Journal of Radiotherapy in Practice

cambridge.org/jrp

Association of survival with stereotactic body radiation therapy following induction chemotherapy for unresected locally advanced pancreatic cancer

Sung Jun Ma[1], Lucas M. Serra[2], Austin J. Bartl[2], Hye Ri Han[2], Fatemeh Fekrmandi[1], Austin J. Iovoli[1], Kavitha M. Prezzano[1], Gregory M. Hermann[1], Han Yu[3] and Anurag K. Singh[1]

[1]Department of Radiation Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [2]Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, Buffalo, NY, USA and [3]Department of Biostatistics and Bioinformatics, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

Original Article

Cite this article: Ma SJ, Serra LM, Bartl AJ, Han HR, Fekrmandi F, Iovoli AJ, Prezzano KM, Hermann GM, Yu H, and Singh AK. (2022) Association of survival with stereotactic body radiation therapy following induction chemotherapy for unresected locally advanced pancreatic cancer. *Journal of Radiotherapy in Practice* **21**: 403–410. doi: 10.1017/S1460396921000212

Received: 14 January 2021
Accepted: 12 February 2021
First published online: 14 April 2021

Key words:
National Cancer Database; pancreas; SABR; SBRT

Author for correspondence:
Dr Anurag K. Singh, Roswell Park Comprehensive Cancer Center, 665 Elm Street, Buffalo, NY 14203, USA. Tel: 716 845 5715. Fax: 716 845 7616.
E-mail: anurag.singh@roswellpark.org

Abstract

Aim: Induction chemotherapy (iC) followed by concurrent chemoradiation has been shown to improve overall survival (OS) for locally advanced pancreatic cancer (LAPC). However, the survival benefit of stereotactic body radiation therapy (SBRT) versus conventionally fractionated radiation therapy (CFRT) following iC remains unclear.
Materials and methods: The National Cancer Database (NCDB) was queried for primary stage III, cT4N0-1M0 LAPC (2004–15). Kaplan–Meier analysis, Cox proportional hazards method and propensity score matching were used.
Results: Among 872 patients, 738 patients underwent CFRT and 134 patients received SBRT. Median follow-up was 24·3 and 22·9 months for the CFRT and SBRT cohorts, respectively. The use of SBRT showed improved survival in both the multivariate analysis (hazards ratio 0·78, $p = 0{\cdot}025$) and 120 propensity-matched pairs (median OS 18·1 versus 15·9 months, $p = 0{\cdot}004$) compared to the CFRT.
Findings: This NCDB analysis suggests survival benefit with the use of SBRT versus CFRT following iC for the LAPC.

Background

Pancreatic cancer is the fourth most common cause of cancer death in the USA with a dismal 5-year survival of less than 8%.[1] While surgery is considered part of the definitive management, only 10–15% of pancreatic cancers present with resectable disease.[2,3] Treatment for unresectable locally advanced pancreatic cancer (LAPC) typically involves chemotherapy with or without radiation therapy. However, nearly half of all patients experience disease progression following conventional chemoradiation.[4] The optimal combination of these modalities remains unclear, though recent literature suggests a role for induction chemotherapy (iC) and stereotactic body radiation therapy (SBRT).

The use of chemoradiation following iC for LAPC has been controversial due to conflicting reports.[5–8] The LAP-07 trial randomised patients with non-progressing LAPC to chemoradiation or chemotherapy after a 4-month period of iC and found no overall survival (OS) benefit with the addition of radiation. Despite this, the study did find significant improvement in rates of local progression (43 versus 36%, $p = 0{\cdot}03$).[6] Contrasting these results are two large retrospective reports from MD Anderson and the Groupe Coopérateur Multidisciplinaire en Oncologie that suggest OS is improved by chemoradiation following iC compared to chemotherapy alone.[7,8] A recent National Cancer Database (NCDB) study similarly showed that chemoradiation following iC improved OS.[5]

The rising utilisation of SBRT has also shown promise in improving outcomes for LAPC. First reported as feasible in patients with LAPC by Koong et al.,[9] SBRT has the advantage over conventionally fractionated radiation therapy (CFRT) of quicker treatment time while still achieving favourable OS and locoregional control.[10] A recent meta-analysis suggested the survival benefit and favourable toxicity profile when treated with SBRT compared to CFRT.[11] Several single-institutional experiences have demonstrated iC followed by SBRT to be well tolerated and exhibit favourable efficacy in LAPC.[12–19] Two recent NCDB analyses have compared outcomes between SBRT and CFRT for LAPC and found improved OS was associated with SBRT.[20,21] However, the survival benefit of SBRT in the setting of iC remains unclear.

CAMBRIDGE UNIVERSITY PRESS

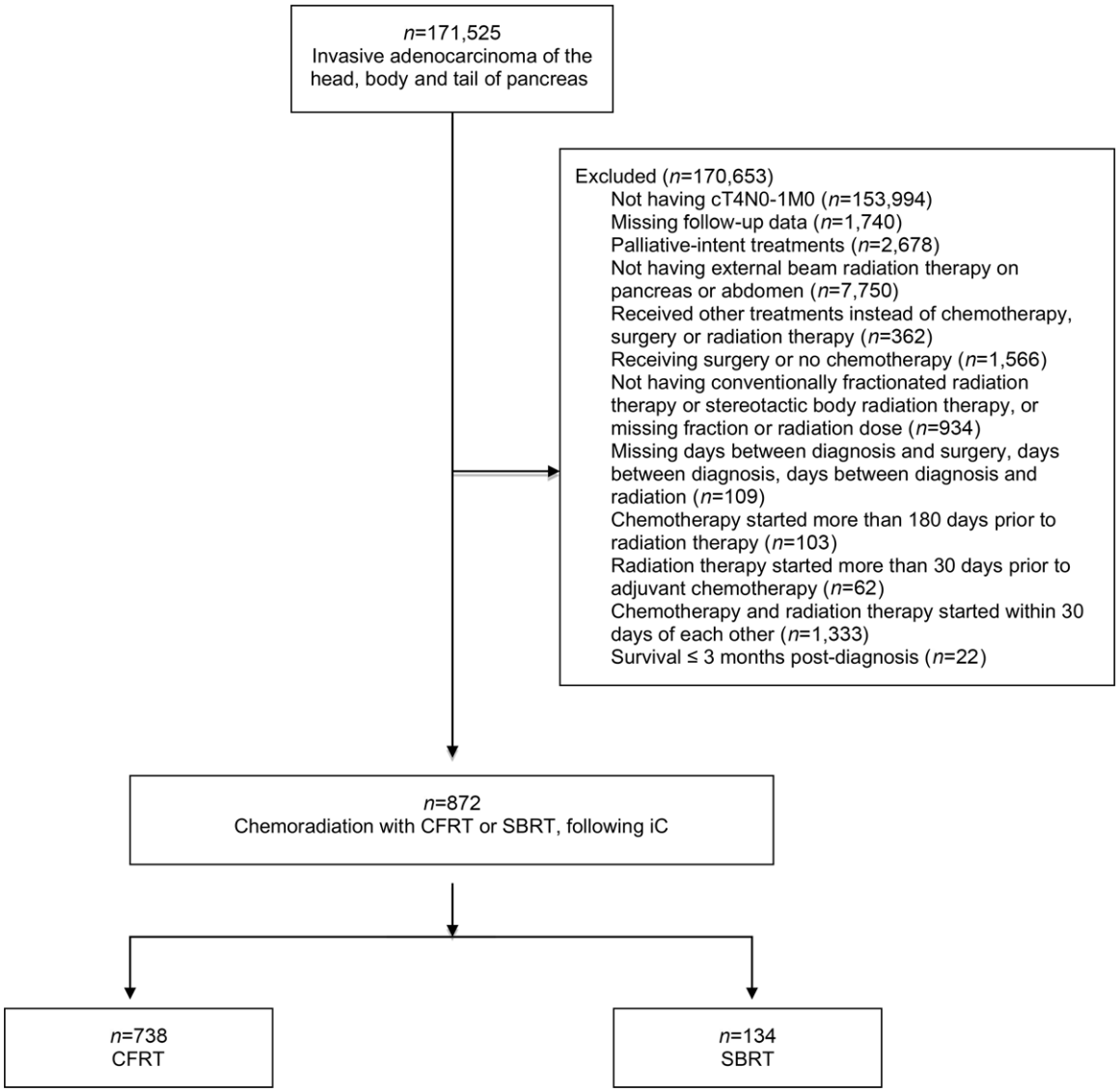

Figure 1. Patient selection diagram. iC, induction chemotherapy; CFRT, conventionally fractionated radiation therapy; SBRT, stereotactic body radiation therapy.

This study compares the outcomes of patients who have received CFRT versus SBRT for stage III LAPC treated with iC.

Methods

Patient population

The NCDB was used to select for LAPC cases diagnosed between 2004 and 2015. It is a national cancer registry database with data gathered from over 1,500 hospitals.[22] This study was exempt from institutional review board review.

Patient selection criteria are shown in Figure 1. Our initial query selected for patients with unresected stage III, clinical T4N0-1M0 pancreatic adenocarcinoma who had been treated with curative-intent iC followed by concurrent chemoradiation with SBRT or CFRT. Stage III disease in 2004–15 was based on American Joint Committee on Cancer 7th editions.

To take into account variability of dose fractionation schedules among hospitals for LAPC, CFRT was defined as 1·8–2·5 Gy/fraction up to a total dose of 45–70 Gy, while SBRT was defined as ≥4 Gy/fraction up to a total dose of 20–60 Gy.[19,23–26] The definition of iC was based on chemotherapy delivered within 31–180 days prior to the radiation therapy.[5] Patients who received chemotherapy more than 180 days prior to the radiation therapy and those who received chemotherapy or radiation therapy within 30 days of each other were excluded from our analysis.

Other patients were also excluded if they had surgery, incomplete follow-up data, missing data regarding radiation dose or fractionation, incomplete data on the number of days between diagnosis and treatments, palliative-intent treatments and any other dose fractionation besides the defined CFRT and SBRT regimens. Those who survived less than 3 months after their diagnosis were excluded.

Baseline characteristics about patients, tumours and treatments were extracted. Based on their median values, age and tumour size were stratified by <65 or ≥65 years and <3·8 or ≥3·8 cm. Relevant prognostic factors and outcomes such as performance status, the number of cycles and type of chemotherapy given, toxicities, and local and distant failure are unavailable in the NCDB. CA 19-9 factor was excluded from analysis, since 340 patients

https://doi.org/10.1017/S1460396921000212 Published online by Cambridge University Press

Table 1. Baseline characteristics before matching

	CFRT		SBRT		
	n	%	*n*	%	*p*
Facility					<0·001
CCP	52	7	0	0	
CCCP	276	37	11	8	
Academic	324	44	117	87	
INCP	78	11	4	3	
NA	8	1	2	1	
Age					0·015
<65	372	50	52	39	
≥65	366	50	82	61	
NA	0	0	0	0	
Gender					0·51
Female	378	51	73	54	
Male	360	49	61	46	
NA	0	0	0	0	
Race					0·28
White	608	82	111	83	
Black	98	13	14	10	
Other	22	3	7	5	
NA	10	1	2	1	
Insurance					0·33
None	14	2	1	1	
Nonprivate	383	52	79	59	
Private	335	45	54	40	
NA	6	1	0	0	
Income					0·043
Above median	479	65	97	72	
Below median	254	34	33	25	
NA	5	1	4	3	
Residential setting					0·099
Metro	602	82	119	89	
Urban	93	13	12	9	
Rural	15	2	0	0	
NA	28	4	3	2	
Charlson–Deyo Score					1
0–1	706	96	129	96	
≥2	32	4	5	4	
NA	0	0	0	0	
Year of diagnosis					0·047
2004–07	59	8	4	3	
2008–11	319	43	53	40	
2012–15	360	49	77	57	
NA	0	0	0	0	

(*Continued*)

https://doi.org/10.1017/S1460396921000212 Published online by Cambridge University Press

Table 1. (*Continued*)

	CFRT		SBRT		
	n	%	*n*	%	*p*
Primary tumour site					0·21
Head	505	68	82	61	
Body	214	29	49	37	
Tail	19	3	3	2	
NA	0	0	0	0	
Tumour size (cm)					0·28
<3·8	330	45	67	50	
≥3·8	347	47	57	43	
NA	61	8	10	7	
Clinical N stage					0·15
0	456	62	92	69	
1	282	38	42	31	
NA	0	0	0	0	
Chemotherapy					0·21
Single agent	196	27	43	32	
Multi-agent	542	73	91	68	
NA	0	0	0	0	
Total radiation dose (Gy)					<0·001
Median	50·4		31·3		
IQR	50·4–54·0		25–36		
Fraction					<0·001
Median	28·0		5·0		
IQR	27·0–30·0		3·0–5·0		

CFRT, conventionally fractionated radiation therapy; SBRT, stereotactic body radiation therapy; CCP, Community Cancer Program; CCCP, Comprehensive Community Cancer Program; INCP, Integrated Network Cancer Program; NA, not available; IQR, interquartile range.

(39·0%) had missing information and another 312 patients (35·8%) had an unknown value above 98·0 U/mL. Tumour grade was also excluded, since 690 patients (79·1%) had missing data. The primary endpoint was OS, defined as the time between the diagnosis and the last follow-up or death.

Statistical analysis

OS was assessed using Kaplan–Meier method and log-rank tests. Categorical and continuous variables between the CFRT and SBRT groups were compared using Fisher's exact and Mann–Whitney U tests, respectively. Logistic regression univariable (UVA) and multivariable analyses (MVA) were used to evaluate potential predictors for the receipt of SBRT and were shown as odds ratio (OR). Cox proportional hazard UVA and MVA were used to examine potential predictors for the OS and were shown as hazards ratio (HR). MVA models were initially constructed with all statistically significant variables from UVA and were finalised based on a backward stepwise elimination. Potential treatment interactions with other variables were examined using Cox MVA with interaction terms.[27]

To minimise selection bias, propensity score matching was used. All matching was performed in a 1:1 ratio without any replacement and was based on nearest neighbour method with a caliper distance of 0·2 of the standard deviation of the logit of the propensity score.[28] After matching, matched-sample Cox UVA was used to evaluate the effect of SBRT on OS. R software (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria) was used to perform all statistical analyses. *p* Values were all two-sided and were considered statistically significant if *p* values were less than 0.·05.

Results

A total of 872 patients with unresected clinical stage III, T4N0-1M0 pancreatic adenocarcinoma treated with iC followed by concurrent chemoradiation with SBRT or CFRT were identified. Of those, 738 patients received CFRT and 134 patients underwent SBRT. The majority of patients had clinical T4N0M0 adenocarcinoma of the pancreatic head (Table 1). The SBRT group included more patients treated at academic facilities, of older age, above median household income and diagnosed between 2012 and 2015. Other variables were well balanced.

On logistic MVA, patients with lower income (OR 0·65, $p = 0·045$) were less likely to receive SBRT, while those aged 65 or older (OR 1·52, $p = 0·031$) and diagnosed between 2012 and

https://doi.org/10.1017/S1460396921000212 Published online by Cambridge University Press

Table 2. Cox UVA and MVA

	Cox UVA			Cox MVA		
	HR	95% CI	*p*	HR	95% CI	*p*
Facility						
CCP	1	Ref				
CCCP	1·11	0·81–1·52	0·52			
Academic	0·81	0·59–1·10	0·17			
INCP	1·18	0·81–1·70	0·39			
Age						
<65	1	Ref				
≥65	1·05	0·91–1·21	0·52			
Gender						
Female	1	Ref				
Male	1·13	0·98–1·31	0·097			
Race						
White	1	Ref				
Black	0·97	0·78–1·21	0·80			
Other	0·74	0·49, 1·12	0·15			
Insurance						
None	1	Ref				
Nonprivate	1	0·55–1·82	1			
Private	0·97	0·53–1·76	0·91			
Income						
Above median	1	Ref				
Below median	1·12	0·96–1·30	0·16			
Residential setting						
Metro	1	Ref				
Urban	1·08	0·87–1·35	0·47			
Rural	1·42	0·85–2·37	0·18			
Charlson–Deyo score						
0–1	1	Ref				
≥2	1·17	0·83–1·65	0·38			
Year of diagnosis						
2004–07	1	Ref		1	Ref	
2008–11	0·88	0·66–1·16	0·35			
2012–15	0·63	0·48–0·84	0·0014	0·61	0·45–0·83	0·0020
Primary tumour site						
Head	1	Ref				
Body	0·86	0·73–1·004	0·056			
Tail	1·25	0·81–1·93	0·32			
Tumour size (cm)						
<3·8	1	Ref		1	Ref	
≥3·8	1·23	1·06–1·43	0·0076	1·20	1·03–1·39	0·023
Clinical N stage						
0	1	Ref				
1	1·14	0·98–1·32	0·080			

(*Continued*)

https://doi.org/10.1017/S1460396921000212 Published online by Cambridge University Press

Table 2. (*Continued*)

	Cox UVA			Cox MVA		
	HR	95% CI	*p*	HR	95% CI	*p*
Chemotherapy						
Single agent	1	Ref		1	Ref	
Multi-agent	0·69	0·59–0·81	<0·001	0·72	0·61–0·86	<0·001
Radiation type						
CFRT		1	Ref		1	Ref
SBRT	0·80	0·65–0·99	0·035	0·78	0·63–0·97	0·025

UVA, univariate analysis; MVA, multivariate analysis; HR, hazards ratio; CI, confidence interval; CFRT, conventionally fractionated radiation therapy; SBRT, stereotactic body radiation therapy; CCP, Community Cancer Program; CCCP, Comprehensive Community Cancer Program; INCP, Integrated Network Cancer Program; Ref, reference.

2015 (OR 2·87, $p = 0·048$) were more likely to be treated with SBRT.

On Cox MVA (Table 2), a larger tumour (HR 1·20, $p = 0·023$) was associated with worse mortality. In contrast, being diagnosed between 2012 and 2015 (HR 0·61, $p = 0·002$) and having received multi-agent chemotherapy (HR 0·72, $p < 0·001$) and SBRT (HR 0·78, $p = 0·025$) were associated with improved OS. After Cox MVA, there was no treatment interaction with age ≥65 versus <65 ($p = 0·47$), Charlson–Deyo Score (CDS) ≥2 versus 0–1 ($p = 0·46$), year of diagnosis (2008–11, $p = 0·17$; 2012–15, $p = 0·44$), tumour size ≥3·8 cm versus <3·8 cm ($p = 0·39$), clinical N1 versus N0 stage ($p = 0·99$) or pancreatic tumour site (body and tail, $p = 0·78$).

The overall median follow-up for all patients was 24·1 months [interquartile range (IQR) 16·1–38·1]. The CFRT and SBRT groups had a median follow-up of 24·3 months (IQR 16·2–38·0) and 22·9 months (IQR 17·2–35·5), respectively. The median OS was 16·0 months (IQR 11·1–23·2) for the CFRT group and 18·3 months (IQR 12·3–25·5) for the SBRT group (log-rank $p = 0·035$). OS at 2 years was 27·0% for the CFRT group and 34·8% for the SBRT group (Figure 2).

A total of 240 patients were matched, with 120 patients in each group. All variables were well balanced (Table 3). The median follow-up of the CFRT group was 21·0 months (IQR 11·6–26·5) and that of the SBRT group was 24·2 months (IQR 19·0–36·9). The median OS was 15·9 months (IQR 10·9–22·9) for the CFRT group and 18·1 months (IQR 12·3–26·3) for the SBRT group (log-rank $p = 0·004$). OS at 2 years was 25·5% for the CFRT group and 37·3% for the SBRT group (Figure 3).

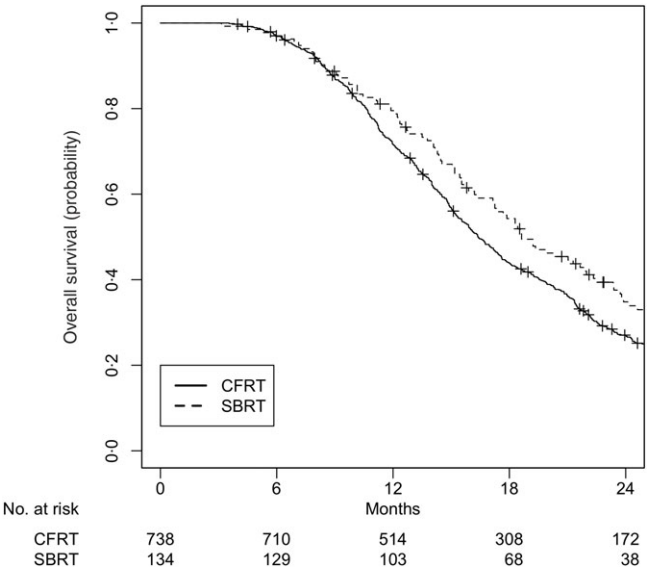

Figure 2. Overall survival before matching. CFRT, conventionally fractionated radiation therapy; SBRT, stereotactic body radiation therapy.

Discussion

To the best of our knowledge, this is the first study using a multi-institutional national registry to evaluate outcomes of concurrent chemotherapy with SBRT compared to CFRT, following iC for patients with LAPC. Our results show that the use of SBRT improved OS after multivariate analysis compared to CFRT (HR 0·78, $p = 0·025$). This is consistent with two prior reports by Doholposki et al. (HR 0·79, $p = 0·010$) and Zhong et al. (HR 0·84, $p < 0·001$) which examined the NCDB, though neither of these reports specifically examined the effects of chemoradiation following iC (20, 21). Upon 1:1 propensity score matching, our results demonstrate significantly improved OS with the use of SBRT compared to the CFRT ($p = 0·004$), with median OS (18·1 months versus 15·9 months) and 2-year OS (37·3% versus 25·5%). These results are comparable to other single-institutional studies investigating SBRT after iC for LAPC (median OS range 11·8–20·0 months).[12–19]

On MVA, patients with lower income were less likely to receive SBRT, while those with age ≥65 and diagnosed in 2012–15 were more likely to be treated with SBRT. Increased SBRT usage in the elderly can be attributed to its favourable toxicity profile, which makes it a reasonable choice for those patients who have multiple comorbidities, poor performance status or for whom a longer course of treatment may not be feasible.[29] Shorter treatment time also permits for easier concurrent chemotherapy management with fewer interruptions, which may contribute to the survival advantage seen in this study. The general trend towards expanded usage of SBRT is likely related to increasing provider comfort level with the technique, the lack of clear benefits with use of CFRT and its favourable toxicity profile.[21]

Worse mortality was associated with larger tumour size (HR 1·20, $p = 0·023$) on Cox MVA, as may be expected, as increased tumour burden likely makes local control more difficult to achieve and poses a greater risk of distant metastasis. In contrast, being diagnosed between 2012 and 2015 (HR 0·61, $p = 0·002$) and having received multi-agent chemotherapy (HR 0·72, $p < 0·001$) were associated with improved OS. These factors suggest recent improvements in chemotherapy regimens and greater utilisation

https://doi.org/10.1017/S1460396921000212 Published online by Cambridge University Press

Table 3. Baseline characteristics, after matching

	CFRT		SBRT		
	n	%	*n*	%	*p*
Facility					1
Nonacademic	12	10	12	10	
Academic	108	90	108	90	
Age					0·69
<65	51	43	47	39	
≥65	69	58	73	61	
Charlson–Deyo score					0·54
0–1	113	94	116	97	
≥2	7	6	4	3	
Year of diagnosis					0·42
2004–07	1	1	4	3	
2008–11	43	36	45	38	
2012–15	76	63	71	59	
Tumour size (cm)					0·52
<3·8	61	51	67	56	
≥3·8	59	49	53	44	
Clinical N stage					0·89
0	84	70	82	68	
1	36	30	38	32	
Chemotherapy					1
Single agent	35	29	35	29	
Multi-agent	85	71	85	71	

CFRT, conventionally fractionated radiation therapy; SBRT, stereotactic body radiation therapy.

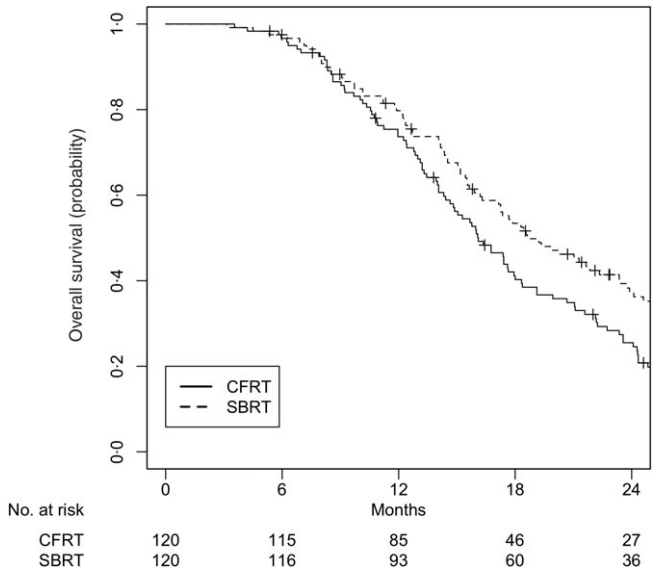

Figure 3. Overall survival after matching. CFRT, conventionally fractionated radiation therapy; SBRT, stereotactic body radiation therapy.

of multi-agent combinations contribute to increased survival. The ESPAC-4 trial and a large meta-analysis both demonstrated that gemcitabine combinations improve survival over gemcitabine alone in advanced disease.[30,31]

As a national registry-based study, our study is limited by missing patient information and documentation error. Relevant prognostic factors such as performance status, the number of cycles of chemotherapy and type of chemotherapy received are unavailable in the NCDB. Although CDS for comorbidity burden and single- versus multi-agent chemotherapy were well balanced in our cohorts both prior to and after matching, there may be unmeasured confounding factors that affected survival outcomes. Important outcomes, including toxicity, local and distant failure rates are also not reported in the NCDB. Despite these factors, the NCDB provides data on large numbers of patients not otherwise available through single-institutional studies.

Conclusions

We believe this is the first study using the NCDB to evaluate outcomes of concurrent chemotherapy with SBRT compared to CFRT, in the setting of definitive management for LAPC following iC. This analysis shows a significant survival benefit with the use of SBRT, though further prospective studies evaluating the use of SBRT in the definitive treatment of this challenging population are warranted.

Acknowledgements. The National Cancer Database is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Financial Support. Dr. Singh is currently supported by the National Cancer Institute (grant number 5P30CA016056-42) Cancer Center Support Grant.

Conflicts of Interest. The authors declare none.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by Clinical Research Services and Office and Office of Research Subject Protection at Roswell Park Cancer Institute. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guides on the care and have been approved by Clinical Research Services and Office and Office of Research Subject Protection at Roswell Park Cancer Institute under the study number STUDY00000621/BDR 099918.

Availability of Data and Materials. The data that support the findings of this study are available from the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The data are publicly accessible by any investigator affiliated with the Fellow of the American College of Surgeons applying to gain access. More information can be found at: http://ncdbpuf.facs.org

References

1. Siegel R L, Miller K D, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018; 68: 7–30.
2. McGuigan A, Kelly P, Turkington R C, Jones C, Coleman H G, McCain R S. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol 2018; 24: 4846–4861.

https://doi.org/10.1017/S1460396921000212 Published online by Cambridge University Press

3. Weledji E P, Enoworock G, Mokake M, Sinju M. How grim is pancreatic cancer? Oncol Rev 2016; 10: 294.
4. Willett C G, Czito B G, Bendell J C, Ryan D P. Locally advanced pancreatic cancer. J Clin Oncol 2005; 23: 4538–4544.
5. Torgeson A, Lloyd S, Boothe D et al. Multiagent induction chemotherapy followed by chemoradiation is associated with improved survival in locally advanced pancreatic cancer. Cancer 2017; 123: 3816–3824.
6. Hammel P, Huguet F, van Laethem J L et al. Effect of chemoradiotherapy versus chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. J Am Med Assoc 2016; 315: 1844–1853.
7. Krishnan S, Rana V, Janjan N A et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. Cancer 2007; 110: 47–55.
8. Huguet F, Andre T, Hammel P et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. J Clin Oncol 2007; 25: 326–331.
9. Koong A C, Le Q T, Ho A et al. Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2004; 58: 1017–1021.
10. Petrelli F, Comito T, Ghidini A, Torri V, Scorsetti M, Barni S. Stereotactic body radiation therapy for locally advanced pancreatic cancer: a systematic review and pooled analysis of 19 trials. Int J Radiat Oncol Biol Phys 2017; 97: 313–322.
11. Tchelebi L T, Lehrer E J, Trifiletti D M et al. Conventionally fractionated radiation therapy versus stereotactic body radiation therapy for locally advanced pancreatic cancer (CRiSP): an international systematic review and meta-analysis. Cancer 2020; 126: 2120–2131.
12. Ch'ang H J, Lin Y L, Wang H P et al. Induction chemotherapy with gemcitabine, oxaliplatin, and 5-fluorouracil/leucovorin followed by concomitant chemoradiotherapy in patients with locally advanced pancreatic cancer: a Taiwan cooperative oncology group phase II study. Int J Radiat Oncol Biol Phys 2011; 81: e749–e757.
13. Mahadevan A, Miksad R, Goldstein M et al. Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer. Int J Radiat Oncol Biol Phys 2011; 81: e615–e622.
14. Mellon E A, Hoffe S E, Springett G M et al. Long-term outcomes of induction chemotherapy and neoadjuvant stereotactic body radiotherapy for borderline resectable and locally advanced pancreatic adenocarcinoma. Acta Oncol 2015; 54: 979–985.
15. Herman J M, Chang D T, Goodman K A et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. Cancer 2015; 121: 1128–1137.
16. Kim J S, Lim J H, Kim J H et al. Phase II clinical trial of induction chemotherapy with fixed dose rate gemcitabine and cisplatin followed by concurrent chemoradiotherapy with capecitabine for locally advanced pancreatic cancer. Cancer Chemother Pharmacol 2012; 70: 381–389.
17. Crane C H, Varadhachary G R, Yordy J S et al. Phase II trial of cetuximab, gemcitabine, and oxaliplatin followed by chemoradiation with cetuximab for locally advanced (T4) pancreatic adenocarcinoma: correlation of Smad4(Dpc4) immunostaining with pattern of disease progression. J Clin Oncol 2011; 29: 3037–3043.
18. Quan K, Sutera P, Xu K et al. Results of a prospective phase 2 clinical trial of induction gemcitabine/capecitabine followed by stereotactic ablative radiation therapy in borderline resectable or locally advanced pancreatic adenocarcinoma. Pract Radiat Oncol 2018; 8: 95–106.
19. Moningi S, Dholakia A S, Raman S P et al. The role of stereotactic body radiation therapy for pancreatic cancer: a single-institution experience. Ann Surg Oncol 2015; 22: 2352–2358.
20. Zhong J, Patel K, Switchenko J et al. Outcomes for patients with locally advanced pancreatic adenocarcinoma treated with stereotactic body radiation therapy versus conventionally fractionated radiation. Cancer 2017; 123: 3486–3493.
21. Dohopolski M J, Glaser S M, Vargo J A, Balasubramani G K, Beriwal S. Stereotactic body radiotherapy for locally-advanced unresectable pancreatic cancer-patterns of care and overall survival. J Gastrointest Oncol 2017; 8: 766–777.
22. Bilimoria K Y, Stewart A K, Winchester D P, Ko C Y. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Ann Surg Oncol 2008; 15: 683–690.
23. Colbert L E, Rebueno N, Moningi S et al. Dose escalation for locally advanced pancreatic cancer: how high can we go? Adv Radiat Oncol 2018; 3: 693–700.
24. Sutera P A, Bernard M E, Gill B S et al. One- versus three-fraction pancreatic stereotactic body radiation therapy for pancreatic carcinoma: single institution retrospective review. Front Oncol 2017; 7: 272.
25. Krishnan S, Chadha A S, Suh Y et al. Focal radiation therapy dose escalation improves overall survival in locally advanced pancreatic cancer patients receiving induction chemotherapy and consolidative chemoradiation. Int J Radiat Oncol Biol Phys 2016; 94: 755–765.
26. Hall W A, Colbert L E, Nickleach D et al. The influence of radiation therapy dose escalation on overall survival in unresectable pancreatic adenocarcinoma. J Gastrointest Oncol 2014; 5: 77–85.
27. Barraclough H, Govindan R. Biostatistics primer: what a clinician ought to know: subgroup analyses. J Thorac Oncol 2010; 5: 741–746.
28. Austin P C. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011; 10: 150–161.
29. Rosati L M, Herman J M. Role of stereotactic body radiotherapy in the treatment of elderly and poor performance status patients with pancreatic cancer. J Oncol Pract 2017; 13: 157–166.
30. Neoptolemos J P, Palmer D H, Ghaneh P et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet 2017; 389: 1011–1024.
31. Sultana A, Smith C T, Cunningham D, Starling N, Neoptolemos J P, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol 2007; 25: 2607–2615.

https://doi.org/10.1017/S1460396921000212 Published online by Cambridge University Press