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Abdominal Paragangliomas: A Single Center Experience

Abdominal Paragangliomalar: Tek Merkez Deneyimi

Ahmet Gökhan Sarıtaş[1], Mehmet Onur Gül[2], Orçun Yalav[1], Zafer Teke[2], İsa Burak Güney[3]

[1]Çukurova University Faculty of Medicine, Department of General Surgery Adana, Turkey
[2]Çukurova University Faculty of Medicine, Department of Oncological Surgery Adana, Turkey
[3]Çukurova University Faculty of Medicine, Department of Nuclear Medicine, Adana, Turkey

ABSTRACT

Objective: Paragangliomas are rare tumors arising from extra-adrenal chromaffin tissue, which are widely distributed near or within the autonomic nervous system in the retroperitoneal sites and in the sympathetic ganglia of various viscera. We present a review of our 18-year institutional experience with resected abdominal paragangliomas.

Methods: The data collected from 12 patients who underwent surgery due to abdominal paraganglioma in our clinic between 2002 and 2020 were analyzed retrospectively.

Results: There were 12 patients in our study. The median age was 44 years (range: 21-81 years). The patients had one or more of the symptoms of headache (n:2, 16,6%), palpitations, abdominal pain (n:5, 41.6%), sweating (n:2, 16.6%) and hypertension (n:5, 41.6%), which are the classic clinical symptoms. One of the cases (1/12; 8,3%) was detected incidentally. The mass location was in the retroperitoneal region in 10 cases (83.3%) and in the pelvic region in 2 cases (16.6%). Five of the patients applied to our clinic with episodes of paroxysmal hypertension, and vanillylmandelic acid and metanephrine levels were found to be high in the blood and 24-h urinary tests. After a median follow-up period of 60 months, only 1 patient (8.3%) had metastasis and required reoperation 2 years after the first operation. One patient (8.3%) died on postoperative 36th month due to cardiac problems.

Conclusion: Abdominal paragangliomas are rare tumors whose optimal management requires the surgeon to be highly attentive to the disease course, from diagnosis of functioning or nonfunctioning lesions, through operative treatment that may require adjacent organ resection, to lifelong follow-up for recurrences.

Keywords: Paraganglioma, Endocrine hypertension, Retroperitoneal, Metastasis, Surgical treatment, Survival

ÖZ

Amaç: Paragangliomalar, retroperitoneal bölgelerde otonom sinir sisteminin yakınında veya içinde ve çeşitli organların sempatik gangliyonlarında yaygın olarak dağılım gösteren ekstra-adrenal kromaffin dokusundan kaynaklanan nadir görülen tümörlerdir. Biz bu çalışmada 18 yıllık abdominal paraganglioma cerrahisine ait klinik deneyimimizi sunuyoruz.

Yöntemler: 2002-2020 yılları arasında kliniğimizde abdominal paragangliomaya bağlı cerrahi uygulanan 12 hastadan elde edilen veriler retrospektif olarak incelendi.

Bulgular: Çalışmamızda 12 hasta vardı. Ortalama yaş 44 (21-81) idi. Hastalarda klasik klinik semptomlar olan baş ağrısı (n: 2,% 16,6), çarpıntı, karın ağrısı (n: 5, 41.6), terleme (n: 2,% 16.6) ve hipertansiyon (n: 5,% 41.6) mevcuttu. Olgulardan biri (1/12;% 8,3) insidental olarak tespit edildi. Kitle yerleşimi 10 olguda (% 83.3) retroperitoneal bölgede, 2 olguda (% 16.6) ise pelvik bölgede idi. Kliniğimize paroksismal hipertansiyon atakları ile başvuran hastaların beşinde kan ve 24 saatlik idrar testlerinde vanil mandelik asit ve metanefrin düzeyleri yüksek bulundu. Ortalama 60 aylık takip süresi boyunca sadece 1 hastada (% 8.3) metastaz gelişti ve bu hasta ilk ameliyatından 2 yıl sonra tekrar ameliyat edildi. Bir hastada (% 8.3) ameliyat sonrası 36. ayda kardiyak problemler nedeniyle mortalite gelişti.

Sonuç: Abdominal paragangliomalar nadir görülen tümörler olup optimal yönetiminde cerrahın hastalık seyri boyunca son derece dikkatli olmasını gerektirir. Bu süreç, fonksiyonel veya non-fonksiyonel lezyonların tanısından başlayarak komşu organ rezeksiyonu gerektirebilecek geniş cerrahi tedavilere ve de nüks açısından yaşam boyu takibe kadar uzanmaktadır.

Anahtar Sözcükler: Paraganglioma, Endokrin hipertansiyon, Retroperiton, Metastaz, Cerrahi tedavi, Sağkalım

Address for Correspondence/Yazışma Adresi: Ahmet Gökhan Sarıtaş, Çukurova University Faculty of Medicine, Department of General Surgery Adana, Turkey
E-mail: drags0001@hotmail.com **ORCID ID:** orcid.org/

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Introduction

Paragangliomas are rare neuroendocrine tumors with an incidence of 1 case per million and are similar to adrenal pheochromocytomas by clinical features. Head and neck paragangliomas are usually parasympathetic type. They are not hormone-releasing type and generally located near the carotid bifurcation (1). The Zuckerkandl's organ, first described by Zuckerkandl in 1901, is located between the inferior mesenteric artery root and the aortic bifurcation on the right edge of the abdominal aorta. It is normally present in the fetus, localized in the para-aortic plexus; however, it is in the form of a residue in the adult and here is the localization where most extra-adrenal pheochromocytomas are frequently located. Subramanian *et al*. identified only 135 abdominal paraganglioma patients in their literature review (2). Paragangliomas with mediastenial localization are generally located along the aortopulmonary window. Paragangliomas developing in the mediastinum are sympathetic type paragangliomas like abdominal paragangliomas (3).

The neoplastic cells found in paraganglioma are positive for immunohistochemical markers of CD56, synaptophysin and chromogranin A, and there is focal S100 protein positivity in sustentacular cells. Histopathological examination is insufficient to predict benign or malignant features. Since there are no histological or molecular markers that distinguish between malignant and benign paragangliomas, malignancy can only be proved by the appearance of metastases that occur during the initial diagnosis or after diagnosis. Tumor size is also not considered as an important factor in determining malignancy (3).

Extra-adrenal paragangliomas occur in individuals of all ages, but mostly occur in the fourth or fifth decades of life. Paragangliomas releasing hormones characterized by excessive catecholamine secretion are called active paragangliomas. Although active paragangliomas are rare in the head and neck region, they are more common in the thoracic, abdominal and retroperitoneal regions (4). The most common clinical symptoms due to catecholamine hypersecretion are headache, palpitations and sweating (5). Cardiac arrest, brain hemorrhage and malignant hypertension are life-threatening complications. Approximately 10% of paragangliomas are clinically silent and are detected incidentally during radiological imaging studies (6-9). Familial paragangliomas account for about 10% of cases, and 35-50% of familial paraganglioma cases are multicentric tumors (9,10). Surgical resection is the most important step in the treatment of paraganglioma. Depending on the location, abdominal paragangliomas can develop hypervascular invasion to the abdominal aorta, inferior vena cava, or other adjacent tissues, and even invasion leading to large vascular resections (10).

In this study, we aimed to present radiological and histological features, surgical treatment strategies and postoperative follow-up results of these very rare abdominal paraganglioma cases in the light of the literature.

Methods

Study Design and Setting

In this study, medical records of 12 patients who were operated on for abdominal mass between January 2002 and January 2020 and diagnosed as paraganglioma in histopathological examination were analyzed retrospectively. This study was approved by the Institutional Review Board of our institute (IRB No. 10.01.2020/95/23). The informed consent was read and signed by all participants. All procedures performed in this study involving human participant were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patients' clinical features as well as biochemical, radiological, surgical and histopathological data were collected and a data set was created. Patients confirmed to had paraganglioma as a result of clinical features, radiological imaging methods and histopathological evaluations were included in the study. Pathologically, tumor size, immunhistochemical analyses of S100, *chromogranin A* , synaptophysin, and neuron specific enolase, and Ki-67 index were investigated. The largest tumor size in the pathological specimens was measured. The patients were followed up for at least 24 months after surgical removal of the tumor. All patients were referred to the medical genetic clinic for their genetic evaluation in terms of neurofibromatosis, von Hippel-Lindau disease, multiple endocrine neoplasia (MEN) syndromes. Cases that could not be confirmed as paraganglioma histopathologically, cases with inaccessible information and cases with adrenal pheochromocytoma were excluded from the study.

Statistical Analysis

Statistical analysis was carried out using IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA). Continuous data were presented as mean (standard deviation) or median (range), and categorical data as frequency. Student's *t*-test was used for comparison of continuous variables. Shapiro-Wilk normality test was performed for numerical variables such as age, tumor size and follow-up time. Student's *t*-test was used to analyze the relationship between tumor size and mortality and recurrence**.** Based on the results of analyses, the p value < 0.05 was considered to be statistically significant.

Results

There were 6 male (50%) and 6 female (50%) in our study. The median age was 44 years (range: 21-81 years) (Table 1). The patients had one or more of the symptoms of headache (*n*:2, 16,6%), palpitations, abdominal pain (*n*:5, 41.6%), sweating (*n*:2, 16.6%) and hypertension (*n*:5, 41.6%), which are the classic clinical symptoms. One of the cases (1/12; 8,3%) was detected incidentally. The mass location was in the retroperitoneal region in 10 cases (83.3%) and in the pelvic region in 2 cases (16.6%). Five of the patients applied to our clinic with episodes of paroxysmal hypertension, and vanillylmandelic acid and

metanephrine levels were found to be high in the blood and 24-h urinary tests. All demographic, clinical, pathological and radiological data for the 12 patients are presented at Table 2.

Table 1. Clinicopathologic characteristics for the 12 patients under study

Characteristic	(n) (%)
Age (year)(median)	44 (range: 21-81)
Gender	
• Male	6 (50%)
• Female	6 (50%)
Clinical presentation	
• Incidentaloma	1 (8.3%)
• Hypertension	5 (41.6%)
• Abdominal pain	5 (41.6%)
• Headache	2 (16.6%)
• Hematuria	1 (8.3%)
Radiological method	
CT	7 (58.3%)
MRI	10 (83.3%)
USG	10 (83.3%)
PET/CT	4 (33.3%)
Localization	
Posterior pancreatic	2 (16.6%)
Paracaval / Para-aortic	2 (16.6%)
Renal hilum	2 (16.6%)
Zuckerkandl's organ	2 (16.6%)
Bladder side wall	2 (16.6%)
Sacral/Sacrococcygeal	2 (16.6%)

The first patient was admitted with high blood pressure attacks. A paracaval paraganglioma was detected on radiological imaging method and then she was operated on. The tumor was resected with the wall of inferior vena cava due to suspicion of tumor invasion and then inferior vena cava was repaired. A tumor invading the vein was detected in the pathological examination. In the second patient, laparoscopic resection was performed for the mass at the level of renal hilus. After the operation, the patient developed a fistula between the left renal artery and vein, and it was observed that the arteiro-venous fistula regressed in the first year of follow-up. The fifth patient had a lesion located lateral to the superior mesenteric vein in the posterior of pancreas. Subtotal pancreatectomy and splenectomy with mass excision were performed due to suspected pancreatic invasion. Fibrosis was revealed by the pathological evaluation of the region considered as tumor invasion to the pancreas in the preoperative radiological imaging method. The patient's disease-free survival is 60 months and follow-up continues. In the sixth patient, 2 years after tumor excision of the Zuckerkandl's organ, total omentectomy was performed due to suspicion of omental metastasis and was followed up by giving 8 cycles of peptide receptor radionuclide therapy (PRRT) with Lutetium 177 (Lu-177) in the postoperative period. The time to metastasis was 24 months and disease-free survival after metastasectomy was 16 months. In the eighth patient, a renal artery injury occurred while removing the paraganglioma mass located at the level of renal hilus. The renal artery was primarily repaired and no additional pathology developed during follow-up. In the ninth patient, the complaint of application was hematuria due to the paraganglioma mass located on the bladder side wall. Thickening was detected on the lateral wall of bladder on the pelvic ultrasonography (USG) and the lesion was excised using

Table 2. Demographic, clinical, pathological and radiological data for the 12 patients under study

Case	Age/ Gender	Clinical presentation	Tumor diamater (cm)	Localization	Operational complication	Metastasis/ Local recurrence	Radiological methods	Follow-up time (month)
1	52/F	Hypertension, Abdominal pain	3x2x0.5	Paracaval	IVC repair	None	USG, MRI, PET/CT	84
2	34/M	Hypertension	3x2x2	Renal hilum	Left renal AVF	None	USG, MRI	84
3	27/F	Hypertension	4x4x3.5	Zuckerkandl's ogan	None	None	USG, MRI	72
4	40/F	Abdominal pain	8x6x5	Posterior pancreatic	None	None	USG, CT, MRI, PET/CT	60
5	81/M	Hypertension	15x5x2.5	Posterior pancreatic	None	None	CT, MRI	60
6	44/F	Hypertension	8x5x5	Zuckerkandl's organ	None	Yes	USG, CT, MRI	40
7	45/M	Incidentaloma	4x2x2	Bladder lateral wall	None	None	CT	84
8	31/M	Weight loss, Nausea and vomiting	6x4x2	Renal hilum	None	None	USG, CT, MRI, PET/CT	24
9	29/M	Hematuria	0.5x0.5x0.3	Bladder lateral wall	None	None	USG, MRI	60
10	45/M	Abdominal pain	3x2x1.5	Para-aortic	None	None	USG, MRI	84
11	81/F	Abdominal pain	5x4x4	Sacral	Pelvic hematoma	None	USG, CT, PET/CT	36
12	21/F	Abdominal pain	3x0.3x2	Sacrococcygeal	None	None	USG, CT, MRI	36

cystoscopy. The patient was followed up through routine annual check-up and no recurrence occurred.

Laparoscopic surgery was performed in 2 of the twelve patients in our study. Surgical, pathological and oncological characteristics for the 12 patients are presented at Table 3. The median follow-up time was 60 months (range: 12-84 months). Metastasis developed in only one patient after the first operation. Despite advanced age and comorbid diseases of the eleventh patient, she lived 36 months without local recurrence and/or metastasis after tumor excision, approximately 5 cm in size, from the sacrococcygeal region. This patient died on postoperative 36th month due to cardiac problems.

When the preoperative radiological imaging methods of the patients were reviewed, 10 patients had abdominal USG and 2 patients had no pathological findings on the ultrasound examination. A paraganglioma in two cases and a lymphadenopathy in one case were reported in the abdominal USG. In one case, bladder wall thickness was reported and cystoscopy was recommended. The remaining patients were described as abdominal mass lesions without being reported as paraganglioma. Abdominal computed tomography (CT) imaging was performed in seven cases in the preoperative period and a mass was detected in all cases. In four patients, the differential diagnosis of paraganglioma was considered, and in 3 patients, only a mass lesion was reported. Magnetic resonance imaging (MRI) was performed in 10 patients and the differential diagnosis of paraganglioma could be made in these patients. Positron emission tomography/computed tomography (PET/CT) examination was performed in four patients and SUVmax value was found to be high in all patients. (SUVmax values; Case 1: 20, Case 4: 21.38, Case 6: 14.84, and Case 8; 14.3). On the PET/CT imaging of the case with metastasis detected in the omentum, the lesion was found to have high SUVmax value (14.84).

The median tumor size was 5.2 cm (range: 0.5-15 cm) in our series (Table 3). There was no statistically significant relationship between the tumor size and mortality (p>0.05) or local recurrence (p>0.05). Histopathological evaluations confirmed the diagnosis of paraganglioma in all of 12 patients. Capsular invasion was positive in 10 patients. *Positive* immunohistochemical staining for S100 was detected in 10 patients, *chromogranin A* in 8 patients, synaptophysin in 5 patients, and neuron specific enolase in 2 patients. Ki-67 index was 6% in one patient and 4% in other patient.

Discussion

Paragangliomas are rare neuroendocrine tumors with similar clinical and histopathological features of pheochromocytomas originating from the adrenal medulla (1). Paraganglioma is mostly located in the region where the organ of Zuckerkandl resides, and it is common in this region due to the development of chromaffin tissue from extra-adrenal paraganglioma cells (1).

Benign or malignant features of paraganglioma are related to the behavioral character of the tumor and cannot be diagnosed histopathologically (11). Abdominal paragangliomas tend to be malignant (2,12,13). Diagnosis of the disease is made by laboratory tests and radiological imaging methods performed in patients presenting with symptoms suggestive of paraganglioma. The most common symptoms are hypertension that occur as sudden attacks and abdominal pain (6-9). In our study, the patients had one or more of the symptoms of headache (n:2, 16,6%), palpitations, abdominal pain (n:5, 41.6%), sweating (n:2, 16.6%) and hypertension (n:5, 41.6%), which are the classic clinical symptoms of paragangliomas.

Radiological imaging methods aid in determining the localization of primary tumor as well as showing metastatic lesions in malignant cases. Combined use of two or more radiological imaging techniques is often required for diagnosis and staging. In these radiological imaging methods, PET/CT examination is recommended when distant metastasis is suspected (14-16). If the lesion cannot be found during the operation, intraoperative USG examination can be useful (17). Dan *et al.* reported that a bladder paraganglioma was detected by pelvic USG preoperatively (18). Malthouse *et al.* used transabdominal USG and determined paragangliomas adjacent to the pancreas (19). In our study, a paraganglioma located on the bladder side wall was detected by pelvic USG. The disadvantage of USG is that it does not show tumor involvement to the organs such as lung, brain and bone, and is dependent on the physcian who does it (20). Ultrasonographic examination was performed in 10 patients in our study. In two patients, the lesions could not be detected on ultrasound. Preliminary diagnosis of paraganglioma was considered in 2 patients, and primary tumor and its localization were reported in the remaining 6 patients. It was thought that the inability to detect the lesion by ultrasound was associated with anatomical localization and radiologist's experience. MRI can detect catecholamine-secreting tumors in 95% of cases and has a sensitivity of 93–100% (21,22). Paragangliomas have a characteristic hyperintensity on T2-weighted images due to the tumor's hypervascularity. In pregnant women, children,

Table 3. Surgical, pathological and oncological characteristics for the 12 patients under study

Characteristic	(n) (%)
Tumor diameter (median) (cm)	5.2 (range: 0.5-15)
Metastasis	1 (8.3%)
Time to metastasis (month)	24
Local recurrence	0
Follow-up time (median) (month)	60 (range: 24-84)
Mortality	0
Mortality related to comorbidities	1 (8.3%)
Surgical procedure	
• Tumor resection	10 (91.6%)
• Subtotal pancreatectomy + splenectomy	1 (8.3%)
• Cystoscopic resection	1 (8.3%)
• Vascular repair	
• (Inferior vena cava / Renal artery)	2 (16.6%)

and patients with an iodine-based contrast allergy, MRI is the test of choice. In our study, 10 patients had MRI, and typical characteristic findings of paraganglioma were detected in all. Despite these advantages of MRI, most of the clinicians still prefer CT scan because it provides better anatomic detail and does not aggravate claustrophobia (23). CT and MRI are considered the gold standard for radiological imaging in hereditary paraganglioma screening (24). Paraganglioma is not the first preliminary diagnosis that comes to mind during the diagnosis of masses located intraabdominally or retroperitoneally, and therefore CT is usually used before MRI. Thin-sliced CT scans have 98% sensitivity and 92% specificity with intravenous contrast enhancement in the diagnosis of paraganglioma (25-27). CT imaging was performed in 7 of the patients in our study, and the preliminary diagnosis of paraganglioma was reported in 4, while others were described only as a mass lesion.

^{18}F-fluoro-2-deoxy-d-glucose (F-18) FDG PET/CT scan guides the diagnosis based on the glucose uptake level of the tumor tissue. Most clinicians use F-18 FDG PET/CT scanning not as the primary localization method, but when ^{123}I-labeled metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy scanning is negative or suspected or when fast growing tumors with high metabolic rate are detected (14-16). Paragangliomas overexpress somatostatin receptors (SSR), especially SSR2 (28). ^{68}Ga-labeled DOTA peptides have been shown to be far superior to ^{111}In-DTPA-octreotide (Octreoscan®) for the detection of neuroendocrine tumor (NET) lesions (29). Additionally, [^{68}Ga]-DOTATATE PET/CT gives the chance to evaluate these patients for their potential eligibility for peptide receptor radionuclide therapy (PRRT), since DOTA peptides can also be labeled with therapeutic β-emitters such as ^{177}Lu and ^{90}Y. Jansen *et al*. reported that ^{68}Ga-DOTATATE PET/CT was superior to all other PET radiopharmaceuticals including ^{18}F-FDOPA and especially ^{18}F-FDG, suggesting that ^{68}Ga-DOTATATE has the potential to affect patient treatment plans and outcomes by identifying not only more metastatic lesions but also additional involved sites of disease as compared with all other functional imaging modalities and CT/MRI (30). In our study, PET/CT was used in 4 patients, and high SUVmax values were detected in all tumor tissues. In one case, it was used to confirm metastasis and to perform another focus scan. In some of our patients, USG, CT, MRI and PET/CT scans were all performed. We thought that the reason for this was difficulties encountered in the diagnosis of this very rare disease and the fact that the patients had admitted to more than one hospital before applying to us.

The risk of life-threatening intraoperative and postoperative complications in symptomatic patients must be reduced, and appropriate preoperative preparations must be provided by taking the recommendations of the endocrinology clinic. In the treatment of paraganglioma, resection is recommended without leaving tumor tissue at the surgical margins. The difficulty of surgery in the anatomical localization of paragangliomas is the most important factor preventing negative surgical margins (31). The treatment method to be applied when tumor recurrence develops is resection. Tumor recurrence was found to be 6-15% in the studies and the average survival was reported to be 47-60 months (32,33). Johnston *et al*. reported that after initial surgery tumour development occurred at 8.6, 12 and 17.7 years respectively (33). This shows that patient's follow-up should not be disrupted and annual follow-up should continue. Although metastases and recurrences are expected to develop in the early period, metastases occurring 41 years after primary surgery have also been reported in the literature (34). In our study, metastasis developed in the 24th month of a patient with a primary tumor diameter of 8 cm after initial surgery, but no local recurrence or metastasis occurred in other patients. Assadipour *et al*. reported that the risk of local recurrence and distant metastasis in paraganglioma and pheochromocytoma is higher in the presence of *SDHB* mutation and/or when the tumor diameter is greater than 5 cm (35). Previously published studies on pheochromocytomas have shown that the risk factors for recurrence are young age, large tumor diameter, extra-adrenal tumor and genetic pheochromocytomas (36,37). Cunningham *et al*. reported that tumor diameter, whether the tumor was symptomatic or not, surgical margin, and lymph node resection did not contribute to survival, and survival was affected only if the tumor had metastasized (38). Due to the lack of adequate prospective studies in the literature on paragangliomas, surgical margins, recurrence, metastasis and other factors affecting the prognosis of disease have not been revealed very clearly. In our study, one patient (8.3%) developed metastasis and the median survival of patients in our study was found to be 60 months.

Currently, there is no reliable histological, immunohistochemical, molecular or radiological imaging criterion for determining malignancy for paragangliomas (39). Hamidi *et al*. found that male gender, advanced age, dopamine hypersecretion, presence of synchronous metastasis, primary tumor size, and those who did not undergo surgical resection for their primary tumor were associated with the aggressive disease course and high mortality (40). In our study, the patient who developed metastasis was 44-years-old female and did not comply with the high-risk group criteria. The small number of patients, the lack of genetic data, and the retrospective design of our study are important limitations of this study. However, large prospective randomized controlled studies with genetic features are needed.

Conclusion

Paragangliomas may occur anywhere paraganglia are found, from the base of the skull to the floor of the pelvis. It should be borne in mind that masses in abdominal localization with hypermetabolic activities in F-18 FDG PET/CT may be paraganglioma. ^{68}Ga-DOTATATE has the potential to affect patient treatment plans and outcomes by identifying not only more metastatic lesions but also additional involved sites of disease as compared with all other functional imaging modalities and CT/MRI. Surgical treatment of these tumors should be done in a way to obtain a negative surgical margin after making preoperative examinations and preparations.

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