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Incidence and Survival Patterns of Rare Anal Canal Neoplasms Using the Surveillance Epidemiology and End Results Registry

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Small cell, neuroendocrine tumors, and melanoma of the anus are rare. Limited data exist on the incidence and management for these rare tumors. A large, prospective, population-based database was used to determine incidence and survival patterns of rare anal neoplasms. The Surveillance, Epidemiology and End Results registry was queried to identify patients diagnosed with anal canal neoplasms. Incidence and survival patterns were evaluated with respect to age, sex, race, histology, stage, and therapy. We identified 7078 cases of anal canal neoplasms: melanoma (n = 149), neuroendocrine (n = 61), and small cell neuroendocrine (n = 26). Squamous cell carcinoma (SCC) (n = 6842) served as the comparison group. Anal melanoma (AM) demonstrated the lowest survival rate at 2.5 per cent. Neuroendocrine tumors (NETs) demonstrated similar survival as SCC (10-year survival for regional disease of 25 and 22.3%, respectively). Ten-year survival of small cell NETs resembled AM (5.3 *vs* 2.5%). Age 60 years or older, sex, black race, stage, and surgery were independent predictors of survival. This study presents the largest patient series of rare anal neoplasms. NETs of the anal canal demonstrate similar survival patterns to SCC, whereas small cell NETs more closely resemble AM. Accurate histologic diagnosis is vital to determine treatment and surgical management because survival patterns can differ among rare anal neoplasms.

NEOPLASMS OF THE anal canal are rare malignancies that account for 1.5 per cent of digestive system cancers in the United States.[1] Approximately 6200 cases of anal cancer are diagnosed annually in the United States, resulting in almost 800 deaths.[2] Both tumor histopathology and anatomic location influence the diagnosis, treatment strategy, and prognosis. A key distinction is drawn between tumors located in the anal canal and those arising from the anal margin. The surgical anal canal begins at the dentate line and extends proximally to the anorectal ring, whereas the anal margin is the perianal skin that extends from the anal verge to 5 cm outward on the perineum.[3] There are a variety of lesions that comprise tumors of the anal canal with squamous cell carcinoma (SCC) being the most frequent. Anal melanoma (AM) and neuroendocrine tumors (NETs) are significantly less common and frequently diagnosed incidentally.

Together, AM and NETs of the anal canal comprise less than 5 per cent of all colorectal malignancies.[3] Both are commonly diagnosed at an advanced stage, rendering poor overall prognoses.[4–9] Only surgical resection offers patients with these histologic subtypes of anal cancer a chance for cure.[10–13] However, the choice of operation and the degree of resection remain controversial as a result of the low overall survival rate associated with these rare neoplasms and the negative changes in quality of life that accompany a more radical resection.

Although surgery has been viewed as the mainstay treatment for AM as a result of its poor response to chemoradiation,[14] there are inconsistencies in the clinical management of patients with anal NETs, likely resulting from the poorly characterized diagnostic categorization of this histologic subtype.[15] This inconsistency is largely the result of the rarity of this anal canal

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neoplasm. It has been recognized in the literature that NETs of the gastrointestinal tract can have a spectrum of morphologic features that range from classic small cell carcinoma to large cell NETs,[4, 16–18] and it has been suggested that small cell carcinoma be separated from large cell NETs as a result of differences in certain pathologic characteristics as well as clinical outcomes.[15] However, patients diagnosed with anal canal neuroendocrine tumors have historically been grouped as one histologic subtype when considering prognosis and potential therapeutic options.

A recent incidental finding of an aggressive small cell NET in the pathologic evaluation of a hemorrhoidectomy specimen obtained from a 64-year-old woman with recurrent anal pain previously diagnosed with a thrombosed external hemorrhoid prompted a literature search. Given the rarity of the disease, the search offered limited clinical guidance, consisting of only small case series reports, rendering it difficult to draw definitive clinical conclusions about optimal treatment, management, and prognostic information for this diagnosis. As a result, an investigation of the incidence and survival of rare anal canal tumors using a cancer registry was conducted. This is the first comparative study examining the incidence and survival patterns of rare anal canal neoplasms using a national cancer registry.

Methods

Surveillance, Epidemiology and End Results Registry and Study Population

The Surveillance, Epidemiology, and End Results (SEER) project is a U.S. population-based cancer registry started in 1973 and is supported by the National Cancer Institute and Centers for Disease Control and Prevention. SEER contains data on cancer incidence, prevalence, mortality, and population-based variables, representing now approximately 28 per cent of the U.S. population sampled across multiple geographic regions. The SEER data set also contains information on the primary characteristics of the tumor, including site, spread, and histology when available as well as limited information regarding treatment, excluding chemotherapy.

Data Collection and Analysis

This study was reviewed and approved by the Institutional Review Board at the University of California, San Diego. We queried the SEER registry of the National Cancer Institute from 1973 to 2008 to identify patients diagnosed with anal canal neoplasm involving the following histologic subtypes: SCC, anal melanoma, neuroendocrine, and small cell neuroendocrine. Incidence and survival patterns were evaluated with respect to age, sex, race and ethnicity, marital status, birthplace, state, country of residence, histologic diagnosis, stage, and therapy.

According to the SEER registry, staging is defined by the presence of local, regional, or distant disease at the time of diagnosis (Table 1). The SEER extent of disease coding scheme incorporates size of the primary tumor, extension of tumor, and lymph node involvement. The code is based on clinical, operative, and pathologic diagnoses of the cancer. The size of the tumor is the size before the administration of chemotherapy or radiation therapy. See Table 1 for definitions of stages. Categories of race/ethnicity as defined in SEER were white, black, Asian, Hispanic, American Indian/Alaskan Native, and other/unknown. Marital status was defined as married, never married, divorced, separated, or widowed.

In univariate analyses, log-rank tests were used to compare survival functions, and Kaplan-Meier curves were used to display these functions. Cox multivariate proportional hazard models were used to generate relative risk of death by any cause with 95 per cent confidence intervals controlling for stage, histology, and surgical and chemoradiation treatment. Subset analyses explored the influence and interaction of other variables, including gender, ethnicity, marital status, stage at diagnosis, age at diagnosis, and treatment modality. Age at diagnosis was categorized into patients diagnosed younger than 30 years of age and then increasing in 10-year intervals beginning at age 30 years.

TABLE 1. *Definition of Staging by Surveillance, Epidemiology and End Results*

Stage	Definition
Localized disease	Incidental finding of malignancy in hemorrhoids, invasive intraluminal extension of tumor confined to the mucosa, and localized NOS
Regional disease	Direct extension or nodal involvement; includes extension to ischiorectal fat, perianal skin, perineum, pelvic floor muscles and anorectal sphincters, and vulva, and/or anorectal hemorrhoidal, hypogastric, lateral sacral, perirectal, and superficial inguinal nodes
Distant disease	Involvement of distant lymph node and extension to bladder, broad ligaments, cervix uteri, corpus uteri, pelvic peritoneum, prostate, urethra, vagina, and metastasis

NOS, not otherwise specified.

Statistics

The data were extracted using the latest SEER*Stat software, Version 6.6.2 (Stata Corp., College Stations, TX). Statistical significance was defined as a Type I error probability of < 0.05; all confidence intervals (CIs) are reported as 95 per cent CI.

Results

Incidence

Using the SEER cancer registry, we identified 7078 neoplasms involving the anal canal, most of which were of epidermoid histology. There were 3347 male and 3731 female cases. Consistent with the existing body of literature, SCC comprised the majority of identified cases (97%, n = 6842) with a statistically comparable incidence occurring among men and women. The number of rare anal canal neoplasms was significantly lower with only 149 AMs, 61 NETs, and 26 small cell NET cases.

Age at diagnosis ranged from 27 to 90 years of age with a mean of 56.3 years (standard deviation, 21.7) and a median of 55 years of age. The bulk of cases occurred in the fourth to seventh decades of life. The majority of cases were diagnosed in non-Hispanic whites at 83.9 per cent followed by blacks at 11.5 per cent with just a handful of cases diagnosed in Asians, Hispanics, and Native Americans/Alaskans (Table 2).

Treatment

Overall, the majority of patients diagnosed with carcinoma of the anal canal underwent surgical resection (69.7%) and radiation therapy (58.8%). Surgery was performed in the majority of patients diagnosed with SCC, AM, and NETs of the anal canal. In contrast, only 36.4 per cent of patients diagnosed with small cell NETs underwent surgical resection. The majority of patients with NETs (65.4%) received radiation treatment as well as patients diagnosed with SCC of the anal canal (60.1%). Surgery was the mainstay treatment for patients with AM (95.5%) and NETs of the anal canal (80.0%). In contrast, radiation was rarely used to treat AM (Table 2).

Stage at Diagnosis

Stage at time of diagnosis was significantly different among the various histologic subtypes (Table 3). Patients with SCC and NETs of the anal canal were more likely to be diagnosed at an early stage of the disease. Sixty-six per cent of patients with SCC had localized disease at the time of diagnosis and 72.1 per cent of patients with NETs of the anal canal were diagnosed with local disease. Only 7 per cent of patients with SCC had evidence of distant metastasis at the time of diagnosis. In contrast, small cell NETs of the anal canal were more likely to be diagnosed at later stages: 38.5 per cent with regional disease and 46.2 per cent

TABLE 2. *General Patient Characteristics*

	Total No. (%)	Squamous Cell Carcinoma (no.) (%)	Anal Melanoma (no.) (%)	Neuroendocrine Tumor of the Anal Canal (no.) (%)	Small Cell Neuroendocrine Tumor of the Anal Canal (no.) (%)
Gender					
Male	3347 (47.3)	3256 (97.3)	50 (1.5)	32 (1.0)	9 (0.3)
Female	3731 (52.7)	3586 (96.1)	99 (2.65)	29 (0.8)	17 (0.5)
Age of diagnosis (years)					
< 30	126 (1.78)	125 (1.8)	0 (0)	1 (1.6)	0 (0)
30–39	824 (11.6)	813 (11.9)	4 (2.7)	5 (8.2)	2 (7.7)
40–49	1733 (24.5)	1688 (24.7)	18 (12.1)	20 (32.8)	7 (26.9)
50–59	1612 (22.8)	1573 (23.0)	22 (14.8)	11 (18.0)	6 (23.1)
60–69	1286 (18.2)	1233 (18.0)	37 (24.8)	9 (14.8)	7 (26.9)
70–79	1005 (14.2)	954 (13.9)	38 (25.5)	10 (16.4)	3 (11.5)
80–89	427 (6.0)	401 (5.9)	22 (14.8)	3 (4.9)	1 (3.9)
≥ 90	65 (0.9)	55 (0.8)	8 (5.4)	2 (3.3)	0 (0)
Ethnicity					
Non-Hispanic white	5485 (83.9)	5326 (84.2)	104 (75.9)	37 (67.3)	18 (75.0)
Black	752 (11.5)	730 (11.5)	9 (6.6)	8 (14.6)	5 (20.8)
Asian	164 (2.5)	137 (2.2)	22 (16.1)	5 (9.1)	0 (0)
Hispanic	96 (1.5)	91 (1.4)	2 (1.5)	3 (5.5)	0 (0)
Native American/Alaskan	31 (0.5)	29 (0.5)	0 (0)	2 (3.6)	0 (0)
Unknown/other	13 (0.2)	12 (0.2)	0 (0)	0 (0)	1 (4.2)
Treatment					
Surgery	2276 (69.7)	2623 (68.9)	107 (95.5)	28 (80.0)	4 (36.4)
Radiation	4101 (58.8)	4052 (60.1)	14 (9.6)	18 (30.5)	17 (65.4)
Both	1157	1,143	9	4	1

TABLE 3. *Tumor Staging Characteristics*

	Total No. (%)	Squamous Cell Carcinoma (no.) (%)	Anal Melanoma (no.) (%)	Neuroendocrine Tumor of the Anal Canal (no.) (%)	Small Cell Neuroendocrine Tumor of the Anal Canal (no.) (%)
Local	4619 (65.3)	4512 (66.0)	59 (39.6)	44 (72.1)	4 (15.4)
Regional	1925 (27.2)	1848 (27.0)	60 (40.3)	7 (11.5)	10 (38.5)
Distant	534 (7.5)	482 (7.0)	30 (20.1)	10 (16.4)	12 (46.2)
Total	7078 (100)	6842 (100)	149 (100)	61 (100)	26 (100)

with distant disease. Patients with AM had a fairly equal distribution across stages at the time of diagnosis. The distribution of stage at diagnosis was not significantly different among the races ($P = 0.281$). However, women were found to present with regional (63.1 *vs* 36.9%) and distant (58.8 *vs* 41.2%) disease more frequently when compared with men ($P < 0.001$).

Regardless of stage, patients were more likely to receive surgical resection, whereas radiation was reserved more often for patients with advanced- or late-stage anal cancers (Table 4). The distribution of stage at the time of diagnosis among the different histologic subtypes of anal cancer could explain differences in the surgical approach selected for these patients. Although the frequency of surgical resection decreased with advancing stage, more than half of the patients in all staging categories underwent an operation to treat their anal cancer. There was, however, a significant increase in the frequency of radiation therapy as stage advanced.

TABLE 4. *Treatment by Staging Characteristics*

	Total No. (%)	Local (no.) (%)	Regional (no.) (%)	Distant (no.) (%)
Surgery	2762 (69.7)	1924 (73.7)	703 (64.3)	135 (52.5)
Radiation	4101 (58.8)	2176 (47.7)	1533 (81.3)	392 (75.1)
Both	1157	644	439	74

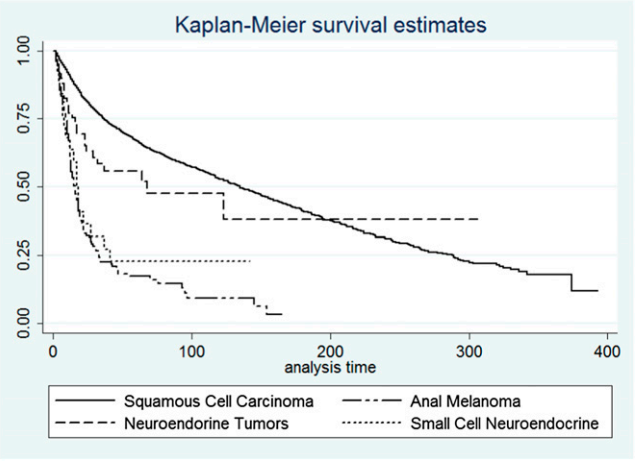

FIG. 1. Kaplan-Meier survival estimates. Kaplan-Meier survival curves illustrate how overall mortality changes with histology. Overall survival of SCC was similar to that of NETs. However, AM demonstrated significantly worse overall survival compared with SCC. Small cell NETs demonstrated a similar survival trend to that of AM rather than with other NETs of the anal canal. Log-rank test, $P < 0.0001$. SCC, squamous cell carcinoma; NETs, neuroendocrine tumors; AM, anal melanoma.

Survival

Survival analysis revealed significant differences in 10-year survival rates among the four histologic subtypes (Fig. 1). SCC had the highest 10-year survival rates (27.8%) followed by NETs of the anal canal (16.7%). Small cell NETs and AM demonstrated dismal 10-year survival rates at 5.3 and 2.5 per cent, respectively. Kaplan-Meier analysis revealed similar survival trends between AM and small cell NETs. Conversely, NETs of the anal canal demonstrated survival trends that more closely resembled that of SCC. In Cox regression analysis, AM was associated with significantly worse prognosis compared with SCC (hazard ratio [HR], 3; 95% CI, 2.3 to 3.8). There was a trend to worsening prognosis of NETs and small cell NETs compared with SCC with small cell NETs demonstrating a slightly worse HR to NETs, although not statistically significant (Table 5). This divergence in 10-year survival by histologic subtype was more significant when reviewed by stage (Table 6). NETs of the anal canal followed a similar trend to that of SCC, whereas small cell NETs more closely resembled AM.

In multivariate analysis, protective demographic factors included only female gender with an odds ratio (OR) of survival at 10 years of 2.0 (95% CI, 1.5 to 2.7; $P < 0.001$) compared with their counterparts (Table 7). However, age older than 60 years, black race, and stage at diagnosis were all found to be poor prognostic factors in predicting 10-year survival. Although surgery was a significant predictor of survival with an OR of 33.6 (95% CI, 13.6 to 83.1; $P < 0.001$), radiation therapy was not.

Discussion

Neoplasms of the anal canal are uncommon and infrequent neoplasms of the digestive tract. SCC, the most common lesion found in the anal canal, comprised 97 per cent of the cases identified using the

TABLE 5. *Survival Analysis by Histologic Subtype*

Histologic Subtype	Cases	10-year Survival	Adjusted HR (95% CI)	*P*
Squamous cell carcinoma	6842	27.8%	—	—
Neuroendocrine	61	16.7%	1.2 (0.7–2.1)	0.457
Small cell neuroendocrine	26	5.3%	1.5 (0.6–3.6)	0.395
Anal melanoma	149	2.5%	3 (2.3–3.8)	< 0.001

HR, hazard ratio; CI, confidence interval.

TABLE 6. *Ten-year Survival of Histologic Subtypes by Stage*

Histologic Subtype	Local Disease	Regional Disease	Distant Disease
Squamous cell carcinoma	36.8%	22.3%	5.1%
Neuroendocrine tumor	23.5%	25%	0%
Small cell neuroendocrine tumor	50%	0%	0%
Anal melanoma	4.7%	2.0%	0%

TABLE 7. *Independent Predictors of Survival*

Predictors	Adjusted R^2 (95% CI)	*P* Value
Age ≥ 60 years	0.4 (0.2–0.9)	0.036
Female	2.0 (1.5–2.7)	< 0.001
Black race	0.6 (0.4–0.8)	0.005
Stage	0.6 (0.4–0.7)	< 0.001
Surgery	33.6 (13.6–83.1)	< 0.001
Radiation	0.8 (0.6–0.97)	0.029

CI, confidence interval.

SEER cancer registry. Rare anal canal neoplasms such as AM, small cell NETs, and NETs comprised the remaining 3 per cent of cases (AM 2%, NETs and small cell NETs 1%). Overall, the optimal treatment strategy and outcome are highly dependent on location and histopathology of the anal neoplasm. As a result of the rare occurrence of AM, NETs, and small cell NETs, limited data exist in the literature, and the literature that is available mostly consists of small case series making it difficult for one to draw definitive conclusions about optimal treatment strategies and prognostic expectations.

Historically, SCCs of the anal canal were treated with abdominoperineal resection (APR) until treatment was revolutionized in the 1970s by Nigro and colleagues,[19, 20] who demonstrated that chemoradiation achieved survival and recurrence rates equivalent to those achieved with surgery and preserved sphincter function. For the approximately 30 per cent of patients with persistent or recurrent disease after chemoradiation, APR is performed and achieves 5-year survival rates between 24 and 58 per cent.[21] The traditional treatment with surgery in patients with SCC could explain our findings of a high surgical intervention rate at nearly 70 per cent in such patients. In addition, we queried the database for rate of surgical procedures performed at the site of diagnosis, defined as a surgical procedure that removes and/or destroys tissue of the primary site, performed as part of the initial workup or first course of therapy. Because a surgical biopsy is included in this definition, it could further explain a higher-than-expected surgical intervention rate in patients diagnosed with SCC.

Anal melanoma does not share the same outcome or prognosis with anal SCC. First reported by Moore[22] in 1857, AM was found to be a rare and aggressive malignancy that accounts for 2 to 4 per cent of all malignant neoplasms of the anus and rectum.[23–25] Diagnosis is often delayed because of nonspecific presenting symptoms indistinguishable from other benign conditions in this region (hemorrhoid, rectal polyp, or rectal prolapse), and thus it is often misdiagnosed.[26, 27] The correct diagnosis is usually established at a late stage, which results in a poor overall survival.[7–9] Because AM responds poorly to chemoradiation, surgery is the mainstay treatment.[10, 14] However, as a result of its poor prognosis, the debate continues as to the optimal surgical management for anorectal melanoma. Initially it was suggested that aggressive surgical intervention resulted in better survival, and local excision led to higher recurrence rates. However, more recent reports have concluded that there is no difference in survival rates in patients with AM treated with wide local excision *versus* APR.[28, 29]

NETs of the anal canal are exceedingly rare, and the histogenesis of these tumors is poorly understood. Traditionally, colorectal NETs were classified as low-grade or high-grade NETs based on number of mitoses per high-power field and degree of tumor necrosis.[15] Current literature, however, suggests that high-grade NETs follow a spectrum of morphologic features, ranging from classic small cell carcinoma to large cell neuroendocrine carcinoma. A retrospective review of the Memorial Sloan-Kettering Cancer Center pathology database by Shia et al.[15, 30–34] revealed different pathologic and clinical characteristics of three subtypes (small cell, mixed-cell, and large-cell NETs), which led the authors to suggest separating small cell carcinoma from large cell and mixed NETs.

The outcome of the case presentation of the patient with an incidental finding of a NET in a hemorrhoidectomy specimen was poor. Further medical evaluation with a positron emission tomography and computed tomography imaging study revealed evidence of widespread metastases. A biopsy of a suspicious left inguinal lymph node confirmed the presence of metastatic small cell NET. Chemotherapy and palliative options were reviewed with the patient in the setting of metastatic disease and the patient elected to

pursue hospice care and died within 4 months of the initial diagnosis.

Our review of the SEER database revealed similarly poor survival rates of AM and small cell NETs. Although not statistically significant, the differences in survival patterns supported the theory of histologically separating small cell from neuroendocrine tumors. Furthermore, these differences may also have a significant impact on the optimal management of patients diagnosed with these rare histologic subtypes. Another reason for the differences in outcome could be related to the late stage at presentation of patients with AM and small cell NETs, further illustrating the importance of early diagnosis and the diagnostic challenge of these rare cancers.

One limitation of this study is that the SEER database represents only 28 per cent of the U.S. population. The National Health Institute collects information from specific geographic regions. Furthermore, changes in the diagnostic criteria since the initiation of SEER data collection may have resulted in underreported anal canal cancer cases in the SEER registry. This, plus the small sample size of NETs of the anal canal, made it difficult to extrapolate true 10-year survival rates to draw definitive conclusions. There is also the inherent recognition that findings from any database are dependent on the quality of the data that are originally entered. Hence, the evaluation of the data in the SEER data set is dependent on the accurate evaluation of each patient's histologic data, underscoring the important role that the surgeon and pathologist play in creating a database that is as accurate as possible. There is also limited information on lymph node status because this information has only recently been collected as part of the SEER database within the past decade. Nevertheless, this is the largest study to analyze the incidence and survival patterns of patients with neoplasms of the anal canal.

Anal melanomas and neuroendocrine tumors of the anal canal continue to be diagnostic and therapeutic challenges. The prognostic considerations and surgical approaches for these tumors should be guided by age, stage, nodal involvement, and tumor histopathology. Early diagnosis and early surgical intervention are imperative.[30–35] It is estimated that a large number of patients with small cell NETs and AM will have evidence of metastatic disease at the time of diagnosis. NETs and AM remain diagnostic challenges as a result of their nonspecific symptoms making early diagnosis extremely difficult. Further investigations are necessary to understand the differences in tumor behavior based on tumor morphology as well as to develop novel diagnostic screening measures and targeted therapies to improve the outcomes of these rare, aggressive anal canal neoplasms.

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