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Survival and prognostic factors in patients with pancreatic squamous cell carcinoma

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ABSTRACT

Objectives: Squamous cell carcinoma (SCC) of pancreas is rare entity with poorly defined prognostic factors and therapeutic outcomes. We sought to determine the overall survival (OS) and prognostic factors of patients with pancreatic SCC using National Cancer Database (NCDB) (2004–15).
Methods: Kaplan-Meier method and log-rank test were used to perform OS analysis. Propensity-matched analysis was used to compare the OS of pancreatic SCC and adenocarcinoma.
Results: Of the 515 cases included in our analysis, 46% were female. Approximately half of the cohort (48%) received chemotherapy or radiation therapy or both. Twenty six percent (33/125) of stage I and II disease (localized disease), 11% (8/72) of stage III, and 2% (6/318) of stage IV disease underwent surgical resection of the primary tumor. Median OS for the entire cohort was 4 months and was significantly higher in patients who underwent surgical resection of the primary tumor (17 vs 4 months, $p < 0.001$). In localized disease, adjuvant chemotherapy was not associated with improved OS in early stage disease (20 vs 24 months, $p = 0.60$). Stage IV patients treated with chemotherapy had a better OS than those without (5 vs 2 months, $p < 0.0001$). Propensity matched analysis demonstrated no significant differences in median OS between pancreatic adenocarcinoma (4.8 months) and SCC (4 months, $p = 0.09$).
Conclusions: Pancreatic SCC had a diverse OS that varied significantly according to increasing age (>70 years) and stage of the disease at presentation ($p < 0.01$). Surgical resection of primary tumor was associated with longer OS in stages I-II, whereas chemotherapy was associated with longer OS in stage IV disease.

Introduction

Pancreatic squamous cell carcinoma (SCC) is a rare form of exocrine pancreatic malignancy with a dismal prognosis [1]. The disease is typically diagnosed after ruling out primary SCC at other locations and pancreatic adeno-squamous carcinoma that typically constitutes ~30% of squamous component [2–4]. Current clinical data are mostly limited to individual case reports, small case series and a Surveillance, Epidemiology, and End Results (SEER) database analysis [1]. As per the recently published SEER analysis, the incidence of pancreatic SCC is about 2 cases per 10,000,000 person-years in the United States (U.S), which has been steadily increasing over the last decade (almost tripled or ~229% increase from 2000 to 2012) [1]. This increase in incidence may be attributed to a better histologic diagnosis and/or reporting to SEER database. Given the uncommon nature of the disease and limited clinical experience in the management of pancreatic SCC, information on the therapeutic patterns and survival outcomes is very limited. Over time, there have been numerous retrospective and prospective studies that determined the predictors of survival of conventional pancreatic adenocarcinoma [5,6]. However, such information is lacking on pancreatic SCC. In this study, we sought to analyze the therapeutic patterns of pancreatic SCC cases in specific and its

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median OS based on the therapies offered to pancreatic SCC at various cancer facilities in the U.S. In addition, this study compared therapeutic patterns and OS outcomes of pancreatic SCC patients with that of the much more common pancreatic adenocarcinoma.

Methods

Data source

In the current study, we utilized the National Cancer Database (NCDB), the largest cancer registry that covers more than 70% of all newly diagnosed cancer cases each year in the U.S. A total of 654 pancreatic SCC cases were identified, encompassing years 2004–2015 by using the third edition International Classification of Diseases for Oncology (ICD-0-3) codes 8070/3–8076/3 (site code: C250–254, C257-259). Patients with unknown stage at diagnosis ($n = 71$) and/or incomplete follow-up data ($n = 68$) were excluded from the final analysis. We also included pancreatic adenocarcinoma cases reported to NCDB using the ICD-0-3 codes of 8140/3–8147/3, to compare the survival between the two groups. Institutional Review Board exempted the study from review as both the facility and patient data was de-identified.

Objectives

The primary outcome of interest was to determine the therapeutic patterns followed in the management of pancreatic SCC in the United States and to analyze any median OS differences based on the therapies. This study censored the patients who were alive at last follow up from the OS analysis. Propensity adjusted analyses was performed, OS patterns were compared with that of pancreatic adenocarcinoma. Factors that were noted to be statistically significant in univariate cox proportional hazard regression model were included in the multivariate model.

Statistical analysis

Statistical analysis was performed by using Statistical Package for Social Sciences (SPSS) (version 24.0; SPSS, Inc., Chicago, IL). Cox proportional-multivariable hazards regression model was used to determine the prognostic factors that influenced the OS. Univariate survival analysis was performed and covariates with significance level <0.05 were included in the multivariate analysis. Descriptive statistics were expressed as median and range (r). Chi-square test and Mann-Whitney *U* test were used to compare the categoric data and continuous variables, respectively. The effect of surgical resection, post-surgical chemo and radiation therapy on OS was investigated using univariate and multivariate analysis. OS analysis was performed separately for stages I-II (localized disease), III and stage IV disease (by using the Kaplan-Meier methods). OS comparison between the groups was performed by log-rank test.

Propensity matched analysis

For propensity score matching, patients with incomplete follow-up data and unknown stage were excluded. A total of 182,090 were included prior to matching, 181,575 with pancreatic adenocarcinoma and 515 with SCC. We estimated the propensity score, or the probability of being in the adenocarcinoma or SCC group, by using a multivariable logistic regression model. Covariates included in the model were age at diagnosis, sex, race, insurance status, Charlson comorbidity score, year of diagnosis, facility type, tumor grade, TNM stage, surgery, radiation administration and chemotherapy use. Each sub-category was entered as a separate variable in the model. A 1:3 matching was then performed by using the nearest neighbor method with a caliper width equal to 0.20 standard deviations using the MatchIt' package in R [7]. A total of 1,545 pancreatic adenocarcinoma cases and 515 pancreatic SCC cases were included in the analysis. The balance in the baseline covariates in the matched data was examined using standardized mean differences (Table 1), histogram (Supplemental Fig. 1) and jitter plots (Supplemental Fig. 2). Unmatched patients were excluded from survival analysis.

Results

Baseline characteristics

A total of 515 patients with pancreatic SCC diagnosed between 2004 and 2015 met the inclusion criteria. Of these 515 patients, 47% were female. The distribution by race was 79% White, 15% Black, 3% Asian-Pacific Islander, and 3% others or unknown. Median age at diagnosis was 69 (range, 36–90) years and did not differ by sex ($p = 0.19$) or stage of disease at diagnosis ($p = 0.63$). Table 1 summarizes the patients' baseline characteristics. The distribution of the primary tumor based on the anatomical location was 42.5%, 14%, and 20% at head, body, and tail of pancreas, respectively. The proportion of patients with stage I, II, III and IV disease at diagnosis were 5%, 19%, 14%, and 62%, respectively. For stage IV disease, the most common distant sites of metastases were liver (32%) and lungs (6%).

Treatment patterns

Forty-eight percent of the patients received chemo or radiation therapy either alone or in combination (without surgery). Twenty-six percent (33 of 125) of stage I and II disease (localized disease), 11% (8 of 72) of stage III, and 2% (6 of 318) of stage IV disease underwent surgical resection of the primary tumor. In the patients who had surgical resection, negative tumor margin (R0) resection was reported for 60% ($n = 28$) of patients. The rate of R0 resection was 73% in stages I and II, and 38% in stage III.

Neo-adjuvant therapy with either chemo or radiation or both was administered to 11% ($n = 5$) of the patients. Given the small number of patients who received neo-adjuvant therapy, we could not evaluate the effect on R0 resection rates. In stage I-II disease, 46% and 21% of patients received post-surgical chemotherapy and radiation therapy, respectively. In stage III disease, 13% and 25% of patients received post-surgical chemotherapy and radiation therapy, respectively.

Prognostic factors

Median OS of pancreatic SCC was 4 months and was not significantly higher among Whites as compared to Blacks (4.4 vs 2.7 months, $p = 0.09$). Similarly, no such survival differences were noted between males and females (median OS: 4.4 vs. 3.7 months; $p = 0.16$). In addition, no difference in median OS based on location of tumor (head *vs* body *vs* tail) in the pancreas ($p = 0.11$).

As expected, patients with stage I/II disease at diagnosis had a better median OS (7 months) as compared to that of stage III (6 months) and stage IV (3 months) ($p < 0.001$ for both comparisons) (Fig. 1A). In stage I/II disease, patients who received surgical therapy, irrespective of chemoradiation therapy utilization, had a better median OS as compared to that of patients who did not receive surgical therapy (21 vs 5 months, $p < 0.01$) (Fig. 1B). However, no such benefit was seen in stage III disease (7 vs 6 months, $p = 0.32$) (Fig. 1C). We could not evaluate the benefit of surgery in stage IV disease as only 6 out of 350 patients with stage IV disease had surgery. In patients with stage I/II disease, patients who underwent

Table 1
Baseline characteristics in the unmatched and matched cohorts.

	Unmatched Cohort				Matched Cohort			
	Adeno Ca (n = 181575)	SCC (n = 515)	SMD	p-value	Adeno Ca (n = 1545)	SCC (n = 515)	SMD	p-value
Age								
>70	79755 (43.9%)	244 (47.4%)	0.069	0.115	746 (48.3%)	244 (47.4%)	0.018	0.722
≤70	101820 (56.1%)	271 (52.6%)	0.069	0.115	799 (51.7%)	271 (52.6%)	0.018	0.722
Sex								
Male	93062 (51.3%)	275 (53.4%)	0.043	0.331	836 (54.1%)	275 (53.4%)	0.014	0.779
Female	88513 (48.7%)	240 (46.6%)	0.043	0.331	709 (45.9%)	240 (46.6%)	0.014	0.779
Race								
White	151223 (83.3%)	409 (79.4%)	0.099	0.019	1252 (81.0%)	409 (79.4%)	0.041	0.421
Black	22160 (12.2%)	79 (15.3%)	0.091	0.030	211 (13.7%)	79 (15.3%)	0.048	0.342
Unknown/other	8192 (4.5%)	27 (5.2%)	0.034	0.425	82 (5.3%)	27 (5.2%)	0.003	0.955
Insurance								
No insurance	5817 (3.2%)	17 (3.3%)	0.005	0.900	40 (2.6%)	17 (3.3%)	0.042	0.394
Private	58275 (32.1%)	143 (27.8%)	0.095	0.036	442 (28.6%)	143 (27.8%)	0.019	0.714
Government	113285 (62.4%)	345 (67.0%)	0.096	0.031	1028 (66.5%)	345 (67.0%)	0.010	0.850
Unknown/other	4198 (2.3%)	10 (1.9%)	0.026	0.577	35 (2.3%)	10 (1.9%)	0.023	0.664
Charlson-Deyo								
0–1	166661 (91.8%)	476 (92.4%)	0.024	0.597	1445 (93.5%)	476 (92.4%)	0.043	0.389
2–3	14914 (8.2%)	39 (7.6%)	0.024	0.597	100 (6.5%)	39 (7.6%)	0.043	0.389
Year of diagnosis								
2004–2007	50090 (27.6%)	126 (24.5%)	0.071	0.114	379 (24.5%)	126 (24.5%)	0.002	0.976
2008–2011	69043 (38.0%)	190 (36.9%)	0.023	0.597	607 (39.3%)	190 (36.9%)	0.049	0.334
2012+	62442 (34.4%)	199 (38.6%)	0.088	0.043	559 (36.2%)	199 (38.6%)	0.051	0.316
Facility Type								
Non-academic	102729 (56.6%)	326 (63.3%)	0.137	0.002	982 (63.6%)	326 (63.3%)	0.005	0.916
Academic	77502 (42.7%)	184 (35.7%)	0.143	0.001	548 (35.5%0	184 (35.7%)	0.005	0.915
Others/Unknown	1344 (0.7%)	5 (1.0%)	0.025	0.545	15 (1.0%)	5 (1.0%)	<0.001	1.000
Tumor Grade								
1–2	33209 (18.3%)	46 (8.9%)	0.275	<0.001	149 (9.6%)	46 (8.9%)	0.025	0.633
3–4	28817 (15.95)	175 (34.0%)	0.428	<0.001	541 (35.0%)	175 (34.0%0	0.022	0.669
Unknown	119549 (65.8%)	294 (57.1%)	0.180	<0.001	855 (55.3%)	294 (57.1%)	0.035	0.489
Stage								
Stage I	14510 (8.0%)	27 (5.2%)	0.111	0.022	92 (6.0%)	27 (5.2%)	0.031	0.549
Stage II	45939 (25.3%)	98 (19.0%)	0.151	0.001	312 (20.2%)	98 (19.0%)	0.029	0.567
Stage III	24379 (13.4%)	72 (14.0%)	0.016	0.713	201 (13.0%)	72 (14.0%)	0.028	0.574
Stage IV	96747 (53.3%)	318 (61.7%)	0.172	<0.001	940 (60.8%)	318 (61.7%)	0.019	0.715
Surgery								
No	147655 (81.3%)	460 (89.3%)	0.227	<0.001	1387 (89.8%)	460 (89.3%)	0.015	0.770
Yes	29476 (16.2%)	47 (9.1%)	0.215	<0.001	124 (8.0%)	47 (9.1%)	0.039	0.433
Unknown	4444 (2.4%)	8 (1.6%)	0.064	0.190	34 (2.2%)	8 (1.6%)	0.048	0.368
Radiation								
No	141666 (78.0%)	409 (79.4%)	0.034	0.445	1231 (79.7%)	409 (79.4%)	0.006	0.900
Yes	35177 (19.4%)	88 (17.1%)	0.059	0.190	276 (17.9%)	88 (17.1%)	0.020	0.689
Unknown	4732 (2.6%)	18 (3.5%)	0.052	0.206	38 (2.5%)	18 (3.5%)	0.061	0.211
Chemotherapy								
No	71452 (39.4%)	246 (47.8%)	0.170	<0.001	728 (47.1%)	246 (47.8%)	0.013	0.799
Yes	103468 (57.0%)	256 (49.7%)	0.146	0.001	769 (49.8%)	256 (49.7%)	0.001	0.980
Unknown	6655 (3.7%)	13 (2.5%)	0.066	0.169	48 (3.1%)	13 (2.5%)	0.035	0.500

Adeno Ca: Adenocarcinoma; SCC: Squamous Cell Carcinoma; SMD: Standardized Mean Difference.

lymph node surgery (n = 33) had a better median OS as compared to that of the counterparts (21 vs 5 months, p < 0.001) (Fig. 1D). Post-surgical chemoradiation therapy was not associated with OS benefit in stage I-II disease (unadjusted) (21 vs 24 months, p = 0.21).

In stage IV disease, a significant difference in median OS was noticed between the patients who received chemoradiation (4.9 months) as compared to that of the patients who did not receive chemoradiation (1.5 months) (p < 0.01).

Older age (ages > 70 years) and advanced stage of the disease (HR for stage IV disease: 1.85 [95%CI:1.45–2.36], p < 0.001; stages I, II as referent) were associated with poorer OS. For patients with localized disease (stages I and II), surgical resection of primary tumor (HR: 0.33 [95%CI: 0.15–0.73], p = 0.006), or surgery in combination with post-surgical chemoradiation (HR: 0.41 [95%CI: 0.22–0.77], p = 0.01) or neoadjuvant chemoradiation (HR: 0.20 [95%CI: 0.05–0.83], p = 0.03) were associated with better OS as compared to that of patients who received chemoradiation only. In stage III disease, ages >70 years (HR: 3.21 [95%CI:1.90–5.42], p < 0.001), higher Charlson comorbidity index (HR: 2.93 [95% CI:1.03–8.31], p = 0.04) were associated with poor OS. In stage IV disease, female gender (HR: 1.30 [95%CI:1.03–1.65], p = 0.03), higher grade (HR: 2.04 [95%CI: 1.27–3.30], p = 0.01), higher Charlson comorbidity index (HR: 1.61 [95%CI: 1.04–2.49], p = 0.03), Medicare insurance (HR: 1.53 [95%CI: 1.13–2.07], p = 0.01) were associated with poor OS (Table 2) (Fig. 2). Patients who received chemoradiation only had a better OS (HR: 0.38 [95%CI: 0.29–0.49], p < 0.01) as compared to that no treatment group whereas surgical resection of primary tumor only, surgery in combination with neoadjuvant or post-surgical chemoradiation did not yield in better OS as compared to that of no treatment group (Table 2) (Fig. 2).

Propensity matching and comparison of therapy patterns and OS estimates with pancreatic adenocarcinoma.

After matching for baseline patient demographics and tumor characteristics, irrespective of the therapeutic patterns, median OS of pancreatic SCC (4 months) was marginally lower than that of

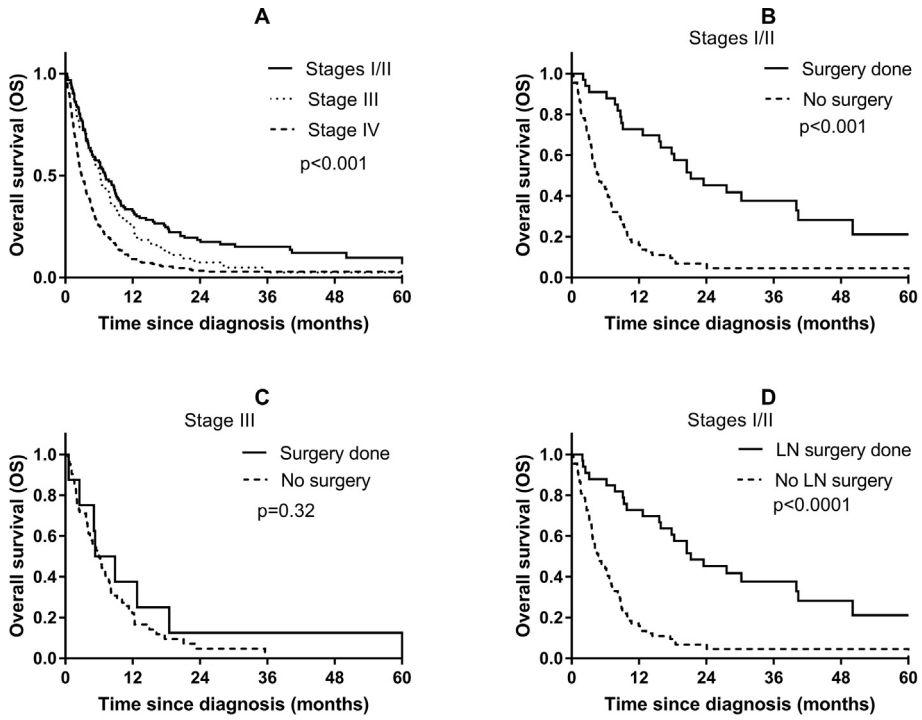

Fig. 1. Kaplan-Meier estimates of overall survival of pancreatic squamous cell carcinoma patients based on the A) stage of the disease at diagnosis; B) receipt of surgery in localized (stages I-II) disease; C) receipt surgery in stage III disease; and D) receipt of lymphadenectomy (prophylactic and therapeutic) in localized disease (stages I-II).

Table 2
Cox multivariate analysis to predict overall mortality in patients with Pancreatic Squamous carcinoma in stage IV disease.

Parameter	Hazard Ratio (HR) [95% CI]	*p*-value
Age	Referent	0.73
≤70 years	1.05 [0.80–1.39]	
≥71 years		
Sex	referent	0.03
Males	1.30 [1.03–1.65]	
Females		
Charlson-Deyo Score	referent	0.03
0–1	1.61 [1.04–2.49]	
2–3		
Race	referent	0.55
White	0.90 [0.64–1.27]	
Black		
Insurance status	referent	0.06
Private	0.88 [0.48–1.62]	
Uninsured	1.09 [0.70–1.69]	
Medicaid	1.53 [1.13–2.07]	
Medicare		
Grade	reference	0.003
1–2	2.04 [1.27–3.30]	
3–4		
Therapy received	referent	<0.001
No treatment	0.38 [0.29–0.49]	
Chemoradiation only	0.48 [0.18–1.33]	
Surgery only	0.46 [0.14–1.48]	
Surgery plus adjuvant chemoradiation		

pancreatic adenocarcinoma (4.8 months), but did not reach the statistical significance ($p = 0.09$) (Fig. 3A). Pancreatic SCC patients who had undergone surgical resection of the primary tumor had similar OS as to pancreatic adenocarcinoma (15.9 vs 16 months; $p = 0.71$) (Fig. 3B). Similarly, there was no noticeable difference in median OS between the two cohorts who received surgery plus chemoradiation (18 months in both cohorts; $p = 0.89$).

Discussion

The current study examined the clinical outcomes, therapeutic patterns, and predictors of survival in pancreatic SCC patients using a national cancer registry. Within the 515 pathologically confirmed pancreatic SCC patients, it was found that elderly age (>70 years) and higher stage of disease were associated with higher mortality risk. Comparable to these findings, a SEER analysis on 214 pancreatic SCC patients previously reported that older age at diagnosis and failure to have surgical treatment of the primary tumor were associated with shorter survival [1]. The SEER analysis showed that majority of patients were of age > 65 years and were of White race. The current analysis found the same demographic distribution, and additionally found that Whites had a better median OS as compared to that of Blacks. However, there was no gender differences in the survival outcomes.

We found that surgery remains the mainstay of treatment of pancreatic SCC and improved OS in localized disease only (stages I-II). Similar better survival rate in the patients who were managed with surgical resection of the primary tumor was seen in prior case reports [8,9]. Though surgery improved median OS, it is important to note that majority of pancreatic SCC cases were diagnosed in advanced stages and in our cohort only 5% and 18% of cases were diagnosed in stages I and II, respectively. Correspondingly, the rate of R0 resection rates decreased with advancing disease. This again signifies the importance of early detection of this rare but fatal cancer in early stages. Earlier studies have found that the pancreatic SCC seems to be more common in patients who suffered from chronic inflammation in pancreas leading to squamous metaplasia thereby causing pancreatic SCC [1,10,11]. Future prospective studies focusing on the importance of screening methods in these high-risk patients might help in early detection of pancreatic SCC [12].

It is interesting that there was no noticeable difference in median OS based on the tumor location-head, body, and tail, which has been reported to be the case with pancreatic adenocarcinoma [13].

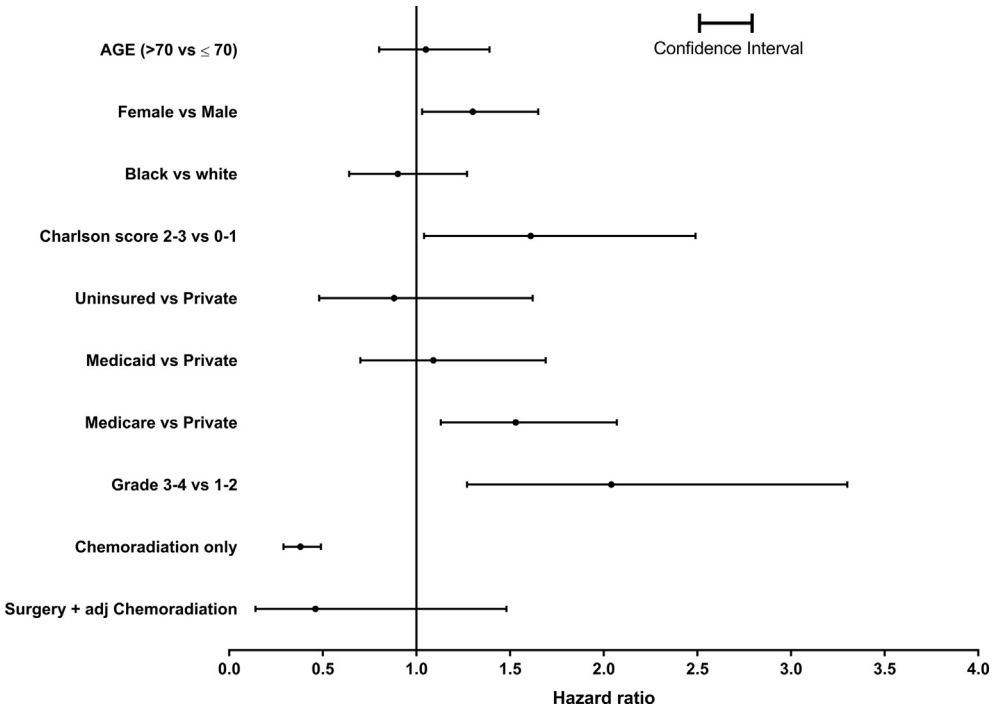

Fig. 2. Forest plot depicting the predictors of survival in patients with stage IV pancreatic squamous cell carcinoma using a Cox proportional hazards model.

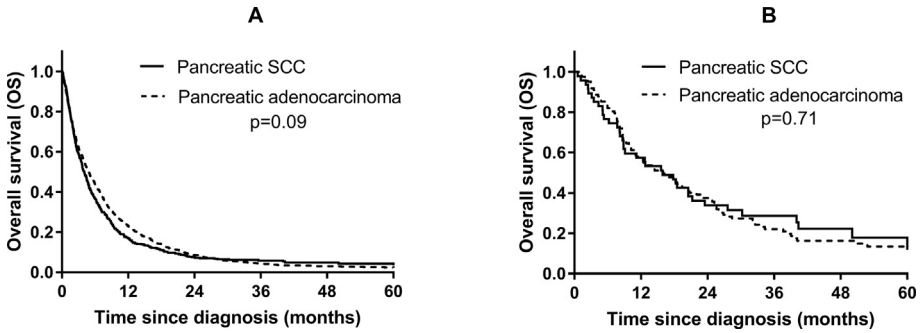

Fig. 3. Kaplan-Meier estimates of overall survival (OS) of propensity matched cohort of pancreatic squamous cell carcinoma (SCC) and pancreatic adenocarcinoma. A) OS difference between pancreatic SCC and pancreatic adenocarcinoma matched cohorts. B) OS difference between pancreatic SCC and pancreatic adenocarcinoma cohorts who received surgical therapy only.

A SEER based study showed that pancreatic adenocarcinoma located at body and tail had poor prognosis as compared to that of lesions located in the head of the pancreas [14]. This difference in OS was thought to be secondary to resectability of lesions located in the head. This non-difference in OS based on the tumor location in pancreatic SCC may be attributed to aggressive nature of the disease, delayed diagnosis in advanced stages, and larger tumor size. A SEER analysis on pancreatic SCC showed that a higher percentage of pancreatic SCC are diagnosed in stage IV disease and fewer patients were managed with surgical resection of the primary tumor as compared to that of pancreatic adenocarcinoma [1].

The importance of post-surgical chemoradiation therapy in localized (stages I-II) and locally advanced disease (stage III) was further analyzed to find no significant difference in OS. One possible explanation is the disease may not be responsive to conventional therapeutic agents used in pancreatic adenocarcinoma, or due to small sample size of the both the study arms. A poor response of pancreatic SCC to various chemotherapeutic agents including gemcitabine-based therapies, combination regimen of cisplatin and 5-flurouracil has been documented in several case reports [2,8,15,16].

The propensity matched analysis with pancreatic adenocarcinoma showed that the OS was only marginally shorter in pancreatic SCC, with no statistically significant difference, which again signifies the dismal prognosis of pancreatic SCC. The median OS in pancreatic adenocarcinoma was much less (~4–5 months) than one would expect, based on reported clinical trials. The majority of the patients in both the cohorts of adenocarcinoma and SCC had stage IV disease. This may have contributed to poor OS in the current analysis. In addition, there might be a component of selection bias in the clinical trials. It is important to note that the median OS in the current study was similar to that of the prior SEER study and case reports [1,17,18]. The SEER study showed that pancreatic SCC had inferior median OS as compared to pancreatic adenocarcinoma, which is not the case in the present analysis [1]. The discrepancy in the findings may be attributed to lack of propensity matched analysis in the SEER study [1].

The limitations of our study are inherent to the registry-based

analysis and retrospective study design [19]. Important clinical characteristics including tumor biology, mitotic count, information on disease recurrence, specific type and duration of chemotherapy, and dose of radiation therapy details were not taken into consideration, due to lack of data in NCDB. In addition, the effects of various therapeutic modalities on progression-free survival are lacking. Nonetheless, NCDB provides the real-world data that is not influenced by biases that may arise from small case series and single institutional studies and information on disease recurrence may not play a significant role given the lethality of cancer and the cancer response to chemotherapy. Such robust database is very much needed for assessing treatment utilization and treatment outcomes in such a rare subtype of pancreatic cancer. Moreover, the data in NCDB are extensively monitored and evaluated for data integrity, which makes it a powerful initiative to improve the cancer care [20]. To our knowledge, ours is the largest reported study till date that provided a focused stage wise analysis of management trends and survival outcomes in pancreatic SCC patients using a national cancer registry.

Conclusions

Patients with pancreatic SCC have diverse median OS, which varies significantly according to age and stage of the disease at presentation. Surgical resection of primary tumor is associated with longer survival in stage I-II disease (localized disease), whereas chemoradiation therapy was associated with OS benefit in stage IV disease. The results of our study underscore the need for evaluating various therapeutic regimens in this fatal malignancy and the role of screening exams in the high-risk patients as identified in this analysis. Multi-institution or global alliance studies may be needed to better analyze the therapeutic agents in this rare but deadly malignancy.

Author contributions

Kommalapati, Tella, Yadav, and Mahipal had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Tella, Kommalapati, Mahipal; Acquisition, analysis, or interpretation of data: Tella, Kommalapati, Yadav, Mahipal; Drafting of the manuscript: Tella and Kommalapati; Critical revision of the manuscript for important intellectual content: All authors; Statistical analysis: Kommalapati and Yadav. All authors approved the final version of the manuscript.

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Disclosure

Authors report no conflicts of interest for this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.05.011.

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