Impact of Regional and Racial Variation in Extent of Lymph Node Dissection on Survival in Pancreatic Adenocarcinoma: A SEER Database Analysis

By

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CERTIFICATE OF APPROVAL

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Fig 7. Kaplan - Meier plot showing survival differences in node negative patients with pancreatic adenocarcinoma who had <12 or ≥12 lymph nodes examined among SEER 9 regions. The median survival for inadequately LNs assessed was highest for Seattle region with 21 months (95%CI: 17.31,24.69), whereas Metropolitan Atlanta and Detroit ranked lowest with 13months(95%CI: 10.24,15.75) and 15months (95%CI: 11.02,18.97) respectively. Overall survival differences between the SEER 9 regions were not significant in node negative patients (Log Rank test, p=0.360).

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Abstract

Background: The survival patterns of patients with pancreatic adenocarcinoma appear to vary between geographical regions and among people of color. A few studies have reported that variations in adequate lymph node assessment (ALNA) across regions have led to poorer survival for several cancers including pancreatic cancer. To date, no study has systematically investigated the variation in the extent of lymph node dissection and impact on overall survival by race and geographic regions in patients with pancreatic adenocarcinoma.

Methods: Using the SEER 9 registry database, we selected 3106 patients who had undergone surgical resection for pancreatic adenocarcinoma between 1988 and 2005. We assessed whether the absolute number of lymph nodes resected and the ratio of positive lymph nodes to resected lymph nodes (LNR) differed by race, or geographic regions. In addition, a Cox proportional hazards model was used to estimate hazard ratio (HR) and compare overall survival.

Results: In the entire cohort, 68% of patients had fewer than 12 lymph nodes resected, and the median number of nodes examined was 8 (range 1-90). Patients without lymph node metastases (node negative) were stratified as adequately assessed (<12 lymph nodes) and inadequately assessed (≥12 lymph nodes) based on the number of nodes resected. In node negative patients, there were no significant differences in adequate lymph node assessment or overall survival between race groups. However, in patients with nodal metastases (node positive), racial variation in extent of lymph node resection was marked (Chi square test, p=0.003). For patients with LNR 0.2-0.4 and LNR >0.4, the median survival significantly varied between White, African American and Asian/Pacific Islander (Log-Rank test, p<0.01). African Americans with LNR >0.4 had significantly worse median survival (5 months, 95%CI: 3.59,6.4) compared to the median survival of Whites (10 months, 95%CI: 8.96,11.0; Log- Rank test, p =<0.001), and Asian/Pacific islanders (12 months, 95% CI: 9.10, 14.90; Log- Rank test, p=0.003) who had LNR>0.4. There were no significant survival differences between Whites and Asian/Pacific Islanders in any LNR groups. In the adjusted Cox proportional model, race was a significant prognostic factor of overall survival with African Americans men having worse survival (HR=1.33;CI: 1.03,1.73) compared to White women. Overall, there were significant differences in average number of lymph nodes resected between the SEER 9 regions (ANOVA, p<0.001). All of the regions had a majority of node negative patients who had inadequate lymph node assessment, which ranged from 82.7% (Iowa) to 63.6% (Hawaii) (Chi square test, p=0.002). Between the SEER 9 regions we found marked survival differences in node positive LNR groups (Log-Rank test, p<0.05) but not in node negative patients.

Conclusions: Majority of patients with pancreatic adenocarcinoma have inadequate lymph node assessment in the United States, which may suggest understaging and under treatment for many patients. Our findings clearly demonstrated racial variation in node positive patients and regional variation in node negative patients with regard to extent of lymph node dissection. African Americans experienced worse survival compared to Whites and Asian/Pacific Islanders. Race and adequate lymph node assessment remained as strong prognostic factors of survival even after adjusting for competing risk factors.

Research Question and Specific Aims

Title

Impact of Regional and Racial Variation in Extent of Lymph Node Dissection on Survival in Pancreatic Adenocarcinoma: A SEER Database Analysis

Research question: For patients who have undergone resection for pancreatic adenocarcinoma, is there variation in the extent of lymph node dissection by race or by geographic region, and does this impact overall survival?

Specific Aims: Using the Nov 2007 release Surveillance, Epidemiology, and End Results (SEER) database, the following main objectives were accomplished:

1. Examined the variation in the absolute number of resected lymph nodes and the ratio of positive lymph nodes to resected lymph nodes (LNR) by race in patients who have undergone resection for pancreatic adenocarcinoma.

2. Assessed the variation in the absolute number of resected lymph nodes, and the positive lymph node ratio (LNR) in patients with resected pancreatic adenocarcinoma by geographic region (SEER 9 regions).

3. Using the Kaplan-Meier estimates, and a multivariate Cox proportional hazards model, assessed the impact of variation in the extent of lymph node dissection among our study subjects of diverse racial backgrounds and between the SEER regions on overall survival.

Background

The Burden of Pancreatic Cancer

Pancreatic cancer is the fourth leading cause of cancer-related deaths among both men and women in the United States, and accounts for about 5 percent of total cancer related deaths.[1] In 2008, an estimated 37,680 new cases and 34,290 new deaths from pancreatic cancer were reported.[2] As seen with other diseases, variations are commonly observed in the incidence of pancreatic cancer among people of different races. Incidence rates for men among Whites, African Americans, Asian/Pacific Islanders, American Indians and Hispanics are 13, 16.2, 10.1, 10.9, and 10.9 per 100,000 men respectively.[2] And for women the incidence rates among Whites, African Americans, Asian Pacific Islanders, American Indians and Hispanics are 10, 14.3, 8.2, 8.2, and 10.3 per 100,000 women respectively.[2] Among all pancreatic cancers, pancreatic adenocarcinoma arising from cells of the pancreatic ducts is the most common.

In general, pancreatic cancer has a very poor prognosis compared to most other cancers and has a high rate of mortality with a 5- year relative survival rate for adenocarcinoma of only about 5% (range 4-10%). [3-6] Among node positive patients, the median survival is reported to be around 1 year.[6-10]

The Importance of Extent of Lymph Node Dissection

It is evident from the literature that prognosis and outcome of most cancers, including adenocarcinoma of the pancreas, depends on the extent of disease spread. In addition, from a treatment perspective, it is recognized that accurate staging of cancer at the time of initial diagnosis or recurrence is key to choosing appropriate, stage-specific treatment options, which affect ultimate prognosis and outcome.[11]

Presently, there still exists controversies across the nation over the current standards of cancer staging; physicians often argue over optimal guidelines to accommodate tumor micometastases.[12] Regardless of these debates, most experts have universally agreed that lymph node status and extent of lymph node resection play a significant role in prognosis and overall survival of pancreatic adenocarcinoma. Based on this rationale, several recent studies have demonstrated that in many cancers including pancreatic adenocarcinoma, the absolute number of lymph nodes resected and the ratio of metastatic to examined nodes (LNR) are significant predictors of cancer outcome. [6 8 9 13-16] Pawlik et al. and Slidell et al. illustrate the advantages of LNR over absolute count in node positive patients with pancreatic adenocarcinoma, indicating that LNR not only accounts for positive nodes (extent of disease spread) but also considers the adequacy of node resection and is not influenced by 'stage migration'.[6 9] A few recent studies have noted that LNR based grouping may be more useful for prognostic comparisons in clinical trials and favorable over the 1997 UICC/AJCC classification for gastric cancer.[6 9 17]

More specifically, many of the recent studies have also shown that the absolute count of positive lymph nodes and LNR are significantly associated with 5-year and 10-year survival rates among patients who had undergone resection for pancreatic adenocarcinoma.[6 8 9 13 16]

Race and the Lymph Node Assessment

Over the years, the existence of health disparities among minorities has been widely demonstrated through extensive research, especially regarding cancer. It is evident in the literature that cancer is the number one killer among minorities, in contrast to heart disease among Whites. The same trend is observed in the incidence and death rates of pancreatic adenocarcinoma for patients of various racial/ethnic backgrounds.

African Americans with pancreatic adenocarcinoma have higher disease incidence and mortality, and significantly lower survival rates compared to all other races, and especially for patients between 55-69 years of age, where incidence rates are about 60 percent higher than the rates for Whites.[18-22]

Several factors may contribute to these differences including diagnosis at an advanced stage, location of the tumor in body and tail of pancreas (which is least approachable for curative resection), aggressiveness of tumor, and potential differences in physicians' practice of staging and treatment for diverse racial groups. [23] In a study conducted by Chang et al. it was observed that African Americans with pancreatic adenocarcinoma were the least likely to receive surgical treatment regardless of stage of disease or the tumor location compared to all other races, despite having access to heath insurance.[23] Similar results were obtained in another study of patients with pancreatic adenocarcinoma, which reported lower rates of resection for African Americans and other non-Whites, and significantly decreased overall survival (HR 1.107,95% CI 1.072-1.143) adjusted for demographic characteristics and tumor stage. However, after further adjusting for the variables socioeconomic status and adjuvant therapy the differences were no longer significant. [20] In addition, although African Americans are more prone to worse outcomes, they are the least likely to receive, and often tend to refuse, radiotherapy or chemotherapy.[15 20 24]

The incidence rate of pancreatic adenocarcinoma seems to remain uniform among other races except African Americans, but the treatment outcomes still tend to vary regardless of similarity in access to health care. One possible explanation for this disparity is possible differences in staging of cancer for people of color especially regarding variations in the extent of lymph node assessment. One study reported that the odds of adequate lymph node assessment (ALNA) for patients of Japanese and other Asian ethnic backgrounds were 1.48-1.80 when compared with White people. [25]

The pattern of disease occurrence, tumor location and spread, aggressiveness of tumor and severity of prognosis vary between races, for reasons that are not understood clearly. [25 26] Presently, there is no specific training and staging or treatment guidelines for physicians treating patients with diverse backgrounds. This lack of specific guidance may have lead to the varied trends of cancer staging, lymph node assessment and treatments between different races ultimately contributing to the overall discrepancies in pancreatic adenocarcinoma outcomes.

Although pancreatic cancer is deadly and studies have shown poor outcomes among patients with diverse backgrounds, there is little existing research attempting to understand the underlying causes. To date, there is no study assessing the differences in physicians' practices of the extent of lymph node resection among patients of different racial backgrounds having undergone resection for pancreatic adenocarcinoma and its impact on overall cancer survival.

Regional Variation in Extent of Lymph Node Resection

There seem to be differences in physicians' patterns of the extent of lymph node resection across various geographical regions among both node positive and node negative patients with some cancers. In a large population-based study using the SEER database, Baxter and Tuttle reported that geographical region is a significant predictor of adequate lymph node assessment and the odds of undergoing adequate lymph node assessment (ALNA) was significantly ($p<0.001$) different for patients with gastric cancer registered in one SEER registry (Hawaii) compared to patients registered in all other registries (56% vs. 30%). [27] Similar results were obtained in another study, where the rate of ALNA was three times higher in SEER region 1(best) as compared to SEER 9 region(worst).[25] In a recent study among patients with pancreatic cancer using SEER database, there was a difference of 81% (95% CI, 50.0-118.3%,) between the regions with the highest and the lowest lymph node count leading to understaging and under treatment among node negative subjects.[28] Coburn et al. demonstrated current level of poor compliance with current American Joint Committee on Cancer (AJCC) /UICC staging guidelines by examining adequate lymph node assessment between the years before and after the publications of fifth edition staging guidelines in patients with gastric cancer.[25]

This wide discrepancy may indirectly reflect the existing differences in the quality of care or the level of experience and expertise of surgeons and pathologists treating these patients undergoing resection for pancreatic cancer. Apart from this several other factors such as local institutional staging guidelines, regional health care, and insurance policies may contribute to varied lymph node examination across geographic regions.

Importantly, some of these studies reported that the odds of survival among patients in regions with better lymph node assessment were significantly higher as compared to regions with poor assessment. Thus, these regional variations raise questions about the current standards and the effectiveness of Tumor Node Metastases (TNM) and American Joint Committee on Cancer (AJCC) classification to maintain uniform standards for cancer staging across the nation, and regarding health care providers compliance with these staging guidelines. To date, no study has examined the variation in the absolute number of resected lymph nodes, and the lymph node ratio (LNR) by geographic region and its impact on overall survival among patients with pancreatic adenocarcinoma.

Adequate lymph node resection among patients of all races and across geographic regions may successfully lead to better treatment outcomes at all stages of pancreatic cancer. After recognizing existing controversies and deficiencies in identifying prognostic factors for pancreatic adenocarcinoma, the main objectives of this study were to assess the variation in the absolute number of resected lymph nodes, and the ratio of positive lymph nodes to resected lymph nodes (LNR) by race and geographic region. In addition we evaluated the impact of these variations on overall survival.

Methods

Overview of the SEER Database

For this particular cross- sectional study design we used an existing large database named SEER (Surveillance, Epidemiology and End Results). The SEER database, renowned as an authoritative data source for designing cross- sectional studies, provided us with a large sample size, reliable data source and diverse study sample covering most regions of the United States.

The SEER registry appropriately simulates national diversity with its well-planned region selection. Presently, about 23 percent of African Americans, 40 percent of Hispanics, 42 percent of American Indians and Alaska Natives, 53 percent of Asians, and 70 percent of Hawaiian/Pacific Islanders are represented in the SEER registries.[29] The National Cancer Institute and the National American Association of Central Cancer Registries work together to maintain high quality and content of national data through providing strict guidelines to all the state registries.[29]

Study Data Collection Method

For this study, data was obtained from the National Cancer Institute's Nov 2007 release SEER 9 registries database, which contains patients registered in the SEER database between 1973 and 2005. The entire sample of patients diagnosed and registered in the SEER 9 registry, who had undergone either a simple pancreatectomy or any extensive surgery for pancreatic adenocarcinoma between 1988 and 2005 were selected. As the SEER coding system on diagnosis and treatments was not available until 1988, our study cohort included only those patients who were diagnosed after the year 1988.[6]

The SEER 2007 program coding and staging manual was referred to in order to identify cancer site codes as well as surgery codes.[30] Initially, patients were selected based on the SEER registry pancreatic cancer site codes (C 25.0, C 25.1-25.2, C 25.3-25.4, C 25.7-25.9,). Patients with histologically diagnosed adenocarcinoma were identified using ICD-O-3 histology type codes defined by the third edition of International Classification of Diseases for Oncology and the SEER manual (refer to Fig 1). Then for cases diagnosed from 1988 to 1997 SEER variable "RX Summary-Surgery Type", for cases from 1998-2002 SEER variable 'RX Summary-Surgery Site", and finally for patients diagnosed from 2003 onwards the variable named "RX Summary-Surgery Primary Site" was used to identify only those subjects who had undergone surgery that includes either simple local excision or any radical surgery for pancreatic adenocarcinoma. All subjects were excluded if they were under 18 years of age or if the histological diagnosis, surgery performed or lymph nodes examined were noted as unknown in the SEER registry.

Description of Variables

The following variables were selected from the SEER database for analysis: patient demographics such as patient ID, age at diagnosis (18-60 years, 61-80, >81years), race, gender, marital status, SEER regions, and tumor characteristics including tumor size (≤ 2 cm, > 2 cm and Not stated), tumor grade, SEER tumor staging, lymph nodes examined, positive lymph nodes, type of surgery and history of radiation use.
Based on the SEER program race recoding method, data was classified in to White, African American and Asian/Pacific Islander. Asian/Pacific Islander category includes

Chinese, Japanese, Hawaiian, Korean, Asian Indian, Pakistani, Vietnamese, Thai, Micronesian, Chamorran, Melanesian, Tahitian, Samoan Tongan, New Guinean Other Asian and Pacific Islander Laotian, Hmong, Kampuchean, Asian NOS (Not Otherwise Specified), and Pacific Islander. There were only 12 cases in American Indian/Alaska category and 5 subjects in others/ unknown category so we reclassified these race codes into Asian and Pacific Islander groups.

The SEER 9 registries database was chosen as it contains complete information on cases diagnosed from 1973 through 2005, whereas, data from the other registries (SEER 13 and 17) are only available from 1992 onwards. Additionally, the 9 regions chosen for our study are widely distributed across the nation so we had the ability to prevent the potential bias such as similarities in diagnosis and treatment methods of pancreatic cancer among the neighboring regions. Also, the patients registered in SEER registries represent 26% of the total US population, including major proportions of minorities in the United States.[29] The 9 SEER regions are Metropolitan Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah.

The primary outcome variables were the absolute number of lymph nodes examined and the lymph node ratio (LNR). The LNR was calculated by dividing the absolute number of positive lymph nodes by the total number of resected nodes. Then patients were divided in to four groups based on the LNR. The criteria used for LNR categorization was as follows: for patients without Lymph node metastases LNR = 0, for patients with nodal metastases- Lymph Node Ratio (LNR) >0-0.2 as LNR 1, LNR >0.2-0.4 as LNR 2, LNR >0.4 as LNR 3. In addition, node-negative patients were categorized based on the number of lymph nodes resected as: <12 nodes resected as Not adequately assessed (or Inadequately assessed) and ≥12 nodes resected as Adequately assessed. We performed descriptive analysis and also reviewed several previous studies to determine the cutoff values for categorization of node positive and node negative groups. Secondary outcome variable overall survival was measured in months.

Statistical Analysis

The initial analysis included descriptive statistics and graphs to understand distribution and characteristics of our study sample. While comparing between groups, Student t test was used for continuous variables, whereas chi-square tests for categorical variables.

In our Univariate Cox proportional analysis those covariates (Appendix A) that achieved the level of significance $p \leq 0.20$ were entered in to the multivariable Cox proportional hazards model. At this step, using the p-values from the Wald test and the p-value of the partial likelihood ratio test, we identified covariates that were not significant, and removed them from the model one at a time.

Once we had the main effects model, possible effect modifiers were identified by adding interaction terms one at a time to the model and tested for their significance using the p-value of the partial likelihood ratio test. In the next step, all the selected interaction terms were entered along with the main effects, and interaction terms that were insignificant were removed individually from the model. Significant effect modifiers were noted, and considering their clinical relevance, measures of effect estimates were presented in our final report. Thus, the Cox proportional hazards model was built, and controlled for the confounders and the effect modifiers manually using the purposeful selection of covariates and backward elimination method in accordance with David W. Hosmer, Stanley Lemeshow, and Susanne May's model building techniques.[31]

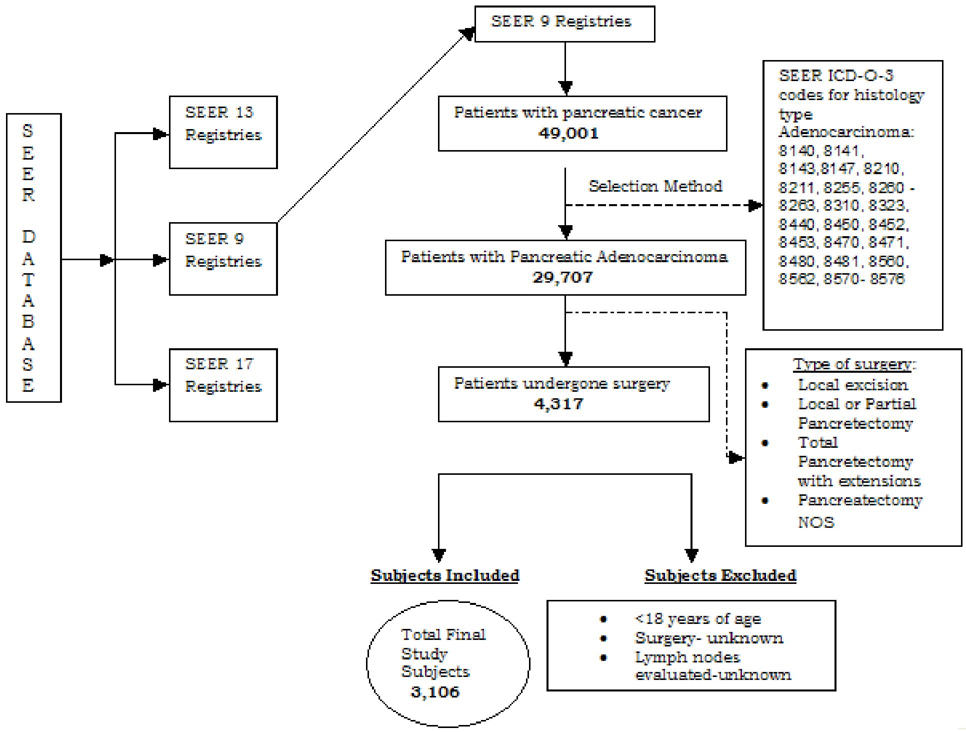
Proportional hazard assumptions were checked using the survival plots and survival probability plots. Using residual and diagnostic plots we identified influential observations. Finally, we assessed the final model for adequacy and for its fit. From the final Cox model, 95% CI and the Hazards ratio were estimated. The Kaplan- Meier analysis, and the log rank test were employed between group comparisons and to estimate median survival.

The statistical package Microsoft Access was used for the initial SEER data extraction and SPSS version. 19.0 (SPSS Inc, Chicago, IL) were used for all the statistical analyses. All the statistical tests were two sided, and a p value of <0.05 was considered significant. Missing values were assigned as such.

Results

Initially, we identified 49,001 patients with pancreatic cancer that were diagnosed between 1988-2005 using the pancreatic cancer site codes (C 25.0- C 25.9). Then using the SEER ICD-O-3 histology type codes, 29,707 patients with pancreatic adenocarcinoma were selected (Fig.1). In the next step we selected 4,317 patients who had undergone surgery that included either simple local excision of tumor or any radical surgery for pancreatic adenocarcinoma. The number of lymph nodes examined was recorded as unknown or incomplete for 1211 patients, these patients were excluded from the final study cohort. Finally, after excluding the patients under 18 years of age or in cases where the histological diagnosis, surgery performed or lymph nodes examined were noted as unknown or incomplete in the SEER registry, our final study sample contained 3,106 patients (Fig.1).

Fig 1. Flowchart indicating steps involved in data extraction from the SEER database, and the study selection criteria used for inclusion and exclusion of patients with pancreatic adenocarcinoma.



Demographic and Clinical Characteristics

The demographic and clinical characteristics of final study subjects (n=3106) are summarized in the Table.2. The final data contained 1592 (51.3%) men and 1514(48.7%) women. There were 1970(63.4%) subjects between the ages of 61 to 80, whereas 979(31.5%) were under 60 years old, and the median age was 66 years (range 18-96). The highest percentage of patients were White (n = 2557, 82.3%); 338(10.9%) were African Americans and 211(6.8%) were Asian /Pacific Islanders. We had 310 subjects that were single (never married), 2026 (65.2%) were married and 770 (24.8%) were classified as “others”. The metropolitan Detroit region had the highest number of patients registered (n = 612, 19.7%), Connecticut (n =535, 17.2%) and San Francisco (n= 477, 15.4%) had relatively high numbers of patients, and Hawaii (n= 139, 4.5%) had the least number of patients registered.

The median tumor size was 3.7cm (0.01-90.0 cm), and 1765 (56.8%) had tumor size more than 2 cm. About half of the tumors were graded as moderately differentiated (n= 1405,45.2%) and poorly differentiated (n= 1338, 43.1%). When staging was assessed, most of the tumors (n= 2286, 73.6%) were in "regional extension" category, 493(15.9%) tumors were localized and only 327(10.5%) had distant metastases. The majority of the subjects (n = 2306, 74.2%) had partial pancreatectomy/Other pancreatectomy, 550(17.7%) had total pancretectomy. More than half of the patients (n = 1804, 58.1%) did not receive adjuvant radiotherapy.

Table 1. Demographic and tumor characteristics of patients who had undergone resectomy for pancreatic Adenocarcinoma

Characteristics	Number of Patients (N = 3106)	Percent (%)
Age		
18-60 years old	979	31.5
61-80 years old	1970	63.4
>80 years old	157	5.1
Med 66 y (18-96 y)		
Gender		
Male	1592	51.3
Female	1514	48.7
Race		
White	2557	82.3
African American	338	10.9
Asian /Pacific Islanders	211	6.8
Marital Status		
Single (never married)	310	10
Married	2026	65.2
Others	770	24.8
SEER Regions		
Hawaii	139	4.5
Connecticut	535	17.2
Utah	176	5.7
New Mexico	178	5.7
Metropolitan Detroit	612	19.7
Metropolitan Atlanta	292	9.4
Seattle (Puget Sound)	342	11
San Francisco-Oakland SMSA	477	15.4

Iowa	355	11.4
SEER Tumor Staging		
In situ/ Localized	493	15.9
Regional Extension	2286	73.6
Distant Spread	327	10.5
Tumor Size		
≤ 2 cm	425	13.7
> 2 cm	1765	56.8
Not stated	411	13.2
Missing value	505	16.3
Tumor Grade		
Well differentiated	363	11.7
Moderately differentiated	1405	45.2
Poorly differentiated	1338	43.1
Type of Surgery		
Local excision of tumor	117	3.8
Partial pancretectomy/Other Pancretectomy	2306	74.2
Total Pancretectomy	550	17.7
Pancretectomy NOS	133	4.3
Adjuvant Radiation Therapy		
Radiation Received	1302	41.9
Not Received	1804	58.1
Lymph Node status		
Lymph Nodes Positive	1785	57.3
Lymph Nodes Negative	1321	42.7
Lymph Node Ratio (LNR)		
LNR0	1321	42.5
LNR1 (>0-0.2)	750	24.1
LNR2 (>0.2- 0.4)	464	14.9
LNR3 (>0.4)	571	18.4
LNs Adequately Assessed		
Adequately Assessed (≥ 12 LNs)	993	32
Not Adequately Assessed (<12 LNs)	2113	68

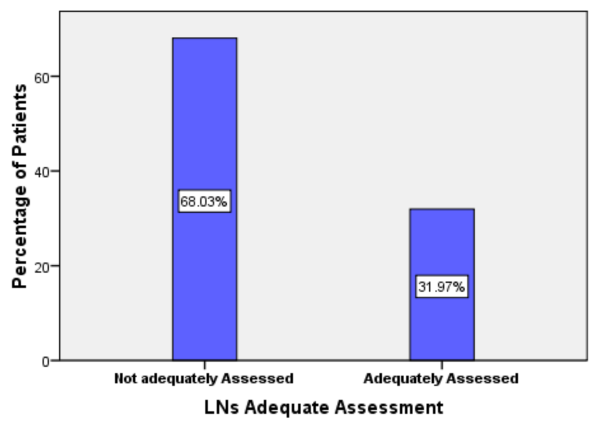
Lymph Node Assessment

Overall, the median number of lymph nodes examined after pancreatic resection were 8 (range 1-90). In maximum number of patients (n = 2113, 68%) lymph nodes were not adequately evaluated (Fig.2). Out of 3106 total study subjects, more than half (n =

1785, 57.3%) had positive lymph nodes and 1321 (42.7%) did not have lymph node metastases.

There were significant differences between the average number of nodes evaluated between node positive patients (11.06; 95%CI: 10.65,11.47) and node negative patients (8.21; 95%CI: 7.84,8.59) (Independent- Samples T Test, p<0.001). Overall, the median survival for the node negative patients (19 months, 95% CI: 17.36,20.64) was significantly higher compared to the median survival (12 months, 95%CI: 11.3,12.73) for the node positive patients (Log- Rank test, p<0.001).

Fig 2. Percentage of patients with pancreatic adenocarcinoma who had an adequate (≥12 lymph nodes examined) and inadequate lymph node assessment in the entire study cohort.



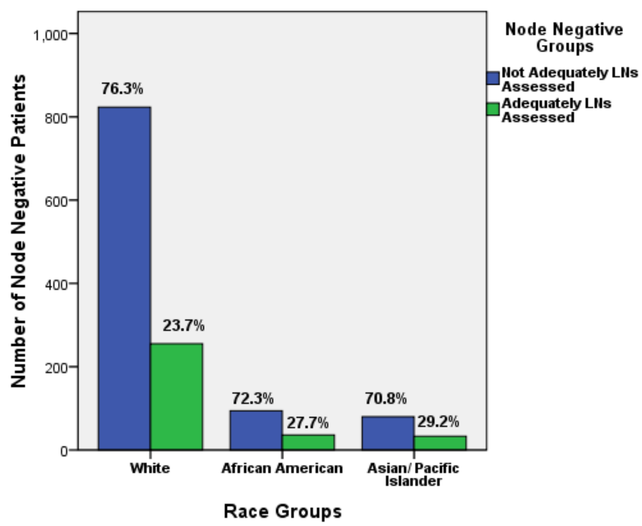
Assessment of Racial Variation

The median number of lymph nodes assessed was 8 (1-90) for both White and Asian/ Pacific Islander and 7(range 1-69) for the African Americans. The average number of lymph nodes examined was not significantly different between race groups (ANOVA test, p= 0.94).

Node Negative Patients

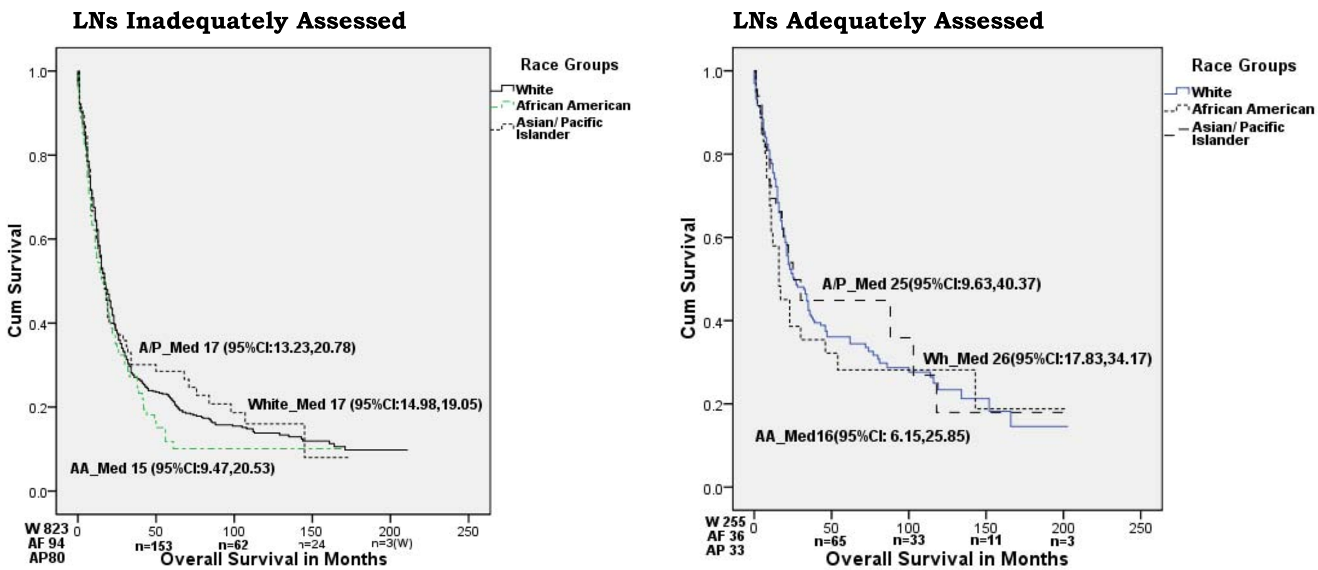
In patients without lymph node metastases, 76.3% among White, 72.3% among African Americans and 70.8% among Asian/Pacific Islanders had < 12 lymph nodes dissected (Fig.3), and there were no significant differences between race groups in respect to adequate lymph node assessment (Chi-square test, p=0.289).

Fig 3. Proportion of node negative patients with pancreatic adenocarcinoma who had adequate (≥ 12 nodes) and inadequate lymph node assessment among race groups. There were no significant differences between race groups in respect to adequate lymph node assessment (Chi-square test, p=0.289).



There were no significant survival differences between race groups (Log-Rank Test, p=0.242)(Fig 4).

Fig 4. Kaplan-Meier estimates of the survival function for node negative patient with pancreatic adenocarcinoma who had adequate and inadequate lymph node assessment among race groups. Survival differences between race groups were not significant (Log-Rank Test, P=0.242)



Node Positive Patients

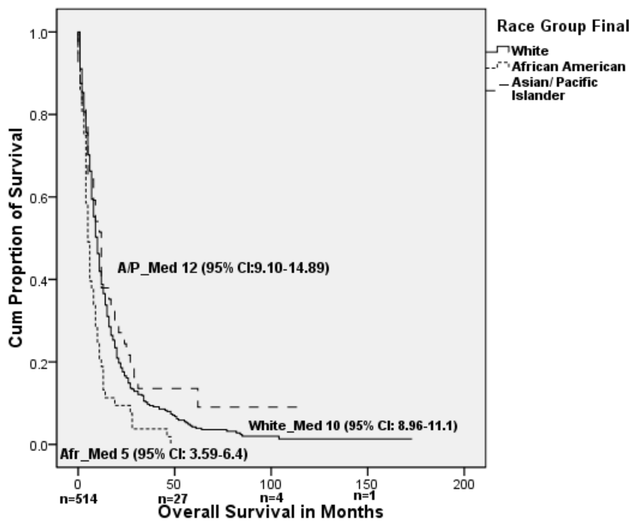
Node positive patients had a higher percentage of patients in the LNR 1 group (>0.0-0.2) compared to the other two LNR groups (LNR2 and 3) for both White and African American, but for Asian/Pacific Islanders there were a greater proportion of patients in LNR 3 group (Chi-square test, p<0.003). We observed marked differences in the distribution of patients between White, African American, and Asian/Pacific islander in the lymph node ratio groups (Chi-square test, p<0.003).

Between White, African American and Asian/Pacific Islanders we observed significant differences in survival among patients with LNR >0.2-0.4 and LNR >0.4 (Fig.5) (Log Rank test, p<0.001). The median survival for African Americans with LNR >0.2-0.4 was significantly lower compared to Whites (Log-Rank test, p= 0.004). African Americans who had LNR >0.4had significantly worse median survival (5 months, 95%CI: 3.59,6.4) compared to the median survival of Whites (10 months, 95%CI: 8.96,11.0; p<0.001) and Asian/Pacific Islanders (12 months, 95% CI: 9.10, 14.90; p=0.003) with LNR >0.4 (Fig. 5).

The classification of node positive patients based on the lymph node ratio indicated a trend of increasing LNR with decreased survival time. On univariate analysis using the Kaplan-Meier log-rank test, among White, the median survival significantly varied from 19 months for LNR 0, 16 months for LNR >0.0-0.2, 13 months for LNR >0.2-0.4, and 10 months for LNR >0.4 (Log Rank test, p<0.001). African Americans had a similar trend of worse median survival (LNR0 16 months, LNR>0.0-0.2 14 months, LNR>0.2-0.4 9 months and LNR>0.4 5 months) with progressive increase in LNR. The 1-year survival rate for subjects with the LNR 3 was 38% for White, 18.9% for African American and 37.9% for Asian/Pacific Islander.

To conclude, in node positive patients we found significant variation in the extent of lymph node resection among race groups and the median survival markedly varied between White, African American and Asian/Pacific Islanders who had LNR >0.2-0.4 and LNR >0.4.

Fig 5. Kaplan–Meier plot of survival in months for node positive patients with pancreatic adenocarcinoma who had Lymph Node Ratio > 0.4 among race groups. There were significant survival differences between race groups who had LNR>0.4 (Log Rank test, p<0.001).



Assessment of Regional Variation

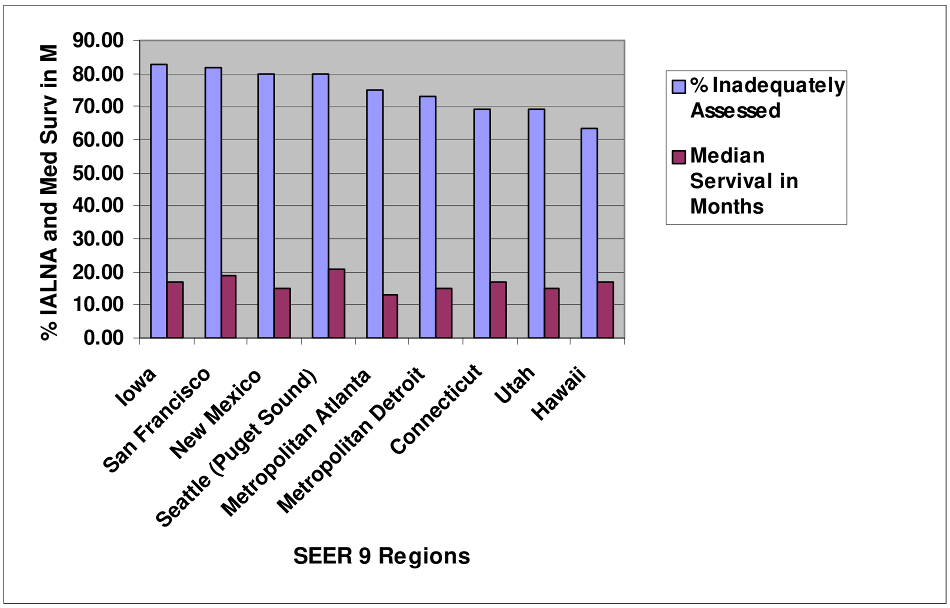
The median number of lymph nodes resected varied from 7(range 1-90) to 9 (range 1-90) between the SEER 9 regions. The mean number of lymph nodes examined among SEER 9 registries varied from 8.66 (95% CI: 7.99, 9.34) in San Francisco to 11.45 (95%CI: 9.58,13.33) nodes in Hawaii, and were significantly different between the SEER 9 regions (ANOVA, p<0.001). A majority of patients registered in most SEER regions had fewer than 12 lymph nodes examined and there was a significant variation in the adequate lymph node assessment between the SEER 9 regions (Chi-square test, p<0.001).

Overall, the median survival was the highest for patients registered in Seattle region (17 months, 95% CI: 14.6,19.4), and was worse (12 months, 95% CI: 10.3,13.7) for patients in Atlanta and Metropolitan Detroit regions.

Node Negative Patients

When compared among node negative groups, the Iowa region was the worst with 82.7% of patients having had fewer than 12 nodes dissected, and Hawaii comparatively better with 63.6% of patients having inadequate lymph node assessment (Fig. 6). Adequate lymph node assessment significantly varied between the SEER 9 regions (Chi-square test, p=0.002) among node negative patients.

Fig 6. Distribution of node negative patients with inadequate (<12 nodes evaluated) lymph node assessment in SEER 9 regions. Adequate lymph node assessment significantly varied between the SEER 9 regions (Chi-square test, p=0.002). Survival differences between regions were not significant (Log Rank test, p=0.360)

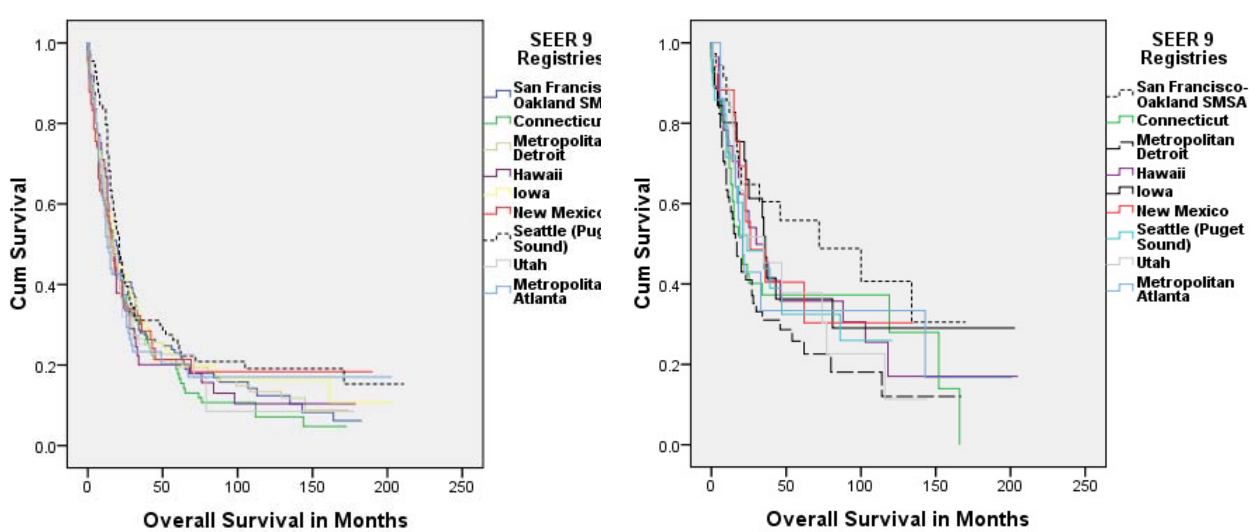


Among node negative patients who had inadequate lymph node assessment, the median survival was highest for the Seattle region with 21 months (95%CI: 17.31,24.69) and for adequately assessed the San Francisco (72 months 95% CI:0. 0,146.45) and Iowa (36 months 95% CI: 31.81,40.19) were highest. Metropolitan Atlanta and Detroit ranked lowest again with 13months(95%CI: 10.24,15.75) and 15months (95% CI: 11.02,18.97) for patients not adequately assessed and 21months (95% CI: 14.96,27.03) and 17 months (95% CI: 11.08,22.9) for adequately assessed patients respectively. The median survival for the SEER region Iowa that had the highest percentage of patients with inadequate lymph node assessment was 17 months (95%CI: 12.72,21.28) and for Hawaii, which had lowest percentage the median survival was 17 months (95%CI: 12.7,21.29).

Overall among node negative patients, there was a significant variation in adequate lymph nodes assessment between the SEER regions (Chi-square test, p=0.002). The survival differences between SEER 9 regions among node negative patients were not significant (Log Rank test, p=0.360)(Fig.7).

Fig 7. Kaplan - Meier plot showing survival differences in node negative patients with pancreatic adenocarcinoma who had <12 or ≥12 lymph nodes examined among SEER 9 regions. The median survival for inadequately LNs assessed was highest for Seattle region with 21 months (95%CI: 17.31,24.69), whereas Metropolitan Atlanta and Detroit ranked lowest with 13months(95%CI: 10.24,15.75) and 15months (95%CI: 11.02,18.97) respectively. Survival differences between the SEER 9 regions were not significant in node negative patients (Log Rank test, p=0.360).

LNs Inadequately Assessed **LNs Adequately Assessed**



Node Positive Patients

There were no significant differences between SEER regions in distribution of node positive patients in each LNR group (Chi-square test, p=0.103).

The survival differences between SEER 9 regions in each of the lymph node ratio group

were significant (Log Rank test, p<0.05). We found significant differences between the node positive patients in SEER regions who had LNR >0-0.2(Log-Rank test, p=0.02). Similarly, survival differed between patients in SEER regions who had LNR 0.2-0.4 (Log-Rank test, p=0.04). Additionally, there were significant differences between patients with LNR >0.4 in SEER regions (Log-Rank test, p=0.02).

When compared between patients with LNR>0.4, the Seattle had the highest median survival of 12 months (95% CI: 9.8,14.1) and Hawaii had the worse median survival of 7 months (95% CI: 2.0,11.9). The 5-year survival rate for patients with LNR >0.04 was 21% for San Francisco, 20% for Atlanta, 19 % for Seattle, 17% for Iowa and 13% for Hawaii.

Results of Cox Regression Analysis

On univariate analysis, factors associated with overall survival included demographic characteristics such as age, gender and race, tumor characteristics including SEER tumor staging, tumor size, grade, and treatment factors such as type of surgery, radiation therapy (all p<0.05)(Appendix A). In addition, lymph node status, adequate lymph node assessment (ALNA) and lymph node ratio (LNR) were also significant predictors of overall survival in univariate analysis (all p<0.001)(Appendix A).

Marital status was not significant in both univariate analysis and the final adjusted model. African Americans had higher death rate compared to Whites (HR = 1.26; 95%

CI: 1.12-1.43). Though the variable SEER 9 regions was not significant in univariate tests we decided to include it in the final model to assess hazard estimates for each region. As anticipated, in the univariate analysis tumor staging was significantly associated with overall survival and the death rate among patients with distant metastases was worse (HR =3.97; 95% CI: 3.36-4.68; p <0.001) compared to patients with in situ/localized tumors. Patients with lymph node metastases had 65% higher risk of death (HR = 1.65; 95% CI: 1.52-1.79; p<0.001) compared to node negative patients. Patients who had adequate lymph node assessment had 18% lower risk of death (HR =0.82; 95%CI: 0.75,0.89) as compared to inadequately assessed subjects.

To adjust for known confounders, a multivariate Cox regression model was developed, and in the final adjusted model gender, age, race, type of surgery, tumor staging, tumor size and grade, radiation therapy, adequate lymph node assessment and LNR remained as important prognostic factors of overall survival (Table.4)

There were significant differences in overall survival between race groups. After adjusting for other factors, African Americans had worse rate of death (HR=1. 35; 95% CI: 1.12,1.63) compared to White, especially African American men had 33 percent higher risk (HR=1.33;CI: 1.03,1.73)) compared to White women. In the final adjusted Cox proportional model, SEER 9 region was not significant, however, rate of death still varied between regions. Age was significantly associated with overall survival, patients more than 60 years old were dying at a significantly higher rate compared to younger patients. As observed in other previous studies, patients with an adequate lymph node assessment were dying at a rate 17 percent lower (HR= 0.83; 95%CI: 0.75,0.91) than subjects who were inadequately assessed in the adjusted model.

As anticipated, patients with more than 2 cm tumor size (HR =1.52; 95% CI; 1.29,1.78) and Not staged groups (HR =1.36; 95% CI: 1.16,1.58), moderately-differentiated tumors

(HR =1.45; 95% CI; 1.26,1.67) and poorly- differentiated tumors (HR =1.62; 95% CI; 1.41,1.86) had significantly worse rates of death. In patients where disease had spread to regional nodes but who had not received radiation therapy, these subjects had lower survival (HR=1.77; 95%CI: 1.34,2.33) compared to patients with in situ/localized tumors and had received radiation treatment. Similarly, patients who had total pancretectomy but had not received radiation therapy had twice the HR of death ((HR= 1.8; 95%CI: 1.12,2.91) compared to patients who received the therapy and had only local excision of tumor. Women who received pancreatectomy (NOS) were dying at a rate twice (HR= 2.07; 95%CI: 1.19,3.58) than that of men who had local excision of tumor. Surprisingly, after controlling for all other factors, patients with lymph node ratio of >0-0.2 and 0.2-0.4 in Connecticut were dying at a rate 50% lower than patients without lymph node metastases (LNR 0) in Hawaii.

Table 2. Factors associated with overall survival in an adjusted Multivariate Cox proportional hazards model for patients who had undergone resectomy for pancreatic adenocarcinoma.

Predictors	Referent	Hazard Ratio (95% CI)	p-Value
Age			
61-80 years old	18-60 years old	**1.26 (1.15,1.38)**	**<0.001**
>81 years old		**1.22 (0.99,1.50)**	**<0.067**
Gender			
Female	Male	**0.77 (0.52,1.16)**	**0.210**
Race			
African American	White	**1.35 (1.12,1.63)**	**0.002**
Asian /Pacific Islanders		**1.20 (0.90,1.60)**	**0.212**
Geographical regions			
Connecticut	Hawaii	**1.09 (0.77,1.53)**	**0.626**
Utah		**1.22 (0.81,1.83)**	**0.336**
New Mexico		**0.94 (0.62,1.41)**	**0.744**
Metropolitan Detroit		**1.22 (0.87,1.71)**	**0.246**
Metropolitan Atlanta		**1.07 (0.73,1.56)**	**0.731**
Seattle (Puget Sound)		**0.91 (0.63,1.30)**	**0.588**
San Francisco-Oakland SMSA		**1.08 (0.77,1.52)**	**0.641**
Iowa		**0.97 (0.68,1.40)**	**0.882**
SEER tumor Staging			
Regional Extension	In situ/ Localized	**1.20 (0.95,1.52)**	**0.125**
Distant Spread		**2.04 (1.47,2.85)**	**<0.001**
Tumor Size			
>2 cm	≤ 2 cm	**1.27 (1.12,1.43)**	**<0.001**
Not stated		**1.36 (1.16,1.58)**	**<0.001**
Grade			
Moderately differentiated	Well differentiated	**1.45 (1.26,1.67)**	**<0.001**
Poorly differentiated		**1.62 (1.41,1.86)**	**<0.001**
Type of surgery			
Partial pancretectomy/Other Pancretectomy	Local excision of tumor	**0.51 (0.35,0.75)**	**0.001**
Total Pancretectomy		**0.45 (0.29,0.68)**	**<0.001**
Pancretectomy NOS		**0.67 (0.40,1.13)**	**0.135**
Adjuvant Radiation			
Not Received	Radiation Received	**0.58 (0.35,0.94)**	**0.028**
Lymph node Ratio (LNR)			
LNR1 (>0-0.2)		**2.04 (1.19,3.48)**	**0.009**
LNR2 (>0.2- 0.4)	LNR0	**2.17 (1.25,3.78)**	**0.006**
LNR3 (>0.4)		**1.44 (0.78,2.67)**	**0.242**
LN Adequately Assessed			
Adequately Assessed (≥ 12 LNs**)**	Not Adequately Assessed (<12 LNs)	**0.83 (0.75,0.91)**	**<0.001**

Table 2. Factors associated with overall survival in an adjusted Multivariate Cox proportional hazards model (contd.)

Predictors (Interaction Terms)	Referent	Hazard Ratio (95% CI)	p-Value
Race*Gender			
African American*Female	White*Male	**0.75 (0.58, 0.98)**	**0.032**
Asian /Pacific Islanders*Female		**0.71 (0.50,1.00)**	**0.054**
Gender*Type of Surgery			
Female*Partial pancretectomy/Other Pancretectomy	Male* Local excision of tumor	**1.22 (0.79,1.86)**	**0.371**
Female*Total Pancretectomy		**1.25 (0.79,1.99)**	**0.341**
Female*Pancretectomy NOS		**2.07 (1.19,3.58)**	**0.01**
Type of Surgery* Adjuvant Radiation			
Partial pancretectomy/Other Pancretectomy*Not Received	Local excision of tumor *Radiation Received	**1.65 (1.06,2.57)**	**0.026**
Total Pancretectomy*Not Received		**1.80 (1.12,2.91)**	**0.015**
Pancretectomy NOS*Not Received		**1.22 (0.69,2.18)**	**0.498**
Tumor Staging* Adjuvant Radiation			
Regional Extension*Not Received	In situ/ Localized *Radiation Received	**1.77 (1.34,2.33)**	**<0.001**
Distant Spread*Not Received		**1.51 (1.03,2.22)**	**0.034**
SEER regions*LNR			
Connecticut*LNR1	Hawaii*LNR0	**0 .50 (0.27, 0.90)**	**0.02**
Connecticut*LNR2		**0.53 (0.28, 1.01)**	**0.053**
Connecticut*LNR3		**1.05 (0.54, 2.05)**	**0.888**
Utah*LNR1		**0.50 (0.24, 1.01)**	**0.052**
Utah*LNR2		**0.76 (0.35, 1.67)**	**0.487**
Utah*LNR3		**1.32 (0.60, 2.93)**	**0.494**
New Mexico*LNR1		**0.76 (0.39, 1.51)**	**0.436**
New Mexico*LNR2		**0.71 (0.33, 1.52)**	**0.377**
New Mexico*LNR3		**1.35 (0.62, 2.95)**	**0.451**
Metropolitan Detroit*LNR1		**0.55 (0.31, 0.98)**	**0.043**
Metropolitan Detroit*LNR2		**0.65 (0.35, 1.20**	**0.173**
Metropolitan Detroit*LNR3		**1.09 (0.57, 2.11)**	**0.794**
Metropolitan Atlanta*LNR1		**0.68 (0.36, 1.29)**	**0.237**
Metropolitan Atlanta*LNR2		**0.90 (0.46, 1.81)**	**0.779**
Metropolitan Atlanta*LNR3		**1.31 (0.64, 2.67)**	**0.457**
Seattle (Puget Sound) *LNR1		**0.80 (0.43, 1.51)**	**0.492**
Seattle (Puget Sound) *LNR2		**0.73 (0.38, 1.41)**	**0.347**
Seattle (Puget Sound) *LNR3		**1.24 (0.62, 2.49)**	**0.548**
San Francisco-Oakland SMSA*LNR1		**0.62 (0.34, 1.13)**	**0.119**
San Francisco-Oakland SMSA*LNR2		**0.54 (0.28, 1.03)**	**0.059**
San Francisco-Oakland SMSA*LNR3		**1.34 (0.69, 2.63)**	**0.39**
Iowa*LNR1		**0.93 (0.50, 1.72)**	**0.809**
Iowa*LNR2		**0.82 (0.43, 1.57)**	**0.546**
Iowa*LNR3		**0.77 (0.38, 1.56)**	**0.462**

95%CI, 95% Confidence Interval; HR, Hazard Ratio; SE, Standard Error; LNR, Lymph Node Ratio; NOS, Not otherwise Specified; SEER, Surveillance, Epidemiology and End Results.

Discussion

Discussion

Pancreatic adenocarcinoma is associated with significant morbidity and mortality. This disease poses a significant burden on public health. Over the last two decades, despite increasing research funding from 21.8 million to 74.2 million dollars (between 2001-2006), the National Cancer Institute (NCI) reports that there is still no considerable decline in the mortality, or improvement in overall survival of pancreatic cancer.[32]

Additionally, there are disparities in survival rates among people with different racial backgrounds and across geographic regions in the United States.[22 25 28 33-34] Some studies have demonstrated that the number of lymph nodes evaluated has prognostic significance in predicting overall survival for several cancers including pancreatic cancer.[8 35-36] This suggests that patients with more lymph nodes resected may have undergone a more thorough resection resulting in more accurate staging. Therefore, we hypothesized that survival disparities in pancreatic adenocarcinoma may be partly due to inconsistencies in surgical resection and lymph node assessment leading to inaccurate staging. This situation has been seen for other cancer sites, such as gastric cancer, where studies have shown that there is a continued trend of inadequate lymph node assessment and understaging despite an AJCC recommendation of at least 15 lymph nodes to be examined for accurate staging.[25]

Some of the recent study findings suggest that the absolute count of lymph nodes evaluated and the lymph node ratio (LNR) are significant predictors of overall survival for pancreatic adenocarcinoma.[68 9 1316] To our knowledge, our large population-based study is the first to systematically examine variation in the absolute number of lymph nodes resected and LNR by race and geographic regions and its impact on overall survival. Our findings demonstrated significant differences in extent of lymph node dissection between races in node positive patients. Survival differences between race groups among node positive patients who had lymph node ratio of >0.2-0.4 or >0.4 were marked. In addition, we found significant regional variations in adequate lymph node assessment in node negative patients. There were profound survival differences between SEER regions in each LNR group.

Minorities seem to carry significantly higher burden of cancer disparities across the United States. African-Americans have higher incidence rates and worse survival for pancreatic cancer.[19-22]We investigated to see if there were any differences in the extent of lymph node resection among patients with diverse backgrounds, and whether these potential differences had any impact on overall survival.

In node negative patients, our study did not find significant differences in lymph node assessment between White, African-American and Asian/Pacific Islander, however, there were significant differences between race groups in node positive patients. The possible explanation to these findings is that the number of lymph nodes harvested may be influenced by body mass index (BMI) differences between race groups.[25 26] BMI differences may potentially influence surgeon's and pathologist's ability to recover all the nodes, and perform thorough evaluation. In addition, the extent of surgery and lymph node dissection may depend on various factors including a surgeon's experience, which may vary based on geographic region, or a patient's health status, which may vary between races. Since the information on BMI and other health conditions were not recorded in the SEER database, we were unable to control for these in our study.

Our study demonstrated significant survival differences between race groups among node positive patients with higher lymph node ratio. The median survival for African Americans who had lymph node ratio (LNR) >0.2-0.4 was significantly lower compared to Whites (Log-Rank test, p= 0.004). African Americans who had LNR >0.4 had significantly worse median survival (5 months, 95%CI: 3.59,6.4) compared to the median survival of Whites (10 months, 95%CI: 8.96,11.0) (Log- Rank test, p =<0.001). Similarly, we found marked survival differences between African Americans (5 months, 95%CI: 3.59,6.4) and Asian/Pacific islanders (12 months, 95% CI: 9.10, 14.90) who had the LNR >0.4 (Log- Rank test, p=0.003). There were no significant survival differences between Whites and Asian/Pacific Islanders in any LNR groups. In the adjusted Cox proportional analysis, race was still a significant prognostic factor of overall survival, and African-Americans men were dying at a rate of 33 percent higher compared to Whites.

These observations of survival disparities and persistent findings showing African Americans having poorer prognosis appear to imply that even after adjusting for the adequacy of lymph node assessment, there may be other factors, including health care access, socioeconomic status, receipt of adjuvant therapy that may have significant impact on survival of patients with various backgrounds.[19,20,23] We found in our study that though relatively higher proportion of Asian/Pacific islanders had LNR>0.4, the median survival (12 months 95%CI: 9.10,14.89) for these patients was better than White and African Americans. This possibly explains that though higher proportion of Asians with advanced disease had not undergone thorough examination but other favorable factors (mentioned above) may have improved their overall survival.

One finding that may partially explain why African Americans had higher risk of death was that higher percentages of African Americans (19.9%) in our study were recorded as “Not Stated” when registering information about tumor size, therefore, most of these patients may be under staged and under treated resulting in poorer survival. Overall, “Not stated” group had worse survival even when compared to patients with >2 cm tumor size.

One study using the large population-based California Cancer Registry (CCR) demonstrated that treatment differences and socioeconomic status are the factors that most likely explain poor survival for African Americans with pancreatic adenocarcinoma.[20] Other studies also found treatment differences between patients with various backgrounds, such as that African Americans were least likely to receive surgical treatment and adjuvant therapy even with equal access to health care.[19 23] One study attributed lower likelihood of receiving radiotherapy and chemotherapy to varied levels of health care, physician bias, and patient rejection.[19]

These studies further strengthen our belief that there are other factors that may contribute to survival experiences of each race group. Since the SEER database does not include information about health care access, socioeconomic status, receival of chemotherapy we were unable to assess their association with race and outcome.

While assessing node positive patients, a number of studies have emphasized the prognostic importance of LNR in patients with colon, and esophageal cancer.[3 7 37 38] Additionally, in recent years several studies have demonstrated the trend of decrease in median survival with increased LNR for patients with pancreatic adenocarcinoma.[6 9 13] Using the SEER database, Slidell et al. demonstrated that in patients with pancreatic cancer who had lymph node metastases, lymph node ratio was an important predictor of overall survival with a trend towards reduced survival with increasing of LNR (15 months for LNR >0-0.2, 12months for LNR >0.2-0.4, 10 months for LNR >0.4). [6]

However, until now no study has investigated this trend among racial groups. Our study results show this trend among all of the three race groups. African-Americans had worse median survival with increased LNR (LNR0 16 months, LNR1 14 months, LNR2 9 months and LNR3 5 months)(P<0.001). This points out that survival experiences of all node positive patients with pancreatic adenocarcinoma were not uniform, and as Pawlik et al. indicate patients with higher LNR ratio may have more aggressive larger tumor with extensive invasion resulting in worse survival as demonstrated in this study.[9]

Prior to performing this study, we hypothesized that the extent of lymph node dissection might vary significantly by geographic region. We theorized that some possible contributing reasons might be the economic stability of a region, rates of referral to tertiary care canters, local institutional staging guidelines, regional health care and insurance policies, and hospital policies that may have significant influence on extent of lymph node resection. In addition, policies and guidelines of local health institution in which medical students are trained or surgeons and pathologists are working may play an enormous role in their ability to resect and evaluate adequate lymph nodes in patients.

Our results, however, showed that, among node negative patients, there was significant variation in the extent of lymph node resection by region. Our results were consistent with a previous study by Govindaraj et al. in finding significant differences in average number of nodes resected between SEER 9 regions (ANOVA, $p<0.001$). [28] When examined in node negative patients, most of the regions had a majority of patients with inadequate lymph node assessment, where Iowa was the worst with 82.7% and Hawaii comparatively better with 63.6% (Chi–square test, $p<0.001$). On the other hand, in node positive patients our study did not find any significant differences in extent of lymph node resection between SEER 9 regions (Chi-square test, $p=0.103$).

Though our study was able to demonstrate significant variability in lymphadenectomy across the geographic regions in node negative patients, we were unable to investigate potential factors contributing to these variations. However, our future prospective study will systematically explore regional variations in lymph node assessment and possibly seek to identify contributing factors.

In contrast to results of a study in gastric cancer patients, in our study the impact of inadequate lymph node assessment on survival was not significant.[25] Coburn et al. had reported that SEER regions with the lowest adequate lymph node assessment (ALNA) had the worst survival however, in our study, Iowa that had the highest percentage of patients with inadequate lymph node assessment, where the median survival was 17 months (95%CI: 12.72,21.28) and for Hawaii, which had lowest percentage, the median survival was still 17 months (95%CI: 12.7,21.29). Though the Seattle region had about 80% of inadequately assessed patients, among all the 9 regions they had the best median survival. In node positive patients the median survival significantly varied across the regions ($p<0.05$). However, in the final adjusted Cox proportional model, the variable SEER region was not associated with overall survival.

Although, these results appear to imply that inadequate lymph node assessment did not result in poor survival among patients in these regions, however there may be other regional-specific factors that may have overwhelming impact on survival. As Coburn et al. indicated race may be one of the important factors.[25] In a study of gastric cancer patients, they demonstrated that survival rates were better in regions that had higher percentages of Asian population.[25] This was also true in our study as we observed highest percentages of African Americans in Metropolitan Atlanta (22.2%) and Metropolitan Detroit regions (24.8%) compared to all other regions, and these regions had the lowest median survival in both node negative and node positive patients. In addition, it was seen in our study that Iowa and Hawaii regions that had the highest percentages of Whites (98.6%) and Asian/Pacific Islanders (75%) respectively, had the best median survival compared to other regions.

Additionally, patterns of treatment, easy access to better treating institutions, high frequency of specialized procedures and experience of an institution may also contribute to survival disparities between regions.[22] In support of this, one study demonstrated that patients receiving treatment in teaching institutions had significantly higher survival than patients who did not.[22]

In our initial analysis, we observed that the type of surgery and tumor staging pattern varied significantly across the SEER 9 regions (Chi-square test, $p<0.05$), however, in the final adjusted model, these interactions were not significantly associated with overall survival. More likely, the effects of these regional variations were explained by other predictors that impacted overall survival. Similar results were obtained by one study using the SEER database, which reported marked variability in the surgical treatment of adenocarcinoma of the pancreatic head across geographic regions but late survival differences were not significant between the types of surgical procedures.[28] These factors need to be further investigated by future studies in order to clearly identify the reasons for these observed regional variations.

In the entire study cohort, 68% of patients had less than 12 nodes resected, which indicates that the majority of patients with pancreatic adenocarcinoma may be understaged. Govindarajan et al. demonstrated that the odds of patients getting diagnosed as node positive is lower for those who had inadequate lymph nodes resected and is associated with worse late survival.[28] Our study results concur with these previous studies.[6 9 13]

In our final adjusted model, adequate lymph node assessment and lower LNR significantly improved survival of patients with pancreatic adenocarcinoma. After adjusting for other risk factors, patients with adequate lymph node assessment had 17% lower risk of death compared to their counterparts.

Though marital status, which acts as a surrogate marker of social support, was reported as an important predictor of survival in some studies, it remained insignificant in both univariate and the multivariate model in our study. [6 25] We found that patients younger than 60 years had significantly improved survival over the other two older age groups, and rate of dying was highest for patients between 60-80 years of age. Similar to other study findings, females in our study had better survival compared to males.[6 23]

Other studies have observed that prognosis of adenocarcinoma of the pancreas depends on several important factors such as size of the tumor at diagnosis, extent of local invasion and distant spread, lymph node status, and the margin status at surgical resection.[6 39-41] In our final adjusted model, type of surgery, tumor size, tumor stage and tumor grade were all important predictors of survival. Margin status is not available in SEER so this predictor could not be included in this analysis.

Limitations

Our study has several limitations. Since we used the SEER database, we had limited capacity in variable selection, and therefore, we were unable to adjust for all known confounders. For example, socioeconomic status and access to health care were important factors that are known to be associated with race and regions, and that have significant impact on overall survival, however, these variables were unavailable in the SEER database. Similarly, adjuvant therapy for pancreatic adenocarcinoma usually includes chemotherapy, which is not available in the SEER database.
Additionally, the SEER database does not collect information on disease recurrence, which is another important end point in outcomes analysis. Other factors, such as the percentage of patient's referrals to tertiary centers, and the overall economic status of a region are important potential confounders, this information was not available in the

SEER database. Although Hispanic population is the majority among many racial classes, we did not consider ethnicity in our study due to the complexity of SEER race recoding methods. Additionally, if ethnicity was considered we had the possibility of reducing the study sample size for African Americans and Asian/Pacific Islanders.

Another limitation to our study was that we had about 500 missing values in the variable tumor size, which were excluded in the Cox regression analysis. However, in order to assess whether missing values were informative, and to identify how they were different from other groups in tumor size, and to assure that excluding missing values did not result in presenting biased estimates, several steps were taken. We compared between patients with missing values and patients with complete data using survival curves and univariate Cox regression analysis. The median survival (20 months) for patients with missing values was similar to patients who had ≤ 2 cm tumor size (22 months, 95%CI: 17.113, 26.887). When compared between the final Cox models with and without missing values, the hazard estimates did not differ markedly. Therefore, for our final model, we only included cases with complete data.

Despite these limitations, SEER is an excellent population-based database that can provide a sufficient sample size to study cancer related issues such as lymph node assessment among minority populations.

Summary

To summarize, a majority of patients with pancreatic adenocarcinoma have inadequate lymph node assessment in the United States. This study demonstrated a significant racial variation in the extent of lymph node resection among node positive patients, and survival differences were profound between patients with various backgrounds who had LNR >0.2-0.4 or LNR >0.4. In the final adjusted Cox regression model, race was a strong predictor of overall survival, and African Americans men were dying at a rate 33 percent higher than white women.

Regional variations in adequate lymph node assessment were clearly observed in node negative patients but not in node positive patients. Differences in survival were marked between the SEER 9 regions in each LNR group. After controlling for other risk factors, race, LNR and adequate lymph node assessment were still important prognostic factors of survival.

Conclusions

Majority of patients with pancreatic adenocarcinoma have inadequate lymph node assessment in the United States, which may suggest understaging and under treatment for many patients. Our findings clearly demonstrated racial variation in node positive patients and regional variation in node negative patients with regard to extent of lymph node dissection. African Americans experience worse survival compared Whites and Asian/Pacific Islanders. Further studies are warranted to identify potential factors contributing to these observed disparities. To stratify node positive patients with pancreatic adenocarcinoma for clinical trials, LNR may be a useful prognostic factor to include.

Public Health Importance

Pancreatic adenocarcinoma is associated with significant mortality and morbidity. This disease poses a significant burden on public health. Currently, there is limited research on pancreatic cancer, and allocated resources are not proportional to the burden of this disease. African Americans most likely experience worse prognosis with pancreatic adenocarcinoma for reasons that are unclear. In addition, there is marked variation in survival of patients residing in various geographic regions. Further studies are warranted to identify factors contributing to survival disparities between race groups and across geographic regions. Proper interventions are necessary to maintain uniform pattern of lymph node evaluation, which is very essential for achieving uniform cancer staging standards across the United States.

This study is an important contribution to public health because it not only adds to the current knowledge of health disparities but also identified existing differences in cancer diagnostic patterns across the United States, and thereby seeks better interventions to improve the overall quality and standards of cancer treatments.

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Appendix A: Univariate Analysis of factors associated with overall survival in patients who underwent resectomy for pancreatic adenocarcinoma

Univariate Analysis				
Predictors	**Reference**	**Hazard Ratio (95% CI)**	**SE (HR)**	**p-Value**
Age 51-80 years old >81 years old	18-50 years old	**1.29 (1.18, 1.40)** **1.45 (1.20, 1.75)**	**0.045** **0.097**	**<0.001** **<0.001**
Gender Female	Male	**0.90 (0.83, 0.97)**	**0.041**	**<0.001**
Race African American Asian /Pacific Islanders	White	**1.26 (1.12, 1.43)** **0.93 (0.79, 1.09)**	**0.063** **0.082**	**<0.001** **0.366**
Marital Status Married Others	Single (never married)	**0.95 (0.83, 1.08)** **1.05 (0.90, 1.21)**	**0.069** **0.076**	**0.419** **0.555**
Geographical regions Connecticut Utah New Mexico Metropolitan Detroit Metropolitan Atlanta Seattle (Puget Sound) San Francisco-Oakland SMSA Iowa	Hawaii	**0.98 (0.80, 1.21)** **1.10 (0.78, 1.29)** **1.07 (0.84, 1.37)** **1.15 (0.94, 1.41)** **1.14 (0.91, 1.43)** **0.90 (0.72, 1.12)** **1.01 (0.82, 1.25)** **1.04 (0.83, 1.29)**	**0.107** **0.129** **0.126** **0.104** **0.115** **0.112** **0.107** **0.112**	**0.862** **0.989** **0.582** **0.178** **0.242** **0.356** **0.924** **0.760**
SEER tumor Staging Regional Extension Distant Spread	In situ/ Localized	**2.15 (1.90, 2.44)** **3.97 (3.36, 4.68)**	**0.064** **0.084**	**<0.001** **<0.001**
Tumor Size >2 CM Not stated Missing value	≤2 CM	**1.43 (1.27, 1.61)** **1.62 (1.40, 1.87)**	**0.060** **0.075**	**<0.001** **<0.001**
Tumor Grade Moderately differentiated Poorly differentiated	Well differentiated	**1.47 (1.29, 1.68)** **1.66 (1.45, 1.90)**	**0.069** **0.069**	**<0.001** **<0.001**
Type of surgery Partial pancretectomy/Other Pancretectomy Total Pancretectomy Pancretectomy NOS	Local excision of tumor	**0.80 (0.66, 0.98)** **0.78 (0.63, 0.97)** **1.59 (1.23, 2.07)**	**0.102** **0.110** **0.133**	**0.030** **0.024** **<0.001**
Adjuvant Radiation Not Received	Radiation Received	**1.37 (1.26, 1.48)**	**0.041**	**<0.001**
Lymph Node status Lymph Nodes Positive	Lymph Nodes Negative	**1.65 (1.52, 1.79)**	**0.042**	**<0.001**
Lymph node Ratio (LNR) LNR1 (>0-0.2) LNR2 (>0.2- 0.4) LNR3 (>0.4)	LNR0	**1.38 (1.24, 1.24)** **1.24 (1.50, 1.90)** **2.12 (1.90, 2.36)**	**0.053** **0.060** **0.056**	**<0.001** **<0.001** **<0.001**
LN Adequately Assessed Adequately Assessed (≥ 12 LNs)	Not Adequately Assessed (<12 LNs)	**0. 82 (0.75, 0.89)**	**0.045**	**<0.001**