Characteristics Associated With Survival in Surgically Nonresected Pancreatic Adenocarcinoma in the Military Health System

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Objectives: Pancreatic cancer is often diagnosed at advanced stages with high-case fatality. Many tumors are not surgically resectable. We aimed to identify features associated with survival in patients with surgically nonresected pancreatic cancer in the Military Health System.

Methods: We used the Military Cancer Epidemiology database to identify the Department of Defense beneficiaries aged 18 and older diagnosed with a primary pancreatic adenocarcinoma between January 1998 and December 2014 who did not receive oncologic surgery as treatment. We used Cox Proportional Hazard regression with stepwise procedures to select the sociodemographic and clinical characteristics related to 2-year overall survival, expressed as adjusted hazard ratios (aHR) and 95% CIs.

Results: Among 1148 patients with surgically nonresected pancreatic cancer, sex, race-ethnicity, marital status, and socioeconomic indicators were not selected in association with survival. A higher comorbidity count (aHR 1.30, 95% CI: 1.06-1.59 for 5 vs. 0), jaundice at diagnosis (aHR 1.57, 95% CI: 1.33-1.85 vs. no), tumor grade G3 or G4 (aHR 1.32, 95% CI: 1.05-1.67 vs. G1/G2), tumor location in pancreas tail (aHR 1.49, 95% CI: 1.22-1.83 vs. head) or body (aHR 1.30, 95% CI: 1.04-1.62 vs. head), and metastases were associated with survival. Patients receiving chemotherapy (aHR 0.66, 95% CI: 0.57-0.76) had better survival compared with no treatment.

Conclusions: In a comprehensive health system, sociodemographic characteristics were not related to survival in surgically nonresected pancreatic cancer. This implicates access to care in reducing survival disparities in advanced pancreatic cancer and emphasizes the importance of treating patients based on clinical features.

Key Words: pancreatic adenocarcinoma, chemotherapy, survival, health disparities, comorbidity

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Pancreatic cancer is the third leading cause of cancer death in US men and women combined.[1] Treatment for pancreatic cancer is largely dependent on the stage at diagnosis and eligibility for surgical resection.[2] Patients with early-stage tumors and those with favorable characteristics are recommended to undergo either upfront surgery followed by adjuvant chemotherapy or neoadjuvant therapy followed by surgery to improve survival.[2] However, only 13% of diagnosed pancreatic cancers qualify for surgery, while the remaining are diagnosed at advanced stages.[1] Patients with advanced or metastatic cancer have tumors that are largely considered surgically unresectable, although these patients may undergo procedures to control disease spread and provide symptom relief.[3,4] Treatment options for advanced and metastatic cancers are limited to chemotherapy, radiotherapy, or enrollment in clinical trials.[4] However, only about 50% of patients in the US receive these treatments.[5] Even with treatment, pancreatic cancer is highly fatal, and the 5-year relative survival across all stages combined is only about 10%.[1,6]

Understanding the factors related to survival in surgically unresectable pancreatic cancer may help patients and clinicians in making treatment decisions to ultimately improve prognosis in these late-stage cancers. There have been few population-based studies to address factors related to survival in patients who do not undergo surgical treatment.[7] Recent studies have focused on clinical features or treatment(s) that may improve survival. These studies support palliative chemotherapy to improve survival in advanced and metastatic pancreatic cancer.[7,8] Comorbidity burden, and especially diabetes mellitus, has also been shown to be independently associated with receiving treatment and decreased survival in patients with all stages of pancreatic cancer.[5,9–11]

Sociodemographic characteristics have been studied in association with pancreatic cancer treatment and survival.

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Patients from racial-ethnic minority groups, including Black and Hispanic, may be less likely to receive pancreatic cancer treatment and have poorer survival than non-Hispanic White patients.[5,12–14] Patient sex may play a role in chemotherapy side effects, response to treatment[15] and differential survival between men and women.[14] Age has also been shown to be related to receipt of pancreatic cancer treatment(s), with older patients being less likely to receive treatment[5,11,16] and survival, with younger patients experiencing better survival given the same treatment.[17] Lastly, marital status has been shown to be associated with treatment and survival in several population-based studies.[18,19] Specifically, patients who were married had better survival outcomes than their single or widowed counterparts, and this was especially true for patients with advanced or metastatic pancreatic cancers.[18,19]

In the general US population, access to care and insurance status has been associated with receiving cancer treatment(s) and overall and cancer-specific survival.[20–23] Insurance status and inadequate coverage for specialty services, such as Radiation Oncology, may present financial barriers to patients in the general US population.[20] Specific to pancreatic cancer, patients with Medicaid, Medicare, or no insurance have been shown to be less likely to receive surgery or systemic therapy compared with patients with private insurance.[5,16,24] Access to care and insurance status may vary across social and demographic groups in the United States,[25,26] making it difficult to study these factors independently in their association with cancer treatment and survival. Thus, studying factors related to survival in pancreatic cancer in a universal health care system may identify independent prognostic factors while minimizing the effects of access to care and insurance status on the results.

The US Military Health System (MHS) beneficiary population is poised to study the topic. The MHS provides universal health care to over 9 million eligible Department of Defense beneficiaries, including active-duty service members, activated National Guard, retirees from active service, and their dependents, regardless of sociodemographic attributes, at little to no out-of-pocket cost.[27,28] The goal of this study is to identify the patient, tumor, and treatment characteristics related to 2-year overall survival among patients with surgically nonresected pancreatic adenocarcinoma in the universal MHS. Two-year survival was selected as the primary outcome because it approximates the median survival time following a pancreatic cancer diagnosis reported in the literature.[8,16,29–31] The outcome of this study may help identify modifiable and nonmodifiable risk factors, which may be targeted for intervention or personalized treatment to improve survival among patients with pancreatic cancer who are poor candidates for upfront surgery.

METHODS

Data Sources

This study was a retrospective analysis of patients in the Military Cancer Epidemiology (MilCanEpi) database, a linked resource containing data from the Department of Defence Central Cancer Registry and the MHS Data Repository.[32] MilCanEpi contains data for persons diagnosed or treated for cancer in military treatment facilities and medical encounters at military treatment facilities and administrative claims from private sector care for any condition. MilCanEpi, its components, and consolidation procedures applied to the data have been described in detail elsewhere.[32,33] The MilCanEpi database was approved for access for research by the Uniformed Services University of the Health Sciences Institutional Review Board.

Study Population

Eligible patients included men and women aged 18 or older with a confirmed diagnosis of pancreatic adenocarcinoma (ICD-O-3 C25.x; histology codes: 8000, 8010, 8020-8022, 8050, 8140, 8141, 8211, 8230, 8255, 8260, 8323, 8441, 8450, 8453, 8470-8473, 8480, 8481, 8500, 8503, and 8521) in the MilCanEpi database between January 1, 1998, and December 31, 2014, and who did not undergo surgical resection as primary treatment. Adenocarcinomas were selected because they represent most pancreatic cancers, and survival has been shown to be worse than other histologic types.[6,34] Patients who were diagnosed by autopsy or death certificate only and patients who were diagnosed with multiple primary tumors were excluded.

Study Variables

Patient characteristics, including age at diagnosis, sex, race, ethnicity, marital status, active-duty status, and military sponsor rank (proxy for socioeconomic status [SES]), were obtained from MilCanEpi. Information on cancer diagnosis, including date, tumor stage, tumor grade, tumor location (eg, head of pancreas), lymph nodes examined and lymph nodes positive, metastatic spread, and metastatic site (if applicable) were also gathered from MilCanEpi. Cancer diagnosis and its date were consolidated from the data.[33] Tumor stage was defined in the data as American Joint Committee on Cancer stage I, II, III, IV, or unknown.[35,36] Tumor grade was defined using the American Joint Committee on Cancer criteria as well-differentiated (G1), moderately differentiated (G2), poorly differentiated (G3), nondifferentiated (G4), or unknown differentiation (Gx).[35,36] Patients with stage IV tumors were considered to have metastasis at diagnosis based on the staging criteria.[36] The metastatic site was determined from the cancer registry records and supplemented with patient encounter data when missing using ICD-9-PCS and ICD-10-PCS diagnosis codes for secondary malignant neoplasms.[37–41] For patients with stage I to III tumors, metastasis during follow-up was identified by diagnosis codes for secondary malignant neoplasms in the patient encounter data occurring from the primary cancer diagnosis date until the study end-point at 2 years postdiagnosis or censor date for patients with less than 2 years of follow-up using established algorithms.[37–41] Cancer treatment with primary chemotherapy or palliative radiation therapy was obtained from the data.[33] Patient pre-existing comorbid conditions were summarized using the Elixhauser Comorbidity Index,[42] modified for use in patients with cancer.[43] In addition, diagnosis with jaundice (ICD-9 CM code 782.4 and ICD-10 CM code R17) in the 90 days before or 30 days after cancer diagnosis was determined from the data since it may be a clinical sign of disease and has been identified in association with pancreatic cancer survival.[44,45] Vital status as all-cause death was obtained from MilCanEpi through the end of the data on December 31, 2015.

Statistical Analysis

First, we examined patient demographic, tumor, and treatment characteristics by vital status using χ^2 statistics. Then, we evaluated each characteristic in relation to 2-year survival using univariable Cox proportional hazards regression models to guide variable consideration in a multivariable time-dependent Cox proportional hazards regression model. Diabetes mellitus was considered separately from other comorbidities in the Elixhauser Index due to its well-studied association with pancreatic cancer survival.[10] The multivariable model applied stepwise procedures to select and retain variables in the model. Entry into the model was set at a probability of 0.25, and

variables were retained if the probability in the model was <0.10. Treatment and metastatic spread variables were modeled as time-dependent to reduce immortal time bias.[46–48] The binary variable for chemotherapy treatment (yes/no) was entered into the stepwise process to assess the overall effects of treatment. After the model-building process, the other chemotherapy variables (ie, modality, duration, and volume) were tested individually in independent models containing the other significant variables from the stepwise procedures. Two-year survival time was calculated from the date of cancer diagnosis until death, last record date, censor at 2 years postdiagnosis, or end of study data on December 31, 2015, whichever occurred first. Analyses were conducted in SAS 9.4 (SAS Institute Inc.).

RESULTS

The study included 1148 patients with surgically nonresected pancreatic cancer (Fig. 1). There were 156 patients alive at 2 years postdiagnosis and 992 patients who died. The median survival time for those who died was 127 days (interquartile range 52 to 260). Comparing patients who were alive and who died, those who died tended to be older or have a sponsor rank of commissioned officer (Table 1). Considering diagnosis factors, those who died had later-stage cancer and were more likely to have metastasis and were less likely to have lymph nodes examined (Table 2). Regarding treatment, patients who died were less likely to receive chemotherapy or radiotherapy, to use multiagent chemotherapy, to be treated with chemotherapy for 6 months or more, or to be treated with more chemotherapy treatment sessions (Table 2).

In the univariable analysis of factors related to 2-year survival, age at diagnosis, comorbid conditions, jaundice at diagnosis, diabetes mellitus, tumor stage, tumor grade, tumor location, lymph node results, metastatic spread, and chemotherapy treatment appeared to have individual associations with vital status ($P < 0.10$ for group effects; Table 3). After conducting stepwise selection into the multivariable model, these variables with the exception of diabetes mellitus and tumor stage were retained as independent predictors of survival (Table 4). Older age (ie, 65 to 79, 80 and older) was associated with a higher risk of death compared with patients aged 18 to 49. This association was also demonstrated using age as a continuous variable (data not shown). Patients with a comorbidity burden of 5 or more conditions (adjusted hazard ratio [aHR] 1.30, 95% CI 1.06-1.59) and those with jaundice at the time of pancreatic cancer diagnosis (aHR 1.57, 95% CI 1.33-1.85) had higher risks of death compared with patients without the conditions (Table 4). Race-ethnicity, sex, marital status, SES, and diabetes mellitus were not selected in association with the risk of death.

Regarding tumor variables, patients with poorly differentiated or undifferentiated tumors (G3 or G4) had 32% worse survival compared with patients with well or moderately differentiated tumors (G1 or G2) (Table 4). Patients with tumors located in the pancreas body or tail had 30% and 49% higher risks of death, respectively, than patients with tumors in the pancreas head. Positive lymph node status was not associated with differences in survival compared with patients with negative lymph nodes. However, patients who did not have lymph nodes examined had a 27% higher risk of death compared with patients with negative lymph nodes (Table 3). Patients with metastasis to the liver (aHR 3.13, 95% CI: 2.57-3.81) or to other (aHR 2.56, 95% CI: 2.05-3.19) or unknown (aHR 2.48, 95% CI: 1.98-3.13) sites had a higher risk of death compared with those with no metastasis (Table 4). Tumor stage was not selected into the model.

Regarding treatment, patients who underwent radiotherapy had a 21% increased risk of death than those without the treatment when adjusted for the other variables selected into the model (Table 4). However, this association did not reach statistical significance at the $P < 0.05$ level. Chemotherapy was associated with a statistically significant 34% reduced risk of death compared with no treatment. In the separate models where chemotherapy treatment variables (eg, modality) were tested individually for effects on survival (Table 5), the benefit of chemotherapy was most pronounced for patients receiving multiagent therapy (aHR 0.50, 95% CI: 0.41-0.60 vs. no chemo), patients receiving treatment for 6 months or longer (aHR 0.28, 95% CI: 0.22-0.34 vs. no chemo), or patients receiving 21 or more sessions of chemotherapy.

DISCUSSION

In this study of the US MHS, we identified characteristics related to 2-year survival of highly fatal pancreatic adenocarcinomas. Our data showed the overwhelming importance of tumor features, chemotherapy treatment, and patient comorbidity status in association with survival. In addition, our study also provided important insight into characteristics not selected in association with survival (such as race) once controlling for tumor and treatment features.

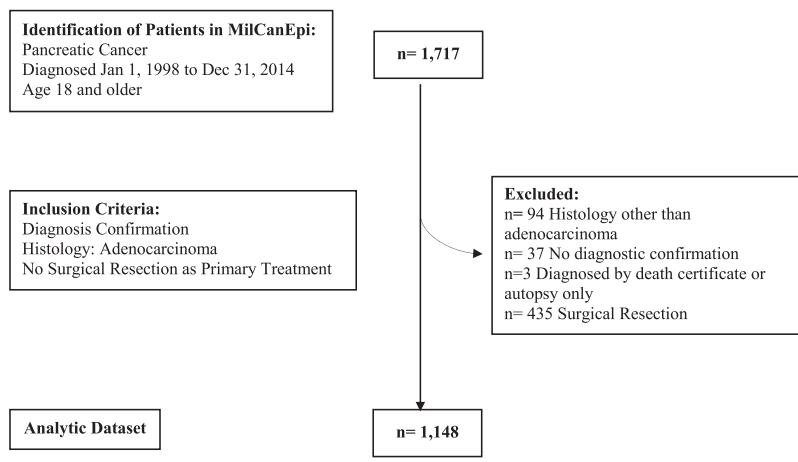

FIGURE 1. Selection of eligible persons into the study of factors related to survival in surgically nonresected pancreatic cancer in the US Military Health System from the Military Cancer Epidemiology database.

TABLE 1. Demographic Characteristics and Comorbidity Status of 1148 Patients With Surgically Nonresected Pancreatic Adenocarcinoma in the US Military Health System, 1998 to 2014 by Vital Status

Characteristic	Patient vital status at 2-y postdiagnosis: Alive N (%)	Died N (%)	*P*
Age at diagnosis	—	—	0.004
18–49	22 (14.1)	68 (6.9)	—
50–64	69 (44.2)	400 (40.3)	—
65–79	50 (32.1)	381 (38.4)	—
80 and older	15 (9.6)	143 (14.4)	—
Sex	—	—	0.709
Men	90 (57.7)	588 (59.3)	—
Women	66 (42.3)	404 (40.7)	—
Race-ethnicity	—	—	0.332
Non-Hispanic White	93 (59.6)	657 (66.2)	—
Non-Hispanic Black	27 (17.3)	154 (15.5)	—
Asian	18 (11.5)	102 (10.3)	—
Other*	18 (11.5)	79 (8.0)	—
Marital status at diagnosis	—	—	0.098
Single	13 (8.3)	41 (4.1)	—
Married	110 (70.5)	754 (76.0)	—
Divorced/widowed/ separated	29 (18.6)	181 (18.2)	—
Unknown	4 (2.6)	16 (1.6)	—
Sponsor rank at diagnosis	—	—	0.018
Enlisted/Warrant Officer	106 (67.9)	646 (65.1)	—
Commissioned Officer	27 (17.3)	254 (25.6)	—
Unknown	23 (14.7)	92 (9.3)	—
Comorbid conditions† at diagnosis	—	—	0.093
0	50 (32.1)	321 (32.4)	—
1	35 (22.4)	194 (19.6)	—
2	35 (22.4)	163 (16.4)	—
3 or 4	22 (14.1)	156 (15.7)	—
5 or more	14 (9.0)	158 (15.9)	—
Diabetes mellitus at diagnosis	—	—	0.190
No	117 (75.0)	693 (69.9)	—
Yes	39 (25.0)	299 (30.1)	—
Jaundice at diagnosis	—	—	0.151
No	126 (80.8)	749 (75.5)	—
Yes	30 (19.2)	243 (24.5)	—

Active-duty status not shown. Frequency of active duty was low in the population (< 5%) and did not differ by vital status ($P = 0.903$).

*Other race-ethnicity includes Hispanic ethnicity, Native American or Alaska Native, multiracial, or unknown race-ethnicity.

†Elixhauser Comorbidity Index, including 24 conditions, exclusive of diabetes mellitus type I or type II, weight loss, lymphoma, metastatic tumor, and solid tumor without metastasis.

TABLE 2. Diagnosis and Treatment Characteristics of 1148 Patients With Surgically Nonresected Pancreatic Adenocarcinoma in the US Military Health System, 1998 to 2014 by Vital Status

Characteristic	Patient vital status at 2-y postdiagnosis: Alive N (%)	Died N (%)	*P*
Tumor stage at diagnosis	—	—	< 0.001
I	15 (9.6)	55 (5.5)	—
II	29 (18.6)	92 (9.3)	—
III	29 (18.6)	87 (8.8)	—
IV	68 (43.6)	695 (70.1)	—
Unknown	15 (9.6)	63 (6.4)	—
Tumor grade	—	—	0.097
G1/G2	32 (20.5)	140 (14.1)	—
G3/G4	21 (13.5)	163 (16.4)	—
Gx	103 (66.0)	689 (69.5)	—
Tumor location	—	—	0.356
Head of pancreas	88 (56.4)	483 (48.7)	—
Body of pancreas	14 (9.0)	105 (10.6)	—
Tail of pancreas	19 (12.2)	147 (14.8)	—
Other	35 (22.4)	257 (25.9)	—
Lymph node results	—	—	< 0.001
Not examined	23 (14.7)	381 (38.4)	—
Positive	44 (28.2)	227 (22.9)	—
Negative	84 (53.8)	365 (36.8)	—
Unknown	5 (3.2)	19 (1.9)	—
Metastatic spread	—	—	< 0.001
None (no metastasis)	56 (35.9)	163 (16.4)	—
Liver	48 (30.8)	480 (48.4)	—
Other site	32 (20.5)	190 (19.2)	—
Unknown metastatic site	20 (12.8)	159 (16.0)	—
Chemotherapy treatment	—	—	0.068
No	77 (49.4)	567 (57.2)	—
Yes	79 (50.6)	425 (42.8)	—
Chemotherapy modality	—	—	0.030
None (no chemotherapy)	77 (49.4)	567 (57.2)	—
Single agent	35 (22.4)	231 (23.3)	—
Multiagent	41 (26.3)	165 (16.6)	—
Not specified or unknown	3 (1.9)	29 (2.9)	—
Chemotherapy duration (mo)	—	—	< 0.001
0 (no chemotherapy)	77 (49.4)	567 (57.2)	—
< 6	16 (10.3)	299 (30.1)	—
6+	63 (40.4)	126 (12.7)	—
Chemotherapy volume (sessions)	—	—	< 0.001
0 (no chemotherapy)	77 (49.4)	567 (57.2)	—
< 10	12 (7.7)	231 (23.3)	—
10-20	16 (10.3)	109 (11.0)	—
21-50	34 (21.8)	82 (8.3)	—
51 or more	17 (10.9)	3 (0.3)	—
Radiation treatment	—	—	0.041
No	130 (83.3)	883 (89.0)	—
Yes	26 (16.7)	109 (11.0)	—

In the MHS, where patients have medical benefits regardless of sociodemographic characteristics, factors such as sex, race-ethnicity, marital status, and sponsor rank (proxy for SES) were not selected in association with survival, despite these factors being identified as possible prognostic indicators in other population-based studies.[12,14,15,18,19,49,50] A study by the California Cancer Registry noted that SES and access to care may help explain disparities in pancreatic cancer treatment and survival between Black and White racial groups.[49] A prior study of the DoD cancer registry data showed no racial differences in treatment or survival for patients with pancreatic adenocarcinomas.[51] Together with our study, this suggests the role of equal access to care in reducing racial health disparities. Factors such as sex and marital status have been less studied,[14,18,19] so the possible role of access to care in reducing observed differences needs more research. Also, there may be no differences in survival by the sociodemographic factors listed above in our study while controlling for tumor and treatment characteristics that were selected into the model.

Regarding treatment, chemotherapy was associated with a 34% reduced likelihood of death at 2 years postdiagnosis. In

TABLE 3. Univariable Associations Between Identified Characteristics and 2-year Overall Survival in Patients With Surgically Nonresected Pancreatic Adenocarcinoma in the US Military Health System, 1998 to 2014

Study characteristic	Hazard ratio (95% CI)	*P*
Age at diagnosis		
18–49	1.00 (reference)	0.086
50–64	1.25 (0.97, 1.62)	<0.001
65–79	1.60 (1.24, 2.07)	<0.001
80 and older	1.98 (1.48, 2.65)	—
Sex		
Men	1.00 (reference)	0.350
Women	0.94 (0.83, 1.07)	—
Race-ethnicity		
Non-Hispanic White	1.00 (reference)	0.115
Non-Hispanic Black	0.87 (0.73, 1.04)	0.654
Asian	1.05 (0.85, 1.29)	0.573
Other	1.07 (0.85, 1.35)	—
Marital status		
Married	1.00 (reference)	0.772
Unmarried*	0.98 (0.84, 1.14)	0.678
Unknown	0.90 (0.55, 1.48)	—
Sponsor rank		
Enlisted (E)/Warrant Officer (WO)	1.00 (reference)	0.964
Officer (O)	1.00 (0.87, 1.16)	0.302
Unknown	0.89 (0.72, 1.11)	—
Comorbid conditions		
0	1.00 (reference)	0.517
1	0.94 (0.79, 1.13)	0.208
2	0.89 (0.73, 1.07)	0.122
3 or 4	1.16 (0.96, 1.41)	0.032
5 or more	1.23 (1.02, 1.49)	—
Diabetes mellitus		
No	1.00 (reference)	0.013
Yes	1.19 (1.04, 1.36)	—
Jaundice at diagnosis		
No	1.00 (reference)	0.019
Yes	1.19 (1.03, 1.38)	—
Tumor stage at diagnosis		
I	1.00 (reference)	0.788
II	0.95 (0.68, 1.34)	0.383
III	0.86 (0.61, 1.21)	<0.001
IV	1.83 (1.38, 2.42)	0.437
Unknown	1.16 (0.80, 1.67)	—
Tumor grade at diagnosis		
G1/G2	1.00 (reference)	<0.001
G3/4	1.55 (1.23, 1.94)	0.003
GX	1.32 (1.10, 1.58)	—
Tumor location		
Head of pancreas	1.00 (reference)	0.047
Body of pancreas	1.24 (1.00, 1.53)	<0.001
Tail of pancreas	1.48 (1.23, 1.78)	0.091
Other	1.14 (0.98, 1.33)	—
Lymph node results		
Negative	1.00 (reference)	0.981
Positive	1.00 (0.84, 1.18)	0.230
Unknown	0.75 (0.48, 1.20)	<0.001
Not examined	1.44 (1.25, 1.67)	—
Metastatic spread		
None (no metastasis)	1.00 (reference)	<0.001
Liver	2.66 (2.22, 3.18)	<0.001
Other site	2.11 (1.71, 2.61)	<0.001
Unknown metastatic site	2.52 (2.02, 3.13)	—
Chemotherapy treatment		
No	1.00 (reference)	<0.001
Yes	0.79 (0.69, 0.91)	—
Radiation treatment		
No	1.00 (reference)	0.056
Yes	0.82 (0.67, 1.00)	—

*Unmarried status includes single, divorced, widowed, or separated.

TABLE 4. Selection of Characteristics Related to 2-year Overall Survival in Patients With Surgically Nonresected Pancreatic Adenocarcinoma Using Stepwise Procedures* in a Time-dependent Cox Proportional Hazard Model

Characteristic	Adjusted hazards ratio (95% CI)†	*P* for overall effect
Age at diagnosis	—	<0.001
18–49	1.00 (reference)	—
50–64	1.04 (0.80, 1.35)	—
65–79	1.40 (1.07, 1.83)	—
80 and older	1.94 (1.43, 2.64)	—
Comorbid conditions	—	0.007
0	1.00 (reference)	—
1	0.90 (0.75, 1.08)	—
2	0.85 (0.70, 1.04)	—
3 or 4	1.16 (0.95, 1.42)	—
5 or more	1.30 (1.06, 1.59)	—
Jaundice at diagnosis	—	<0.001
No	1.00 (reference)	—
Yes	1.57 (1.33, 1.85)	—
Tumor grade	—	0.056
G1/G2	1.00 (reference)	—
G3/G4	1.32 (1.05, 1.67)	—
Unknown	1.20 (0.99, 1.45)	—
Tumor location	—	<0.001
Head of pancreas	1.00 (reference)	—
Body of pancreas	1.30 (1.04, 1.62)	—
Tail of pancreas	1.49 (1.22, 1.83)	—
Other	1.12 (0.96, 1.32)	—
Lymph node results	—	0.006
Negative	1.00 (reference)	—
Positive	1.01 (0.85, 1.19)	—
Not examined	1.27 (1.09, 1.48)	—
Unknown	0.84 (0.53, 1.35)	—
Metastatic spread	—	<0.001
None (no metastasis)	1.00 (reference)	—
Liver	3.13 (2.57, 3.81)	—
Other site	2.56 (2.05, 3.19)	—
Unknown metastatic site	2.48 (1.98, 3.13)	—
Chemotherapy treatment	—	<0.001
No	1.00 (reference)	—
Yes	0.66 (0.57, 0.76)	—
Radiation treatment	—	0.074
No	1.00 (reference)	—
Yes	1.21 (0.98, 1.49)	—

*Entry into the model was set at a probability of 0.25, and variables were retained if the probability was <0.10.

†Model includes adjustment for factors identified in stepwise selection included in Table 4.

further analysis, the greatest risk reductions compared with no treatment occurred for those who received multiagent chemotherapy, received treatment for at least 6 months, or received 21 or more sessions (albeit duration and volume are highly related). This supports the treatment guidelines of using multiagent chemotherapy administered for several cycles as tolerated.[2,4]

Concerning clinical presentation, patients who had metastasis experienced worse survival compared with those with localized disease that did not spread during follow-up. Independent of metastasis, patients who did not have lymph nodes examined had a 27% greater risk of death compared with those who had negative lymph nodes. Tumor stage was not selected into the final model, likely as a result of being highly correlated to and dependent on both metastasis and lymph node involvement as part of staging

TABLE 5. Chemotherapy Treatment Effects Considered in Final Model Created by Stepwise Procedures

Treatment characteristic*†	Adjusted hazards ratio (95% CI)‡	*P* for overall effect
Chemotherapy modality	—	< 0.001
No chemotherapy	1.00 (reference)	—
Single agent	0.80 (0.67, 0.95)	—
Multiagent	0.50 (0.41, 0.60)	—
Administered, modality unknown	0.78 (0.53, 1.15)	—
Chemotherapy duration	—	< 0.001
No chemotherapy	1.00 (reference)	—
< 6 mo	1.16 (0.99, 1.36)	—
≥ 6 mo	0.28 (0.22, 0.34)	—
Chemotherapy volume (sessions)	—	< 0.001
No chemotherapy	1.00 (reference)	—
< 10	1.27 (1.07, 1.50)	—
10-20	0.61 (0.49, 0.77)	—
21-50	0.29 (0.22, 0.37)	—
51 or more	0.06 (0.02, 0.19)	—

*Each treatment characteristic is modeled independently of other treatment characteristics (ie, the model contains 1 treatment characteristic at a time).

†Treatment effects are included as time-dependent variables in the regression model.

‡Model containing individual treatment characteristic and adjustment for age at diagnosis, comorbid conditions, jaundice at diagnosis, tumor grade, tumor location, lymph node results, metastatic spread, and radiation treatment.

criteria.[36] Patients with tumors located in the pancreas body or tail had worse survival compared with patients with tumors in the pancreas head, which has been attributed to differential symptom presentation and treatment receipt by tumor location in the literature.[52,53] Our findings further emphasize the importance of determining disease extent (ie, whether lymph nodes are involved or metastasis has occurred) at diagnosis and tumor location to develop appropriate treatment plans.

A high comorbidity burden and clinical presentation with jaundice at the time of pancreatic cancer diagnosis were associated with a 30% and 57% higher risk of death, respectively. The increased risk of death associated with jaundice has been previously shown[44,45] but generally understudied. Jaundice may develop from biliary obstruction caused by the large head of pancreas tumors and worsen as the tumor persists. Combined with the previous reports, our study data support the importance of managing jaundice symptoms while delivering chemotherapy to improve survival. Diabetes mellitus was not selected into the final model when other factors, such as total comorbidity burden and jaundice, were included. Other studies have demonstrated reduced overall and cancer-specific survival for patients with diabetes and its importance as a prognostic indicator.[9,10,54,55] In our study, it may be that pre-existing diabetes was not selected in association with survival when jaundice was included, as jaundice at the time of cancer diagnosis may be a more relevant clinical indicator of aggressive disease. Nevertheless, our results emphasize the importance of comorbidity in relation to survival after diagnosis of pancreatic cancer.

Patient age at diagnosis was also identified in association with survival, as demonstrated in other population-based studies.[16,17] In our study, patients aged 65 and older had a higher risk of mortality independent of tumor and treatment factors and comorbidities. This finding emphasizes the importance of counseling patients on appropriate treatment options and setting expectations for prognosis in the context of competing health risks.

Although this study provides important insight into potential prognostic indicators among patients with surgically nonresected pancreatic cancer, it is not without limitations. First, we included patients in the study who did not receive surgery as a primary treatment with the assumption that the patients were poor candidates for surgery. It is possible that some patients included in the sample were candidates for surgery, but the surgery was not performed or documented in the data. Next, we cannot exclude the effects of survivor treatment selection bias or immortal time bias on the secondary assessment of chemotherapy duration and volume in relation to survival.[46,56] Although we used a time-dependent Cox regression model, which may reduce survivor treatment selection bias[56,57] and immortal time bias,[46,47] there still remains the possibility that patients who live longer have greater opportunity to receive more sessions and longer duration of chemotherapy, thus affecting the results. Lastly, the demographic attributes of the MHS population may differ from the general US population, affecting the generalizability of the results. However, our study did include a diverse pool of patients in age, race, and sex.

CONCLUSIONS

In a universal health system, sociodemographic characteristics were not related to survival in surgically nonresected pancreatic cancer. Clinical features such as patient comorbidity and jaundice at diagnosis, as well as tumor features such as grade and metastatic spread, were identified in relation to survival. This suggests the potential role of equal access to care in reducing survival disparities in advanced pancreatic cancer observed in the general US population and emphasizes the importance of treating patients based on clinical features.

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