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Early Onset Pancreatic Cancer: Clinical Characteristics and Survival Associations by use of the National Cancer Data Base

By
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Degree to be awarded: Master in Public Health
Global Health

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Early Onset Pancreatic Cancer: Clinical Characteristics and Survival Associations by use of the National Cancer Data Base

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Abstract

Early Onset Pancreatic Cancer: Clinical Characteristics and Survival Associations by use of the National Cancer Data Base

By Betsy Dewey

Background: A scarcity of data exists in younger patient populations with pancreatic ductal adenocarcinoma (PDAC) regarding their overall survival and patient characteristics as compared to typically aged patients with PDAC. This report compares a large cohort of patients with PDAC <=50 years of age compared to patients diagnosed after 50 from the National Cancer Data Base (NCDB) over a 10-year period.

Methods: A retrospective analysis of Continuum of Care (CoC) accredited facilities who report their data to the NCDB identified PDAC cases <=50 years on the date of diagnosis and compared the tumor characteristics and survival associations to PDAC cases diagnosed at >50 years of age, between the years of 2004 through 2014, was performed. Covariates reviewed included demographics, clinical and pathological staging, receipt of surgery, and death or last date of follow-up. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test.

Results: A total of 166,728 PDAC cases were identified for analysis. 13,103 (12.72%) cases were determined early onset pancreatic cancer due to diagnoses before or at the age of 50 years and 153,625 (87.28%) cases diagnosed after the age of 50 years. Age range: 18-90. Men in the sample accounted for 7,615 (58.12%) and 77,686 (50.57%) for early onset and typical onset cases, respectively. Women represented 5,488 (41.88%) and 75,939 (49.43%) for early onset and typical onset cases, respectively. Early onset cases were more frequently diagnosed with late stage PDAC and metastatic disease; however, overall survival was better for the younger patient population compared to the older patient population. For every one-year increase in age, the hazard of death increased by 9.7%. African-Americans, both early onset and typical onset, had worse survival compared whites in both age subgroups.

Conclusions: This is the first study using the NCDB to compare clinical characteristics and survival associations among early onset pancreatic cancer patients. The data suggests that despite being diagnosed with similar advanced stage disease, EOPC patients appear to have better overall survival compared to TOPC, which may reflect other causes of death among older patients. The data also provide evidence that highlights the racial disparity among survival of African-Americans compared to whites.

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Author

Betsy Dewey

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Introduction and Rationale:

Pancreatic cancer is one of the most fatal malignancies due to lack of effective screening methods, and the fact that symptoms do not appear until very late in the process of tumor growth so early intervention is difficult. Although the incidence of pancreatic cancer increases with age, younger patients diagnosed with pancreatic cancer have been the subject of limited investigations. This unique cohort of individuals diagnosed with pancreatic cancer at 50 years or younger, classified as early onset pancreatic cancer (EOPC) is a subset of patients who often lack comorbidities. However, survival rates for EOPC compared to typical onset pancreatic cancer patients (TOPC) remain unknown.

Problem Statement:

Early onset pancreatic cancer represents a significant impact in public health due to the high mortality rates that lead to increased numbers of years of potential life lost. There is currently no recommended screening method for pancreatic cancer even though early detection in most cancers is the best chance for a patient's survival. This thesis will aid to fill the knowledge gap of early onset pancreatic cancer patients compared to typical onset patients in terms of demographic and clinical characteristics and their overall survival.

Research Question/Hypothesis:

Research question: Do patients with early onset pancreatic cancer have more severe tumor types and shorter survival compared to typical onset of pancreatic patients?

Hypothesis: There will be no difference in clinical characteristics and survival in early onset pancreatic cancer patients (<=50 years old) versus typical onset of pancreatic cancer patients (>50 years old).

Aim: Compare clinical characteristics and associated outcomes (survival) of early onset pancreatic cancer patients to typical onset of pancreatic cancer patients.

Aim: If survival or clinical differences are found, factors will be determined that predict these outcomes.

Background:

Pancreatic cancer represents one of the deadliest prognoses for a patient and one of the few cancers whose mortality rate is higher than its incidence rate in the United States (Beeghley-Fadiel, 2016). While the disease is relatively rare, approximately 12.5/100,000 cases diagnosed annually, pancreatic cancer is one of the most fatal cancers among older adults in the United States (SEER, 2017 and Brotherton, et al. 2016). Ranking 9th for women and 11th for men in incidence, pancreatic cancer comes in 4th for mortality related to its dismal 5-year survival rate of less than 5% (Beeghly-Fadiel, 2016 and McWilliams, 2016). Compared to other cancers, the survival rate for pancreatic cancer has not improved substantially in over 40 years and could soon surpass mortality rates for breast and colon malignancies (McWilliams, 2016 and Muniraj, 2013). There are currently no recommendations by any major health professional group for routine screening for pancreatic cancer, simply because imaging modalities have very limited diagnostic accuracy (Poruk, et al. 2014) and the preliminary stages of tumor growth are asymptomatic (ACS, 2013). Without detectable symptoms by the patient, the majority of pancreatic cases have late clinical diagnoses are not diagnosed until Stages III and IV (Duffy, et al. 2009). Established factors that promote survival rely on resectability (Ries, 2007), although only about 20% of patients are candidates for surgery at the time of their diagnosis (Tamburrino, et al. 2014). Due to a lack of detectable symptoms and pancreatic cancer's aggressive tendency to

metastasize to other adjacent organs, early detection remains the greatest advantage for a patient's survival (Brune, et al. 2010). Despite the few occasional cases of early disease detection, nearly all patients die from pancreatic cancer within the first two years (Chakraborty, et al. 2011).

Typical onset pancreatic cancer (TOPC) cases are diagnosed in older adults (over age 50), with a mean age at diagnosis of 71 (McWilliams, 2016). Because most patients are older, research is extremely limited in examining pancreatic cancer cases among younger patients, termed early onset pancreatic cancer (EOPC), which encompasses patients diagnosed at 50 years and younger (Eguchi, 2016). EOPC cases are a unique subset to analyze within a rare disease in an attempt to understand the clinical outcomes and differing survival rates when compared to a TOPC case. Nonetheless, EOPC contributes to the total burden of pancreatic cancer because of the increased number of years of potential life lost (Raimondi, et al. 2007). Many publications on EOPC are merely descriptive and their samples lack diversity. Some studies theorize that EOPC has specific risk factors such as inherited genetic syndromes, obesity, and tobacco smoking; however, publications have failed to show statistically significant associations with prognostic factors in EOPC (Duffy, et al. 2009). Furthermore, because clinical outcomes of patients with EOPC have not been clearly established, it is unknown if treatment plans for EOPC should align with the same methods as older patients receive with TOPC. In addition, racial disparities also persist in mortality among almost all cancer mortalities, especially in gastrointestinal malignancies (Shavers, et al. 2002). African Americans display the highest death rate and shortest survival of any racial group for most cancers, including pancreatic cancer, in the United States (DeSantis, et al. 2013).

Early Onset versus Typical Age of Onset Pancreatic Patients:

Epidemiologic studies comparing EOPC to TOPC at diagnosis have limited data regarding etiology; therefore, it is important to attempt to identify potential prognostic factors regarding patient's survival of pancreatic cancer between EOPC and TOPC cases. A Swedish, controlled study aimed to recognize EOPC-specific prognostic factors, despite their small sample size of only 576 pancreatic ductal adenocarcinoma (PDAC) patients, with 33 cases being EOPC patients. The younger cohort was significantly associated with an advanced stage with distant metastasis (52% vs. 25%) (p=0.001) (Tingstedt, et al. 2011). Also, EOPC received statistically significant results in more frequent of radiotherapy (both intra and post-operatively) compared to the older cohort (36% vs. 9%) (p=0.002) (Tingstedt, et al. 2011). While the Swedish study did not find statistically significant differences in median survival between the two subgroups, EOPC cases had higher rates of both resection and radiotherapy. Reasons for these differences have no been extensively explored, but it may be that EOPC patients, because they are younger, may be overall in better health and be able to tolerate surgery and other therapies better than older patients. To further highlight the scarcity of research done with this young patient population, only one other publication has analyzed this subgroup on its clinicopathological characteristics by use of nationwide registry in Japan (Eguchi, 2016).

Methods:

National Cancer Data Base

The National Cancer Data Base (NCDB) contains approximately 70% of newly diagnosed cancer cases in the United States. At 26 million patient records, the NCDB is 2.5 times larger than the widely utilized Surveillance, Epidemiology and End Results (SEER)

database. The NCDB provides patient-linked treatment information that is unavailable in the SEER database outside of SEER-Medicare linked data. However, the NCDB, unlike SEER, is not a population-based database. The NCDB is maintained by the American College of Surgeons and the American Cancer Society and includes more than 1500 Commission on Cancer (CoC)-approved hospitals in the United States. The NCDB Participant Use Data File (PUF) contains de-identified patient level data that do not identify hospitals, healthcare providers, or patients as agreed to by each CoC-accredited program. Data available include extensive patient demographics (including insurance status, county of residence, race, age, etc.) tumor characteristics, pathologic characteristics, overall survival data, treatment center type, and detailed treatment information (including sequencing, types of treatments, treatment intent, radiation dose, types of surgical procedures, and other important factors), although some variables remain optional for data entry. Overall survival is calculated as the number of months between the date of diagnosis and the date on which the patient was last contacted or died. Overall survival (OS) differs from cancer-specific survival in that the reasons for death is not documented. However, in pancreatic cancer, cause of death is often due to the pancreatic cancer since prognosis tends to be very poor.

Study Population

From a total of 309,709 patients in the NCDB pancreatic cancer PUF from 2004 through 2014, cases were selected that had survival data available at the time of analysis and the primary tumor site was coded as exocrine pancreas. Cases coded with histology type as PDAC were included in the analysis. After assessing inclusion criteria and exclusion of cases with missing information, the total sample accounted for 166,728 cases applicable for this analysis.

Statistical Analysis

Statistical analysis was conducted using SAS Version 9.3.

Descriptive Analysis: Categorical variables were summarized as frequencies per cohort by age of onset, and the median and range was reported for each continuous variable (age, crowfly, last contact or death). The univariate survival analyses were conducted by associating overall survival with each variable individually, using both the Kaplan-Meier method (with log rank test *p* values) and a Cox proportional hazard model (yielding hazard ratios [HR]. The association between age of onset (EOPC vs. TOPC) and each of potential confounder variables was examined by the chi-square test for categorical covariates or ANOVA for continuous covariates.

Results

Demographics:

A total of 166,728 patients were analyzed based on inclusion and exclusion criteria. Among them, 13,103 patients were identified as EOPC or the younger group being diagnosed at age 50 or less, representing 12.72% of the sample. The EOPC patients included 7,615 (58.12%) men and 5,488 (41.88%) women. The TOPC, or the older group, being diagnosed after the age of 50 years was composed of 153,625 patients, representing 87.28% of the total sample. In the TOPC subgroup, men made up only 50.57%, indicating that EOPC patients are more likely to be male (*P*=<.0001). In contrast, TOPC for women comprised 75,939 (49.43%) cases of the sample, thereby indicating women are more frequently diagnosed after the age of 50 years old.

The sample consisted mostly of older Caucasians, which led to a poor representation of non-white, young survivors. Whites made up the majority of cases in both age subgroups. Blacks represented 17.35% of the EOPC group and only 12.28% of the TOPC cohort highlighting racial disparities among black patients diagnosed at a younger age (*P*=<.0001).

Table 1 shows the descriptive statistics for each covariate by the two age groups. EOPC patients were found to travel a farther distance statistically in miles from their home residence to the hospital compared to TOPC patients (m=48.43 std=157.5 versus m=40.11 std=136.3, respectively). These findings agree with Jindal et al. who found evidence of patients who travel longer distances for a pancreatectomy attribute to more beneficial outcomes pertaining to mortality (Jindal, et al. 2017). As for clinical stage, EOPC were more likely to be diagnosed at a later stage (12.72%, stage 3 and 51.35%, stage 4) compared to TOPC (11.79%, stage 3 and 46.04%, stage 4). EOPC cases were more frequently positive for nodes compared to TOPC cases (30.87% versus 25.80%, respectively). Chemotherapy (70.93% versus 54.40%) and radiation were more frequently in the treatment plan for to EOPC patients as compared to TOPC patients.

Hazard Ratio by Age of Diagnosis:

TOPC patients ultimately had the higher risk of death between the two age subgroups. For every one-year increase in age, the hazard of death increases by 9.7% (P=0.0007, Table 2).

Survival by Clinical Stage and Age Subgroups:

Overall survival (OS) was significantly better in the younger group than the older group (P= 0.0007; Fig. 1). For clinical stages 2 and 3, those in the younger cohort were significantly more likely to have better OS than the older group (P= 0.0425, P= 0.0095; Fig. 2 and 3, respectively). No statistically significant differences were found when comparing stage 1 and stage 4 survival by each age subgroup (P=0.8816, P=0.0521 respectively).

Survival by Race and Age Subgroups:

Survival for white patients with EOPC was significantly better than whites diagnosed at TOPC (P=<.0001; Fig. 4). Survival for African-American (AA) patients with EOPC did not differ significantly compared to the older cohort of AA patients (P=0.2989; Fig. 5). Figure 6 are both whites and AA sub-grouped by age, totaling four-overlaid survival curves to show all four subgroups.

Survival by Pancreatic Anatomic Site and Age Subgroups:

Survival for each anatomic site for pancreatic tumors was assessed for both age groups. There were no significant differences in survival between the EOPC and TOPC groups with regard to tumors located in the body of the pancreas, tail, and overlapping lesions (P=0.2583, P=0.8911, P=0.0877 respectively). Patients with a tumor located at the head of the pancreas were the only anatomical tumor site that had statistically significant differences in survival between the age groups (P=0.0037; Fig. 7).

Survival by Resected Patients and Age Subgroups:

TOPC patients underwent tumor resection more often than EOPC, perhaps because TOPC were less likely to have metastatic disease. Surgery was less likely common for EOPC cases compared to TOPC cases (80.78% versus 83.81%) respectively. However, EOPC patients who were eligible for surgery were more likely to receive a Whipple procedure compared to TOPC patients (8.78% versus 7.45%). Survival for resected patients with EOPC had slightly better survival than the resectable TOPC cases (P=0.455; Fig. 8).

Discussion:

This study retrospectively analyzed data from one of the largest hospital-based databases in the United States. Despite the 13,103 EOPC cases being diagnosed at a later stage and having higher rates of metastatic disease, EOPC patients had better overall survival compared to TOPC perhaps due to higher rates of resectability and

administration of chemotherapy and radiation. Despite being diagnosed at later stages, EOPC cases received more systemic treatment and surgical procedures than TOPC cases. This may be due to doctors creating more aggressive treatment plans for EOPC patients than they do for TOPC patients (Wheeler, et al. 2014). TOPC patients, who can be expected to have more comorbidities than EOPC patients, may not be able to tolerate treatments with significant toxicities or complications due to potential frailty. EOPC patients were found to travel farther distances than TOPC to their chosen cancer center with slightly more EOPC patients going to academic/research programs. This may be due to younger patients with PDAC being more likely to travel to an accredited research institution as opposed to their local cancer hospital, which coincides with Jindal's study findings. Male patients were more frequently diagnosed with EOPC, which coincide with the results found in the Japanese nationwide pancreatic cancer registry (Eguchi 2016).

Racially, African-Americans were more likely to be diagnosed as EOPC whereas whites were more likely diagnosed as TOPC. More importantly, African-Americans whether EOPC or TOPC, experienced worse survival than whites in both age groups. These findings contribute to the overwhelming amount of evidence of racial disparities in cancer mortality, including pancreatic malignancies (Brotherton, 2016). Through the cancer-care continuum, disparities lie within unequal distribution of cancer risk factors to inequities in timing of and stage of diagnoses, and appropriate treatment plans (Ward, et al. 2004). A population-based SEER study conducted by Shavers, et al. found no significant differences in mortality among African Americans with regard to overall or disease-specific survival (Shavers, et al. 2009). For clinical stages II and III, EOPC patients had significantly better survival than TOPC patients, however, this was not the case for all clinical stages. Stage I and IV patients, regardless of EOPC or TOPC age subgroup, did not have a

significant difference in survival when diagnosed at these stages, at both an early stage and at a late stage. This analysis coincides with Piciucchi, et al. that also found no statistical differences among stage-specific survival between EOPC and TOPC (Piciucchi, et al. 2016). These findings are most likely due to EOPC patients diagnosed at more advanced clinical stages and metastatic disease (Piciucchi, et al. 2016 and Eguchi 2016), but at the same time possibly lacking comorbidities and consequent eligibility to more aggressive treatment plans outlined by the provider.

Strengths of this study include being the first to use the NCDB in assessing the unique cohort of EOPC's clinical characteristics and overall survival associations with a large sample size of over 10,000 cases for this young subset. The NCDB requires an annual follow-up of at least 90% of patients to capture quality-care metrics and assess performance at the hospital or system level (Mandelson, 2017). This strength provides insight into the quality of cancer care that is mandatory to keep up the standards for the database. Results from the study are useful and important in order to generate hypotheses for future prospective studies and clinical trials (Bilimoria, et al. 2008). This study contributes to relative pancreatic cancer epidemiology literature and should serve as supportive evidence in assessing age of onset diagnoses for this fatal disease. Additional limitations of this study include the retrospective nature of the data. Additionally, the cohorts are not population-based, but rather identified from hospitals where they present for diagnosis and/or treatment, thereby limiting the generalizability of the patient population and management algorithms.

Conclusions:

In conclusion EOPC patients, while diagnosed at later stages with more metastatic disease, experience improved overall survival compared to TOPC patients. Further studies should investigate stage IV EOPC patients who may undergo surgical

resection with more aggressive tumor behavior compared to TOPC. Racial disparities remain highly consistent with the literature in pancreatic cancer in general when focused on comparisons between EOPC and TOPC overall survival within the NCDB. As seen with other types of cancers, the racial survival differences in pancreatic cancer outcomes could be explained by failure to access or undergo suitable cancer care, rather than clinical stage at diagnosis or response to treatments. Future studies must account for socio-demographic, physician, and hospital factors needed to identify modifiable patient and health system factors that could better explain persistent racial disparities for survival.

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