Clinical and Translational Radiation Oncology 35 (2022) 9–16

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Contemporary use and outcomes of radiation and chemotherapy for unresectable pancreatic cancer

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ARTICLE INFO

Keywords:
Pancreatic cancer
Stereotactic body radiation treatment
SBRT
Complications
Toxicity
Gastrointestinal
Cost

ABSTRACT

Background: We assessed radiation treatment (RT) use and complications for unresectable pancreatic cancer in the US, comparing conventionally fractionated (CFRT) and stereotactic body radiation treatment (SBRT) to inform real-world expected outcomes and practice.
Material and Methods: We analyzed 5,624 patients with non-metastatic, unresectable pancreatic cancer (2,522 older patients age > 65, diagnosed 2006–2013 in Medicare linked data; and 3,102 younger patients age < 65, diagnosed 2006–2016 in MarketScan data), comparing CFRT vs. SBRT vs. chemotherapy alone. Cochran-Armitage tested temporal trends. Fisher's Exact Test and proportional hazards models compared gastrointestinal (GI) complications. Healthcare payments (Consumer Price Index adjusted to 2015) through 12 months were compared using generalized linear regression models with log link and gamma distribution.
Results: RT use declined from 55% to 45% of older patients (2006–2013) and 52% to 47% of younger patients (2006–2016) (Ptrend < 0.001 both). Among RT patients, SBRT use increased to 10% of older patients and 12% of younger patients in the most recent years (Ptrend = 0.04 and < 0.001 respectively). Addition of RT was associated with more frequent GI bleeds, strictures, and fistulas (Δ= +3% to 9% excess events, all $P \leq 0.05$). Temporal patterns suggested decreasing complications over time (Ptrend = 0.05 and 0.05 for older and younger patients). Among younger patients, there was no difference in GI complications for SBRT vs. CFRT ($P > 0.05$, all comparisons). Among older patients, increased complications were seen for SBRT in 1–4 fractions vs. CFRT ($P < 0.05$), but not SBRT in 5 fractions ($P = 0.72$). Healthcare payments were greatest for SBRT when compared with CFRT or chemotherapy under US Medicare ($P < 0.001$) and employer-based insurance ($P < 0.001$).
Conclusion: Real-world treatment has shifted toward more selectivity for RT in unresectable pancreatic cancer. However, SBRT uptake and improving trends in complications profiles represent opportunities to optimize current use and benefit. Findings are applicable to inform future comparative and cost effectiveness models of RT for this disease.

Introduction

For patients with unresectable pancreatic cancer, radiation treatment (RT) after induction chemotherapy aims to reduce the risk of local disease progression that contributes to disease morbidity and mortality [1,2]. Current national guidelines support the options of adding conventionally fractionated chemoradiation (CFRT) or stereotactic body radiation therapy (SBRT) for select patients with unresectable disease after induction chemotherapy [3]. While a recent analysis of US National Cancer Data Base patients with unresectable pancreatic cancer demonstrated a comparable, favorable survival profile for patients treated with either CFRT or SBRT [4], similar comprehensive analysis of "real-word" treatment complications and costs outcomes of RT, including SBRT, for unresectable pancreatic cancer are still needed. Such data are critical to inform a balanced and thorough understanding of comparative effectiveness of these therapy options for treatment

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https://doi.org/10.1016/j.ctro.2022.04.007
Received 15 October 2021; Received in revised form 15 April 2022; Accepted 16 April 2022
Available online 19 April 2022

patient and physician decision-making. Such data will also help identify current opportunities for improving RT related toxicities for patients with unresectable pancreatic cancer in practice. Accordingly, we comprehensively evaluated contemporary RT practice and complications outcomes in a large, diverse sample of US patients with unresectable pancreatic cancer derived from the Surveillance, Epidemiology, and End Results and Texas Cancer (TCR) registries linked with the Medicare database and the Marketscan Commercial Claims and Encounter database.

Material and Methods

Patients

This retrospective cohort study was an exempted study by the XXXXX Institutional Review Board. The study was performed in a total of 5,624 patients, including an older patient cohort and a younger patient cohort.

Older patients with pancreatic cancer, age > 65 diagnosed from 2006 to 2013 were identified from the Surveillance, Epidemiology, and End Results (SEER)/Texas Cancer Registry (TCR) databases linked with the Medicare database using the following criteria. We included 5,671 older patients with pathologically confirmed primary cancer diagnosis of localized or regional pancreatic adenocarcinoma, with continuous Medicare non-HMO Part A & B coverage from 12 months prior to diagnosis to 12 months after diagnosis, who survived at least 3 months since diagnosis. We excluded patients who received a pancreaticoduodenectomy (Whipple procedure) within 10 months of diagnosis date (n = 481) and patients who failed to complete at least 1 cycle of chemotherapy (1,668). Our analytic sample thus included 2,522 older patients.

Younger patients with pancreatic cancer, age 18–64 years diagnosed from 2006 to 2016 were identified from the national, employment-based MarketScan Commercial Claims and Encounter database (Truven Health Analytics, Ann Arbor, MI) [5]. These data include individual medical and drug insurance claims. The claims are acquired from large employers and health insurance companies that provide insurance coverage for employees and family members [5]. Beneficiaries originated from 45 US employers and corresponded with approximately 100 payers derived is a convenience sample of 28 million insured US lives, with data obtained from employers, health plans, and state Medicaid agencies. Identification of the cohort used the following criteria: We included 6,043 patients with an International Classification of Diseases (ICD)-9/10 diagnosis code of non-metastatic pancreatic cancer (157.XX or C25) (1 inpatient or ≥ 2 outpatient claims ≥ 30 days apart), with valid Healthcare Common Procedure Coding System (HCPCS) chemotherapy codes (claims-based cohort definition was required in MarketScan due to lack of pathologic diagnosis date information in MarketScan) [5,6] and continuous insurance coverage 3 months prior to 3 months post-chemotherapy initiation. We excluded patients who received pancreaticoduodenectomy within 1 year prior to and 1 year after chemotherapy initiation (2,843), patients who had a code for death within 3 months in the inpatient claims file (24), and patients who did not have at least 9 months of follow up to determine treatment use and complication events in that time frame(i.e. diagnosis and first chemotherapy cycle after March 2016) (74). Our analytic sample thus included 3,102 younger patients.

Treatment and covariates

Claims codes **(**eTable 1**)** identified radiation treatment (RT) within 9 months of SEER/TCR diagnosis date or within 12 months of the earliest chemotherapy date in MarketScan (since pathologic diagnosis date is not available in MarketScan). RT was classified as conventionally fractionated (CFRT) vs. stereotactic body radiation therapy (SBRT) based on unique codes for SBRT in International Classification of Diseases (ICD)-9/10 procedure and CPT codes. RT fractions were determined using radiation delivery/treatment management codes. Patients treated without any RT were categorized as having received chemotherapy alone, defined by systemic therapy and National Drug codes in inpatient, outpatient and Part D Medicare files. Chemotherapy delivery claims dates were used to define duration of chemotherapy received (categorized using 2-month, 4-month, and 6-month intervals). Age, gender, and treatment year were derived from source datasets; cancer stage, grade, and tumor location were available in SEER/TCR. Claims-derived covariates included: modified Charlson comorbidity score based on diagnosis claims and performance status indicators based on durable medical equipment claims [7–12,13] **(**eTable 1**).**

Outcomes and statistical analyses

Our objectives were to analyze: 1) frequency and trends in use of chemotherapy, CFRT, and SBRT; 2) gastrointestinal (GI) complications; and 3) healthcare costs among these patients considered unresectable. Unresectable in this analysis was defined based on the patient not undergoing resection. Univariate associations were examined using Pearson's Chi-square tests. Temporal trends were examined using Cochrane-Armitage tests, and where the sample size was limited in the period January-March 2016, data for patients treated during these 3 months were collapsed in a category with 2015.

Post-treatment GI complications in older and younger cohorts were defined from last claims date of RT if RT was delivered, and from 84 days of chemotherapy alone through death or last follow-up (time zero definition in this cohort chosen as a comparable follow-up period to observe for complications vs. RT groups). To compare GI complications by treatment groups, we used univariate Pearson's Chi-square (or Fisher's test when appropriate) and multinomial logistic regression models based on backward selection. Multivariate Cox proportional hazards models accounted for death as a competing risk in the cohort of older patients with available vital status (Medicare-linked cohort) and adjusted for demographic and clinical covariates as well as diagnosis year. In addition, survival estimates and 95% confidence intervals were calculated for patients in each treatment category using the Kaplan-Meier log method and log-rank tests.

To compare healthcare costs through 12-month follow-up by treatment group, we implemented multivariate generalized linear regression models with log link and gamma distribution. Payments were adjusted to 2015 dollars using the Consumer Price Index. Analyses were performed using SAS® version 9.3 (SAS Institute, Cary, NC). P-values ≤ 0.05 were considered significant using two-sided tests.

Results

Patient characteristics

Of 2,522 *older patients* with unresectable pancreatic cancer: 53% received RT after induction chemotherapy and 47% received chemotherapy alone, with 86% receiving gemcitabine-based chemotherapy, and 13% who received protein-bound paclitaxel, 36% who received oxaliplatin, and 32% irinotecan as part of their chemotherapy regimen. Among those receiving RT, 92% were treated using CFRT (median 28 fractions, IQR 24–28) and 8% using SBRT (median 5 fractions, IQR 3–5). SBRT was more likely used in elderly patients (P < 0.001) with worse comorbidities (P < 0.001).

Of 3,102 *younger patients:* 51% received RT after induction chemotherapy and 49% chemotherapy alone with 68% gemcitabine-based chemotherapy, and 15% who received albumin-bound paclitaxel, 41% oxaliplatin, 29% irinotecan as part of their chemotherapy regimen. Among those receiving RT, 94% were treated using CFRT (median 25 fractions, IQR 10–29) and 6% SBRT (median 4 fractions, IQR 3–5). (Table 1).

Table 1
Patient characteristics in older patient cohort and younger patient cohort.

Older Patients, Age > 65 years						Younger Patients, Age < 65 years				
	Total N = 2522	CFRT N = 1230	SBRT N = 105	Chemo N = 1187	P	Total N = 3102	CFRT N = 1482	SBRT N = 101	Chemo N = 1519	P
Age (years)										
18–49	–					454 (14.6%)	237 (15.9%)	18 (17.8%)	199 (13.1%)	0.32
50–54	–				–	570 (18.4%)	259 (17.4%)	18 (17.8%)	293 (19.2%)	
54–59	–					896 (28.9%)	431 (29.0%)	26 (25.7%)	439 (28.9%)	
60–64	–					1182 (38.1%)	555 (37.4%)	39 (38.6%)	588 (38.7%)	
66–70	652 (25.9%)	348 (28.3%)	22 (21.0%)	282 (23.8%)	**0.05**	–				
71–75	649 (25.7%)	350 (28.5%)	21 (20.0%)	278 (23.4%)		–				–
76–80	606 (24.0%)	279 (22.7%)	28 (26.7%)	299 (25.2%)		–				
>80	615 (24.4%)	253 (20.6%)	34 (32.4%)	328 (27.6%)		–				
Gender										
Female	1418 (56.2%)	683 (55.5%)	58 (55.2%)	677 (57.0%)	0.74	1398 (45.1%)	669 (45.1%)	47 (46.5%)	682 (44.9%)	0.95
Charlson Comorbidity Score										
0	1029 (40.8%)	472 (38.4%)	50 (47.6%)	507 (42.7%)	**<0.001**	2186 (70.5%)	1030 (69.5%)	79 (78.2%)	1077 (70.9%)	0.20
1	799 (31.7%)	405 (32.9%)	22 (21.0%)	372 (31.3%)		553 (17.8%)	284 (19.2%)	13 (12.9%)	256 (16.8%)	
2+	559 (22.2%)	251 (20.4%)	30 (28.6%)	278 (23.4%)		363 (11.7%)	168 (11.3%)	9 (8.9%)	186 (12.2)	
Unknown	135 (5.4%)	102 (8.3%)	3 (2.9%)	30 (2.5%)						
Performance Status Indicator										
0	2273 (90.1%)	1119 (91.0%)	90 (85.7%)	1064 (89.6%)	0.37	2945 (94.9%)	1404 (94.7%)	98 (97.0%)	1443 (95.0%)	0.59
1+	219 (8.7%)	97 (7.9%)	<15 (14%)	108 (9.1%)		157 (5.1%)	78 (5.3%)	3 (3.0%)	76 (5.0%)	
2	30 (1.2%)	14 (1.1%)	NR	15 (1.3%)						
Chemotherapy Duration (months)										
< 2	925 (36.7%)	502 (54.3%)	33 (31.4%)	390 (32.9%)	**<0.001**	693 (22.3%)	333 (22.5%)	13 (12.8%)	347 (22.8%)	0.002
2 to 4	851 (33.7%)	408 (47.9%)	45 (5.3%)	398 (46.8%)		1124 (36.2%)	501 (44.6%)	40 (3.6%)	583 (51.9%)	
>4 to 6	423 (16.8%)	204 (48.2%)	17 (4%)	202 (47.8%)		562 (18.1%)	289 (51.4%)	28 (5%)	245 (43.6%)	
>6	323 (12.8%)	116 (35.9%)	10 (3.1%)	197 (61%)		723 (23.3%)	359 (49.7%)	20 (2.8%)	344 (47.6%)	
Chemotherapy Agents										
Gemcitabine	2177 (86.3%)	959 (78.0%)	96 (91.4%)	1122 (94.5%)	**<0.001**	2095 (67.5%)	1032 (69.6%)	79 (78.2%)	984 (64.7%)	**0.001**
Capecitabine	586 (23.2%)	401 (32.6%)	18 (17.1%)	167 (14.0%)	**<0.001**	818 (26.4%)	512 (34.5%)	25 (24.7%)	281 (18.5%)	**<0.001**
5-Fluoruracil	776 (30.8%)	548 (44.5%)	17 (16.2%)	211 (17.8%)	**<0.001**	1500 (48.4%)	822 (55.5%)	56 (55.4%)	622 (41.0%)	**<0.001**
Oxaliplatin	895 (35.5%)403 (32.8%)39 (37.1%)453 (38.2%)	403 (32.8%)	39 (37.1%)	453 (38.2%)	**<0.001**	1266 (40.8%)	592 (39.9%)	51 (50.5%)	623 (41.0%)	0.11
Irinotecan	799 (31.7%)	405 (32.9%)	22 (21.0%)	372 (31.3%)	0.10	901 (29.0%)	405 (47.3%)	46 (45.5%)	450 (29.6%)	**<0.001**
Protein-bound paclitaxel	339 (13.4%)	77 (6.3%)	13 (12.4%)	114 (9.6%)	0.003	483 (15.6%)	199 (13.4%)	35 (34.7%)	249 (16.4%)	**<0.001**

Abbreviations CFRT, SBRT, Chemo NR, Not reported, for cell sizes less than n = 11.

Temporal patterns of chemotherapy and RT use

Overall selection for use of RT declined slightly but significantly over time, from 55% to 45% of older patients from 2006 to 2013 (P_{trend} = 0.002) and from 52% to 47% of younger patients from 2006 to 2016 (P_{trend} = 0.004). Among RT patients, the proportion selected for SBRT increased from no use (older P_{trend} = 0.04; younger P_{trend} = 0.004), with SBRT used in 10% of older RT patients by 2013 and 12% of younger RT patients by 2015–6. (Table 1).

GI complications after treatment

After RT, older patients demonstrated Δ= +6% excess gastric bleeding frequency compared with the negative control patients treated with chemotherapy alone; +9% excess duodenal bleeding; and + 3% excess biliary stricture. Younger patients demonstrated + 5% excess gastric bleeding, +5% excess duodenal bleeding, and + 4% excess biliary stricture frequencies through follow-up. Other GI complications frequencies are detailed in Table 2**.** Over time, the unadjusted test of temporal trend identified the frequency of GI complications decreasing in more recent years of treatment, particularly among younger patients

Table 2
Frequency of gastrointestinal (GI) complications by treatment group, with follow-up until death or last date of follow up. P-values compare all three treatment groups and between radiation treatment groups.

GI Complications in Older Patients, Age > 65	CFRT N = 1230	SBRT N = 105	Chemo alone N = 1187	P-value‡ 3-Way	P-value‡ CFRT vs. SBRT
Bleeding with Ulcer/Perforation					
Gastric	100 (8.1%)	12 (11.4%)	37 (3.1%)	**<0.01**	0.24
Duodenal	160 (13%)	15 (14.3%)	50 (4.2%)	**<0.01**	0.71
Other intestinal	15 (1.2%)	NR	NR	**0.03***	0.06*
Stricture					
Duodenal	129 (10.5%)	15 (14.3%)	101 (8.5%)	0.07	0.23
Biliary	391 (31.8%)	45 (42.9%)	337 (28.4%)	**<0.01**	**0.02**
Fistulas§					
Biliary	8 (0.7%)	NR	NR	**<0.01***	**0.05***
GI Complications in Younger Patients, Age < 65	**CFRT N = 1482**	**SBRT N = 101**	**Chemo alone N = 1519**	**P-value‡ 3-Way**	**P-value‡ CFRT vs. SBRT**
Bleeding with Ulcer/Perforation					
Gastric	115 (7.8%)	8 (7.9%)	36 (2.4%)	**<0.01**	0.95
Duodenal	117 (7.9%)	7 (6.9%)	45 (3.0%)	**<0.01**	0.73
Other intestinal	19 (1.3%)	0 (0%)	6 (0.4%)	**0.02***	0.63*
Stricture					
Duodenal	101 (6.8%)	8 (7.9%)	65 (4.3%)	**0.01**	0.67
Biliary	365 (24.6%)	29 (28.7%)	308 (20.3%)	**0.01**	0.36
Fistulas§					
Biliary	7 (0.5%)	1 (1%)	1 (0.1%)	**0.03***	0.41*

Abbreviations CFRT, SBRT.
* Fisher's exact test; † NR, Not reported, for cell sizes less than n = 11; ‡P-value 3-way compares CFRT, SBRT and Chemo alone; P-value for RT groups compares CFRT vs. SBRT patients; §There was no significant difference (P > 0.05) in frequencies of gastric, duodenal, and other intestinal fistulas with absolute of event counts not reported due to cell sizes n < 11.

treated with RT (P_{trend} = 0.05). In older patients, a trend toward decreased GI complications was also identified, especially for patients treated after 2011 (P_{trend} = 0.05). Even after adjusting for covariates such as age, chemotherapy, and comorbidity and the competing risk of death in older patients, this association by time era remained for GI bleed (P = 0.05) (Table 3).

SBRT vs *CFRT*. In younger patients, there were no significant differences identified in the frequency of GI complications for SBRT vs. CFRT. In older patients, an increased frequency, especially GI bleeding was observed for SBRT vs. CFRT, which persisted in a multivariate model adjusting for the competing risk of death (OR = 4.13 95% CI 2.58–6.61, P < 0.001) (Table 3). However, in this group of older patients, when stratified by SBRT fractionation, those receiving SBRT in 1 to 4 fractions had higher frequencies of gastric bleeding (P = 0.04), biliary strictures (P = 0.01), and biliary fistulas (P = 0.01) compared to those receiving CFRT. There were no significant differences in these frequencies of complications for SBRT delivered in 5 fractions vs. CFRT (P = 0.72). Survival by treatment category is described in Fig. 1a-d. Survival was not significantly different for patients by RT technique, median 11.5 months after CFRT and 12.0 months with SBRT. (Fig. 1**a-d**).

Table 3
Multivariate proportional hazards models for GI complications, using death as a competing risk (in Medicare-linked data for older patients).

Covariate	Bleed HR	95% CI	P	Stricture HR	95% CI	P
Treatment						
Chemotherapy only	1			1		
CFRT	2.93	2.24 to 3.84	<0.001	1.1	0.95 to 1.27	0.2
SBRT	4.13	2.58 to 6.61	<0.001	1.58	1.18 to 2.12	0.002
Year of diagnosis						
2006–2010	1			1		
2011–2013	0.79	0.63 to 1	0.05	0.92	0.8 to 1.05	0.21
Age group (years)						
66–70	1			1		
71–75	1.08	0.81 to 1.46	0.59	1.04	0.87 to 1.25	0.66
76–80	0.94	0.68 to 1.29	0.69	0.98	0.81 to 1.19	0.88
> 80	1.06	0.76 to 1.48	0.75	0.85	0.7 to 1.04	0.11
Tumor location						
Head	1			1		
Body / tail	0.63	0.46 to 0.86	0.004	0.26	0.20 to 0.34	<0.001
Other	0.63	0.45 to 0.89	0.008	0.61	0.51 to 0.74	<0.001
Gemcitabine						
Yes	1			1		
No	1.33	0.95 to 1.87	0.10	1.04	0.83 to 1.30	0.75
Chemo cycles						
1–5	1			1		
6–12	1.40	1.02 to 1.91	0.038	1.20	1.00 to 1.44	0.046
13–18	1.62	1.14 to 2.31	0.007	1.37	1.12 to 1.68	0.003
19+	2.14	1.47 to 3.10	<0.001	1.41	1.14 to 1.76	0.002

Abbreviations HR Hazards Ratio, CI Confidence Interval, CFRT Conventionally fractionated radiation treatment, SBRT Stereotactic body radiation treatment.
*Also adjusted for race, comorbidity, stage, size, and grade.

Costs

Median 12-month total payments per patient (fee-for-service Medicare insurance coverage) were: $57,502 for chemotherapy alone (IQR $34,179, $84,888); $66,366 for CFRT (IQR $60,645, $118,298); and $80,282 for SBRT (IQR $45,244, $93,684) (P < 0.001). Median payments per patient (under employer-based insurance coverage) were $127,438 for chemotherapy alone (IQR $76,001, $194,98); $172,547 for CFRT (IQR $117,987, $248,735); and $212,579 for SBRT (IQR $144,177, $303,268) (P < 0.001)). Age-adjusted models did not significantly impact mean cost differences by treatment.

Discussion

As the optimal role of RT after induction chemotherapy in unresectable pancreatic cancer has been debated [14–20], our results

eTable 1
Claims codes.

Description	ICD-9 Diagnosis	ICD-9 Procedure	HCPCS Codes
Codes			
Gastric bleeding/ ulcer/perforation	531, 531.0–531.9 (531.0, 531.00, 531.01, 531.1, 531.10, 531.11, 531.2, 531.20, 531.21, 531.3, 531.30, 531.31, 531.4, 531.40, 531.41, 531.5, 531.50, 531.51, 531.6, 531.60, 531.61, 531.7, 531.70, 531.71, 531.9, 531.90, 531.91)		
Duodenal bleeding/ ulcer/perforation	532, 532.0–532.9 (532.0, 532.00, 532.01, 532.1, 532.10, 532.11, 532.2, 532.20, 532.21, 532.3, 532.30, 532.31, 532.4, 532.40, 532.41, 532.5, 532.50, 532.51, 532.6, 532.60, 532.61, 532.7, 532.70, 532.71, 532.9, 532.90, 532.91)		
Perforation of intestine	569.83		
Biliary endoscopy with dilation of biliary duct stricture			47555, 47,556
EGD with dilation of gastric/duodenal stricture			43,245
Duodenal obstruction/ stricture	537.3		
Stricture of bile duct	576.2		
Biliary fistula	576.4		
Intestinal fistula	569.81		
Stomach or duodenal fistula	537.4		
Treatment codes			
CFRT	92.21,92.22,92.23,92.24,92.25,92.26,92.29		77418,G0174,77422,77423,77401,77402,77403,77404,77406,77407,77408,77409, 77411,77412,77413,77414,77416,77418,77520,77522,77523,77525,77301,0073 T,77380,77381,77305,77310,77315,77321,77295
CFRT Delivery	92.21,92.22,92.23,92.24,92.25,92.26		G0174,77402,77403,77404,77406,77407,77408,77409,77411,77412,77413,77414,77416,77418, 0073 T
IMRT			77418, 0073 T
SBRT	92.3,92.30,92.31,92.32,92.33,92.39		77373,77435,G0339,G0340,G0173,G0251,61793,0082 T,0083 T
Surgery (Whipple Procedure)		52.51–52.53, 52.59, 52.6, 52.7	48120, 48145, 48146, 48150, 48152–48155, 48,160
Chemotherapy	V581,V662,V672	99.25	96400–96549, J9000 - J9999,Q0083 - Q0085,J8520,J8521,J8530,J8540,J8560,J8597,J8610 Excluding J9217,J9218,J9219,J9220,J9221,J9222,J9223,J9224,J9225,J9226,J9240,J9295,J9381,J9395,J8499, J3590,J8999,J9355,J9354,J9306, J9055,J9303,C9235,J8565,S0116,C9257,J9035,J9399

Abbreviations: ICD International Classification of Diseases, HCPCS Healthcare common procedure coding, EGD Esophagogastroduodenoscopy, CFRT Conventionally fractionated radiation treatment, IMRT Intensity modulated radiation therapy/ treatment, SBRT Stereotactic body radiation treatment.

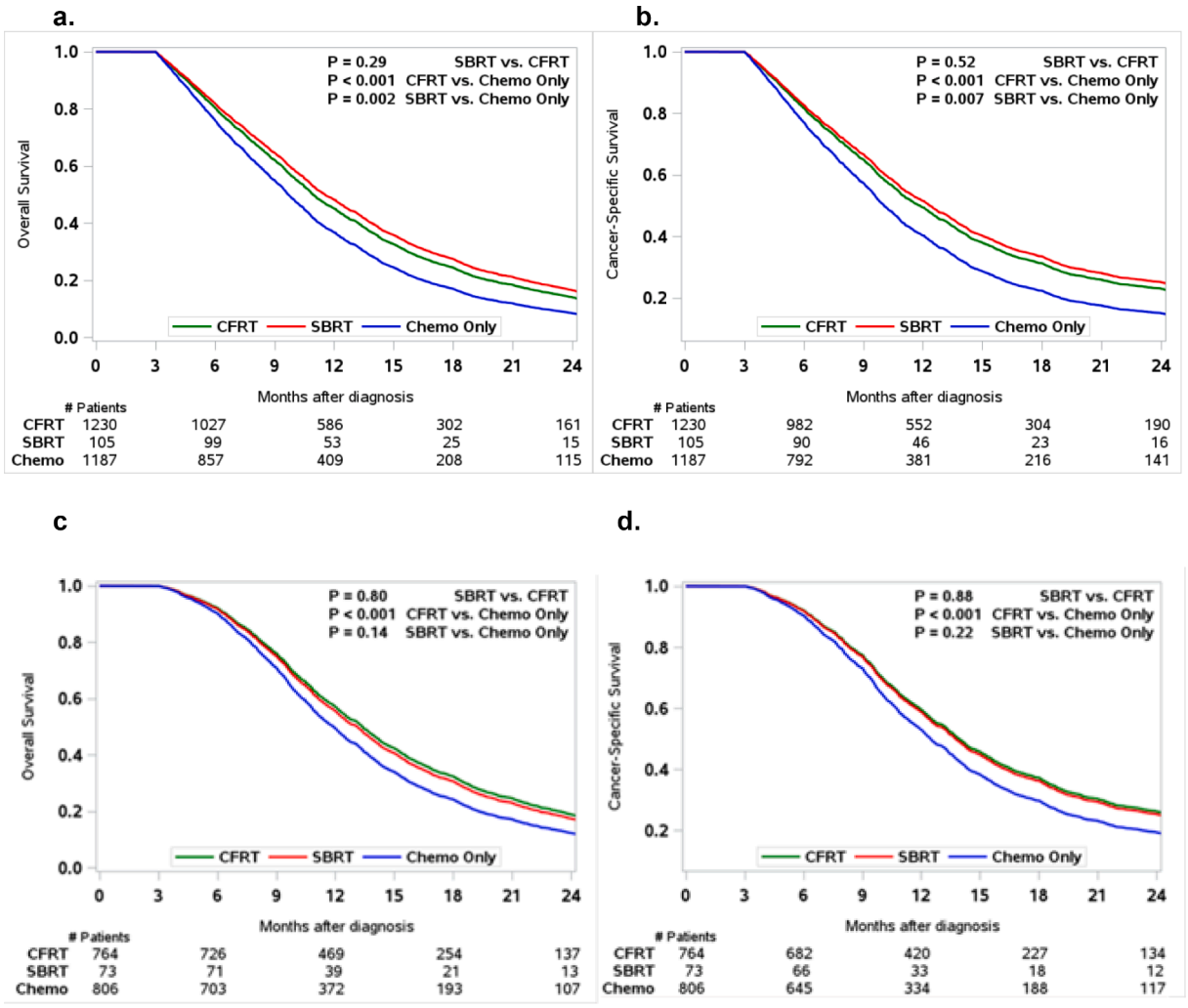

Fig. 1. a-d. Kaplan-Meier survival curves by treatment with chemotherapy only, conventionally fractionated radiation treatment (CFRT), or stereotactic body radiation treatment (SBRT) (among Medicare-linked patients, age > 65 years). 1a. Age-adjusted overall survival (all patients N = 2,522) 1b. Age-adjusted cancer-specific survival (all patients N = 2,522) 1c. Age-adjusted overall survival (in patients who received at least 2 months of chemotherapy N = 1,597) 1d. Age-adjusted cancer-specific survival (in patients who received at least 2 months of chemotherapy N = 1,597).

delineating real-world patterns of treatment for unresectable pancreatic cancer help elucidate contemporary GI complications outcomes profiles and demonstrate potential opportunities for optimizing the use of RT in this context. These data reflect such patterns of treatment in patients who ultimately did not undergo surgery and thus include the spectrum of patients who present with up front unresectable disease as well as borderline resectable or technically resectable (but medically inoperable) who did not proceed to surgery. The contraction over time by 5–10% in use of RT likely reflects improved selection of appropriate patients over the last decade—most likely more accurately excluding patients who developed distant metastases after up front cycles of chemotherapy who were less likely to benefit from additional local therapy.

While local therapy is often thus considered in patients with unresectable pancreatic cancer who do not immediately develop distant metastases after initial chemotherapy [21]—comprising about 60% of patients in prior studies, [2,22] nevertheless, the persistent limited survival time after RT in many patients thus highlights the importance of ongoing uptake and assessment of shorter-course (e.g. hypofractionated) RT and SBRT strategies in patients with unresectable pancreatic cancer, with the goals of optimizing treatment convenience, quality of life, and time off systemic therapy, along with local control [23,24]. de Geus and colleagues recently provided a comprehensive analysis of survival of unresectable pancreatic cancer patients treated with SBRT, CFRT, or only up front chemotherapy using the National Cancer Data Base (NCDB) [4]. In that study, using a matched survival analysis, authors found that patients who received SBRT demonstrated favorable survival. Nevertheless, because NCDB may not represent the full spectrum of practice types and do not have detailed toxicity and complications outcomes [25], these additional data from the population-based registries or community practice presented in our current study are additive for providing insight on "real-world" uptake patterns and GI complications risks for SBRT.

Ongoing prospective randomized trials have recently focused on assessing survival and disease outcomes with or without SBRT after chemotherapy with contemporary regimens of systemic therapy (e.g. FOLFIRNOX) to advance practice [26–32]. Results of the present analysis suggest that assessing GI complications outcomes thus remains a critical priority for ongoing prospective studies, especially as there has been continued uptake of SBRT—including among the oldest elderly with highest frequencies of comorbidities and limitations in performance status. Results suggest an excess of complications after RT compared with chemotherapy alone, but trends toward achieving lower frequencies of GI complications during more contemporary years of treatment. Such trends are consistent with contemporary improvements in RT planning, on-board imaging, respiratory management during RT

delivery, and more precise RT delivery. Nevertheless, results emphasize the importance of ongoing studies to optimize the therapeutic ratio of pancreatic SBRT, such as delivery with radiomodulator/ radioprotector agents (NCT03340974) [26–33]. Finally, healthcare costs per patient were higher with treatment using SBRT or CFRT compared with chemotherapy alone. The introduction of novel reimbursement and delivery models, such as the CMS alternative payment and oncology care models, may signal a shift in anticipated cost-effectiveness and value of short-course RT strategies [34].

The main limitation to this study is that the Medicare and Marketscan claims-based datasets lack the specific clinical details underlying the rationale for selection for RT, specifically, type of RT selection. Unresectable in this analysis was defined based on the patient not undergoing resection, but this definition includes patients who presented as borderline resectable or technically resectable but with excessive comorbidities (medically unresectable), and the current databases do not have the clinical detail to distinguish between these categories. These claims-based datasets also did not have detailed data on detection or development of distant metastases, restaging imaging results, or biomarker data. Also, grading of GI toxicities under schema such as Common Terminology Criteria for Adverse Events (CTCAE) were not available in the claims, and therefore future analyses with datasets having this level of clinical detail (such as institutional chart review) may help provide complementary detailed toxicity details and outcomes trajectories. Survival analyses were limited to the SEER-Medicare database, as survival data were not available for the Marketscan cohort, and therefore, additional “real-world” validation of descriptive survival patterns by treatment selection for this younger group is still needed. For survival analyses among patients in the SEER-Medicare database, it must be emphasized that since patients were not randomized to treatment type, so characteristics that influenced selection for (or against) RT, such as absence or presence of distant metastatic disease development, may drive the survival differences described by treatment modality in these data. Finally, we acknowledge that actual costs for treatment vary in different countries. Within different healthcare systems, for RT in particular, higher costs may or may not be driven by complexity of treatment and/or number of fractions of treatment as with this study of US costs, and therefore additional studies of costs within different delivery settings is needed to expand generalizability of findings.

Conclusion

Debate on the optimal use and benefits of RT, especially SBRT, after induction chemotherapy for unresectable pancreatic cancer has prompted this comprehensive examination of contemporary U.S. practice patterns and outcomes, especially with uptake of contemporary systemic treatment and newer RT technologies/ techniques in patients with unresectable disease. Our “real-world” cohort of US patients demonstrated an increase over time in selectivity for RT in patients with unresectable pancreatic cancer with parallel trend toward decrease in frequency of GI complications after treatment. While selectiveness remains important for identifying appropriate candidates for RT in patients with unresectable pancreatic cancer, the steady uptake of advanced technologies using SBRT, even in elderly patients, underscores the ongoing opportunities to optimize contemporary use and benefit of RT. Findings from this study are applicable for future modeling of comparative and cost effectiveness of SBRT for this disease.

Funding

This research was supported by the MD Anderson Cancer Center grant P30 CA016672.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. SHG reports research funding from CPRIT, Komen. Dr. PD reports payment or honoraria from Adlai Nortye, ASTRO, ASCO, Leidos/NCI, Conveners LLC, Physicians Education Resource. Dr. GLS reports research funding from NIH. Dr. EBL reports research funding from the Fund for Innovation in Cancer Informatics. Dr. EJK reports research funding from the Department of Defense, NIH, Philips, Elekta, GE Healthcare, Siemens, EMD Serono; royalties from Taylor and Francis, LLC; consulting for RenovoRx, Augmenix, MD Anderson Physicians Network and equity ownership in Quantum Aurea. Dr. CT reports research funding from NIH, Mark Foundation, V Foundation, Galera Therapeutics, 4D Therapeutics, Patent licensed by Xerient, consult fees from Phebry Ltd, and Xerient, and patent issued for radioprotection of the intestines. Data used in this study was accessed from the SEER database and Texas cancer registry linked to the Medicare database.

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