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Original Article

Adrenalectomy for incidental and symptomatic phaeochromocytoma: retrospective multicentre study based on the Eurocrine® database

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Abstract

Background: Phaeochromocytoma is sometimes not diagnosed before surgery and may present as an adrenal incidentaloma. The aim of this study was to investigate differences in clinical presentation and perioperative outcome in patients with subclinical and symptomatic phaeochromocytoma, and in patients operated with and without preoperative α-blockade.

Methods: This was a retrospective observational study of patients with a histopathological diagnosis of phaeochromocytoma registered in Eurocrine®, the European registry for endocrine tumours, between 1 January 2015 and 31 March 2020. Patient characteristics, clinical presentation, tumour detection, and perioperative variables were analysed.

Results: Some 551 patients were included. Of these, 486 patients (88.2 per cent) had a preoperative diagnosis of phaeochromocytoma. Tumours were detected as incidentalomas in 239 patients (43.4 per cent) and 265 (48.1 per cent) had a preoperative diagnosis of hypertension. Preoperative α-blockade was more frequently used in patients with a known phaeochromocytoma (350, 90.9 per cent) than in patients with other indications for adrenalectomy (16, 31 per cent). Complications did not differ between patients who had surgery because of catecholamine excess compared with those who had other indications for surgery (19 (3.9 per cent) *versus* 2 (3 per cent); $P = 0.785$), nor did the conversion rate from minimally invasive to open surgery differ between the groups. There were no obvious differences in complications, according to the Clavien–Dindo classification, based on preoperative α-blockade or not.

Conclusion: Subclinical phaeochromocytoma detected incidentally is common. A significant proportion of patients with phaeochromocytoma did not have α-blockade before surgery, without an apparent effect on complications.

Lay summary

Phaeochromocytoma is an unusual adrenal tumour with hormonal overproduction of catecholamines leading to a severe condition, including extreme hypertension in some situations. It is treated with surgery. Medical treatment before surgery is used to minimize surgical complications related to high blood pressure. A large proportion of phaeochromocytomas are detected incidentally, without symptoms, on radiological examination for other reasons. The aim of this study was to investigate differences in patient characteristics and surgical results in patients operated with or without symptoms of phaeochromocytoma. Patients registered in the large, European database, Eurocrine®, between 2015 and 2020 were included in the study. The study showed that phaeochromocytoma without symptoms is common. Medical treatment before surgery does not seem to affect complications.

Introduction

Phaeochromocytoma is a neuroendocrine, catecholamine-secreting tumour, arising from chromaffin cells of the adrenal medulla. Clinical presentation is variable, and depends on the magnitude, type, and pattern of hormone release (adrenaline, noradrenaline, and dopamine), as well as individual sensitivity to catecholamines and their metabolites[1,2].

Clinical presentation includes a triad of symptoms: headache, sweating, and palpitations[1]. Other symptoms include anxiety, tremor, nausea, dyspnoea, and abdominal pain. Hypertension is

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a common sign of phaeochromocytoma, reported in up to 78–93 per cent of patients with adrenal and extra-adrenal phaeochromocytoma[3,4]. Only 0.04 per cent of patients with hypertension are, however, diagnosed with a phaeochromocytoma[5]. Paroxysmal catecholamine release may cause sudden peaks in BP, leading to severe cardiovascular events. Preoperative α-adrenergic blockade is recommended by guidelines to prevent vasoconstriction, and perioperative cardiovascular complications and death[6]. With improvements in anaesthetic methods and minimally invasive surgery, this practice has recently come under scrutiny. A meta-analysis by Schimmack and colleagues[7] demonstrated a lack of evidence for preoperative α-blockade. Most larger series of patients who had surgery for phaeochromocytoma have, however, been reported from high-volume tertiary centres and the results might therefore suffer from selection bias[8,9].

An increasing proportion of phaeochromocytomas are discovered as adrenal incidentalomas. Phaeochromocytomas without clinical symptoms represent 4–7 per cent of adrenal incidentalomas[10–12]. Among histologically diagnosed phaeochromocytomas, up to 29 per cent were detected as incidentalomas[3].

The aim of this study was to investigate contemporary clinical features, evaluation, preoperative medical treatment, surgery, and outcome in patients undergoing adrenalectomy for phaeochromocytoma. A special focus was to analyse outcomes for those diagnosed by clinical symptoms compared with incidentalomas, and in patients with or without preoperative treatment with α-blockers. Data were retrieved from Eurocrine®, a pan-European quality registry for endocrine tumours.

Methods

Eurocrine® is a pan-European registry for endocrine surgical procedures, with a special focus on rare tumours. The database was established in 2015 with a grant from the European Union health programme. Currently, the database is run by the non-profit Eurocrine Society with its seat in Vienna. The aim of the register is to improve clinical standards and reduce differences between hospitals, thereby diminishing morbidity and mortality[13]. The register also supports research within the field.

Patients with a histologically confirmed diagnosis of phaeochromocytoma were included in the study. Patients undergoing reoperation were excluded. The study period was 1 January 2015 to 31 March 2020. Data were extracted on 28 May 2020. The study was approved by the ethical committee at Lund University (2018/1054).

Data variables

Predefined preoperative variables were: sex, age, BMI, systolic and diastolic BP, preoperative diabetes and hypertension, type of detection (incidentaloma or adrenal-related symptoms), hereditary disease, indication for surgery (catecholamine excess, suspected malignancy on imaging, suspected metastasis, tumour size), preoperative imaging, preoperative biochemical evaluation (free metanephrine/normetanephrine in plasma or fractionated adrenaline/noradrenaline in urine), preoperative treatment for hormone excess, and tumour laterality.

Perioperative variables included: time on waiting list before surgery, surgical technique (open adrenalectomy, laparoscopic transabdominal adrenalectomy, posterior endoscopic adrenalectomy, robot assisted transabdominal adrenalectomy, robot assisted posterior adrenalectomy), conversion from endoscopic to open surgery, and surgical complications. Information on complications was retrieved from predefined data fields and from free-text fields, and also based on a Clavien–Dindo severity grade of II or more[14].

Postoperative variables were final histology, tumour size, postoperative duration of hospital stay, postoperative treatment owing cortisol insufficiency, and residual tumour (R) classification.

Statistical analysis

Descriptive statistics are presented as number with percentage, mean (s.d.) or median (i.q.r), as appropriate. Missing values were excluded from frequency calculations. Differences between patient groups in perioperative and tumour characteristics were analysed using the χ^2 test, independent-samples *t* test or Mann–Whitney *U* test, as appropriate. Analyses were conducted using SPSS® for Mac® version 26.0 (IBM, Armonk, New York, USA). $P < 0.050$ was considered significant.

Results

Some 2904 patients underwent adrenalectomy during the study period. A total of 2353 patients were excluded: 2336 patients with adrenal disease other than phaeochromocytoma and 17 who had reoperation. Finally, 551 patients with phaeochromocytoma confirmed on histology were included in the study. Data were registered by 48 surgical departments in 11 European countries. The majority of patients underwent surgery at eight hospitals. The distribution between centres is shown in *Table S1*.

Preoperative characteristics

Preoperative characteristics of the cohort are shown in *Table 1*. The mean(s.d.) age was 53.2(16.0) years, and 319 (57.9 per cent) were women. Some 75 patients (13.6 per cent) were diagnosed with hereditary disease, and 23 had bilateral tumours. Thus, a total of 574 tumours were operated. The tumours were detected incidentally in 239 patients (43.4 per cent). Almost half of the patients had a preoperative diagnosis of hypertension. Hormone evaluation was undertaken before surgery in 491 patients (89.1 per cent). Twelve of 491 patients (2.4 per cent) had normal catecholamine levels in both plasma and urine. Imaging methods used were CT in 258 patients (46.8 per cent), MRI in 180 (32.7 per cent), metaiodobenzylguanidine (MIBG) imaging in 172 of 549 (31.3 per cent), and fluorodeoxyglucose PET in 75 of 504 (14.9 per cent). The median tumour attenuation value was 30 (i.q.r. 21–40) Hounsfield units (HU), and only 4 of 181 patients (2.2 per cent) had a value below 10 HU.

Perioperative characteristics

Perioperative characteristics are summarized in *Table 2*. Indications for surgery (1 and/or several), were catecholamine excess (486 patients, 88.2 per cent), suspicion of malignancy on imaging (178 patients, 33.0 per cent), size (16 patients, 3.2 per cent), and suspicion of metastasis (6 patients, 1.1 per cent). The median time on the waiting list for surgery was 28 (14–47) days. Preoperative α-blockade was used in 366 patients (83.8 per cent).

Endoscopic adrenalectomy was performed in 483 patients (89.1 per cent) and more than half of these operations were carried out using a posterior technique. Conversion from endoscopic to open adrenalectomy was done in 22 patients (4.6 per cent) (*Table S2*). Complications occurred in 22 patients (4.0 per cent) based on registry data field, and 21 (3.8 per cent) based on a Clavien–Dindo grade of II or above (*Table S2*).

Table 1 Characteristics of 551 patients with phaeochromocytoma included in the study

	No. of patients* (*n* = 551)
Age (years)†	53.2(16.0)
Sex ratio (F : M)	319 : 232
Hypertension	265 (48.1)
Diabetes	93 (16.9)
BMI (kg/m^2) (*n* = 543)†	25.1(5.0)
Hereditary disease	75 (13.6)
MEN2	44
Neurofibromatosis 1	16
von Hippel–Lindau syndrome	7
MEN1	3
Other	5
Pathological biochemical result‡§	
Urinary adrenaline	232 of 329 (70.5)
Urinary noradrenaline	261 of 331 (78.9)
Plasma metanephrine	317 of 393 (80.7)
Plasma normetanephrine	344 of 392 (87.8)
Normal biochemical evaluation on all biochemical investigations‡¶	12 of 491 (2.4)

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.). ‡Owing to differences in the biochemical assays used, levels were registered as subnormal, normal or increased in the database. §Patients with pathological result as a proportion of those tested. ¶Patients with normal result as a proportion of those tested.
MEN, multiple endocrine neoplasia.

Postoperative characteristics

The median size of the tumour on histology was 40 (30–60) mm. Malignant phaeochromocytoma was diagnosed in 16 patients (2.9 per cent), and a suspected malignancy on imaging was the indication for surgery for all of these. Median duration of hospital stay was 3 (2–5) days. Postoperative treatment for adrenal insufficiency was prescribed to 61 of 459 patients (13.3 per cent) at discharge, and 66 of 518 (12.7 per cent) at first follow-up.

Conversion and complications in relation to characteristics

There were no obvious differences in outcomes according to whether preoperative α-blockade was given (366 patients) or not (71) (data missing for 114 patients). Complications with a Clavien–Dindo grade of II or higher were registered in 12 of 366 patients (3.3 per cent) with blockade *versus* no patients without blockade ($P = 0.625$). Conversion from a minimally invasive to an open technique was necessary in 13 of 327 patients (4.0 per cent) with blockade *versus* 3 of 56 (5.4 per cent) without ($P = 0.633$).

Of 12 patients (2.4 per cent) who had normal levels in all preoperative biochemical evaluations, of whom two had hereditary disease, MIBG imaging was undertaken in three patients and MRI in three. In this subgroup of patients, there were no complications according to the predefined data fields, no complication was registered as Clavien–Dindo grade II or more, and there were no conversions from endoscopic to open surgery.

Hormone evaluation was not registered for 60 patients (10.9 per cent). MIBG imaging was performed in one of these patients (2 per cent) and MRI in nine (15 per cent). Complications were uncommon; one patient (2 per cent) had complications according to predefined data fields and none based on Clavien–Dindo grade II or more.

Analysis based on indication for surgery

Catecholamine excess was the indication of surgery in 486 patients, and 65 (11.8 per cent) had other indications for surgery. Comparisons between these groups are shown in *Table 3*. Suspected malignancy on imaging was more frequent in patients with an indication for surgery other than catecholamine excess. There was a larger proportion of incidentally detected tumours among patients with an indication for surgery other than catecholamine excess, and consequently preoperative α-blockade was used less often in these patients. In 16 patients (31 per cent), preoperative treatment with α-blockade was not registered. In this subgroup of patients, 14 patients presented with increased catecholamine levels, although these were not registered before operation as the indication for surgery.

Table 2 Perioperative characteristics of 551 patients with phaeochromocytoma

	n	No. of patients*
Indication		
Catecholamine excess	551	486 (88.2)
Suspicious for malignancy on imaging	539	178 (33.0)
Size only	500	16 (3.2)
Suspicion of metastasis	551	6 (1.1)
Tumour side	551	
Left		243 (44.1)
Right		285 (51.7)
Bilateral		23 (4.2)
Preoperative α-blockade	437	366 (83.8)
Surgical approach	542	
Open		59 (10.9)
Transabdominal laparoscopic		276 (50.9)
Posterior endoscopic		153 (28.2)
Transabdominal robotic		47 (8.7)
Posterior robotic		2 (0.4)
Other endoscopic		5 (0.9)
Conversion from endoscopic to open surgery	483	22 (4.6)
Complication‡	551	22 (4.0)
Clavien–Dindo complication grade	551	
I		48 (8.7)
II		13 (2.4)
III		4 (0.7)
IV		4 (0.7)
Duration of hospital stay (days)†	548	3 (2–5)
Malignant phaeochromocytoma on histology	551	16 (2.9)
Tumour size (mm)†	515	40 (30–60)
Resction margin status	551	
R0		535 (97.1)
R1		14 (2.5)
R2		2 (0.4)
Postoperative treatment owing to adrenal insufficiency		
At discharge	459	61 (13.3)
At first follow-up	518	66 (12.7)
Time on waiting list (days)†	414	28 (14–47)
Time until first postoperative follow-up (days)†	519	18 (10–37)

*With percentages based on number with data available (*n*) in parentheses unless indicated otherwise; †values are median (i.q.r.). ‡Complications according to predefined variables and free text.

Analysis based on tumour detection

Preoperative and perioperative characteristics based on incidental tumour detection (239 patients) or adrenal-related symptoms (312) are shown in *Table 4*. Patients diagnosed with incidentaloma were slightly older and had a higher BMI. Patients with adrenal symptoms more often had hereditary disease. Importantly, 91 patients with adrenal incidentaloma (38.1 per cent) had a preoperative diagnosis of hypertension compared with 174 (55.8 per cent) with adrenal-related symptoms. As stated above, types of indication for adrenalectomy other than catecholamine excess were more frequent among patients with incidentaloma.

Table 3 Characteristics and outcomes for patients who had surgery for phaeochromocytoma diagnosed before operation or another indication

	Phaeochromocytoma diagnosed before operation ($n = 486$)	Other indications ($n = 65$)	P[††]
Age (years)*	52.7(15.9)	56.7(16.0)	0.058[‡‡]
Sex ratio (F : M)	280 : 206	39 : 26	0.714
Hypertension	238 (49.0)	27 (41.5)	0.260
Diabetes	82 (16.9)	11 (16.9)	0.992
BMI (kg/m^2)*[§]	24.9(4.7)	26.2(6.9)	0.053[‡‡]
Incidentaloma	182 (37.4)	57 (87.7)	<0.001
Hereditary disease	71 (14.6)	4 (6.2)	0.353
MEN2	43	1	
Neurofibromatosis 1	15	1	
von Hippel–Lindau syndrome	6	1	
MEN1	3	0	
Other	4	1	
Tumour side			0.142
Left	210 (43.2)	33 (50.8)	
Right	253 (52.0)	32 (49.2)	
Bilateral	23 (4.7)	0	
CT	215 (44.2)	43 (66.2)	0.001
Attenuation on CT (HU)[†¶]	30 (21.75–40)	34 (20–38)	0.928[§§]
Positive MIBG imaging	153 of 164 (93.3)	7 of 8 (87.5)	0.021
MRI	159 (32.7)	21 (32.3)	0.947
Positive FDG-PET	56 of 64 (88)	11 of 11 (100)	0.441
Other indications for surgery			
Suspicious for malignancy on imaging	139 of 475 (29.3)	39 of 64 (60.9)	<0.001
Size only	10 of 441 (2.3)	6 of 59 (10.2)	0.001
Suspicious for metastasis	4 (0.8)	2 (3.1)	0.100
Preoperative α-blockade	350 of 385 (90.9)	16 of 52 (30.8)	<0.001
Surgical approach			0.623
Open	51 (10.6)	8 (12.7)	
Endoscopic	428 (89.4)	55 (87.3)	
Conversion	18 of 428 (4.2)	4 of 55 (7.3)	0.304
Complication[‡]	19 (3.9)	3 (4.6)	0.785
Clavien–Dindo complication grade			0.808
I	41 (8.4)	7 (10.8)	
II	11 (2.3)	2 (3.1)	
III	4 (0.8)	0 (0)	
IV	4 (0.8)	0 (0)	
Duration of hospital stay (days) [†]	($n = 483$) 3 (2–5)	3 (2–5.25)	0.779[§§]
Malignant phaeochromocytoma on histology	13 (2.7)	3 (4.6)	0.382
Tumour size (mm)[†#]	40.5 (30–60)	40 (25–60)	0.392[§§]
Resction margin status			0.463
R0	473 (97.3)	62 (95.4)	
R1	11 (2.3)	3 (4.6)	
R2	2 (0.4)	0 (0)	
Postoperative treatment owing to adrenal insufficiency			
At discharge	54 of 407 (13.3)	7 of 52 (13.5)	0.969
At first follow-up	57 of 458 (12.4)	9 of 60 (15.0)	0.577
Time on waiting list (days)[†]**	28 (14–47)	28 (15–48)	0.922[§§]

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (i.q.r.). [‡]Complications according to predefined data fields and free text. Data available for §479 and 64, [¶]154 and 27, #452 and 63, and **365 and 49 in groups with a preoperative diagnosis of phaeochromocytoma and other indications respectively. MEN, multiple endocrine neoplasia; HU, Hounsfield units; MIBG, metaiodobenzylguanidine; FDG, fluorodeoxyglucose. [††]χ^2 test, except [‡‡]independent-samples t test and [§§]Mann–Whitney U test.

Consequently, preoperative α-blockade was used in 150 patients with incidentaloma (75.8 per cent) *versus* 216 (90.4 per cent) with adrenal symptoms. Symptomatic patients more often had abnormal hormone levels than those with incidentaloma (*Table 5*). Incidentalomas were more often registered as suspicious for malignancy on imaging, although there were no differences in attenuation on CT.

There were no major differences in surgical approach between the two groups. Endoscopic procedures were used in 216 patients with incidentaloma (90.8 per cent) *versus* 267 (87.8 per cent) with symptoms. There was no difference in conversion rate. A slight difference was noted in the number of complications registered in data fields: 6 of 239 patients (2.5 per cent) with adrenal incidentaloma *versus* 16 of 312 (5.1 per cent) with adrenal-related symptoms ($P = 0.120$). There was, however, no difference in complications based on Clavien–Dindo grade, and no difference in duration of hospital stay.

Discussion

A non-negligible proportion of phaeochromocytomas are detected incidentally on imaging for non-adrenal indications[3,11]. The present registry-based retrospective observational study included a large collection of clinical data on phaeochromocytomas from almost 50 departments in 11 European countries. The general outcome was good: almost 9 in 10 patients were operated endoscopically, and the conversion rate was approximately 5 per cent. The median duration of hospital stay was 3 days;

Table 4 Characteristics and outcomes for patients with phaeochromocytoma diagnosed as incidentalomas or with symptoms

	Incidentaloma ($n = 239$)	Symptoms ($n = 312$)	P[¶¶]
Age (years)*	56.8(15.1)	50.4(16.1)	<0.001[##]
Sex ratio (F : M)	147 : 92	172 : 140	0.133
Hypertension	91 (38.1)	174 (55.8)	<0.001
Systolic BP (mmHg)*[§]	136(20)	144(31)	0.002[##]
Diastolic BP (mmHg)*[¶]	80(15)	84(16)	0.001[##]
Diabetes	37 (15.5)	56 (17.9)	0.443
BMI (kg/m^2)*[#]	25.8(5.2)	24.5(4.8)	0.002[##]
Hereditary disease	17 (7.1)	58 (18.6)	0.004
MEN2	9	35	
Neurofibromatosis 1	5	11	
von Hippel–Lindau syndrome	1	6	
MEN1	0	3	
Other	2	3	
Indication			
Catecholamine excess	182 (76.2)	304 (97.4)	<0.001
Suspicious for malignancy on imaging	119 of 232 (51.3)	58 of 306 (19.0)	<0.001
Size only	7 of 222 (3.2)	9 of 278 (3.2)	0.958
Suspicious for metastasis	3 (1.3)	3 (1.0)	0.742
Tumour side			0.024
Left	103 (43.1)	140 (44.9)	
Right	132 (55.2)	153 (49.0)	
Bilateral	4 (1.7)	19 (6.1)	
CT	154 (64.4)	104 (33.3)	<0.001
Attenuation on CT (HU)[†,]**	30 (22–40)	33 (20–40)	0.617***
Positive MIBG imaging	51 of 57 (89.5)	109 of 115 (94.8)	0.002
MRI	61 (25.5)	119 (38.1)	0.002
Positive FDG-PET	29 of 31 (93.5)	38 of 44 (86.4)	0.052
Preoperative α-blockade	150 of 198 (75.8)	216 of 239 (90.4)	<0.001
Surgical approach			0.173
Open	22 of 238 (9.2)	37 of 304 (12.2)	
Endoscopic	216 of 238 (90.8)	267 of 304 (87.8)	
Conversion	8 of 216 (3.7)	14 of 267 (5.2)	0.420
Complication[‡]	6 (2.5)	16 (5.1)	0.120
Clavien–Dindo complication grade			0.810
I	20 (8.4)	28 (9.0)	
II	4 (1.7)	9 (2.9)	
III	2 (0.8)	2 (0.6)	
IV	1 (0.4)	3 (1.0)	
Duration of hospital stay (days)[†,††]	3 (2–5)	3 (2–5.25)	0.400***
Malignant phaeochromocytoma on histology	8 (3.3)	8 (2.6)	0.587
Tumour size (mm)[†,‡‡]	40 (26.25–55)	40 (30–60)	0.060***
Resction margin status			0.463
R0	233 (97.5)	302 (96.8)	
R1	6 (2.5)	8 (2.6)	
R2	0	2 (0.6)	
Postoperative treatment owing to adrenal insufficiency			
At discharge	23 of 203 (11.3)	38 of 256 (14.8)	0.271
At first follow-up	25 of 230 (10.9)	41 of 288 (14.2)	0.254
Time on waiting list (days)[†,§§]	28 (14–47.25)	27 (14–46.75)	0.556***

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and [†]median (i.q.r.). [‡]Complications according to predefined data fields and free text. Data available for [§]226 and 276, [¶]226 and 273, [#]236 and 307, **123 and 58, [††]238 and 310, [‡‡]232 and 283, and [§§]186 and 228 in groups with incidentaloma and symptoms respectively. MEN, multiple endocrine neoplasia; HU, Hounsfield units; MIBG, metaiodobenzylguanidine; FDG, fluorodeoxyglucose. [¶¶]χ^2 test, except ##independent-samples *t* test and ***Mann–Whitney *U* test.

complications occurred only in 4.0 per cent of patients, and severe complications as graded according to the Clavien–Dindo classification were rare. These results compare favourably with previous published series[15–18].

Almost half of the tumours (43.4 per cent) were detected as incidentalomas. This is in agreement with other reports[3,4,19], where 23–51 per cent incidentally detected phaeochromocytomas have been described.

Hypertension is frequent in patients with phaeochromocytomas and paragangliomas, with a prevalence of 78–94 per cent[3,4]; the definition varies between studies. In the present study, the diagnosis was based on preoperative data on medical treatment for hypertension, and on measured BP. Hypertension was found in approximately half of the patients (48.1 per cent), and more often in patients with symptoms of catecholamine excess. Catecholamine secretion can be continuous or episodic, and the pattern affects the variation in clinical presentation. Some of the normotensive patients might therefore have had a paroxysmal hypertension that was not registered. Other symptoms described typically related to catecholamine release are headache, sweating, and palpitations[20]. In this cohort with predefined data fields, detailed information regarding such typical symptoms was not available.

Almost 90 per cent of the patients with phaeochromocytoma were diagnosed before operation. The diagnosis was usually based on biochemical evaluation of plasma free metanephrines or urinary fractionated metanephrines, as recommended in clinical guidelines[6]. These patients were mostly detected based on adrenal-related symptoms.

Table 5 Preoperative hormone evaluation in patients with phaeochromocytoma diagnosed as adrenal incidentalomas or with adrenal-related symptoms

	Incidental ($n = 239$)			Adrenal-related symptoms ($n = 309$)			$P^{\dagger}$
	Abnormal*	Normal*	Not performed	Abnormal*	Normal*	Not performed	
Urinary adrenaline	69 (62.7)	41 (37.3)	129 (54.0)	163 (74.4)	56 (25.6)	90 (29.1)	<0.001
Urinary noradrenaline	74 (67.3)	36 (32.7)	129 (54.0)	187 (84.6)	34 (15.4)	88 (28.5)	<0.001
Plasma metanephrine	122 (78.2)	34 (21.8)	83 (34.7)	195 (82.3)	42 (17.7)	72 (23.3)	0.005
Plasma normetanephrine	128 (82.1)	28 (17.9)	83 (34.7)	216 (91.5)	20 (8.5)	73 (23.6)	<0.001
All methods	175 (95.1)	9 (4.9)	55 (23.0)	285 (99.0)	3 (1.0)	21 (6.8)	<0.001

Values in parentheses are percentages; *based on tests performed. $^{\dagger}\chi^2$ test.

It is recommended that patients with hormonally functional phaeochromocytoma undergo preoperative blockade, preferably with α-adrenergic receptor blockers[6]. This was done in 90.9 per cent of the procedures in the present study. Of patients with indications for surgery other than increased catecholamine levels, only 31 per cent were prepared with α-blockers. Despite this, no major differences in the frequency of conversion from endoscopic to open surgery, or intraoperative or postoperative complications was noted in this subgroup. Outcome was favourable for the 71 patients who underwent adrenalectomy without preoperative α-blockade, and no different from that of patients who had received α-blockers. The clinical impact of preoperative treatment with α-blockers has been questioned in observational studies[8]. One recent meta-analysis[7] provided no evidence to support preoperative α-blockade, but not enough evidence to recommend abstaining either. Given the present results, the value of preoperative treatment with α-blockers needs to be tested in prospective trials.

Non-contrast CT is the suggested imaging modality of choice for phaeochromocytomas[6]. A tumour attenuation value of less than 10 HU indicates that an adrenal tumour is benign[11]. The median attenuation value for phaeochromocytomas in the present study was 30 HU and only four patients (2.2 per cent) had values below 10 HU. In a recent, large population-based study[21] of adrenal tumours, the attenuation value of phaeochromocytomas was 33 HU and none of the tumours had a value below 10 HU. The need for biochemical evaluation of adrenal incidentalomas with an attenuation value less than 10 HU, and using this as evidence of benign adrenal adenoma, has been discussed, but clear evidence is lacking[11,22]. Here, CT was performed in only 46.8 per cent of the patients, and interestingly, more often in patients without adrenal-related symptoms and those with other indications for surgery than those with catecholamine excess.

Subclinical phaeochromocytoma is defined as an incidentally detected phaeochromocytoma with no clinical signs of catecholamine excess. Adrenaline-producing tumours often exhibit paroxysmal hormonal release, with a clinical picture varying from hypertensive crisis to clinical silence, whereas tumours with predominantly noradrenaline excess have a more continuous release and sometimes symptoms resembling essential hypertension[2]. Downregulation of adrenoceptors can sometimes produce a milder response[23]. In the present investigation, patients with clinical phaeochromocytoma had higher levels of catecholamines than those with incidentaloma. This strengthens the theory that catecholamine levels matter in the clinical presentation, although the absolute hormone levels were not registered in the database. In a study by Haissaguerre and colleagues[4], patients with phaeochromocytomas and hypertension had higher levels of catecholamines than patients without hypertension. In contrast to a previous report which indicated that measurement of free plasma metanephrines may predict tumour size[24], clinical presentation was not influenced by tumour size in the present study.

The clinical consequences of untreated subclinical phaeochromocytoma are not known. Adrenalectomy is recommended for all phaeochromocytomas, as these tumours may cause hypertensive crises in stressful situations[6]. In agreement with previous reports[3], patients with clinical phaeochromocytoma were younger and more often had a preoperative diagnosis of hypertension.

Phaeochromocytomas are products of genetic mutations in approximately 60 per cent of patients, of which two-thirds are hereditary[25,26]. Germline and somatic mutations in combination with epigenetics in phaeochromocytoma is a fast-growing research field[27,28]. In the present study, hereditary disease was diagnosed in 13.6 per cent of the patients. This is a fairly low figure, and most likely postoperative genetic evaluation was not captured fully owing to a comparatively short follow-up time. Therefore, the number of patients with different mutations is probably underestimated.

Most phaeochromocytomas are benign, but about 10 per cent are malignant[3]. Histological appearance does not, however, clearly distinguish benign from malignant tumours, and the malignant potential is defined by the presence of distant metastasis. Only malignant tumours in the final histological evaluation were included here.

Postoperative adrenal insufficiency was noted in more than 10 per cent of patients in the present study. The reason for this is unknown but, of note, glucocorticoid excess in patients with phaeochromocytoma has been discussed recently[29].

A number of limitations of the present study should be acknowledged. Eurocrine® is a quality registry and data were analysed retrospectively. Exact biochemical data are not registered, which is a drawback for analysis of the value of preoperative treatment with α-blockers. Some 48 centres in 11 different countries are included, and thus probably a fairly wide variation in patient management. The strength of the present study is that it is a large, international series and data fields were predefined. Outcome is therefore likely to reflect current clinical presentation and practice.

Collaborators

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Supplementary material

Supplementary material is available at *BJS* online.

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Snapshots Quiz

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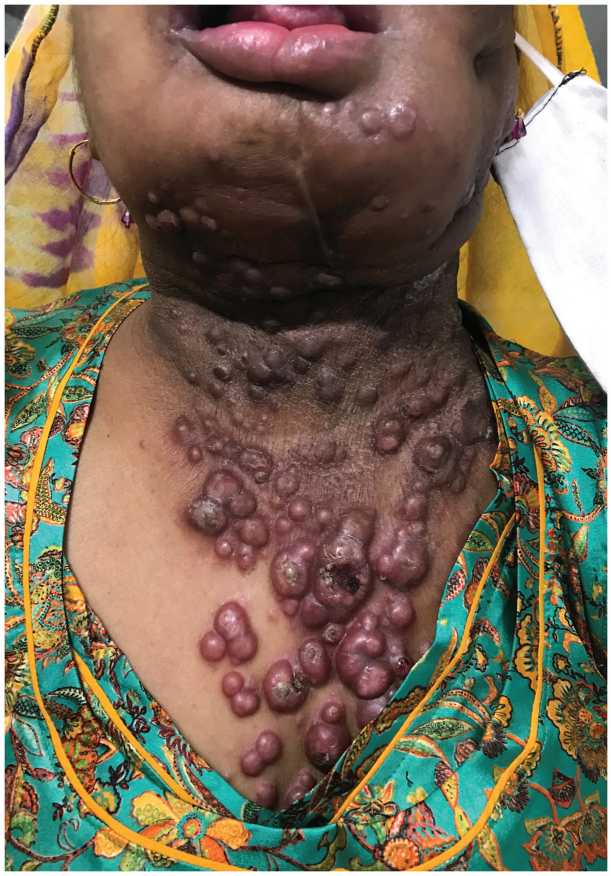
Question: A 45-year-old woman presented with decreased mouth opening, foul smell from the oral cavity and a chain of nodular swellings over chin, neck and chest region for 3 months. These had increased in size and number over the past month. Dimpling over her left cheek and scar marks over her neck and chin region were also noted. What is the diagnosis?



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Answer: Recurrent oral cavity carcinoma with multiple subcutaneous metastases, with a previous history of surgery followed by adjuvant radiotherapy.

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