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Trends in the clinical presentation, treatment, and survival for pancreatic adenocarcinoma☆

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ABSTRACT

Background: We assessed trends in the clinical presentation, treatment, and survival for pancreatic adenocarcinoma.

Methods: A retrospective cohort study using data from the SEER program (2004–2014). All patients diagnosed with pancreatic adenocarcinoma over 2 eras were included (A: 2004–2009 vs. B: 2010–2014). Outcomes of interest were the likelihood of metastatic disease at diagnosis, utilization of resection, and overall survival.

Results: A total of 62,201 patients were included in this study [Era B - 31,998 (51.4%)]. Patients diagnosed in Era B were significantly less likely to have metastatic pancreatic cancer at diagnosis, and demonstrated improved long-term survival after risk-adjustment. Similarly, patients with non-metastatic pancreatic cancer that were diagnosed in Era B were independently more likely to undergo resection. The observed association between era of diagnosis and survival was independent of resection status and the presence of metastatic disease.

Conclusions: There have been significant improvements in pancreatic cancer care over the last decade, as evidenced by earlier diagnosis, increased utilization of surgery, and improvement in overall survival for both resected and un-resected patients.

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Introduction

Pancreatic cancer remains a leading cause of cancer death in the United States, among both men and women.[1] In 2018, it is estimated that 55,440 new cases of pancreatic cancer will be diagnosed in the United States, and more than 44,330 patients will die of the disease.[1] An overwhelming majority (about 85%) of pancreatic cancer diagnoses are adenocarcinomas, which arise from the ductal epithelium. Survival outcomes for pancreatic cancer is closely related to the underlying stage at diagnosis with surgical resection offering the best chance for long-term survival when feasible.

For early-stage pancreatic cancer, pancreatectomy is considered standard of care.[2] However, pancreatectomy is underutilized with previous studies revealing that a little over a third of patients with resectable pancreatic cancer undergo curative resection.[3–5] On the other hand, for patients with metastatic disease not amenable to surgery, chemotherapy confers some survival benefit.[6,7] Based on the profound disparity in survival outcomes between non-metastatic and metastatic pancreatic cancer, efforts have been channeled towards screening high-risk patients to facilitate the timely diagnosis and prompt treatment of this aggressive disease.[8–10] However, it remains unclear if trends in the clinical presentation of pancreatic cancer have changed over the last decade. Specifically, it is unknown if patients are more likely to present with potentially resectable (stage I – III) tumors at diagnosis. Furthermore, recent population-level data on trends in the utilization of pancreatectomy and survival for pancreatic adenocarcinoma are scarce.

Using data from the Surveillance, Epidemiology, and End Results program (SEER), we sought to compare trends in the clinical presentation, treatment, and survival for pancreatic adenocarcinoma. We hypothesized that outcomes of pancreatic cancer have improved over the last decade, in terms of stage of initial presentation, treatment, and survival outcomes.

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Methods

Data source

This retrospective study was conducted using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program (SEER). The SEER program collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 28% of the United States population. SEER routinely collects data on patient demographics, primary tumor site, tumor morphology, tumor stage, treatment characteristics and follow-up for vital status.[11]

Study population

The SEER database was used to identify patients from all cancer registries captured in the SEER 18 program (San Francisco, Connecticut, Detroit, California, Kentucky, Louisiana, New Jersey, Greater Georgia, Hawaii, Iowa, New Mexico, Seattle, Utah, Alaska, San Jose-Monterey, Los Angeles, Rural Georgia, and Metropolitan Atlanta) who had a histologic diagnosis of pancreatic adenocarcinoma (SEER histology code 8140) between the year 2004 and 2014. Patients with unstaged tumors were excluded.

Exposure and endpoints

Using the year of diagnosis, patients were classified into 2 groups: Era A (years 2004–2009) and Era B (years 2010–2014). The geographic location of the index registry was used in classifying patients into various geographic regions: Midwestern region (Detroit and Iowa), Western region (California, Los Angeles, San Francisco, Hawaii, New Mexico, Seattle, Utah, Alaska, and San Jose-Monterey), Southern region (Rural Georgia, Kentucky, Louisiana, Metropolitan Atlanta, and Greater Georgia) and North-Eastern region (New Jersey and Connecticut). The primary outcome of interest was the likelihood of having metastatic (stage IV) pancreatic cancer at diagnosis. The secondary endpoints of interest were the utilization of resection (pancreatectomy) and overall survival. Overall survival was estimated in months from the date of pancreatic cancer diagnosis to the date of last follow-up (for survivors), or the date of death for non-survivors.

The SEER registries continue to code and submit both AJCC 6th and 7th edition stages to the SEER program for all cancers diagnosed in 2010 and beyond. However, patients diagnosed prior to 2010 only have AJCC 6th edition staging available. Since we examined patients diagnosed from 2004 to 2014 in this study, we opted to use the AJCC 6th edition staging system for our analyses as this approach helped standardize the staging system over the study period and offered the additional benefit of having fewer patients with un-staged tumors.

Statistical analysis

Baseline characteristics were compared using the Pearson's χ^2 test for proportions, Student's t-test for continuous variables and Mann Whitney-U test for non-parametric variables. Survival analysis was performed using the Kaplan Meier method, while the log-rank test for equality in survival functions was used in assessing for survival differences between patients diagnosed in Era A and B. Stepwise multivariable Logistic and Cox regression models were built, adjusting for baseline demographic, tumor, and treatment characteristics. All variables included in the multivariable models had a p-value <0.01 on univariate analysis for the outcome of interest, and were kept in the final model if they remained statistically significant. A p-value <0.05 was deemed statistically significant in this study. All statistical analyses were performed using Stata version 13.1 (StataCorp, College Station, Texas, USA).

Results

Study population

Overall, 62,201 patients were included in this study [Era B - 31,998 (51.4%)]. On crude analysis, a significant higher proportion of patients diagnosed in Era B were older, non-Caucasian, Hispanic, and insured. Patients diagnosed in Era B were also significantly more likely to have tumors located in the body/tail of the pancreas, and less frequently underwent surgical resection ($p < 0.05$ for all). No significant gender differences were observed between the study groups. Baseline demographic, tumor, clinical and treatment characteristics are presented in Table 1.

Likelihood of metastatic disease

A total of 36,550 (58.8%) patients had metastatic (Stage IV) pancreatic cancer at diagnosis. On univariate analysis, patients diagnosed with pancreatic cancer in Era B had a decreased likelihood of presenting with metastatic disease at diagnosis (OR: 0.95, CI: 0.92–0.98, $p = 0.002$). After multivariable adjustment for significant demographic, tumor, and clinical characteristics, this association persisted (OR: 0.92, CI: 0.88–0.96; $p < 0.001$). The other independent predictors for metastatic disease at diagnosis were age, gender, race, ethnicity, insurance status, tumor location and grade (Table 2).

Utilization of resection

Overall, a total of 8279 (13.3%) patients underwent pancreatectomy during the study period [Era A: 14.1% vs. Era B: 12.6%; $p < 0.001$]. Similarly, among patients with non-metastatic tumors (stage I – III) which potentially are amenable to resection per guideline recommendations, pancreatectomy was more frequently performed in Era A [Era A: 32.0% vs. Era B: 28.2%; $p < 0.001$]. However, after multivariable adjustment for confounding variables on this subset of patients, we found that those diagnosed in Era B were independently more likely to undergo pancreatectomy (OR: 1.12, CI: 1.04–1.20; $p = 0.002$). Other independent predictors for surgical resection amongst patients with non-metastatic disease (Stage I – III) were age, marital status, race, ethnicity, geographic region, tumor stage, location, and grade (Table 3). Sub-analysis was performed on patients with stage I and II tumors (for whom the data overwhelmingly recommend pancreatectomy) and revealed a persistence of this association.

Overall survival

A total of 55,420 (89.1%) patients died during the study period [Era A: 29,426 (97.4%) and Era B: 25,994 (81.2%); $p < 0.001$]. Overall median survival was 5 months (Era A: 4 months vs. Era B: 5 months; $p < 0.001$). Patients with metastatic pancreatic adenocarcinoma had significantly worse overall survival compared to those with non-metastatic cancer (3 months vs. 10 months; $p < 0.001$). Compared to patients that did not undergo surgery, those who underwent surgical resection had significantly superior survival outcomes (18 months vs. 4 months; $p < 0.001$). On univariate analysis, patients diagnosed in Era B had superior long-term survival (HR: 0.91, CI: 0.90–0.93; $p < 0.001$), and this association persisted following multivariable adjustment (HR: 0.88, CI: 0.86–0.89; $p < 0.001$). The other independent predictors for survival were age, marital status, race, geographic region, tumor stage, tumor grade,

Table 1
Demographic and tumor characteristics.

Variables	Era A N = 30,203 (%)	Era B N = 31,998 (%)	*P*
Age ≥ 65 Years	18,794 (62.2)	20,433 (63.9)	<0.001
Female	14,569 (48.2)	15,321 (47.9)	0.375
Caucasian	24,299 (80.5)	25,535 (79.8)	0.042
Hispanic	2774 (9.2)	3227 (10.1)	<0.001
Married	17,279 (57.2)	17,420 (54.4)	<0.001
Insured	15,529 (51.4)	30,480 (95.3)	<0.001
Geographic Region			<0.001
Midwest	3357 (11.1)	3344 (10.4)	
West	14,792 (49.0)	15,580 (48.7)	
South	6335 (21.0)	7319 (22.9)	
Northeast	5719 (18.9)	5755 (18.0)	
Tumor Size, mm (SD)	43.7 (55.5)	45.2 (66.4)	0.006
AJCC Clinical Tumor Stage 6th Edition			<0.001
I	1738 (5.7)	2167 (6.8)	
II	7351 (24.3)	7932 (24.8)	
III	3178 (10.5)	3285 (10.3)	
IV	17,936 (59.4)	18,614 (58.2)	
No of Lymph Nodes Examined, Median (Range)[a]	11 (0–85)	15 (0–90)	<0.001
No of Positive Lymph Nodes, Median (Range)[a]	1 (0–24)	1 (0–27)	<0.001
Tumor Location			0.002
Body/Tail	14,952 (49.5)	16,236 (50.7)	
Head	15,251 (50.5)	15,762 (49.3)	
Tumor Grade			<0.001
Low	5617 (18.6)	4862 (15.2)	
High	4921 (16.3)	4140 (12.9)	
Unknown	19,665 (65.1)	22,996 (71.9)	
Resection	4261 (14.1)	4018 (12.6)	<0.001

[a] - Resected patients only.

tumor location, and resection (Table 4). The association between era of diagnosis and survival was independent of resection status (resected patients – HR: 0.80, CI: 0.76–0.85; $p < 0.001$ and unresected patients – HR: 0.89, CI: 0.87–0.91; $p < 0.001$) and the presence of metastatic disease (non-metastatic disease – HR: 0.87, CI: 0.85–0.90; $p < 0.001$ and metastatic disease - HR: 0.89, CI: 0.87–0.91; $p < 0.001$).

Discussion

In this retrospective cohort study, we examined recent trends in the clinical presentation of pancreatic adenocarcinoma and found that over the last decade, there has been a significant decrease in the likelihood of metastatic disease for patients with newly diagnosed pancreatic cancer. Furthermore, our analyses revealed a significant improvement in the utilization of pancreatectomy and survival for patients with pancreatic cancer over the same period.

Table 2
Independent predictors for metastatic disease at diagnosis.

Variables	Odds Ratio	Confidence Interval	*P*
Era B	0.92	0.88–0.96	<0.001
Age ≥65 years	0.80	0.77–0.83	<0.001
Female	0.88	0.85–0.91	<0.001
Non-Caucasian	1.10	1.05–1.15	<0.001
Hispanic	1.18	1.11–1.26	<0.001
Insured	0.82	0.72–0.92	0.001
Geographic Region (Midwest)	Ref		
West	1.01	0.95–1.07	0.844
South	0.91	0.86–0.98	0.007
Northeast	0.99	0.92–1.06	0.705
Tumor Location (Body/Tail)	Ref		
Head	0.24	0.23–0.26	<0.001
Tumor Grade (Low)	Ref		
High	1.79	1.69–1.91	<0.001

Likelihood of metastatic disease

Like previous studies, most patients included in this study presented with metastatic pancreatic cancer.[12–14] However, contrary to previous reports,[12] we found that patients diagnosed in Era B were 8% less likely to present with metastatic disease at diagnosis. These results suggest a significant increase in the proportion of patients with newly diagnosed pancreatic cancer in the US who present with tumors that are potentially amenable to curative resection, and may be reflective of notable improvements in pancreatic imaging using a multi-modality approach,[15] and concerted efforts towards screening in patients at high risk for pancreatic cancer.[8–10] Furthermore, this trend may be reflective of changes in insurance coverage related to the implementation of the Patient Protection and Affordable Care Act in 2010.[16] Of note,

Table 3
Independent predictors for the utilization of resection[a].

Variables	Odds Ratio	Confidence Interval	*P*
Era B	1.12	1.04–1.20	0.002
Age ≥65 years	0.54	0.50–0.59	<0.001
Married	1.51	1.40–1.62	<0.001
Non-Caucasian	0.78	0.71–0.86	<0.001
Hispanic	0.84	0.74–0.96	0.009
Geographic Region (Midwest)	Ref		
West	0.77	0.68–0.88	<0.001
South	1.08	0.95–1.24	0.243
Northeast	1.36	1.18–1.56	<0.001
AJCC Clinical Tumor Stage (I)	Ref		
II	1.95	1.76–2.16	<0.001
III	0.19	0.16–0.21	<0.001
Tumor Location (Body/Tail)	Ref		
Head	1.15	1.06–1.25	0.001
Tumor Grade (Low)	Ref		
High	0.84	0.77–0.91	<0.001

[a] Patients with non-metastatic disease only.

Table 4
Independent predictors for survival.

Variables	Hazard Ratio	Confidence Interval	*P*
Era B	0.88	0.86–0.90	<0.001
Age ≥65 years	1.36	1.34–1.39	<0.001
Married	0.83	0.81–0.84	<0.001
Non-Caucasian	1.04	1.01–1.06	0.003
Geographic Region (Midwest)	Ref		
West	0.96	0.93–0.99	0.009
South	1.07	1.04–1.11	<0.001
Northeast	0.87	0.84–0.90	<0.001
AJCC Clinical Tumor Stage (I)	Ref		
II	1.18	1.14–1.23	<0.001
III	1.08	1.03–1.13	0.002
IV	1.98	1.90–2.06	<0.001
Tumor Location (Body/Tail)	Ref		
Head	0.95	0.93–0.97	<0.001
Tumor Grade (Low)	Ref		
High	1.31	1.27–1.36	<0.001
Resection	0.41	0.40–0.43	<0.001

compared to Era A, a significant higher proportion of patients diagnosed in Era B had some form of health insurance coverage (95.3% vs. 51.4%). We found advanced age and female gender to have an inverse relationship with the likelihood of metastatic disease, a trend previously described by Jacobson and Kamisawa et al.[17,18] On the other hand, non-Caucasian racial groups and a lack of insurance were associated with an increased the risk of metastatic pancreatic cancer at diagnosis which confirmed findings from historic studies.[19,20] There is a need for further research into determinants of prevailing disparities in access to care for pancreatic cancer, with a view to identifying strategies that will mitigate them.

Utilization of resection

Despite being endorsed as standard of care for resectable pancreatic adenocarcinoma, pancreatectomy remains underutilized for this purpose.[3–5] Concurrent with reports from previous studies, we found that only a third of patients with non-metastatic pancreatic cancer undergo curative resection. Despite historic studies demonstrating superior outcomes with acceptable perioperative mortality risk following pancreatectomy at high volume centers,[21–23] a substantial proportion of physicians tend to underestimate the survival benefit of surgical resection, while overestimating the morbidity and mortality associated with these procedures.[24] Adjusted for confounding factors, we found a 12% increase in the likelihood of pancreatectomy for non-metastatic pancreatic cancer (Stage I – III) in Era B, a trend that may be explained by the corresponding decrease in the incidence of metastatic pancreas cancer at diagnosis which makes more patients potential candidates for resection. Furthermore, vascular reconstructions are being performed more frequently on highly selected patients with borderline tumors who previously were not considered candidates for resection.[25] These results are similar to those described in a recent retrospective study that observed a 16% increase in the utilization of cancer-directed surgery over the span of 15 years.[12] Elderly, non-Caucasian, and Hispanic patients were independently less likely to undergo pancreatectomy, which was concurrent with results from previous studies.[17,20]

Overall survival

We found an independent association between era of diagnosis and survival, as patients diagnosed in Era B demonstrated significantly improved long-term survival. Furthermore, this association was independent of resection status and the presence of metastatic disease. These results are indicative of advances in the care of patients with pancreatic cancer, irrespective of course of therapy or tumor stage. The safety of pancreatectomy for resectable pancreatic cancer has previously been reported.[21–23] Despite survival outcomes being generally poor, some studies have described improved survival for pancreatic cancer following pancreatectomy in selected patients.[12–14] Furthermore, there has been a trend towards the regionalization of care for patients with pancreatic cancer, as several studies have demonstrated improved outcomes for patients treated at high volume centers.[26,27] For patients who are not candidates for resection, the efficacy of chemotherapeutic agents for advanced disease have been reported in recent trials.[6,7] Concurrent with reports from other studies, elderly and non-Caucasian patients were independently more likely to have poor survival outcomes.[28,29] Furthermore, geographic disparities persist in the stage of presentation, utilization of resection and survival for pancreatic adenocarcinoma (Tables 2–4). We found that although patients from the southern region of the US tend to present with early, non-metastatic pancreatic cancer, they are relatively more likely to suffer poor survival outcomes.

Limitations

The results of this study must be interpreted within the context of its limitations. Firstly, this was a retrospective cohort study and so would be liable to some selection bias. We used multivariable analysis to control for potential confounders when elucidating associations, but there remains the risk of residual confounding. Secondly, we did not have access to data on baseline comorbidities which strongly influences treatment decision making as relatively healthier patients are more likely to undergo cancer-directed therapies for pancreatic adenocarcinoma. Similarly, due to inaccuracies with data reporting for non-surgical cancer therapies, the SEER database does not capture data on chemotherapy and radiation therapy utilization, which both influence survival outcomes. Hence, we could not perform risk-adjustment for these variables. Lastly, the SEER program collects data from population based cancer registries covering approximately 28% of the US population, and so the results from this study may not be generalizable to the entire US population.[11] Despite the noted limitations, this study provides a unique perspective on the prevailing trends in the clinical presentation, treatment, and survival for pancreatic adenocarcinoma.

Conclusion

There have been significant improvements in pancreatic cancer care over the last decade, as evidenced by earlier clinical stage at diagnosis, increased utilization of surgery, and improvement in overall survival, irrespective of resection status or the presence of metastatic disease. However, survival outcomes remain poor and notable disparities in access to care and outcomes persist based on sociodemographic characteristics. Elderly and non-Caucasian populations continue to be undertreated and demonstrate worse long term survival. There is a need to bridge existing disparities in access to pancreatic cancer care, while intensifying efforts at early diagnosis and treatment to optimize outcomes.

Conflicts of interest

The authors' have no disclosures.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amjsurg.2018.05.017.

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