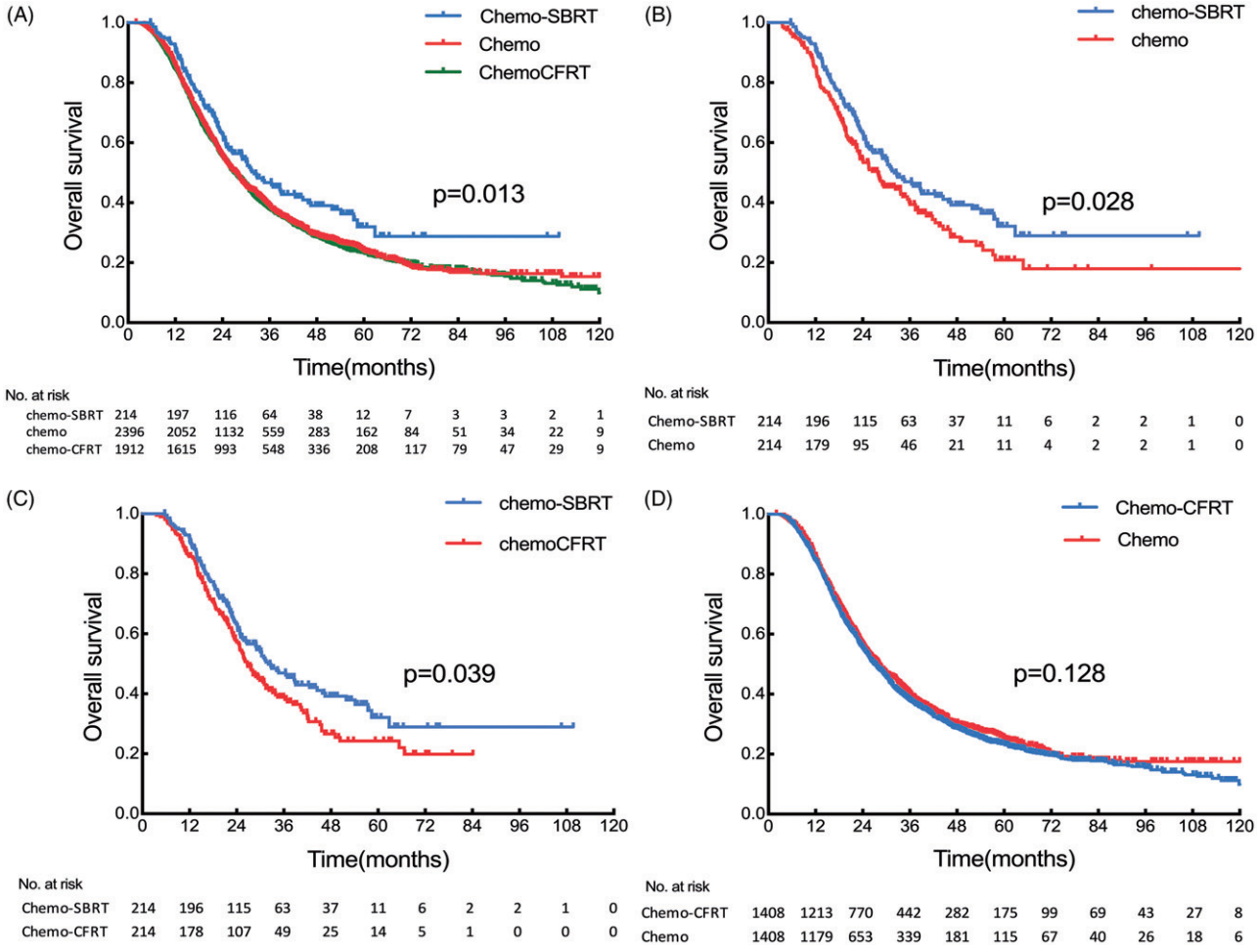

Figure 2. Kaplan–Meier overall survival curves of three cohorts of pancreatic adenocarcinoma. (a) Before propensity score matching; (b) After propensity score matching between chemo-SBRT and chemo cohorts; (c) After propensity score matching between chemo-SBRT and chemo-CFRT cohorts; (d) After propensity score matching between chemo-CFRT and chemo cohorts. chemo-SBRT: chemotherapy combined with stereotactic body radiotherapy; chemo: chemotherapy; chemo-CFRT: chemotherapy combined with conventionally fractionated radiotherapy.

analysis was performed to determine characteristics associated with improved OS.

To reduce bias caused by baseline differences, a propensity score matching was performed between the chemo-SBRT and chemo-CFRT cohorts, the chemo-SBRT and chemo cohorts, and again between the chemo-CFRT and chemo cohorts, in order to compare the OS. Each matching was performed at a 1:1 ratio without replacement using the nearest

Table 3. Prognostic factors for non-metastatic pancreatic adenocarcinoma in NCDB.

Characteristic	HR	95%CI	*p* Value
Modality			
Chemo-SBRT	1 (reference)		
Chemotherapy	1.295	1.071–1.567	.008
Chemo-CFRT	1.330	1.098–1.610	.003
Age			
≥70	1 (reference)		
51–69	0.816	0.753–0.884	<.001
<50	0.757	0.664–0.864	<.001
Gender			
Male	1 (reference)		
Female	0.966	0.899–1.038	.342
Race			
White	1 (reference)		
African American	0.993	0.875–1.128	.920
Other/ not recorded	0.739	0.597–0.915	.005
Charlson Deyo score			
0	1 (reference)		
1	1.059	0.975–1.150	.176
2	1.081	0.915–1.278	.359
3	1.041	0.752–1.441	.808
Facility Type			
Academic	1 (reference)		
Nonacademic	1.230	1.142–1.324	<.001
Not recorded	0.811	0.558–1.178	.272
Insurance			
Private	1 (reference)		
Medicaid	0.797	0.633–1.005	.055
Medicare	0.858	0.645–1.142	.294
Not insured	0.960	0.762–1.209	.727
Other/not recorded	0.997	0.702–1.417	.989
Income			
<$62999	1 (reference)		
≥$63000	0.895	0.829–0.966	.004
Not recorded	1.773	1.328–2.369	<.001
No high school education %			
< 14.0	1 (reference)		
14.0–19.9	1.054	0.960–1.157	.269
20.0–28.9	1.202	1.092–1.325	<.001
≥29.0	1.070	0.949–1.207	.268
Unknown	1.123	0.928–1.359	.234
Distance from facility			
<20 miles	1 (reference)		
≥20 miles	1.061	0.987–1.141	.109
Not recorded	2.116	1.567–2.856	<.001
Year of diagnosis			
2010–2015	1 (reference)		
2004–2009	1.170	1.080–1.267	<.001
cT stage			
T1	1 (reference)		
T2	1.082	0.908–1.288	.377
T3	1.121	0.949–1.323	.178
T4	1.160	0.967–1.392	.110
Tx	1.195	0.979–1.459	.081
N stage			
N0	1 (reference)		
N1	1.097	1.012–1.188	.025
Nx	1.254	1.108–1.418	<.001
Primary location			
Head	1 (reference)		
Body	0.962	0.837–1.106	.586
Tail	0.968	0.817–1.147	.709
Other/NOS	0.869	0.771–0.978	.02
Chemotherapy agent			
Multiagent	1 (reference)		
Single-agent	1.314	1.219–1.416	<.001
Chemotherapy, NOS	1.397	1.177–1.658	<.001
Surgical margin			
Negative	1 (reference)		
Microscopic	1.620	1.453–1.806	<.001
Macroscopic	1.932	1.443–2.587	<.001
Residual, NOS	1.728	1.509–1.979	<.001
Unknown	1.248	0.995–1.564	.055

chemo-SBRT: chemotherapy combined with stereotactic body radiotherapy; chemo-CFRT: chemotherapy combined with conventionally fractionated radiotherapy; HR: Hazard ratio; CI: Confidence interval; NOS: Not Otherwise Specified.

neighbor method. The caliper width was equal to 0.2 of the standard deviation of the logit of the propensity score [23]. Overall survival (OS) was estimated in the matched sample with Kaplan–Meier method and log-rank test.

All statistical tests were two-sided, and a value of $p < .05$ was considered statistically significant. Analyses were performed using IBM SPSS, version 24.0 (IBM, Armonk, NY, USA), R version 3.4.3(www.R-project.org) and Joinpoint Regression Program Version 4.5.0.1, June 2017, National Cancer Institute (http://srab.cancer.gov/joinpoint/).

Results

Baseline characteristics

The patient inclusion criteria are depicted in Figure S1; a total of 5,828 patients met the inclusion criteria. Of these, 332 (5.7%), 3234 (55.5%) and 2262 (38.8%) were in the chemo-SBRT, chemo-alone and chemo-CFRT groups, respectively. Table 1 presents baseline characteristics of patients and compares them based on treatment modality. The chemo-SBRT cohort had the highest proportion of white patients, T3–T4 disease, and patients treated with multi-agent chemotherapy. Additionally, nearly 90% of patients in the chemo-SBRT cohort received treatment at academic facilities, the greatest proportion amongst all three groups.

Trends and predictors of upfront SBRT utilization

As shown in Figure 1, utilization of neoadjuvant chemo-SBRT increased from 0% in 2004 to 9.5% in 2015, with an APC of 28.3% ($p < .001$). Neoadjuvant chemotherapy alone steadily increased from 44.5% in 2010 to 64.1% in 2015, with an overall APC of 6.4%. Meanwhile, chemo-CFRT decreased significantly after 2010 from 51.0% to only 26.5% in 2015, with an overall APC of −7.8% ($p < .001$).

On multivariable analysis to assess for factors predictive of SBRT treatment (eTable 1), diagnosis after 2010, T3–4 disease, N1 disease, treatment at academic centers, residence in higher-educated regions and residence >20 miles from the treatment facility were all predictive of SBRT use ($p < .05$ for all).

Response and postoperative complications

A total of 79.3% ($n = 4621$) of the patients were found to have negative surgical margins. As recorded in Table 2, the use of any RT (SBRT or CFRT) was associated with higher R0 resection rates, T-stage downstaging, N-stage downstaging, and NCDB analytic stage downstaging ($p < .001$) when compared to neoadjuvant chemotherapy alone. Treatment with chemo-SBRT was associated with a higher rate of T-stage downstaging and N-stage downstaging than chemo-CFRT (both $p < .001$), but not R0 resection rate ($p = .678$).

After neoadjuvant therapy, the mean postoperative length of stay (LOS) was 10.0 ± 7.9 days. Chemo-CFRT prolonged the LOS compared to chemotherapy alone ($p < .001$), though there were no differences in LOS between chemo-CFRT and chemo-SBRT patients ($p = .268$). Chemo-CFRT patients were also observed to have higher 30-day readmission and 90-day mortality than chemo-SBRT and chemotherapy only patients ($p = .014$), but no difference was observed for readmission and perioperative mortality rates between chemo-SBRT and chemotherapy only cohorts ($p > .8$).

Survival outcomes

At a median follow-up of 47.0 months, the overall median OS of all patients was 27.6 months. When dividing patients by treatment type, the median OS was 32.1 months, 27.5 months and 27.1 months for the chemo-SBRT, chemo, and chemo-CFRT cohorts, respectively ($p = .013$). The survival improvement for the chemo-SBRT cohort was statistically significant (Figure 2(a)). Predictors of OS are depicted in Table 3.

Following propensity score matching, the clinical and demographic characteristics were well balanced between the groups, as shown in Tables S2–S4. The survival benefit of chemo-SBRT persisted after propensity score matching when compared to the chemo only and the chemo- CFRT cohorts (Figure 2(b,c)). There was no difference in OS following propensity score matching between the chemo-CFRT and chemo cohorts (Figure 2(d)). The propensity score matching was repeated using a different categorical variable for time (2004–2011 vs. 2012–2015) in order to account for the change in chemotherapy in this time period, and again found a similar result with superior OS found when comparing chemo-SBRT to patients treated with either chemo only or chemo-CFRT.

Subgroup analysis

To better address the potential heterogeneity of patients most and least likely to benefit from SBRT, subgroup analysis were undertaken on OS for chemo-SBRT and chemotherapy or chemo-CFRT (e Figures 2 and 3). Treatment with chemo-SBRT was associated with improved survival (over both chemo-CFRT and chemotherapy) for several subsets: age 51–69 years, Charlson-Deyo index of 1, T3/T4 tumors, N1 disease, and pancreatic head tumors.

Discussion

While neoadjuvant therapy may lead to improved outcomes for selected patients with pancreatic adenocarcinoma [8], challenges remain with this approach, such as delays to undergo definitive surgery and an increased risk for perioperative complications [24–27]. The use of SBRT in the neoadjuvant setting is promising owing to the small volumes treated (which minimize toxicities), as well as the relatively short course of treatment (which minimize delays to surgery and/or chemotherapy). It is in this setting that the present report, the largest study to date evaluating nationwide trends of neoadjuvant SBRT utilization for pancreatic cancer, provides evidence for the clinical efficacy of SBRT for pancreatic cancer in the neoadjuvant setting.

The utilization of SBRT in the neoadjuvant setting has increased consistently from 2004 to 2015, with an APC of 28.3%. Additionally, the use of SBRT in the neoadjuvant setting was associated with improved OS in both the unmatched and matched cohorts. Interestingly, the utilization of neoadjuvant chemo-CFRT decreased nearly 50% over this same time period.

While CFRT in addition to chemotherapy improved R0 resectability and improved tumor downstaging when compared to chemotherapy alone, no differences were observed in OS. These findings are concordant with another study utilizing the NCDB (2006–2011), that similarly showed no OS benefit with the addition of CFRT to neoadjuvant chemotherapy [28]. Randomized trials are needed to identify the benefit of CFRT in the neoadjuvant setting, and we anticipate the results of the ongoing CONKO-007 and ESPAC-5F to more fully answer this question.

The rapid increase in utilization of SBRT is likely due to the maturation of technique, the lack of clear benefit with CFRT, and the minimal toxicity associated with its use. Three NCDB analyses had revealed its use and confirmed its benefit in locally advanced unresectable pancreatic carcinoma from a nationwide review [29–31]. Neoadjuvant SBRT has been demonstrated to be correlated with improved survival in single institution studies [20,32,33]. The results of the present study are similar to previous NCDB studies comparing the efficacy of SBRT to CFRT for patients with unresectable pancreatic cancer and concordant with the aforementioned results from single institution studies.

Negative surgical margins have been reported to be an important prognostic factor for patients with pancreatic cancer undergoing surgical resection [24,34]. The addition of radiotherapy, whether delivered in CFRT or SBRT, renders an improved negative surgical margin resection rate and may also improve resectability. The survival benefit observed with neoadjuvant SBRT suggests a better local regional control which is a big concern for small volume irradiation, and, due to the shorter length of treatment, may be associated with decreased interruptions in systemic therapy [35].

An additional advantage to use of SBRT is the potential decrease of toxicities when compared with treatment using CFRT. Though severe toxicities have been reported with the use of CFRT, perhaps due to the large volume irradiated, with rates of grade 3 or greater toxicity up to 64% observed in the Alliance trial A021101, minimal toxicity has been described in the modern SBRT experience [17,27]. Toxicity data was not explicitly reported in this study due to limitations within the NCDB, but we examined postoperative mortality and 30-day readmission as a surrogate for treatment associated toxicity, and found that chemo-CFRT patients had a higher 30-day readmission and 90-day mortality than chemo-SBRT and chemo only patients. The worse postoperative outcomes associated with patients undergoing neoadjuvant CFRT may be due to high rates of toxicity caused by CFRT and the larger treatment volumes associated with its use. Therefore, an additional benefit afforded by use of SBRT may be decreased toxicity, allowing for the more aggressive, effective chemotherapy, mFOLFIRINOX, to be administrated following SBRT, which may further improve clinical outcomes.

Our study has limitations inherent to studies from large databases, such as coding error, an inability to determine the reason for the treatment delivered, and incomplete information regarding treatment details and patient characteristics. First, this study excluded patients not found to be resectable after neoadjuvant therapy, and was thus restricted to a group of patients who did not progress during neoadjuvant treatment. Additionally, there was a lack of information regarding chemotherapy regimens. This study included cases spanning over a period of 12 years during which there has been an evolution in systemic chemotherapy regimens, with newer regimens such as mFOLFIRINOX improving resectability and survival compared to a gemcitabine-based regimen [36,37]. Additionally, there has been an evolution in the ability to precisely deliver RT in recent years, which is part of the reason for the increased SBRT utilization demonstrated in the present study and in other similar NCDB studies in more recent time periods [29–31]. The potential bias of more effective systemic therapy in the SBRT group due to the increased utilization of SBRT in recent years was controlled by rigorous propensity matching and multivariable analysis, but some differences in chemotherapy regimens in the different groups remained. The heterogeneity of radiotherapy and surgeons' experience should also be considered. Additionally, since this study used data from the NCDB, information regarding local control was not available, and it is also possible that there may have been a miscoding of margin status. Moreover, the present study was retrospective in nature and while an OS was observed with the use of neoadjuvant SBRT, this does not necessarily imply causation. Therefore, the neoadjuvant SBRT paradigm should be defined with prospective randomized trials. The authors eagerly await the results of the Alliance A021501 trial, which is comparing neoadjuvant FOLFIRINOX to neoadjuvant FOLFIRINOX and SBRT for borderline resectable pancreatic cancer patients.

Conclusions

Utilization of neoadjuvant SBRT for pancreatic cancer is increasing. Neoadjuvant Chemo-SBRT may improve R0 resection and/or OS over chemotherapy alone and chemo-CFRT, although confirmatory prospective studies are needed to confirm these results.

Disclosure statement

No potential conflict of interest was reported by the authors.

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