Original Article

DOI: 10.14235/bas.galenos.2020.4082
Bezmialem Science 2021;9(2):205-11

Abdominal Paragangliomas: A Single Center Experience

Abdominal Paragangliomalar: Tek Merkez Deneyimi

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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

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

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Received: 23.01.2020
Accepted: 14.05.2020

Cite this article as: Sarıtaş AG, Gül AO, Yalav O, Teke Z, Güney İB. Abdominal Paragangliomas: A Single Center Experience. Bezmialem Science 2021;9(2):205-11.

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

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

Introduction

Paragangliomas are rare neuroendocrine tumors with an incidence of 1 case per million and are similar in their clinical features to adrenal pheochromocytomas. Head and neck paragangliomas are usually of the parasympathetic type. They are not the hormone-releasing type and are 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, in the adult, it takes the form of a residue and is the most frequent location of extra-adrenal pheochromocytomas. Subramanian and Maker (2) identified only 135 abdominal paraganglioma patients in their literature review. Mediastinal paragangliomas are generally located along the aortopulmonary window. Paragangliomas developing in the mediastinum are sympathetic-type paragangliomas, such as abdominal paragangliomas (3).

The neoplastic cells found in paragangliomas are positive for the immunohistochemical marker 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 malignant and benign paragangliomas, malignancy can only be proven 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 most often 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 approximately 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 paragangliomas. 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, the medical records of 12 patients who were operated on for an abdominal mass between January 2002 and January 2020 and diagnosed with paragangliomas on histopathological examination were analyzed retrospectively. This study was approved by the Institutional Review Board of our institute (IRB No. 10.01.2020/95/23). An informed consent was read and signed by all participants. All procedures performed in this study involving human participants were performed 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 with confirmed paragangliomas as a result of clinical features, radiological imaging methods, and histopathological evaluations were included in the study. Pathologically, tumor size, immunohistochemical analyses of S100, *chromogranin A*, synaptophysin, and neuron-specific enolase, as well as the 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 genetics clinic for genetic evaluation in terms of neurofibromatosis, von Hippel-Lindau disease, and multiple endocrine neoplasia syndromes. Cases that could not be confirmed histopathologically as paragangliomas, 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 Corp., 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. A 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, a p value <0.05 was considered to indicate statistical significance.

Results

There were six male (50%) and six female (50%) patients in our study. The median age was 44 years (range: 21-81 years) (Table 1). The patients had one or more of headaches (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 paraganglioma. One of the cases (1/12; 8.3%) was detected incidentally. The mass was located 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 in Table 2.

The first patient was admitted with high blood pressure attacks. A paracaval paraganglioma was detected on radiological imaging, and then she was operated on. The tumor was resected with the wall of the inferior vena cava due to suspicion of tumor invasion, and then the 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 the renal hilus. After the operation, the patient developed a fistula between the left renal artery and vein, and the arterio-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 the pancreas. Subtotal pancreatectomy and splenectomy with mass excision were performed due to suspected pancreatic invasion. Fibrosis was revealed by a pathological evaluation of the region considered as tumor invasion to the pancreas on preoperative radiological imaging. 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 with eight cycles of peptide receptor radionuclide therapy consisting of 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 during removal of the paraganglioma mass located at the level of renal hilus. The renal artery was repaired, and no additional pathology developed during follow-up. In the ninth patient, the initial complaint was hematuria due to a paraganglioma mass located on the bladder side wall. Thickening was detected on the lateral wall of the bladder on pelvic ultrasonography (USG), and the lesion was excised using cystoscopy. The patient was followed up through routine annual check-ups, and no recurrence occurred.

Table 1. Clinicopathologic characteristics for the 12 patients under study

Characteristic	(n) (%)
Age (year) (median)	44 (range: 21-81)
Gender	
Male	6 (50%)
Female	(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%)

CT: Computed tomography, MRI: Magnetic resonance imaging, USG: Ultrasonography, PET/CT: Positron emission tomography/computed tomography

Laparoscopic surgery was performed in 2 of the 12 patients in our study. The surgical, pathological, and oncological characteristics of the 12 patients are presented in 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 the advanced age and comorbid diseases of the 11th patient, she lived for 36 months without local recurrence and/or metastasis after excision of a tumor, approximately 5 cm in size, from the sacrococcygeal region. This patient died in the 36th postoperative month from cardiac problems.

When the preoperative radiological imaging methods used on all 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' conditions 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 three 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/CT (PET/CT) examination was performed in four patients, and the SUVmax value was found to be high in all patients (20 in Case 1, 21.38 in Case 4, 14.84 in Case 6, and 14.3 in Case 8). On PET/CT imaging of the case with metastasis detected in the omentum, the lesion was found to have a 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 tumor size and mortality (p>0.05) or local recurrence (p>0.05). Histopathological evaluations confirmed the diagnosis of paraganglioma in all 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. The Ki-67 index was 6% in one patient and 4% in another patient.

Discussion

Paragangliomas are rare neuroendocrine tumors with similar clinical and histopathological features of pheochromocytomas originating from the adrenal medulla (1). Paragangliomas are

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

CT: Computed tomography, MRI: Magnetic resonance ımaging, USG: Ultrasonography, PET/CT: Positron emission tomography/computed tomography, IVC: Inferior vena cava, AVF: Arterio-venous fistula

Table 3. Surgical, pathological, and oncological characteristics of 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%)

usually located in the vicinity of the organ of Zuckerkandl, and they are common in this region due to the development of chromaffin tissue from extra-adrenal paraganglioma cells (1).

The benign or malignant character of a paraganglioma is related to the behavioral features 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 headaches (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 primary tumor localization and show metastatic lesions in malignant cases. The 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. (18) reported that a bladder paraganglioma was detected by pelvic USG preoperatively. Malthouse et al. (19) used transabdominal USG and determined paragangliomas adjacent to the pancreas. 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 of organs such as the lung, brain, and bone and is dependent on the physician who performs 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 two patients, and the primary tumor and its localization were reported in the remaining six patients. It was thought that the inability to detect the lesion by ultrasound was associated with anatomical localization and the 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, 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; 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 seven of the patients in our study, and the preliminary diagnosis of paraganglioma was reported in four, 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 a 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 opportunity to evaluate these patients for their potential eligibility for peptide receptor radionuclide therapy, 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 four 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 been 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 following 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. (33) reported that after initial surgery, tumor development occurred at 8.6, 12, and 17.7 years. This shows that the 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 in 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. (35) reported that the risk of local recurrence and distant metastasis in paraganglioma and pheochromocytoma

is higher in the presence of an *SDHB* mutation and/or when the tumor diameter is greater than 5 cm. 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. (38) 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. 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 in paragangliomas (39). Hamidi et al. (40) found that male gender, advanced age, dopamine hypersecretion, the presence of synchronous metastasis, primary tumor size, and not undergoing surgical resection for the primary tumor were associated with an aggressive disease course and high mortality. In our study, the patient who developed metastasis was a 44-year-old female who did not fit the high-risk group criteria. The small number of patients, the lack of genetic data, and the retrospective design are important limitations of this study. However, large, prospective randomized controlled studies including 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 paragangliomas. ^{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 performed in such a way as to obtain a negative surgical margin after preoperative examinations and preparations are conducted.

Ethics

Ethics Committee Approval: Approval was obtained from the Non-invasive Clinical Research Ethics Committee of Çukurova University Faculty of Medicine (date: 10.01.2020).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.G.S., M.O.G, O.Y., Z.T., İ.B.G., Concept: A.G.S., M.O.G., O.Y., Z.T., İ.B.G., Design: A.G.S., M.O.G., O.Y., Z.T., İ.B.G., Data Collection or Processing: A.G.S., M.O.G., O.Y., Z.T., İ.B.G., Analysis or Interpretation: A.G.S., M.O.G., Z.T., İ.B.G., Literature Search: A.G.S., M.O.G., Z.T., İ.B.G., Writing: A.G.S., M.O.G., Z.T., İ.B.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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