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Original article

Genitourinary paraganglioma: Demographic, pathologic, and clinical characteristics in the surveillance, epidemiology, and end results database (2000–2012)

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Abstract

Background: Extra-adrenal paragangliomas (PGLs) are infrequent, benign, and neuroendocrine tumors arising from chromaffin cells of the autonomic nervous system. Most PGLs are sporadic, but up to 32% are associated with inherited syndromes such as neurofibromatosis type 1, von Hippel-Lindau disease, and familial PGL. Although most PGLs develop above the umbilicus, they have been reported in the genitourinary (GU) tract. Owing to the paucity of literature on the rates of GU PGL, the objective of our study is to describe the demographic, pathologic, and clinical characteristics of GU PGL, and compare them to non-GU sites of PGL using the surveillance, epidemiology, and end results (SEER) database.

Methods: The SEER 18 database was used to identify all cases of PGL from 2000 to 2012. Demographic, pathologic, and clinical characteristics were described using chi-square and *t*-test for categorical and continuous variables, respectively. The Kaplan-Meier method was used to compare overall survival (OS) between GU and non-GU PGL. Statistical significance was defined as $P < 0.05$. All analyses were performed using excel and SAS/Stat version 9.4.

Results: A total of 299 cases of PGL were retrieved from SEER, and 20 (6.7%) of the total PGL arose from the GU tract. The mean age at diagnosis was higher in non-GU than GU PGL (50.4 ± 17.2 vs. 40.8 ± 15.6, $P = 0.026$). Furthermore, 83.3% of GU PGLs developed in the bladder, followed by the kidneys/renal pelvis (16.7%), and spermatic cord (2%). Non-GU PGL developed most frequently within the endocrine system (43%). PGL, overall, was more common in men than in women, and it was more common in whites than all other races. Although 55.5% of GU PGLs were organ confined, only 22.2% of non-GU PGLs were localized at diagnosis. All cases of PGL were treated with surgery. There were 2 cause-specific deaths in the GU PGL groups between 2000 and 2012. The 5-year OS was 93.3% for GU PGL vs. 65.5% in non-GU PGL ($P = 0.062$).

Conclusions: GU PGL remains rare with low incidence (6.7% of all PGL cases) in the US population between 2000 and 2012. Bladder PGL represents just 5% of all PGL. Moreover, GU PGL had better OS compared to PGL developing outside of the GU tract although the *P*-value only approached statistical significance. The bladder represents the most common site of involvement, and surgery is the mainstay of treatment for GU PGL. Clearer prognostic factors, including tumor grade and stage, are needed to better elucidate PGL management in the future; thus, pooled studies from various institutions with detailed clinical information are needed to delineate these prognostic factors.

Keywords: Paraganglioma; Genitourinary tumors; Bladder cancer; SEER database; Epidemiology

1. Introduction

Extra-adrenal paragangliomas (PGLs) are infrequent, benign, and neuroendocrine tumors arising from neural crest–derived cells of the autonomic nervous system. PGLs can be further classified into sympathetic or parasympathetic types [1–4]. Sympathetic PGLs arise from chromaffin cells distributed along the sympathetic chain and typically secrete catecholamines [4]. Parasympathetic PGLs arise from the ganglia distributed along the parasympathetic chain, are usually nonfunctional, and are

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generally localized in the base of the skull and neck [1,5,6]. Most PGLs are sporadic, but up to 32% are associated with inherited syndromes such as neurofibromatosis type 1, von Hippel-Lindau disease, and familial PGL [5,7].

The rarity of PGLs makes prevalence difficult to predict particularly in locations such as the genitourinary (GU) tract [5]. PGLs have been found in the kidney and renal pelvis, ureters, urethra, prostate gland, as well as in the bladder [8–10]. Of these sites, the bladder is the most common (79.2%) [9,10]. Regardless, bladder PGLs remain extremely rare, accounting for less than 0.06% of all bladder neoplasms and 6% of PGLs [4,10–18]. Approximately 17% of bladder PGLs are nonfunctional, while the majority cause paroxysmal symptoms such as headache, diaphoresis, and palpitations [9]. The triad of hypertension, intermittent painless hematuria, and the aforementioned paroxysmal symptoms upon micturition or sexual activity is considered nearly diagnostic of bladder PGLs and is present in roughly 50% of patients [4,6,9,10].

Most bladder PGLs are benign but 13% to 20% have been reported as malignant, when malignancy is defined as metastases in areas where chromaffin tissue is uncommon [3,9,11,19]. Most PGLs are treated conservatively, with surgery [1–20] which is typically curative in nonmetastatic disease [10]. Owing to the paucity of literature on PGLs in GU tract, our study aims to describe demographic, pathologic, and clinical characteristics of GU PGLs and compare them with PGLs occurring at non-GU sites using a population-based database.

2. Methods

The National Cancer Institute developed the surveillance, epidemiology, and end results (SEER) program that remains the leading comprehensive population-based cancer incidence and survival registry in the United States. The SEER 18 database was used to identify all cases of PGL from 2000 to 2012. This database uses the International Classification of Disease for Oncology, third edition (ICD-O-3) for histology coding and collects data from 18 state registries representing approximately 27.8% of the US population. Histology codes used for identification of PGL cases were 8680, 8683, 8690, 8691, 8692, or 8693.

Demographic information in this population-based study included patient sex, race, age at diagnosis, year of diagnosis, and survival status as of December 31, 2012. Race was classified into white, black, and other (American Indian/Alaska Native, Asian or Pacific Islander, and unknown). Age at diagnosis was divided into 3 groups: 0 to 29, 30 to 59, and 60 to 85+.

Pathologic characteristics included tumor stage, grade, and location. Tumors were categorized as localized, regional, distant, unknown, or missing according to the SEER staging system. Location was categorized by region: eye and orbit, brain and nervous system, oral cavity and pharynx, digestive system, respiratory system, bone and joints, and soft tissue including the heart, endocrine system, female genital system, male genital system, urinary system, and miscellaneous. Subcategorization of tumors by exact location was done for the male genital system (subcategorized into prostate, testis, penis, and spermatic cord) and the urinary system (subcategorized into bladder, kidney and renal pelvis, ureter, and others).

Clinical variables included radiation therapy, surgery, or both, lymph node (LN) dissection, and 5-year relative survival. Radiation therapy was defined by 3 categories: performed, unknown, and none. Surgery was defined as performed or none. LN dissection was defined by 3 categories: performed, unknown, and none.

SEER*Stat software (Surveillance Research Program, National Cancer Institute SEER*Stat software, seer.cancer.gov/seerstat, version 8.3.2, NCI) was used to analyze incidence rates and trends from 2000 to 2012. All incidence data were age adjusted and normalized to the 2000 U.S. standard population. Demographic, pathologic, and clinical characteristics were described using chi-square and *t*-test for categorical and continuous variables, respectively. The Kaplan-Meier method was used to compare overall survival (OS) between GU and non-GU PGLs. The log rank test was used to determine statistical significance of the unadjusted comparison. All analyses were performed using excel and SAS/Stat version 9.4. Statistical significance was defined as $P < 0.05$.

3. Results

3.1. GU and non-GU PGL

A total of 299 patients with PGL were identified in the SEER database between 2000 and 2012. Furthermore, 279 (93.3%) were non-GU PGLs, whereas GU PGLs were found in 20 (6.7%) cases (Table 1). The median age at diagnosis was 43 years for GU PGLs and 47 years for non-GU PGLs ($P = 0.989$). Most PGLs (70% vs. 58.4% in GU and non-GU, respectively) were diagnosed in patients with ages between 30 and 59 years. Table 1 describes the demographic, pathologic, and clinical characteristics of patients with GU and non-GU PGLs.

Compared to non-GU PGLs, more GU PGLs were described as localized (55.5% vs. 22.2%, $P = 0.002$). The urinary bladder was the most common site of GU PGLs with 83.3% of GU PGLs developing in the urinary bladder. The most common site for non-GU PGLs was the endocrine system (43% of all non-GU PGLs).

Radiation was performed on 37.6% of non-GU PGLs but on none of the GU cases ($P = 0.002$). LN dissection was performed in 30% ($n = 6$) of GU PGLs and 27.6% ($n = 77$) of non-GU PGLs. There were 2 deaths (10%) due