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Research Article

Clinical and Paraclinical Metabolic Outcomes in Patients with Pheochromocytoma

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ABSTRACT

Background and aim: Pheochromocytoma is a rare endocrine tumour that originates from the chromaffin cells of the sympathetic and parasympathetic nervous system. Pheochromocytoma has been called the "Great Mimic" because its clinical manifestations range from an adrenal gland accident to hypertensive crises with associated cerebral or cardiovascular complications.

Patients and Methods: A total of 70 patients were initially considered eligible, of which 60 cases were available for further post-treatment real-time assessment who had pathologically confirmed pheochromocytoma and underwent surgery between March 2006 and March 2021, in Ghaem Hospital of Mashhad University of Medical Sciences (MUMS), Mashhad, Iran, were enrolled in this retrospective cross-sectional study. For each patient, demographic and clinical information were retrieved from hospital records.

Results: The average age of the patients was 40.2 ± 14.9 years (13-80 years). Most patients were female (58.3%, 35 people). The diagnosis of the disease in 28 patients was random (46.7%) and in 32 patients it was based on clinical symptoms (53.3%, 32 people).Diagnoses of diabetes and high blood pressure were reported in 13.3% of patients (8 people) and 68.3% of patients (41 people). MEN syndrome was reported in 11 patients (18.3%). The size of the tumoral mass was equal to 7.1 ± 3.5 cm (1.4-16 cm). Tumours were mostly unilateral (88.3%, 53 people) and were discovered on the right and left sides (26 people and 27 people, respectively). With an average survival of 4.8 ± 5.4 years (1-32 years), 9 cases of mortality due to pheochromocytoma and 11 cases of recurrence due to pheochromocytoma were reported.

Conclusion: The results of the present study suggest that lifelong follow-up of patients with pheochromocytoma and paraganglioma through repeated examination of their serum markers and follow-up in terms of the occurrence of related tumours in hereditary cases and cardiovascular disorders.

INTRODUCTION

Pheochromocytoma (PCC) is a rare endocrine tumour that originates from the chromaffin cells of the sympathetic and parasympathetic nervous system. Tumours

caused by pheochromocytoma are chromaffin cells, post-ganglionic sympathetic neurons that produce catechol amines [1,2]. These cells are mainly located in the adrenal medulla (approximately 85-95% of pheochromocytomas are located in the adrenal medulla). Tumours caused by extra-adrenal chromaffin cells are called paragangliomas and can be seen along the paravertebral and para-aortic axes [3]. These tumours are similar in origin, but their clinical manifestations, prevalence and management are different. About four percent of incidentally found adrenal masses are pheochromocytomas. Pheochromocytoma has been called the "Great Mimic" because its clinical manifestations range from an adrenal gland accident to hypertensive crises with associated cerebral or cardiovascular complications [4]. Most of the signs and symptoms of pheochromocytoma, which are caused by excessive catecholamine secretion by tumours, include headache, palpitations, high blood pressure, and high blood pressure. Most of the secreted catechol amines are epinephrine, norepinephrine and dopamine. Most pheochromocytomas mainly secrete norepinephrine. About 15% of secretions are mostly epinephrine [5].

The prevalence of pheochromocytoma in the world is estimated to be 2 to 8 cases per million people, which is gradually increasing over time. Also, the screening studies that have been conducted to investigate the secondary causes of hypertension show the prevalence of pheochromocytoma among patients with high blood pressure between 0.1% and 0.6%. Timely diagnosis of this disease is very important because 10% of tumours caused by it are malignant [3]. In addition to these cardiovascular complications, metabolic disorders and mortality are also seen in patients due to excessive catecholamine secretion [6]. An adrenal incidentaloma is a mass lesion greater than 1 cm in diameter, serendipitously discovered by radiologic examination. This entity is the result of technological advances in imaging such as CT and MRI [7]. All patients with adrenal incidentalomas should be evaluated for the possibility of malignancy. The size and imaging characteristics ("imaging phenotype") of the mass may help determine whether the tumor is benign or malignant [7-9].

Benign cortical adenoma – A homogeneous adrenal mass <4 cm in diameter, with a smooth border, and an attenuation value <10 Hounsfield Unit (HU) on unenhanced CT is very likely to be a benign cortical adenoma [7].

Adrenal carcinoma or metastases – The imaging characteristics that suggest adrenal carcinoma or metastases include irregular shape, inhomogeneous density, high unenhanced CT attenuation values (>20 HU), diameter >4 cm, and tumour calcification. Other characteristics are described above.

All patients with adrenal incidentalomas should be evaluated for the possibility of subclinical hormonal hyper function.

Pheochromocytoma should be excluded in all patients with adrenal incidentalomas with unenhanced CT attenuation >10 HU by measuring 24-hour urinary fractionated metanephrines and catecholamines or plasma fractionated metanephrines [10].

Subclinical Cushing syndrome should be ruled out by measuring baseline Dehydroepiandrosterone Sulfate (DHEAS) and performing the 1 mg overnight Dexamethasone Suppression Test (DST). To detect clinically significant glucocorticoid secretory autonomy, the post-overnight 1 mg DST 8 AM serum cortisol concentration cut off is >1.8 mcg/dL (>50 nmol/L). An abnormal 1 mg overnight DST is consistent with corticotropin (ACTH) - independent cortisol production, a finding that should be confirmed with 24-hour urinary free cortisol, serum ACTH concentration, and a high-dose (8 mg) overnight DST [11]. If the adrenal incidentaloma patient has hypertension or hypokalemia, a plasma aldosterone level and plasma renin activity should be measured to screen for primary aldosteronism [7-12].

In the 2017 World Health Organization (WHO) classification, pheochromocytoma is considered an adrenal tumour and paraganglioma is an extra-adrenal tumour. Since the two types of tumours cannot be differentiated based on histological findings, anatomical location is used to differentiate between them [13,14]. Tumour growth shows the so-called zellballen pattern, which actually consists of well-developed tumour cells with nested growth, with an intervening stromal component of fibro vascular tissue and peripheral smooth cells. Immunohistochemical examination shows that malignant cells are stained with chromogranin and S100 [14].

The prevalence of pheochromocytoma and paraganglioma is about 0.6 cases per 100,000 people per year [15]. There is a wide range of potential symptoms associated with this disease,

including the classic triad of headache, palpitations, and profuse sweating [16]. Considering the significant prevalence of anxiety symptoms and panic attacks in the general society, identifying a rare patient with pheochromocytoma or paraganglioma is a challenge for doctors. However, with the widespread use of imaging, the incidental discovery of an adrenal mass is increasing [17]. In addition, asymptomatic cases of pheochromocytoma and paraganglioma are increasingly being discovered based on evaluation of other family members and germ line mutation screening [3].

The diagnosis of pheochromocytoma or paraganglioma requires proof of excess release of catechol amines and anatomical documentation of the tumour. The increase in plasma metanephrines (metanephrine and normetanephrine) has a sensitivity of 97% and a specificity of 93%, which has been confirmed in various studies [5]. On the other hand, the measurement of fragmented catechol amines (epinephrine, norepinephrine and dopamine) is less sensitive. Although it is clear that increased values of any of these (> 2 times the upper limit of the normal range) are also diagnostic [18,19].

For medical imaging of pheochromocytoma or paraganglioma, the following scenarios should be considered: First, typical symptoms with detectable elevation of metanephrine or catecholamine levels. Second, the incidental diagnosis of a yarteroperitoneal adrenal mass and third, the discovery of a germline mutation in the susceptibility gene in the molecular genetics test and the related syndrome. In scenario 1, the primary location of the tumor should be discovered using contrast-enhanced Computed Tomography (CT) or T2-weighted Magnetic Resonance Imaging (MRI). Standard imaging includes examination of the entire retroperitoneal space because almost all catecholamine-secreting extra-adrenal tumors are located in the retroperitoneal space rather than the pelvis or chest. In scenario 2, a non-contrast CT scan is important because when a mass with an attenuation of 10 Hunsfield units or less is detected on a CT scan; the primary diagnosis is a lipid-rich mass, and therefore it rejects the diagnosis of pheochromocytoma or paraganglioma, and biochemical testing is not necessary in this situation [20]. For masses with an attenuation of more than 10 Hounsfield units on CT scan, biochemical testing should be performed. When biochemical tests are abnormal, cross-sectional imaging with contrast-enhanced CT or MRI should be performed.

Once a pheochromocytoma or paraganglioma is identified, additional whole-body imaging is required [21]. Functional imaging (with scintigraphy with 123I-labeled metaiodobenzylguanidine, positron-emission tomography [PET]-CT labelled with DOTATATE and l-DOPA) is very effective in discovering the main site of pheochromocytoma and paraganglioma [22]. The main use for functional imaging is to look for metastatic disease or identify multiple chromaffin tumours. In contrast, head and neck paragangliomas usually appear as painless, slow-growing masses, mainly identified as carotid body tumours and vagal paragangliomas, or with conductive hearing loss and pulsatile tinnitus caused by jugulotympanic paragangliomas. Become Lower cranial nerve defects are often seen in patients with advanced paraganglioma of the head and neck. Increased excretion of catecholamine is rarely found in such patients [23,24]. Finally, although pheochromocytoma disease has been known as one of the causes of diabetes and secondary hypertension for many years, some researches showed that about 50% of pheochromocytoma cases are diagnosed in autopsy, of course, with the improvement of laboratory diagnostic methods. And the imaging accuracy of diagnosing this disease has improved significantly compared to the past decades [25]. The risk of recurrence of the disease (usually with distant involvement) in people with pheochromocytoma during a long-term follow-up is approximately 15%, so it is necessary to measure the 24-hour urinary secretion of catecholamine and urinary metanephrines or plasma metanephrines of affected people annually during the patient's life as be monitored continuously. For this reason, due to the possibility of disease recurrence or the remaining diseases caused by the complications of pheochromocytoma, our purpose of conducting this research is to investigate the metabolic and laboratory consequences and determine the cases of recurrence in patients with pheochromocytoma.

MATERIALS AND METHODS

All patients who had pathologically confirmed pheochromocytoma and underwent surgery between March 2006 and March 2021, in Ghaem Hospital of Mashhad University of Medical Sciences (MUMS), Mashhad, Iran, were enrolled in this retrospective cross-sectional study. The study

protocol was reviewed and approved by the Ethics Committee of MUMS (IR.MUMS.MEDICAL.REC.1399.480). A total of 70 patients were initially considered eligible, of which 60 cases were available for further post-treatment real-time assessment. For each patient, demographic and clinical information including age and gender, past medical history, clinical complications like as diabetes, hypertension, cardiovascular involvement, imaging data, unilateral or bilateral, frequency of malignancy, syndromic, and disease recurrence as well as laboratory parameters including urinary catecholamine, blood sugar, urea, creatinine, complete blood cell count, type of medical or surgical treatment were retrieved from hospital records. All 60 available patients were revisited and rechecked for paraclinical tests. Any evidence of disease recurrence was confirmed using CT scan.

Statistical analyses were performed using IBM SPSS version 22 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used and categorical data was presented as frequencies and percentages. Continuous variables with normal distribution were reported in terms of mean ± Standard Deviation (SD); otherwise, they were given as median (IQR). In case of subgroup analysis, chi-square, independent and unpaired t-tests were used to compare the qualitative and quantitative variables respectively. In all calculations, a significance level of 0.05% was considered.

RESULTS

In this study, 60 patients with pheochromocytoma were examined. The average age of the investigated patients at the time of diagnosis was 40.2 ± 14.9 years (13-80 years). Most patients were female (58.3%, 35 people). The diagnosis of the disease in 28 patients was random (46.7%) and in 32 patients it was based on clinical symptoms (53.3%, 32 people).Diagnoses of diabetes and high blood pressure were reported in 13.3% of patients (8 people) and 68.3% of patients (41 people) at the time of diagnosis, respectively. MEN syndrome was reported in 11 patients (18.3%). The size of the tumoral mass in the examined patients was equal to 7.1 ± 3.5 cm (1.4-16 cm). Tumours were mostly unilateral (88.3%, 53 people) and were discovered on the right and left sides in the same proportion (26 people and 27 people, respectively). In total, with an average survival of 4.8 ± 5.4 years (1-32 years), 9 cases of mortality due to pheochromocytoma and 11 cases of recurrence due to pheochromocytoma were reported (Tables 1 and 2).

Table 1: Background characteristics of patients.

Characteristic	Standard deviation ± mean Middle(IQR)	N	%
Age Less than 45	40.2+_14.9	41	68.3
Male		25	41.7
type of action			
laparoscopy		42	72.4
open		16	27.6
Cause of diagnosis			
Accidental		28	46.7
Marked		32	53.3
Diabetes Before surgery		8	13.3
Diabetes after surgery		7	11.6
Hypertension Before surgery		41	68.3
Hypertension after surgery		4	6.7
MEN syndrome		11	18.3
Tumour size (cm)			
Less than 5	7.1+_3.5		
side involved			
One side		53	88.3
Tow side		7	11.7
mortality		9	15
relapse		11	18.3

Table 2: Laboratory characteristics of patients at diagnosis and after treatment.

laboratory characteristic	Get diagnosed Standard deviation ± mean	after treatment Standard deviation ± mean	P-VALUE
Hb(g/dL)	13/6 ± 1/1	13/4 ± 1/5	0.9
FBS(mg/dL)	103/1 ± 22/0	94/2 ± 11/2	0.045
Creatinine(mg/dL)	0/91 ± 0/13	0/88 ± /2	0.8
Methanephrin(mg/24h)	812)1659/85(	52)122/35(	Less than 0.0001
nor methanephrin(mg/24h)	1450)1277/35(	150)208/50(	0.033
Ca(mg/dL)		9/33 ± 0/5	

Table 3: Comparison of the type of background characteristics according to the mortality event.

Variable	with mortality (Abundance %)	Without mortality (Abundance %)	p-value
gender			0/58 *
female	6)66/7(	29)56/9(	
male	3)33/3(	22)43/1(	
age category			0/90 *
Less than 45 years	6)66/7(	35)68/6(	
more than 45 years	3)33/3(	16)31/4(	
Diabetes before surgery	0)0(	8)15/7(	0/20 *
HTN before surgery	0)0(	8)15/7(	0/20 *
HTN after surgery	0)0(	4)7/8(	0/38 *
MEN syndrome	7)77/8(	34)66/7(	0/50 *
Cause of diagnosis			0/56 *
Accidental	5)55/6(	23)45/1(	
Marked	4)44/4(	28)54/9(	
Two-sided conflict	9)100(	44)86/3(	0/23 *
The size of the malignant mass			0/01 *
less than 5 cm	0)0(	21)41/2(	
more than 5 cm	9)100(	30)58/8(	
Type of surgery			0/006 *
laparoscopy	2)28/6(	40)78/4(	
open	5)71/4(	11)21/6(	

* Chi-square test

Table 4: Comparing the type of laboratory variables according to the mortality event.

characteristic	with mortality (Standard deviation ± mean) Middle(IQR)	without mortality (Standard deviation ± mean) Middle(IQR)	P-Value
Hb(g/dL)	12/5 ± 1/1	13/7 ± 1/1	0/02 *
FBS(mg/dL)	95/8 ± 4/4	104/1 ± 23/6	0/4 *
Creatinine(mg/dL)	1/02 ± 0/11	0/89 ± /13	0/03 *
Methanephrin(mg/24h)	2260/5)1013(	624)1406/5(	0/01 **
nor methanephrin(mg/24h)	2189)2751(	1329/5)1115/8(	0/1 **

* Independent T-test

** U-Man-Whitney test

Table 5: Comparison of the type of background characteristics according to the presence of MEN syndrome.

Variable	MEN syndrome Frequency (%)	Sporadic Frequency (%)	p-value
gender			0/69 *
female	7)63/6(	28)57/1(	
male	4)36/4(	21)42/9(	
age category			0/72 *
Less than 45 years	8)72/7(	33)67/3(	
More than 45 years	3)27/3(	16)32/7(	
Diabetes before surgery	0)0(	8)16/3(	0/15 *
HTN before surgery	9)81/8(	32)65/3(	0/28 *
HTN after surgery(cronic)	0)0(	4)8/2(	0/32 *
Cause of diagnosis			
Accidental	2)18/2(	26)53/1(	0/03 *
Marked	9)81/8(	23)46/9(	
Two-sided conflict	5)54/5(	1)2(	>0/001 *
The size of the malignant mass			
less than 5 cm	6)54/5(	15)30/6(	0/13 *
More than 5 cm	5)45/5(	34)69/4(	

* Chi-square test

Table 6: Comparison of laboratory variables among patients with and without MEN syndrome.

laboratory characteristic	MEN syndrome Standard deviation ± mean(IQR)	Sporadic Standard deviation ± mean(IQR)	P-VALUE
Hb(g/dL)	13/6 ± 0/9	13/5 ± 1/2	0/8 *
FBS(mg/dL)	92/3 ± 4/1	104/7 ± 23/4	0/2 *
Creatinine(mg/dL)	0/86 ± 0/12	0/92 ± /13	0/3 *
Methanephrin(mg/24h)	970)2074/6(	812)1862/7(	0/9 **
nor methanephrin(mg/24h)	2550)4191/3(	1329/5)1031/5(	0/06 **

* Independent t-test ** U-Man-Whitney test

Table 7: Comparison of background characteristics according to the presence of diabetes.

Variable	Diabetic (Frequency)	Non Diabetic (Frequency)	p-value
female	4(50)	31(59.6)	0/6 *
male	4(50)	21(40.4)	
Less than 45 years	4)50(	37(71.2)	0/2 *
More than 45 years	4)50(	15(28.8)	
Cause of diagnosis			
Accidental	6)75(	22)42/3(	0/08 *
marked	2)25(	30)57/7(	
Two-sided conflict	0)0(	7)13/5(	0/2 *
The size of the malignant mass			
Less than 5 cm	3)37/5(	18)34/6(	0/8 *
More than 5 cm	5)62/5(	34)65/4(	

Table 8: Comparison of test results in patients with and without diabetes.

laboratory characteristic	With DM	Without DM	P-VALUE
Hb(g/dL) [SD standard deviation]	13/3 ± 1/1	13/5 ± 1/1	0/9 *
Creatinine(mg/dL) [SD standard deviation]	0/86 ± 0/12	0/92 ± /13	0/3 *
Methanephrin(MG/24HOURS) [median (IQR)]	710)816/6(	)1943/6(1000	0/6 **
nor methanephrin(MG/24HOUR) [median (IQR)]	1082/5)1167/3(	)1427/9(1500	0/1 **

* Comparison with T-test ** Comparison with Mann-Whitney

Table 9: Comparison of background characteristics according to the presence of HTN.

Variable	HTN (Frequency)	Non HTN (Frequency)	p-value
female	25)71/4(	16)64(	0/5 *
male	10)28/6(	9)36(	
Less than 45 years	30)73/2(	11)57/9(	0/2 *
More than 45 years	11)26/8(	8)42/1(	
Cause of diagnosis			
Accidental	9)32/1(	32)100(	0/001 *
marked	19)67/9(	)0((	
Two-sided conflict	35)66(	6)85/7(	0/2 *
The size of the malignant mass			
Less than 5 cm	13)61/9(	28)71/8(	0/4 *
More than 5 cm	8)38/1(	11)28/2(	

Table 10: Comparison of test results in patients with and without HTN.

laboratory characteristic	With HTN	Without HTN	P-VALUE
Hb(g/dL) [SD standard deviation]	13/4 ± 1/1	13/5 ± 1/2	0/9 *
FBS(mg/dl) [median (IQR)]	96)29(	92/5)7/2(	0/3 **
Creatinine(mg/dL) [SD standard deviation]	0/9)0/2(	0/9)0/1(	0/5 **
Methanephrin(MG/24HOURS) [median (IQR)]	1020)2110(	)1720/5(645/5	0/1 **
nor methanephrin(MG/24HOUR) [median (IQR)]	1450)1937/7(	)866/2(1307	0/5 **

* Comparison with T-test ** Comparison with Mann-Whitney

Table 11: Comparison of high blood pressure frequency before and after surgery.

	HTN after surgery	No HTN after surgery	p Value
Preoperative HTN	3	38	* >0/0001
No HTN before surgery	1	18	

* McNemar's test

Table 12: Comparison of the prevalence of diabetes before and after surgery.

	DM after surgery	No DM after surgery	p Value
Preoperative DM	0	8	0/999 *
No DM before surgery	8	44	

* McNemar's test

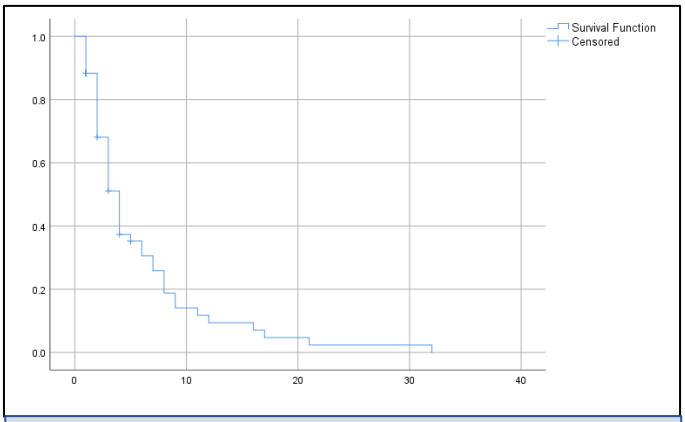

Chart 1: Survival chart of patients with pheocrocytoma.

DISCUSSION

In this study, 60 patients with pheochromocytoma were examined. The average age of the investigated patients at the time of diagnosis was 40.2 ± 14.9 years (13-80 years). Most patients were female (58.3%, 35 people). In the study of Leung et al, the epidemiology of pheochromocytoma and paraganglioma in the province of Alberta, Canada during 2012 to 2019 was investigated and the incidence of these patients in the studied community was 0.66 per 100,000 people per year. The frequency of this group of diseases increases with age, so that the highest prevalence rate was reported in the age group of 60-79 years old [26].

In the study of Sohail et al, 69% of patients were women [27].

In our study the diagnosis of the disease in 28 patients was random (46.7%) and in 32 patients it was based on clinical

symptoms (53.3%, 32 people). Diagnoses of diabetes and high blood pressure were reported in 13.3% of patients (8 people) and 68.3% of patients (41 people) at the time of diagnosis, respectively.

MEN syndrome was reported in 11 patients (18.3%).

In the study of Sohail et al, The most common symptoms of pheochromocytoma in the investigated patients were abdominal pain (51.7%), high blood pressure (44.8%) and headache (41.4%). Most pheochromocytomas were sporadic (82.8%), all adrenal gland tumours and 89.7% were unilateral [27].

In the study of Rafiq et al. [28], 14 patients with pheochromocytoma were examined in the period from 2010 to 2019 in India. Out of 14 patients, 10 were women and 4 were men. The average age of the patients was 38 ± 16 years. The most common symptoms at the time of diagnosis were headache (96.6%), heart palpitations (64.3%), abdominal pain (64.3%) and sweating (57.1%). While there were triple signs in 8/42. High blood pressure was the predominant clinical finding (92.8 percent), followed by orthostatic and increased blood sugar, which were reported in 35.7 percent of patients. Most pheochromocytomas were sporadic (85.7%), and most cases of tumours were discovered in the adrenal gland (78.6%) and were benign histologically (92.8%). Two cases were familial (one each due to neurofibromatosis and von Hippel-Lindau type) [28].

In our study Most of the patients underwent laparoscopic surgery (72.4%, 42 people). The size of the tumour mass in the examined patients was equal to 7.1 ± 3.5 cm (1.4-16 cm). Tumours were mostly unilateral (88.3%, 53 people) and were discovered on the right and left sides in the same proportion (26 people and 27 people, respectively). In the study of Rafiq et al, More than half of the tumours (54.5%) were located on the left side and 36.4% on the right side, and one patient had a bilateral tumour [28].

In our study, a significant difference was observed in the proportion of blood pressure before and after surgery ($p<0.0001$). This was despite the fact that no such significant difference was observed regarding diabetes ($p=0.999$). In the study of Khorram Menesh et al, at diagnosis, 85% of patients had high blood pressure. One year after surgery, more than half of them still had high blood pressure. However, preoperative and postoperative hypertension did not affect the risk of death compared to the control group. This study concluded that pheochromocytoma and paraganglioma can be safely treated with surgery [29]. In the study of Rafiq et al, Improvement of blood pressure after surgery was observed in 35.7% of patients with high blood pressure [28].

In Elenkova et al. [30] study, the frequency of carbohydrate disorders was investigated in 204 patients with pheochromocytoma and paraganglioma over a 40-year period. Carbohydrate disorders were diagnosed in 49.5% of patients, most of whom had diabetes (30.4%) and pre-diabetes (19.1%). Compared to patients with normal glucose tolerance, people with carbohydrate disorders had higher age at diagnosis and 24-hour urine metanephrine and normetanephrine concentrations. A third of patients with diabetes achieved good glycaemic control when receiving oral therapy (54% received monotherapy with metformin). One-third of patients in total required preoperative insulin treatment. Postoperative follow-up (100 patients; average duration of 5 years) showed a decrease in the prevalence of diabetes (13% vs. 33%; $P = 0.0007$) and prediabetes status (12% vs. 24%; $P = 0.027$). Shows. Approximately 60% of people initially diagnosed with carbohydrate disorders regain normal glucose tolerance after surgery. Preoperative urinary metanephrine/normetanephrine levels in these subjects were significantly higher than those with persistent diabetes/prediabetes. Correlation analysis showed a moderate negative relationship between urinary metanephrine/urine normetanephrine concentration and the outcome of carbohydrate disorders (Spearman's $r=0.507$ and $p=0.013$). There was no significant difference in the prevalence of obesity before or after surgery (15% vs. 16%; $P=0.845$) or dyslipidaemia (46% vs. 39%; $P=0.316$). The study concluded that carbohydrate disorders affect approximately half of patients with pheochromocytoma. 30% of patients develop overt diabetes, which may be the only clinical manifestation in some rare cases. Diabetes associated with pheochromocytoma is more likely to affect patients with adrenal glands. It is often easy to control and usually requires oral antidiabetic therapy. The reversibility of carbohydrate disorders depends on its severity at the time of diagnosis, preoperative metanephrine level, age and weight [30].

In our study Incidence of MEN syndrome according to gender (p=0.69), age (p=0.72), symptoms before and after surgery (for diabetes and HTN before surgery, respectively, p=0.15 and p=0.28, and blood pressure chronic (p=0.32), and tumour mass size (p=0.13) had no significant difference. Bilateral involvement was reported in more than half of patients with MEN syndrome, while only one patient without this diagnosis had bilateral involvement (54.5% and 2%, respectively, p<0.001). Also, 81.1% of patients with MEN syndrome were treated due to the presence of clinical symptoms, while only 46.9% of patients without such a diagnosis were treated due to clinical symptoms (p=0.03).

In our study in total, with an average survival of 4.8 ± 5.4 years (1-32 years), 9 cases of mortality due to pheochromocytoma and 11 cases of recurrence due to pheochromocytoma were reported.

In the study of Khorram Menesh et al. [29], 121 patients with pheochromocytoma and paraganglioma who were examined in a period of 47 years in Sweden. During the follow-up of 15 ± 6 years, 42 patients died, which was twice the number expected in the general population (P < 0.001). There were no intraoperative or postoperative deaths. Four patients with sporadic disease due to malignant paraganglioma and six patients with hereditary disease of neuroectoderm-related tumours died. . Five patients died due to other malignancies, 20 patients died due to cardiovascular diseases and seven patients died due to other causes. In addition to old age at the initial surgery, increased excretion of methoxy-catecholamines through urine was the only risk factor for death (P = 0.02). The death of malignant pheochromocytoma and paraganglioma is an unusual event, although in general, this malignancy is associated with an increased risk of mortality compared to the general population [29].

In our study, in deceased patients, the size of all malignant masses was above 5 cm (100%, 9 people), while in living patients, only 58.8% of patients (30 people) had a tumour size of 5 cm. Also, among deceased patients, 71.4% underwent open surgery, while 78.4% of living patients underwent laparoscopic surgery. In the study of Hue et al. [31], the outcome of malignant pheochromocytoma in the United States in a 6-year period was investigated in patients undergoing open or less invasive surgery. Using the national database, patients who underwent adrenalectomy for the treatment of malignant pheochromocytoma in the period of 2010-2016 were included in the study. A total of 276 patients were included in the study, of which 50.7% underwent open surgery and 49.3% underwent laparoscopic surgery. Tumour size in open surgery patients was significantly higher than laparoscopic group (8.2 cm vs. 4.7 cm, p<0.001). Other demographic and disease characteristics were similar between the two groups. The probability of a positive surgical margin was similar between the two groups. Five-year survival was 74.3% in patients undergoing open surgery and 79.1% in patients undergoing laparoscopic surgery, which were similar and the type of surgery did not affect the survival of patients [31].

In our study,). The level of metanephrine in patients with mortality was also significantly higher (2260.5 vs. 624 micrograms in 24-hour urine, p=0.01). The mortality rate in the present study was 15%. Also, in terms of tumour characteristics, tumoral lesions were mostly larger than five centimetres and unilateral. Larger tumour size and open surgery were more frequent in deceased patients. In the study of Rafiq et al. (2020), Metanephrine and non-metanephrine secretion patterns were observed in 58.3% of patients, while increased metanephrine was reported only in 41.7% of patients. Biochemical treatment was achieved in 85.7% and surgical treatment in 78.5% of patients. The survival of patients varied from 2 months to 9 years [28]. In our study, with a median follow-up of three years, the 5- and 10-year survival in the studied patients was 35% and 11.7%, respectively. Also, the median overall survival of the examined patients was 4 years (CI95% - 4.8 - 1.3)

In the study of Hamidi et al. [32] 272 patients with malignant pheochromocytoma referred to the Mayo Clinic of America were followed up for a period of 55 years. Malignant paraganglioma was diagnosed at a mean age of 39 years (range, 7-83 years), with simultaneous metastasis in 96 patients (35%). In 176 patients (65%), metastases developed at a median of 5.5 years (range 0.3 to 53.4 years) from initial diagnosis. The average follow-up was 8.2 years (range 0.01 to 54.1 years). The average overall survival and disease-specific survival were 24.6 and 33.7 years, respectively. Poor survival with male sex (P=0.014), older age at the time of

primary tumour (P=0.0011), concurrent metastasis (p<0.0001), larger size of primary tumour (p=0.0039), increased Dopamine was associated with the initial diagnosis (p=0.0195) and incomplete resection of primary tumour (p<0.0001). There was no difference in primary tumour type or presence of SDHB mutation. This study finally concluded that the clinical course of patients with malignant paraganglioma is significantly variable. Rapid disease progression is associated with male gender, older age at diagnosis, concurrent metastasis, larger tumour size, increased dopamine, and failure to resection the primary tumour [32].

Also, researchers recommend lifelong follow-up of patients with pheochromocytoma and paraganglioma through repeated examination of their serum markers and follow-up in terms of the occurrence of related tumours in hereditary cases and cardiovascular disorders [29].

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