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Genitourinary Paraganglioma: Demographic, Pathologic, and Clinical Characteristics in the Surveillance, Epidemiology, and End Results (SEER) Database (2000–2012)

Stephanie Purnell¹, Abhinav Sidana¹, Mahir Maruf¹, Campbell Grant², and Piyush K. Agarwal¹

¹Urologic Oncology Branch, National Cancer Institute, Bethesda, MD

²Department of Urology, George Washington University Hospital, Washington, DC

Abstract

Background—Extra-adrenal paragangliomas (PGLs) are infrequent, benign, neuroendocrine tumors arising from chromaffin cells of the autonomic nervous system. The majority of PGLs are sporadic but up to 32% are associated with inherited syndromes such as neurofibromatosis type 1, von Hippel-Lindau disease, and familial paraganglioma. While most PGLs develop above the umbilicus, they have been reported in the genitourinary (GU) tract. Due to the paucity of literature on the rates of GU paraganglioma, 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 utilized to identify all cases of PGL from 2000–2012. 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 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—299 cases of PGL were retrieved from SEER. 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 , $p=0.026$). 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 women, and it was more common in whites than all other races. While 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 overall survival was 93.3% for GU PGL versus 65.5% in non-GU PGL ($p=0.062$).

Corresponding Author: Dr. Piyush K Agarwal, Urologic Oncology Branch, National Cancer Institute, 10 Center Drive 2W-5940, Building 10, MSC 1210, Bethesda, MD 20892, Office: 301-496-6353, Fax: 301-480-5626, piyush.agarwal@nih.gov.

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Conclusions—Genitourinary 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. Also, GU-PGL had better overall survival 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.

Introduction

Extra-adrenal paragangliomas (PGLs) are infrequent, benign, 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 catecholamines⁴. Parasympathetic PGLs arise from the ganglia distributed along the parasympathetic chain, are usually non-functional, and are generally localized in the base of the skull and neck^{1,5,6}. The majority of PGLs are sporadic but up to 32% are associated with inherited syndromes such as neurofibromatosis type 1, von Hippel-Lindau disease, and familial paraganglioma^{5,7}.

The rarity of PGLs make prevalence difficult to predict particularly in locations like the genitourinary (GU) tract⁵. Paragangliomas have been found in the kidney and renal pelvis, ureters, urethra, prostate gland, as well as in the bladder^{8,10,12}. Of these sites, the bladder is the most common (79.2%)^{10,12}. Regardless, bladder PGLs remain extremely rare, accounting for less than 0.06% of all bladder neoplasms and 6% of paragangliomas^{4,9,12–19}. About 17% of bladder PGLs are nonfunctional, while the majority cause paroxysmal symptoms such as headache, diaphoresis, and palpitations¹⁰. 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^{4,6,10,12}.

Most bladder PGLs are benign but 13–20% have been reported as malignant, when malignancy is defined as metastases in areas where chromaffin tissue is uncommon^{3,9–11}. Most PGLs are treated conservatively, with surgery^{1–20} which is typically curative in non-metastatic disease¹². Due 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 to PGLs occurring at non-GU sites using a population based database.

Methods

The National Cancer Institute (NCI) developed the Surveillance Epidemiology and End Results (SEER) program which remains the leading comprehensive population-based cancer incidence and survival registry in the United States (US). The SEER-18 database was utilized to identify all cases of paraganglioma from 2000–2012. 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 gender, 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 three groups: 0–29, 30–59, and 60–85+.

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, 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 other).

Clinical variables included radiation therapy and/or surgery, lymph node (LN) dissection, and 5-year relative survival. Radiation therapy was defined by three categories: performed, unknown, and none. Surgery was defined as performed or none. Lymph node dissection was defined by three 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 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 $p < 0.05$.

Results

GU and non-GU paraganglioma

A total of 299 patients with paraganglioma were identified in the SEER database between 2000 and 2012. 279 (93.3%) were non-genitourinary (non-GU) PGLs while genitourinary 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 ($p = 0.989$). The majority of PGLs (70% vs. 58.4% in GU and non-GU, respectively) were diagnosed in patients with ages between 30 to 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 ($p = 0.002$). Lymph node 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 to GU PGLs and 67 (24%) deaths due to non-GU PGLs during the study period. The 5-year cause-specific survival (CSS) for GU PGLs was 100%; the two patients that died from GU PGLs died at 69 and 72 months. Overall survival (OS) was greater for the GU PGLs group compared to the non-GU PGLs group (5-year OS 93.3% and 65.5% respectively, $p = 0.0624$) as seen in Figure 1.

Bladder paraganglioma

Fifteen cases of bladder PGLs, representing 5% of all paragangliomas, were documented in the SEER database between 2000 and 2012. The demographic and clinical findings of those patients with paraganglioma of the bladder are summarized in Table 2. In the bladder, paraganglioma was most commonly treated with partial cystectomy (40%), followed by transurethral resection of the bladder (20%), complete cystectomy with reconstruction (13.3%), radical cystectomy plus ileal conduit (6.7%), radical cystectomy plus continent diversion (6.7%), and radical cystectomy plus orthotopic diversion (6.7%). Lymph nodes were removed in 40% of bladder PGLs. One patient died during the study period with the overall 5-year survival of 93.3%.

Discussion

Consistent with current literature, GU PGLs remains a rare neoplasm representing 6.7% of all paragangliomas and 0.002% (20/1,157,760) of all GU cancers in the SEER database between 2000 and 2012. The most common location of non-GU PGLs was the endocrine system including the carotid and aortic bodies as well as the thyroid gland. This finding correlates well with published studies which report the head and base of the skull as the most common sites of PGL development^{1,5-6,26}. The digestive system was the second most common location of non-GU PGL development. Within that system, the retroperitoneum developed the most (77%) PGLs. This finding is noteworthy as most abdominal PGLs arise around the organ of Zuckerkandl which commonly presents as a retroperitoneal mass¹⁵.

Overall, extra-adrenal paragangliomas represent ~15% of adult and 30% of childhood PGLs²³, with the primary treatment being surgery^{12,25}. Variation in treatment, using radiation or chemotherapy, is at times useful in patients with advanced disease or those who are elderly²⁶. In our analysis, all patients with GU PGLs were treated surgically. Those with non-GU PGLs were also treated with surgery, but 37.6% of cases also had radiation. This finding is likely partially explained by the fact that up to 34.7% of non-GU PGLs cases were diagnosed at the distant stage; radiotherapy has typically been relegated to the treatment of advanced disease or for the elderly or medically unstable²⁶.

Bladder paraganglioma makes up less than 1% of all bladder neoplasms^{11,13,17,21}, and is the most common site of GU PGLs. Our findings are consistent with other studies that have shown that the urinary bladder is the most common site for PGLs in the genitourinary tract^{11,13,21}. The urethra, renal pelvis, and the ureter are the next most common sites, respectively, for PGLs in the GU tract^{11,13}.

While most cases of bladder PGL involve the submucosa and lamina propria^{4,12}, the most common location of involvement within the bladder is less clear. One case series reported PGL distribution throughout the bladder wall¹⁷, while another case series found PGL to be located in the anterior, lateral, and posterior walls as well as the trigone¹¹. Bladder PGLs have been described as most prevalent in the lateral and posterior walls and can be multifocal¹⁶, however, others have also reported that they are most commonly situated at the dome or trigone¹¹. In our investigation, PGLs were found throughout the bladder, except in the anterior wall and trigone.

Pal and Priyadarshi, Ranaweera and Chung, Cheng et al, and Pastor-Guzmán et al agree that bladder PGLs are more common in women^{11,16–17,21}. Our study determined that PGLs in all locations, including the bladder, are more frequent in men. Alternatively, there is general disagreement about the age of diagnosis among patients with bladder PGLs. Hereditary paraganglioma is believed to present earlier than the sporadic type⁸ but autopsy series have shown that many PGLs remain undiagnosed⁵ which has implications for the time of presentation and the age of diagnosis. The mean age at diagnosis for bladder PGLs is 44 years based on SEER 18 data. This is similar to what was found by Cheng et al who reported a mean age of 45 years at diagnosis¹⁶.

Martucci et al found patients with bladder PGLs to have a mean age of 29.4 years at diagnosis⁹. The patients in this study were followed closely due to inherited conditions associated with mutations of genes including von Hippel-Lindau and succinate dehydrogenase. As a result, it is possible that these patients were diagnosed earlier in life due to frequent evaluations and imaging studies earlier on in life. Without a hereditary condition being regularly monitored, bladder PGLs may go undiagnosed until later in life when symptoms present. Studies also suggest that, if questioned, patients may recall the presence of non-specific symptoms (i.e. paroxysmal headache or palpitations) as early as the first and second decades of life and that the development of other more troublesome symptoms associated with PGLs may not occur or be reported until later on in life^{17,21}. Coupled with the fact that this neoplasm is rare, bladder PGLs may not be properly suspected in a patient with the tumor prolonging an investigation and the diagnosis of PGL. Given this variability, it is important that physicians are attentive to unexplained hypertension, headache, palpitations, hematuria and other nonspecific but associated symptoms.

As with other types of PGLs, surgery is the primary treatment for localized bladder PGLs. Surgical resection with partial or complete cystectomy combined with pelvic lymph node dissection is advised⁴. Surgical management is mainly dictated by the size and location of the tumor. In our study, partial cystectomy was most commonly performed followed by TURBT and then complete cystectomy. Radiation is not employed often, unless there is

advanced disease, because it is less effective¹⁵. Our data support this as none of the bladder paragangliomas in Table 1 were treated with radiation therapy.

Intraoperative risks can be limited using the appropriate preoperative medical treatment to block the effects of catecholamines 10 to 14 days prior to surgery^{15,19}. All patients with paraganglioma, including those with normal catecholamine levels, should receive appropriate preoperative medical management to block the effects of released catecholamines^{15,26}. Phenoxybenzamine, an alpha adrenoceptor blocker, is most commonly used for preoperative control of blood pressure. A beta adrenoceptor blocker may be used for preoperative control of tachyarrhythmias or angina^{18,19}. Finally, volume contraction associated with chronic vasoconstriction can be seen in patient with paraganglioma; thus, preoperative volume expansion with saline infusion is recommended to decrease postoperative hypotension²⁷. Intra-operative intervention may be necessary for excess catecholamine release. Phentolamine or nitroprusside can be used prior to removing the tumor^{21,26}. Vasopressin may be used subsequent to tumor if there is catecholamine deficiency²⁷. This is a carefully orchestrated process requiring communication between the surgeon and anesthesiologist.

To determine if paraganglioma resection is complete, the patient should have a 24-hour urinary catecholamine and catecholamine metabolite test two weeks after their surgery; if the levels are normal, the resection is complete^{9,16}. Lastly, because recurrence is possible, periodic follow-up is recommended for all cases of PGLs with plasma metanephrines, and CT or MRI as indicated^{13,14,16}. Since most cases of bladder PGL are localized, the prognosis is generally excellent. Only one patient died due to bladder PGL in our study, which correlates with the high (100%) cause-specific 5-year survival ascertained.

Our investigation has numerous limitations. SEER 18, as a database, represents 27.8% of the US population and does not capture all the cases of PGLs in the US as evidenced by the 27 cases of bladder PGLs described in the study by Martucci et al⁹. In addition, SEER only roughly characterizes the US population because most cancers reported likely represent patients who live in urban areas and are foreign-born because SEER has a higher proportion of US Native Hawaiian, Pacific Islander, Asian, American Indian, Alaskan native, and Hispanic populations as compared to the white and black populations²². This retrospective study also lacks many very important parameters on diagnosis and treatment of paraganglioma leading to potential bias in our analysis. As is typical with many large database studies, preoperative data, immunohistochemistry, TNM stage, grade, biological and genetic assessment, co-morbidities, concomitant treatment, and radiographic findings were incomplete preventing us from being able to more precisely describe the paragangliomas. There also appears to be underreporting of radiation therapy within the SEER database²¹. Other limitations of using SEER 18 for our analysis include the absence of data on the rates of primary cancer recurrence, site(s) of metastases, patient comorbidities, reoperations, and relevant biochemical laboratory studies. In order to better understand PGLs, pooled analyses of cases from several large centers in the US are needed.

Conclusion

In conclusion, GU paragangliomas are rare neoplasms in the US population with a better 5-year survival than PGLs developing outside of the genitourinary tract. The urinary bladder is the most common site of GU PGLs while GU PGLs represents roughly 20% of all PGLs. Clear prognostic factors must be established to better elucidate the management of PGLs. Due to the limited scope of data available in SEER, it is difficult to give consistent conclusions based on this data alone. Resultantly, pooled studies from various institutions with detailed clinical information, including but not limited to tumor stage, grade, immunohistochemistry, and treatment are needed to delineate these prognostic factors. Future studies should incorporate this pooled data with that found in SEER to comprehensively describe genitourinary paragangliomas.

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Highlights

- Genitourinary paragangliomas are rare, representing 20% of all paragangliomas.
- Common paraganglioma signs: paroxysmal hypertension, tachycardia, and diaphoresis.
- Diagnosis of paraganglioma is made based on urine or blood levels of metanephrines.
- Surgery is the mainstay of treatment for genitourinary paraganglioma.
- Preoperative management with α -blockers limits the effects of catecholamine excess.

Figure 1.
Overall Survival of Patients with GU and Non-GU paraganglioma.

Table 1

Demographic, pathologic, and clinical characteristics of 299 patients with paraganglioma in SEER (2000–2012).

	Genitourinary Paragangliomas	Non-Genitourinary Paragangliomas	p-value
DEMOGRAPHIC			
N	20 (6.7%)	279 (93.3%)	
Gender			0.361 ^a
Male	13 (65%)	152(54.5%)	
Female	7 (35%)	127 (45.5%)	
Median Age at Diagnosis (IQR)	43 (17.25)	47 (25)	0.989 ^c
Age at Diagnosis			0.214 ^a
0–29	4 (20%)	39 (14%)	
30–59	14 (70%)	163 (58.4%)	
60–85+	2 (10%)	77 (27.6%)	
Race			0.064 ^a
White	11 (55%)	213 (76.3%)	
Black	5 (25%)	45 (16.1%)	
Other	4 (20%)	21 (7.5%)	
PATHOLOGIC			
Stage	n=18	n=72	0.002 ^a
Local	10 (55.5%)	16 (22.2%)	
Regional	5 (27.8%)	27 (37.5%)	
Distant	–	25 (34.7%)	
Unknown	3 (16.7%)	4 (5.5%)	
Grade			0.559 ^a
I	–	5 (1.8%)	
II	1 (5%)	5 (1.8%)	
III	–	10 (3.6%)	
IV	1 (5%)	5 (1.8%)	
Unknown	18 (90%)	254 (91%)	
Location			
	By System: Male Genital System- 2 (10%) Urinary System-18 (90%) By Organ: Spermatic Cord - 2 Bladder - 15 Kidney & Renal Pelvis - 3	Bone & Joints - 3 (1.1%) Brain & Nervous System- 11 (3.9%) Digestive System - 57 (20.4%) Endocrine System - 120 (43%) Eye & Orbit - 1 (0.4%) Female Genital System- 1 (0.4%) Oral Cavity & Pharynx - 4 (1.4%) Respiratory System - 18 (6.5%) Soft Tissue & Heart - 42 (15.1%) Miscellaneous - 22 (7.9%)	
CLINICAL			
Radiation			0.002 ^a

	Genitourinary Paragangliomas	Non-Genitourinary Paragangliomas	p-value
Performed	–	105 (37.6%)	
Unknown	–	8 (2.9%)	
None	20 (100%)	166 (59.5%)	
Surgery	20 (100%)	279 (100%)	
Lymph Node Dissection			0.143 ^a
Performed	6 (30%)	77 (27.6%)	
Unknown	2 (10%)	83 (29.7%)	
None	12 (60%)	119 (42.7%)	
Death Due to PGL	2 (10%)	67 (24%)	

^a Chi-Square test

^b t-test

^c Wilcoxon rank sum

^d log rank test

N/A not applicable

SD Standard deviation

LN lymph node

Table 2

Demographic, pathologic, and clinical data on bladder paraganglioma in SEER (2000–2012).

DEMOGRAPHIC	Count (n=)	%
Total	15	5 (15/299)
Gender		
Male	10	66.7
Female	5	33.3
Age		
0–29	3	20
30–59	10	66.7
60–85+	2	13.3
Race		
White	8	53.3
Black	4	26.7
Other	3	20
PATHLOGIC		
Location		
Dome	2	13.3
Lateral Wall	2	13.3
Posterior Wall	2	13.3
Neck	2	13.3
NOS	7	46.7
Stage		
Localized	11	73.3
Regional	2	13.3
Unknown	2	13.3
Grade		
I	–	–
II	1	6.67
III	–	–
IV	1	6.67
Unknown	13	86.7
CLINICAL		
Surgery		
Partial Cystectomy	6	40
Trans-Urethral Resection of Bladder Tumor	3	20
Complete Cystectomy with Reconstruction	2	13.3
Radical Cystectomy plus Ileal Conduit	1	6.67
Radical Cystectomy with Continent Reservoir	1	6.67
Radical Cystectomy plus in Situ Pouch	1	6.67

DEMOGRAPHIC	Count (n=)	%
NOS	1	6.67
Death due to this cancer	1	6.67

Other: American Indian/Alaskan Native, Asian/Pacific Islander, and unknown

NOS: Not otherwise specified