Prognostic Factors of Malignant Pheochromocytoma and Paraganglioma: A Combined SEER and TCGA Databases Review

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ABSTRACT

Pheochromocytoma (PCC) and paraganglioma (PGL) are rare malignancies while pathogenesis is strongly influenced by genetics. The prognostic factors of these patients remain poorly defined. We aim to study the epidemiology and survival pattern by analyzing the combination of SEER and Cancer Genome Atlas (TCGA) database. Primary outcome was overall survival (OS) and disease specific survival (DSS). Between 1973 and 2013, a total of 1014 patients with PGL or PCC were analyzed. Younger age and female were associated with better outcomes. The incidence of second primary malignancy in PGL/PCC patients was about 14.6 %. This population had a significant longer DSS. Other factors, including surgical resection and origin from of aortic/carotid bodies, conferred remarkable survival advantage. In contrast, distant spread portended worse prognosis. Laterality, race, positive serum catecholamine marker did not demonstrate a significant association with OS and DSS. By analyzing TCGA database with total 184 patients were identified. Eighty out of 184 patients (43.5 %) had at least one pathogenic mutation. Female had higher ratio of pathogenic mutations than male (58.7 % vs. 41.3 %) and *NF1* mutation was associated with elderly population. *SHDB* mutation had higher percentage in male. Twenty-nine patients (15.8 %) had 2 or more primary. *ATRX* was the most common oncogenic mutations in metastatic cohort. In conclusion, younger age, female sex, origin from aortic/carotid bodies, complete surgical resection, regional disease, as well as concomitant second primary malignancies were associated with better prognosis. The prognostic value of radiotherapy and oncogenomics warrants further investigation.

Introduction

Pheochromocytoma (PCC) and paraganglioma (PGL) and are rare neuroendocrine malignancy arising from neural crest cells of adrenal medulla and extra-adrenal autonomic nervous system, respectively [1]. It is estimated with annual incidence of ~0.8 per 100 000 person, and approximately 500–1600 new cases per year in the United States [2, 3]. PCC is highly vascular and secreting catecholamine, presenting with over-activation of sympathetic nervous system. PGL, commonly arise in the head and neck area, is usually nonfunctioning and cause local compressive symptoms. These tumors are predominantly benign, but 10–15 % behave malignant features, with metastases to lymph node, liver, lung, or bone [1]. It is difficult to differentiate them from morphology, unless metastases is shown. PCC and PGL are also known for their high heritability and unique genetic background [4]. The comprehensive molecular characterization of Cancer Genome Atlas (TCGA) have provided us a sophisticated molecular signature of PCC and PGL, including pseudohypoxia, Wnt signaling and kinase signaling pathways [5]. Although it has been known for over 100 years, the prognostic factors of PCC and PGL have been largely unknown and there

are no reliable clinical, radiological, molecular, biochemical or histopathological marker to forecast malignant potential. In addition, due to unidentified genetic causes, PCC or PGL may present with second primary neoplasm, with unclear prognostic meaning. Owing to the rarity of the disease, previous studies only have small number of subjects with controversial result. Limited evidence suggest that gender, anatomical location, stage, age and surgical resection may be associated different outcome [2, 6–8]. Recently, emerging evidence indicated that tumor size [9], germline mutations [10], age at diagnosis [11] and age-related gene penetrance [12] were associated with prognosis and these results warranted further validation. In this study, we aim for investigating the prognostic factors from population-based and oncogenomic data. In particular, we will focus on secondary malignancies and radiotherapy which have not been reported before based on our knowledge.

Methods and Statistical Analyses

The Surveillance, Epidemiology and End Results (SEER) database was utilized to identify patients diagnosed with malignant PCC and PGL between 1973 and 2013, collecting from 18 state registries. SEER incorporate cancer incidence, prevalence, and survival data which collectively cover ~28 % the United States population. Patient demographics, primary tumor site, tumor stage and treatment of primary site are also included in the database. Histology code (ICD-O-3) used for identification of PCC and PGL cases were 8680, 8683, 8693, or 8700.

Demographic information in this population-based study included patient gender, age at diagnosis, race, and survival status as of December 31, 2013. Age at diagnosis was divided into 3 groups: 0–30, 30–60, and over 60. Race was classified into Caucasian, African American, Hispanic, and other (American Indian, Alaska Native, Asian, Pacific Islander, and unknown). Survival was analyzed both as overall survival (OS) and disease-specific survival (DSS).

Pathologic variables and included laterality, tumor stage, metastasis at diagnosis, and anatomical location. Laterality was categorized as unilateral (non-paired site) or bilateral tumor. Tumor stage was described as “localized” if it is entirely confined to the organ of origin, “regional” if it extends to regional lymph nodes and/or surrounding organs or tissues, and “distant” if it has metastasized to distant organs or lymph nodes according to SEER staging system. Anatomical location was subdivided into adrenal gland origin, aortic/carotid bodies, and other/unknown.

Clinical characteristics of interest incorporated second or more primary malignancies, tumor biomarker, radiotherapy, and surgery. Prior radiotherapy included external bream radiation therapy (EBRT), radioactive isotopes, implants, or combination. Surgery was defined as performed or none.

The cBioPortal for Cancer Genomic (http://www.cbioportal.org/) provides large-scale cancer genomic data. We obtained RNA-Seq data and the corresponding clinical record of 184 PCC and PGL patients. It is reported by Fishbein et al. [5]. Fifteen genes categorized into pseudohypoxia (*SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *FH*, *VHL*, and *EPAS1*), Wnt pathway (*CSDE1* and *MAML3*) and Kinase signaling (*RET*, *NF1*, *MAX*, *HRAS*, *TMEM127*) were queried. The associated clinical information regarding gender, second primary malignancy, and age of diagnosis were studied.

SEER * Stat software (version 8.3.4) was used to download parameters from 1973–2013. Demographic, pathological and clinical data were assessed. Categorical and continuous variables were analyzed by chi-square and analysis of variance (ANOVA) respectively to determine statistical significance. The Kaplan–Meier method was employed to compare the univariate analysis of prognostic factors. Log-rank test was used to evaluate statistical significance of OS and DSS. For multivariate analysis, Cox proportional hazards regression modeling was performed based on the result of univariate study. Hazard ratios (HR) and 95 % confidence intervals were calculated. GraphPad Prism 6 was used to perform statistical analysis and made figures. All tests were 2-sided, and statistical significance was set as p-value of < 0.05.

Results

Demographics

A total of 1074 patients with histologically confirmed malignant PCC and PGL were identified in the SEER database between 1973 and 2013. The incidences of different age at diagnosis were 15.3, 55.6 and 29.1 % for age ≤ 30, 30–60 and > 60 respectively, with median OS 298, 114 and 63 months (▶ **Table 1** and ▶ **Fig. 1a)**. Median DSS was not reached for group of age ≤ 30, while 207 and 78 months for group with age 30–60 and over 60 ($p < 0.01$). Elderly population (age > 60) has less surgery rate than younger population (≤ 60) (33.1 vs. 53.3 %, $p < 0.05$). These tumors were equally distributed between male and female, with 52.1 and 47.8 % respectively (▶ **Table 1**). Male had significantly shorter median OS and DSS (OS: 108 vs. 117 months, HR: 1.26, 95 % CI: 1.05–1.51, $p = 0.01$; DSS: 141 vs. 282 months, HR: 1.27, 95 % CI: 1.02–1.60, $p = 0.03$; ▶ **Fig. 1b**). Due to the substantial disparities of different races and ethnicities regarding cancer incidence and survival in the United States [13], it was also evaluated in our study. The percentage of non-Hispanic Caucasian, African American, Hispanic and other population were 63.0, 16.5, 11.8, and 8.7 %. There was no statistical significance of median OS and DSS in these 4 groups (▶ **Table 1**).

Pathological variables

Unilateral tumor was the predominant initial presentation and accounted for 94.4 % compared to 5.6 % of patients with bilateral tumors. Neither OS nor DSS was observed between these 2 populations (▶ **Table 1**). The incidence of different locations was 54.8, 18.2, and 26.9 % for adrenal gland, aortic/carotid bodies, and other sites respectively. Aortic/carotid bodies had significant longer median OS and DSS compared to tumor origin from adrenal gland (OS: 279 vs. 114 months, HR: 0.62, 95 % CI: 0.50–0.84, $p < 0.01$; DSS: 341 vs. 141 months, HR: 0.67, 95 % CI: 0.51–0.96, $p = 0.03$; ▶ **Table 1**). However, there was no statistical advantage of tumor origin from other sites in terms of OS and DSS (▶ **Fig. 2a**, ▶ **Table 1**). Regional or distant stage was equally distributed at initial diagnosis, corresponding to 35.5 and 32.8 % of total cases. As expected, distant stage portended worse outcome compared to regional tumor (OS: 38 vs. 272 months, HR: 3.18, 95 % CI: 2.69–4.81, $p < 0.01$; DSS: 36 vs. not reached, HR: 4.24, 95 % CI: 3.38–6.72, $p < 0.01$; ▶ **Fig. 2b**, ▶ **Table 1**).

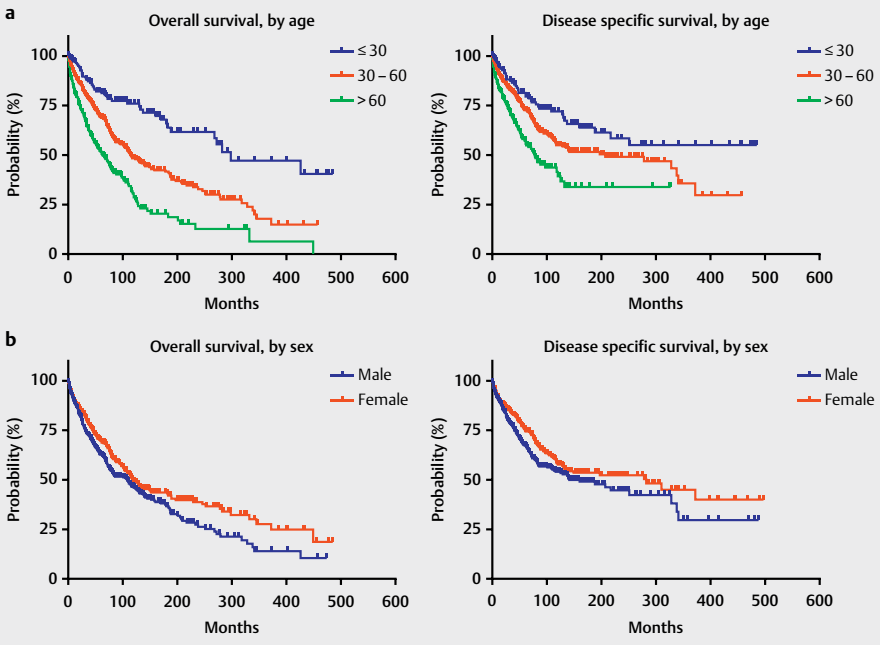
▶ **Table 1** Patient demographics, pathological variables, clinical characteristics, and survival.

Characteristics	Number of cases (%)	Overall Survival (months)	Hazard ratio (95% CI)	p-Value	Disease-specific survival (months)	Hazard ratio (95% CI)	p-Value
Age							
≤30	146 (15.3)	298	Reference		Not reached	Reference	
30–60	530 (55.6)	114	2.13 (1.45–2.44)	0.00*	207	1.53 (1.08–2.00)	0.01*
>60	277 (29.1)	63	3.43 (2.37–4.09)	0.00*	78	2.40 (1.71–3.37)	0.00*
Gender							
Female	456 (47.8)	117	Reference	0.01*	282	Reference	0.03*
Male	497 (52.1)	108	1.26 (1.05–1.51)		141	1.27 (1.02–1.60)	
Laterality							
Unilateral	900 (94.4)	114	Reference	0.90	160	Reference	0.19
Bilateral	53 (5.6)	149	0.98 (0.68–1.41)		207	0.90 (0.54–1.47)	
2nd Primary malignancy							
No	866 (85.4)	114	Reference	0.07	188	Reference	0.00*
Yes	148 (14.6)	178	0.78 (0.62–1.02)		Not reached	0.19 (0.28–0.58)	
Race/Ethnicity							
Caucasian	639 (63.0)	111	Reference		137	Reference	
African American	167 (16.5)	184	0.83 (0.65–1.07)	0.15	372	0.71 (0.54–1.00)	0.04
Hispanic	120 (11.8)	130	0.87 (0.66–1.18)	0.39	341	0.85 (0.60–1.20)	0.36
Other	88 (8.7)	107	1.06 (0.77–1.47)	0.69	Not reached	0.84 (0.57–1.26)	0.43
Tumor biomarker							
No/Unknown	703 (69.3)	114	Reference	0.41	251	Reference	0.26
Yes	311 (30.7)	111	1.07 (0.90–1.30)		139	1.13 (0.91–1.44)	
Radiotherapy							
No	740 (79.0)	129	Reference	0.00*	328	Reference	0.00*
Yes	197 (21.0)	68	1.66 (1.42–2.32)		75	1.94 (1.66–3.00)	
Surgical resection							
No	367 (58.5)	49	Reference	0.00*	77	Reference	0.00*
Yes	518 (41.5)	139	0.41 (0.31–0.44)		Not reached	0.38 (0.30–0.47)	
Primary location							
Adrenal gland	479 (54.8)	114	Reference		141	Reference	
Aortic/carotid bodies	159 (18.2)	279	0.62 (0.50–0.84)	0.00*	341	0.67 (0.51–0.96)	0.03*
Other	230 (26.9)	84	1.04 (0.84–1.29)	0.72	125	1.05 (0.80–1.37)	0.74
Stage							
Regional	171 (52.0)	272	Reference		Not reached	Reference	
Distant	158 (48.0)	38	3.18 (2.69–4.81)	0.00*	36	4.24 (3.38–6.72)	0.00*

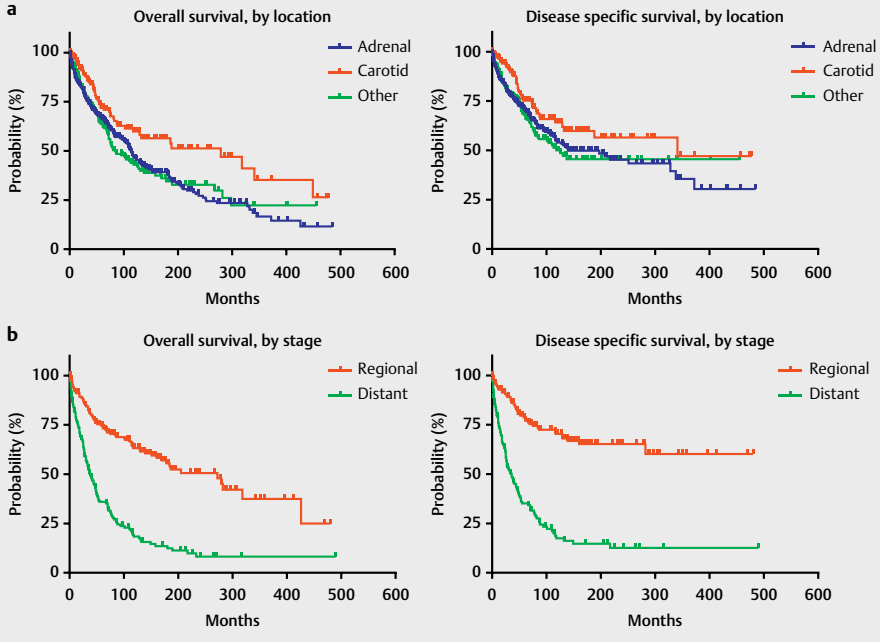
*P<0.05

Clinical characteristics

The incidence of second or more primary malignancies was found in 14.6% of patients. It was associated with considerably longer median DSS (not reached vs. 188 months, HR: 0.19, 95% CI: 0.28–0.58, p<0.01) but not OS (178 vs. 114 months, HR: 0.78, 95% CI: 0.62–1.02, p=0.07), though there was a trend favoring second primary malignancy group (▶ **Fig. 3a**, ▶ **Table 1**). It was evenly distributed in both male (49%) and female (51%). Serum tumor biomarkers were evaluated in this study as well. Approximately 30% patients had positive biomarkers, however, it was not correlated with median OS or DSS compared to non-secreting or unknown patients (▶ **Table 1**). Prior radiotherapy was administrated in 21.0% of population. It was related to worse outcome compared to non-radiation group (OS: 68 vs. 129 months, HR: 1.66, 95% CI: 1.42–2.32, p<0.01; DSS: 75 vs. 328 months, HR: 1.94, 95% CI: 1.66–3.00, p<0.01; ▶ **Fig. 3b**, ▶ **Table 1**). Moreover, surgical resection was performed in 41.5% of patients. Among patients who underwent surgery, it was associated with better overall survival (139 months)



▶ **Fig. 1** Overall survival and disease-specific survival Kaplan–Meier curves by patient demographics: **a** By age, **b** by sex.



▶ **Fig. 2** Overall survival and disease-specific survival Kaplan–Meier curves by pathological variables: **a** By anatomical location, **b** by SEER stage.

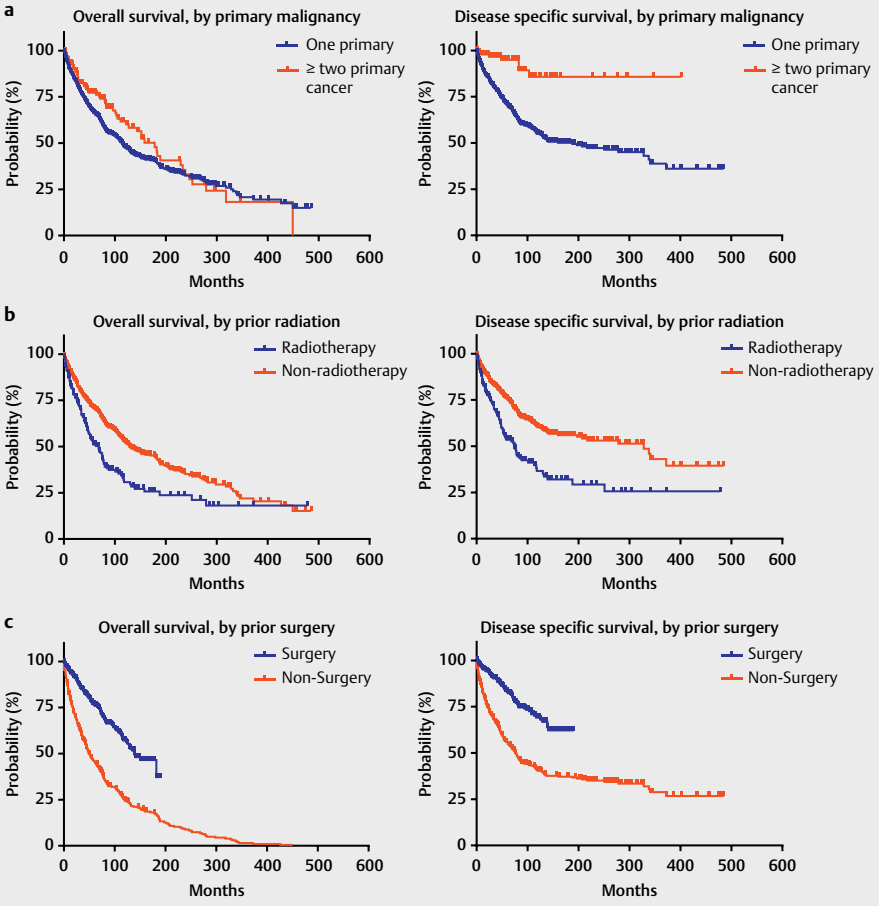
compared to non-surgical cases (49 months) (HR: 0.41, 95 % CI: 0.31–0.44, p < 0.01), as well as DSS (not reached vs. 77 months, HR: 0.38, 95 % CI: 0.30–0.47, p < 0.01; ▶ **Fig. 3c**, ▶ **Table 1**).

Multivariate analysis

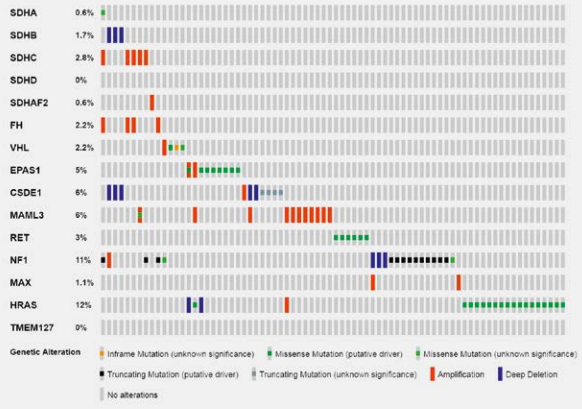
Cox proportional hazards regression modeling was performed. All above-mentioned parameters, including age, sex, anatomical location, stage, second or more primary malignancies, prior radiotherapy or surgery, continued to show the same trends or statistical significance when compared to the results of univariate analysis.

Oncogenomic data

Total 184 cases were analyzed by accessing the cBioPortal TCGA database, in which 13 (7.0 %) of them were malignant metastatic



▶ **Fig. 3** Overall survival and disease-specific survival Kaplan–Meier curves by clinical characteristics: **a** By number of primary malignancy, **b** by prior radiotherapy, **c** by prior surgery.



▶ **Fig. 4** The genetic alteration of 15 genes were analyzed by cBioportal TCGA database. The alternation percentage was present proportionally.

PCC/PGL. As mentioned above, 15 genes had been queried, associated with pseudohypoxia, Wnt pathway and kinase signaling [4]. Eighty out of 184 patients (43.5 %) had at least one pathogenic mutation (▶ **Fig. 4**). In this population, 17 patients (21.3 %) had 2 or more mutations and female had higher ratio than male (58.7 vs. 41.3 %). Four *SDHB*-mutated cases are all male. Twenty-nine patients had secondary primary malignancies, which account for 15.8 % of total cases. However, the presence of genetic alteration was only 17.2 %. *NF1* mutation was significantly associated with the age of diagnosis, compared to non-*NF1*-mutated population (age of diagnosis: 54.8 ± 2.8 vs. 46.2 ± 1.2, p = 0.01). While, it was not observed with other genes, though *MAML3* had the similar tendency without significance yet (p = 0.06). Specifically for malignant PCC/PGL cohort, 7 out of 13 cases (53.8 %) had identified oncogenic mutations, with the most common mutation located at *ATRX*, with 15.4 % (2/13). The rest of mutations included *SDHAF2*, *SDHB*, *NF1*, *EPAS1* and *MAML3*.

Discussion

Due to lack of large randomized prospective studies, the survival outcome and optimal treatment of malignant PCC and PGL have not been well established, in part because of the rarity of disease. SEER database, a large population-based resource, provides valuable information of these low incidence malignancies. In addition,

recent published molecular characterization of PCC and PGL provides us a different view from oncogenomic standpoint. In this study, we assess over one thousand cases, which is one of the largest cohorts by our knowledge and combined with TCGA database. We found that clinical behavior of PCC and PGL is dramatically variable and multiple factors, including molecular signature play diverse roles in affecting their outcomes.

Among patient demographics, male population indicates worse OS and DSS, with the HR of 1.26. It is consistent with other reports [2, 6, 14]. However, the reason is unclear. Our results do not show the sexual difference of incidence in second primary malignancy. Several studies indicate male patients have propensity to develop tumor at difficult location [7], or harbor succinate dehydrogenase subunit B (SDHB) [12] or SDH subunit D (SDHD) [15] mutational penetrance. In our study, we do find that all 4 *SDHB*-mutated PCC/PGLs were all male, which is associated with an aggressive course. While, female patients have high ratio of head and neck PGL [16], which is validated by our result having favorable outcome as well. As we expected, older age at diagnosis is correlated with worse prognosis. We report the hazard ratio is 3.43 for patients older than 60. Similar result from Goffredo et al. found the hazard ratio was 2.58 for patients older than 76 [6]. Patients with older age tend to have PCC or PGL without appreciable catecholamine production or no established mutation [17]. *VHL*, *SDHB*, and *SDHD* mutations represent the group with younger ages, while tumors associated with multiple endocrine neoplasia type 2 (MEN2) and neurofibromatosis type 1 (NF1) happen more frequent in older population [17]. Additionally, gene mutational penetrance, particularly those portended worse prognosis, was reported to be age-related [12]. Recent identification of *MAML3* fusion as a novel factor portending tumor aggressiveness was also found in older patients [5, 18]. We validated in this study that NF1 mutation had high ratio in elderly population. *MAML3* had the tendency of high mutational rate in elderly population as well, though it is non-significant ($p = 0.06$). Likely due to other comorbidities, elderly population (>60) in our study has less surgical resection rate than younger population (33.1 vs. 53.3 %, $p < 0.05$), which might be another reason contributing to the poor survival. Race plays important role in multiple types of cancer. For example, the prostate cancer mortality rate is 2.4 times higher in black men than the rate in white men [13]. Our data do not show any racial disparities regarding both OS and DSS. Likewise, genomic expression from TCGA analysis do not demonstrate significant difference between races [19].

Pathologic variables, like laterality, tumor stage and anatomical location, are also explored in our research. Bilateral PCC or PGL manifested in about 5.6 % of all cases. Although it is frequently considered as a sign of germline genetic aberrancy, such as mutations of *VHL*, *RET*, or *NF1*[4], no distinctive survival discrepancies are observed in our study and low incidence (17.2 %) of genetic alteration. Tumor stage is another well-known prognostic factor. We do not enroll localized stage in our study, since it is hard to differentiate it from benign disease. It is well advocated that metastatic disease at the time of diagnosis is a poor prognostic factor as validated from us as well. However, localized or regional stages share similar clinical outcome [6]. This interesting finding might reflect the unique genetic background of malignant PCC and PGL. Another presentation highly related to tumor genetic context is the anatomical location. PGL, which is normally originated from extra-adrenal chromaffin cells or paraganglia, has worse outcome than PCC arising from the adrenal medulla [6]. Nevertheless, the majority of head and neck PGLs represent parasympathetic profile and have benign behavior [20], with extremely rare propensity of distant metastasis [21]. Minority of this population has strong familial predisposition, as the result of germline mutation of *SDHB*[22]. We first time unravel that PGLs with aortic/carotid bodies origination bestow survival advantage compared to adrenal gland tumors. However, tumor grow out of adrenal gland other than aortic/carotid bodies has the worse survival.

In addition, clinical characteristics exert crucial effect for disease outcome. Approximately 15 % of PCC or PGL is accompanied with second or more primary malignancies. Paralleling evidence from TCGA database showed similar percentage with 15.8 %, suggesting many PCC or PGLs are associated with inherited cancer susceptibility syndromes. Again, it reiterates the substantial influence of disease by underlying genetic status. Surprisingly, our data shows cases have second or more primary malignancies tend to have better DSS, and marginal insignificance of OS as well. We believe germline mutations, such as *VHL*, *EPAS1*, *RET* or *NF1*, in this group drive the tumor underwent an indolent process. Meanwhile, these mutations increased the risk of secondary malignancies. Elevated catecholamine level is utilized to the diagnosis of PCC and PGL. It is linked to cell differentiation, metastatic potential, and even as a prognostic marker. Hamidi et al. summarized 272 patients who were treated at Mayo Clinic over 55 years and they found catecholamine secretion was associated more aggressive disease with HR of 3.93 [2]. In contrast, we do not observe such relationship, partially because of high percentage of unknown status in the SEER database. Surgery remains the cornerstone of PCC and PGL treatment. Failure to undergo surgery is a major adverse predictive factor for survival [2], which is in agree with our results. On the contrary, the benefit of radiation therapy in PCC and PGL treatment is controversial. Lee et al. reported 5-year overall survival was inferior of surgery and radiation (33 %) versus surgery alone (78 %) [23]. However, argument can be made that radiotherapy is often used in patients with positive margin, frail performance status, non-surgical candidate, or dearth of modern radiotherapy techniques, consequently confer the worse outcome. Therefore, we further investigate the database stratified by other factors using multivariate analysis by Cox proportional hazards regression modeling. Similar result is recapitulated, displaying the worse prognosis in patients underwent radiotherapy. Due to the nature of retrospective study and absence of pathological/genomic result, we cannot draw the conclusion regarding the role of radiation. Further randomized prospective trials are warrant to clarify this question.

Recent released TCGA database provides a novel view with in-depth oncogenomic information [5]. Somatic *SDHB*[12], *NF-1*[17], and *MAML3*[5] mutations were well-known associated with unfavorable survival. Although 93 % of them were benign PCC/PGLs, we were able to identify 13 metastatic cases. Only 7 patients (53.8 %) had these known oncogenic mutations. Besides well-established aberrancy of pseudohypoxia, Wnt and kinase signaling pathways, *ATRX* was the most common oncogenic mutation. The ratio of PGL was significantly higher than PCC [19]. It was reported that somatic mutations of cell cycle pathway, calcium signaling, regulation of

cytoskeleton, gap junction and phosphatidylinositol pathway are upregulated in malignant PGL/PCC [19]. However, the pathogenic mechanism is still unknown. The linkage of oncogenomic profile with clinicopathological features warrants further investigation.

We acknowledge several limitations to this study. First, SEER database only covers ~28 % of population in the United States. Although major demographical information, clinical course and prior surgical or radiation therapy are included in this database, details of chemotherapy, pathology, molecular result, and radiotherapy (dosage, fraction, and field etc.) are missing, thereby could create bias. Second, about 16 % of cases are diagnosed or treated before 1990, when radiation was less conformal and peri-operative morbidity was high. Third, the extent of surgical resection is not available, which may underestimate the efficacy of other approaches. Finally, cBioportal TCGA database does not provide survival data, which makes us hard to interpret the linkage of molecular features and clinical outcomes.

Conclusion

In conclusion, malignant PCC and PGL are rare disease with highly variable clinical course. In our population-based retrospective study, over 1000 cases are analyzed from SEER database and 184 cases are analyzed from cBioportal TCGA database. Younger age, female sex, origin from aortic/carotid bodies, complete surgical resection, early stage, and concomitant second or more primary malignancies are associated with better survival result. It is associated with underlying genetic signatures. There is no significant impact of patient race, tumor laterality, or tumor markers. The influence of radiotherapy warrants further investigation. Again, surgery remains major curative treatment, and multidisciplinary approaches should be consider for every patient. In the future, integration of cancer genomic test will further help us for risk stratification and applying individualized treatment.

Conflict of Interest

The authors declare that they have no conflict of interest.

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