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Clinical Study

Factors Associated with Survival of Veterans with Gastrointestinal Neuroendocrine Tumors

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Background. Gastrointestinal (GI) neuroendocrine tumor (NET) incidence has been increasing; however, GI NET within the national Veterans Affairs (VA) health system has not been described. *Methods*. We used the VA Central Cancer Registry to identify the cohort of patients diagnosed with GI NET in 1995–2009. Cox regression models were constructed to explore factors associated with survival. *Results*. We included 1793 patients with NET of the stomach (9%), duodenum (10%), small intestine (24%), colon (19%) or rectum (38%). Twenty percent were diagnosed in 1995–1999, 35% in 2000–2004, and 45% in 2005–2009. Unadjusted 5-year survival rates were: stomach 56%, duodenum 66%, small intestine 52%, colon 67%, and rectum 84%. Factors associated with shorter survival were increasing age, hazard ratio (HR) 1.05 (95% CI 1.04–1.06), NET location [compared to rectum: stomach HR 2.26 (95% CI 1.68–3.05), duodenum HR 1.70 (95% CI 1.26–2.28), small intestine HR 1.85 (95% CI 1.42–2.42), and colon 1.83 (95% CI 1.41–2.39)], stage [compared to *in situ*/local: regional HR 1.15 (95% CI 0.90–1.47), distant HR 2.38 (95% CI 1.87–3.05)], and earlier period of diagnosis [compared to 1995–1999: 2000–2004 HR 0.70 (95% CI 0.59–0.85), 2005–2009 HR 0.43 (95% CI 0.34–0.54)]. *Conclusions*. The incidence of GI NET has also increased over time in the VA system with similar survival rates to those observed in non-VA settings. Worsened survival was associated with older age, tumor site, advanced stage, and earlier year of diagnosis.

1. Introduction

Neuroendocrine tumors (NETs) arise from the embryologic neuroendocrine system and thus can occur in any location in the body. The gastrointestinal (GI) tract and lungs are the most common primary tumor sites. Based on Surveillance Epidemiology and End Results (SEER) data, NET incidence has increased 300%, up to 5.3 per 100,000, in the last three decades [1]. International data also suggest similar increases, as more recent studies have observed higher incidences than previous studies [2–4]. NET prevalence has also increased to 103,312 in the US population making it more prevalent than adenocarcinoma of the stomach and pancreas combined [1, 5]. Much of the apparent rise in new diagnoses may reflect incidental detection of NET through the increased use of imaging modalities such as computed tomography (CT) scans and endoscopic procedures for other indications rather than a true increase in tumor incidence. NETs are relatively slow growing tumors usually diagnosed late in the clinical course. Retrospective analysis suggests an average delay of nine years between initial onset of symptoms and final diagnosis [6]. Despite the long delay in diagnosis and advanced stage of the disease, the 5-year survival rates are relatively high which also contributes to the disease prevalence [7]. Based on autopsy data, the true prevalence may be closer to 65 to 120 in 100,000 [1, 8–10].

Most information regarding the epidemiology of NET has been derived from the SEER database. Tumor location, size, and histopathology and patient factors such as age, sex, and race have previously been shown to predict survival [1, 9, 10]. While this database is extensive, it is limited to certain regions of the United States. In addition, heterogeneity of patient populations and health care delivery systems could confound some outcomes such as survival. The Veterans Affairs (VA) health system is the largest integrated health system in the US and includes patients from allover the country, and a single healthcare system may provide more homogeneous data. Thus, the Veterans Affairs (VA) population provides an attractive alternative population in which to examine NET characteristics and survival. In addition, factors associated with the survival of patients in a large, integrated system could be used to improve the care of patients within that system. The purpose of this study is to characterize patients with GI NET in the VA system and explore factors associated with survival.

2. Methods

2.1. Setting and Sample. We conducted a retrospective cohort study of VA patients with a new diagnosis of GI NET as identified in the VA Central Cancer Registry (CCR). Patients in the VA CCR with a histological diagnosis of a primary malignant GI neuroendocrine tumor between January 1995 and November 2009 were included in this study. There were no exclusion criteria on the preliminary collection of data. Some subjects were not included in all analyses because of missing data. The cohort began with the year 1995 because only 6 patients with GI NET were identified prior to 1995.

2.2. Data Sources. The VA CCR includes data from 143 VA facilities across the United States. Case ascertainment at each facility was accomplished by searching cytology, pathology, and microscopic data for various specimens by histologic codes, including neuroendocrine tumors. In addition, cancer cases are ascertained by searching clinical data such as radiology. Data for each cancer case were abstracted from clinical records using standardized coding and uploaded to the VA CCR every 6 months. The method of tissue diagnosis, however, is not available in the administrative database [11].

Date of death was ascertained from the VA Vital Status File. The Vital Status File uses data from the Veterans Benefits Administration's (VBA) Beneficiary Identification Records Locator subsystem Death File (BIRLSDF), the Social Security Administration (SSA) Death Master File (DMF), the Medical SAS Inpatient Datasets (MSID), and Medicare database to determine a patient's date of death. The cause of death was not available; therefore, the study outcome was all-cause death. Use of these four sources to ascertain death (BIRLSDF, MSID, SSADMF, and Medicare) was shown to identify 98.3% of all National Death Index (NDI) deaths where NDI is considered the gold standard for mortality data [12].

2.3. Predictor Variables. The CCR database provided patient-level covariates: age, gender, race (which we collapsed into white and nonwhite due to low numbers in some of the nonwhite racial categories), marital status (married, not married), and diagnosis date which we divided into 5-year increments: 1995–1999, 2000–2004, and 2005–2009. Specific tumor data were also obtained including primary tumor location, tumor size, tumor extent (classified as localized, regional, or distant), and treatment.

2.4. Statistical Analysis. Demographic and baseline clinical characteristics were summarized using frequency and percent for categorical characteristics, and means and standard deviations for continuous descriptors. Unadjusted 5-year survival rates from time of diagnosis by NET site were estimated using the Kaplan-Meier method. Unadjusted and adjusted hazard ratio estimates and 95% confidence intervals were also generated using Cox proportional hazards models where patients that were still alive on August 6, 2010 were censored. We ran unadjusted models including each predictor separately and then ran two multivariable survival models. Predictors we evaluated were age, race, marriage status, tumor location, year of diagnosis, cancer stage, and tumor size. In the first adjusted model (Table 2, adjusted model 1), we included all predictors except for tumor size because of the large number of patients missing tumor size data ($n = 818$). As a sensitivity analysis we also ran a multivariable model removing cancer stage as we had about 170 missing a tumor stage diagnosis (Table 2. Adjusted Model 2). The proportional hazards assumption was assessed for all covariates. SAS, Version 9.2 (Cary, NC), was used for all analyses.

3. Results

From 1995 to 2009, there were 1855 patients diagnosed with a primary NET of a digestive organ. We excluded 62 cases that involved the pancreas (38), liver (19), anus (4), and esophagus (1), because the incidences of NET in these organs were small. The remaining 1793 patients had been diagnosed with NET of the stomach, duodenum, small intestine, colon or rectum. The baseline characteristics of this cohort are provided in Table 1. As is typical for a VA population, the subjects were predominantly men, but there was racial diversity. There were 35% non-white subjects, 98% of which were African American. Table 1 lists NET characteristics for the cohort. The most common GI site was the rectum (38%) and the small intestine (24%). The tumor size ranged from 1 mm to 280 mm with a mean of 19.4 mm. Most of the NETs were diagnosed at an early stage, 62% *in situ*/local, but 12% had distant metastasis at diagnosis. Among patients with metastasis, the most common sites were liver (69%), unknown (11%), peritoneum (9%), lung (5%), and lymph nodes (4%).

Sixty nine percent (69%) of patients with GI NETs underwent tumor resection, 3% had unspecified surgery, <1% had tumor destruction, and 0.1% ($n = 2$) were missing information on treatment. In the resection group, there was a negative margin rate of 61%, positive margins of 11%, and 28% with unknown margin status.

There was a steady increase in incidence over time. The incidence increased by 256 cases between 1995–1999 and 2000–2004 time periods. The incidence increased further

Table 1: Demographic and baseline clinical characteristics of veterans with gastrointestinal neuroendocrine tumors ($n = 1793$).

Characteristic	n (%)	Deceased $N = 647$	Not deceased $N = 1146$
Age (years), mean (SD)	62.6 (11.0)	67.2 (11.1)	60.0 (10.0)
Gender			
Male	1725 (96.3%)	635 (98.2%)	1090 (95.1%)
Female	67 (3.7%)	12 (1.9%)	55 (4.8%)
Race			
White	1156 (65.5%)	452 (70.3%)	704 (62.8%)
Non-white	608 (34.5%)	191 (29.7%)	417 (37.2%)
Ethnicity			
Hispanic	88 (4.9%)	22 (3.4%)	66 (5.8%)
Non-Hispanic	1705 (95.1%)	625 (96.6%)	1080 (94.2%)
Marital status			
Married	893 (51.1%)	302 (48.6%)	591 (52.4%)
Not married	856 (48.9%)	319 (51.4%)	537 (48.6%)
GI NET location			
Stomach	166 (9.3%)	71 (11.0%)	95 (8.3%)
Duodenum	186 (10.4%)	70 (10.8%)	116 (10.1%)
Small intestine	431 (24.0%)	229 (35.4%)	202 (17.6%)
Colon	336 (18.7%)	133 (20.6%)	203 (17.7%)
Rectum	674 (37.6%)	144 (22.3%)	530 (46.3%)
Cancer stage			
In situ and localized	1106 (61.7%)	304 (47.0%)	802 (70.0%)
Regional	298 (16.6%)	131 (20.3%)	167 (14.6%)
Distant metastases	218 (12.2%)	136 (21.0%)	82 (7.2%)
Missing	171 (9.5%)	76 (11.8%)	95 (8.3%)
Tumor size (mm), mean (SD)	19.4 (26.4)	24.6 (31.8)	16.9 (23.0)
Treatment			
Surgery	1309 (73.0%)	399 (61.7%)	910 (79.4%)
Radiation	21 (1.2%)	16 (2.5%)	5 (0.4%)
Chemotherapy	71 (4.0%)	45 (7.0%)	26 (2.3%)
Hormone	1(0.1%)	0 (0%)	1 (0.1%)
Biological response modifiers	26 (1.5%)	14 (2.2%)	12 (1.1%)
Year of diagnosis			
1995–1999	363 (20.3%)	260 (40.2%)	103 (9.0%)
2000–2004	619 (34.5%)	262 (40.5%)	357 (31.2%)
2005–2009	811 (45.2%)	125 (19.3%)	686 (59.9%)

Missing data occurred as follows: gender ($n = 1$), race ($n = 29$), marital status ($n = 44$), tumor size ($n = 818$), surgery ($n = 2$), radiation ($n = 5$), chemotherapy ($n = 4$), hormone ($n = 5$), and biological response modifiers ($n = 1$).

with an additional 192 cases between 2000–2004 and 2005–2009 time periods. Thus, the largest percentage of cases (45%) occurred during 2005–2009.

Unadjusted 5-year survival rates from time of diagnosis by site were stomach 56%, duodenum 66%, small intestine 52%, colon 67%, and rectum 84%. In the unadjusted model that included race, non-whites had decreased survival compared to whites; however, in adjusted models, there are no racial differences (Table 2). Survival rates of patients with a rectal tumor site were higher than each of the 4 other sites in both unadjusted and adjusted models (Table 2). Increasing age, not being married, NET location [compared to rectum], stage compared to in situ/local, and earlier period of diagnosis were associated with decreased survival in the adjusted analysis. When cancer stage is removed from the model, the magnitude of the hazard ratio for comparing small intestine and colon to rectum is increased somewhat.

4. Discussion

This study provides the largest sample from a single health-care system and represents a national sample of patients. These data add to our knowledge of GI NET within the VA by providing data on treatment and outcomes. This study adds to our general knowledge of GI NET by providing important information on survival trends and by confirming

Table 2: Descriptives of demographic, clinical factors of survival and Cox regression model results.

	Unadjusted		Adjusted model 1 ($n = 1721$)		Adjusted model 2 ($n = 1721$)	
Characteristic	Hazards ratio	95% CI	Hazards ratio	95% CI	Hazards ratio	95% CI
Age (years)	1.05	1.05-1.06	1.05	1.04–1.06	1.05	1.04-1.05
Race						
White	1.00 (ref)	—	1.00 (ref)	—	1.00 (ref)	—
Non-white	0.79	0.67–0.94	1.02	0.86–1.22	1.02	0.85–1.22
Marital status						
Married	1.00 (ref)	—	1.00 (ref)	—	1.00 (ref)	—
Not married	1.17	1.00–1.37	1.41	1.20–1.65	1.35	1.15–1.58
GI NET location						
Rectum	1.00 (ref)	—	1.00 (ref)	—	1.00 (ref)	—
Stomach	2.48	1.86–3.29	2.26	1.68–3.05	2.38	1.77–3.20
Duodenum	2.26	1.70–3.01	1.70	1.26–2.28	1.79	1.33–2.41
Small intestine	3.16	2.56–3.89	1.85	1.42–2.42	2.45	1.95–3.06
Colon	2.08	1.64–2.63	1.83	1.41–2.39	2.09	1.63–2.68
Year of diagnosis						
1995–1999	1.00 (ref)	—	1.00 (ref)	—	1.00 (ref)	—
2000–2004	0.64	0.54–0.77	0.70	0.59–0.85	0.70	0.58–0.85
2005–2009	0.36	0.28–0.45	0.43	0.34–0.54	0.41	0.32–0.52
Stage						
In situ/localized	1.00 (ref)	—	1.00 (ref)	—		
Regional	1.71	1.40–2.10	1.15	0.90–1.47		
Distant	2.95	2.41–3.61	2.38	1.87–3.05		
Missing	1.72	1.34–2.21	1.67	1.29–2.17		
Tumor size (mm)	1.01	1.00-1.01	—	—		

previous results. We provide results from published studies using SEER data as the context of what is currently known about the survival of patients with GI NET; however, the different methods of collection between the databases do not allow for direct comparisons of the data.

The incidences rates of the stomach, duodenum, small intestine, colon, or rectum were comparable to the most recent review of the SEER data [13]. The only potential discrepancy involves the smaller incidence of pancreatic NET (2%) compared to SEER data (11% of GI NET). The reason remains unclear, but it may be that in the past, the VA did not commonly document pancreatic NET as suggested by the trend of more diagnosis in the latest 5-year period. We did not include the pancreatic NET as well as the liver, esophagus, and anus NET because of the smaller incidences. The incidence rates of the other organs did, however, correlate with new SEER data [13].

Our study shows a 223% increase in incidence GI NET from the time period of 1995–1999 to 2005–2009. Our adjusted analysis found an increased all-cause mortality rate associated with older age, tumor site (compared to rectum), and advanced cancer stage. As expected, those diagnosed in earlier time periods have worse survival than those diagnosed in later time periods.

The increased GI NET incidence is consistent with previous SEER database analyses [1, 10, 13]. In part, this increase is likely related to the increased use of endoscopy. The VA, in particular, has had increased use of colonoscopy for screening and surveillance [14]. Thus, there has been an increased opportunity to incidentally diagnose colon and rectal NET, and this may in part explain the higher percentage of rectal NET in this population (38%) compared to the previous SEER database analysis which has also shown a steady increase in rectal NET [9, 13, 15]. In addition, this VA study cohort had a higher percentage non-white population compared to the previous SEER data analysis by Modlin et al. [9]. Blacks made up the majority of the 35% non-white population in our study, and the Modlin study found the black population to have 2.3 times more rectal NET per population than whites [9].

The unadjusted 5-year survival rate was consistent with previous SEER data, with the rectal NET having the highest survival of 84% (versus 88% 1992–1999 SEER), followed by duodenum at 66%, then small intestine with 52% (1992–1999 SEER data with 63% but did not differentiate between small bowel and duodenum), and colon with 67% (versus 62% 1992–1999 SEER). Classically, rectal NETs have been associated with better survival than NETs from other locations, and this was observed in our population. The better survival is likely due in part to increased incidental diagnosis from endoscopic exams as previously noted. Also, they may have earlier symptoms such as rectal bleeding that would lead to further evaluation and subsequent diagnosis.

The older SEER analysis showed a small and often nonstatistically significant difference in survival between the time period of 1973–1991 and 1992–1999, with an overall 5-year survival of 59.5% and 67.2%, respectively [9]. Another study compared the time period of 1973–1987 and 1988–2004 and found a hazard ratio of 0.73 (95% CI 0.69 to 0.77) for 1988–2004 [1]. The most recent SEER analysis

confirms a trend of increasing 5-year survival in the last 30 years [13]. Our results suggest improved survival when the diagnosis was made in 2005–2009 versus previous time periods. Perhaps this was in part due to the increased incidental findings through increased use of endoscopy and radiographic imaging studies. Part of the improved survival may also reflect that there was a longer period of observation after a diagnosis resulting in an increased opportunity of death during that time period.

Two-thirds of patients diagnosed with GI NET in the VA system had local disease and 70% underwent resection or tumor destruction. We found no difference in survival rates between patients with local disease as compared to those with regional. Although the distribution of stage at diagnosis (i.e., local, regional, and distant metastasis) was similar in this VA population compared to the SEER database, the differences in 5-year survival rates between stages appear attenuated.

Our results should be interpreted in the context of the study's strengths and limitations. VA databases provide considerable linked data, and by examining patients in a single health care system, there may be fewer confounders to outcomes such as survival than in other databases. With its many facilities distributed throughout the country, the cohort we obtained provides a national sample of patients. Admittedly, VA patients are a select population and thus may not be generalizable to other populations. Interestingly and contrary to popular belief, the VA patient life expectancy is very similar to the general US population. A 2009 VA report found that the life expectancy of male veterans was 75.6 years and 80.3 years for female veterans [16]. By comparison, Central Intelligence Agency (CIA) data indicate that the life expectancy of the general US population is 75.8 years for men and 80.8 years for women [17]. There are also limitations of cancer registries that include the observational design, the lack of some clinical details that may also impact survival such as comorbidity status, method of diagnosis (e.g., incidental findings on endoscopy), and missing data for some potentially important covariates (tumor size, treatment). Also, we were not able to subtype the NETs into categories such as insulinoma, gastrinoma, or VIPoma which limits our ability to understand the different types of NET.

In conclusion, the incidence of GI NET has recently increased in the VA population. Our findings indicate that the incidence and prognosis of NETs in veterans are similar to patients in non-VA settings. Since many patients with GI NET have a good prognosis, future studies should examine the role of surveillance after tumor resection or destruction.

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