ORIGINAL PAPER

UROLOGICAL ONCOLOGY

# The effect of surgical treatment of phaeochromocytoma on concomitant arterial hypertension and diabetes mellitus in a single–centre retrospective study

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Article history
Submitted: Aug. 11, 2014
Accepted: Sept. 1, 2014

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**Introduction** Phaeochromocytoma is one of the numerous causes of secondary hypertension. Furthermore, phaeochromocytoma may first present with type 2 diabetes mellitus. The objective of our study was to evaluate the effects of adrenalectomy on patient recovery with regards to normotension and well–controlled glycaemia.

**Material and methods** The retrospective analysis involved 67 patients with phaeochromocytoma operated between 2006 and mid-2012. The pre–operative diagnoses were made in the departments of internal medicine and endocrinology. Based on laboratory tests and diagnostic imaging, we were able to confirm the diagnosis of phaeochromocytoma in 42 (62.7%) patients. We verified the influence of adrenalectomy on the level of patient recovery, with regards to normotension and glycaemic control: arterial pressure and fasting glycaemia levels were obtained on the day of hospital discharge, at follow–up 3 months post–operatively and 1 year after surgical intervention.

**Results** Of the 67 patients operated for phaeochromocytoma, 48 (71.6%) were treated laparoscopically, whereas 19 (28.4%) underwent open adrenalectomy. Arterial hypertension was recorded in 53 (79.1%) cases. Furthermore, among this group, diabetes mellitus coexisted in 21 (31.3%) cases. Postoperatively, 70% of cases of arterial hypertension and 90% of type 2 diabetes mellitus were cured. Additionally, a high rate of patients reported a quantitative reduced use of antihypertensive medicines.

**Conclusions** In the majority of patients, surgical treatment of symptomatic phaeochromocytoma leads to a regression of arterial hypertension, or a reduction of the number or doses of medicines taken in one's treatment, and glucose–intolerance symptoms.

Key Words: phaeochromocytoma ‹› hypertension ‹› diabetes

## INTRODUCTION

Adrenal and extra–adrenal phaeochromocytomas comprise the numerous causes of secondary hypertension. It is estimated that they are the single cause of secondary hypertension in 0.1% to 0.6% of patients with paroxysmal hypertension [1, 2, 3].

An escalated burst of catecholamines results in hypertensive emergency and its consequences that involve various types of cardiac rhythm disturbances, pseudo–coronary syndromes (e.g. Takotsubo syndrome) and cerebral strokes. The incidence of acute coronary syndromes such as Takotsubo is thought to be approximately 1.7–2.2% in all patients hospitalised with phaeochromocytoma [4, 5]. Clinical experience indicates that hypertension concomitant with phaeochromocytoma varies in intensity. However, 5% to more than 30% of patients exhibit subclinical phaeochromocytoma with no associated hypertension [6–9].

According to a range of authors, phaeochromocytoma may first present with glucose intolerance and type


10.5173/ceju.2014.04.art9

2 DM. The above symptoms are recorded in approximately 50% of phaeochromocytoma patients. Elevated blood glucose levels and type 2 DM in the course of phaeochromocytoma result from both increased gluconeogenesis and, glycogenolysis, and decreased tissue glucose uptake. Additionally, serum catecholamine concentration growth suppresses insulin secretion by antagonising pancreatic beta–cells [10, 11, 12]. Increased catecholamine release may lead to a number of pathological, systemic symptoms, which initially may not be suggestive of phaeochromocytoma [13, 14].

From a clinical point of view, the key disorders are paroxysmal hypertension, with its systemic consequences, and carbohydrate metabolism disorders, including type 2 DM. The objective of our study was to evaluate the effects of adrenalectomy on the level of patient recovery, with regards to normotension and glycaemic control.

## MATERIAL AND METHODS

The retrospective analysis involved a group of 67 patients with phaeochromocytoma operated between 2006 and mid–2012 in the local academic centre. All patients were hospitalised and diagnosed in the departments of internal medicine and endocrinology in the pre–operative period. Based on test findings of serum adrenaline, noradrenaline, and chromogranin, and of methoxy–catecholamines in 24–hour urine specimens, in association with diagnostic imaging (ultrasound examination – USG, computed tomography of the abdomen and pelvis with contrast – CT, magnetic resonance imaging of the abdomen and pelvis with contrast – MR, positron emission tomography – PET), we were able to confirm the diagnosis of phaeochromocytoma in 42 (62.7%) patients. The remaining 37 (35.7%) patients were suspected of phaeochromocytoma based on patient medical history and the results of diagnostic imaging. Hence, all patients were administered alpha–adrenolytic treatment and other hypotensive medicines, if needed, in the 3–4–week period prior to the planned surgical intervention. The final confirmation of phaeochromocytoma was based on pathological examination.

Hypertension associated with phaeochromocytoma is characteristic due to its paroxysmal nature and usually reaches high values [1]. The hypertension attack lasts a few minutes until the catecholamines are removed from the circulation. These findings are suggestive for medical professionals to start diagnostics aimed at secondary hypertension. Prior to the surgery, all patients underwent 24–hour Holter monitoring of arterial blood pressure, which confirmed the diagnosis. The definition of hypertension was based on 2003 World Health Organization/International Society of Hypertension statement on management of hypertension, whose recommendations set systolic and diastolic pressure thresholds as 160 mmHg and 90 mmHg, respectively. Furthermore, the WHO definition of diabetes mellitus used in this paper was as follows: fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) or 2–h plasma glucose ≥11.1 mmol/l (200 mg/dl).

We evaluated arterial pressure and fasting glycaemia levels on the day of hospital discharge, at follow–up 3 months postoperatively and 1 year after surgical intervention. As the patients were qualified based on medical indications, no approval by local ethical committee was necessary. For the statistical analysis of the length of surgery and correlation of diameter of the tumor and length of surgery, the Student's t–test using Statistica Software® was performed. Furthermore, for analysis of statistical differences in arterial hypertension and diabetes mellitus post–surgery the Mann–Whitney U test was used.

## RESULTS

There were sixty–seven patients treated surgically due to phaeochromocytoma. The group consisted of 40 (59.7%) women and 27 (40.3%) men, aged 16 to 80 (mean age 44.5). Forty–eight (71.6%) of the patients were treated laparoscopically, and 19 (28.4%) underwent open adrenalectomy. All the laparoscopic procedures were performed via the transperitoneal approach. One patient died (1.5%) on the second day after laparoscopic adrenalectomy as a result of a prolonged hypotension following phaeochromocytoma excision. This patient suffered an extensive myocardial infarction, which was determined the cause of death. Blood transfusions were not required in either group of patients. The operative time was similar and did not exceed 240 minutes in both groups; no statistical differences were found ($p > 0.05$, Student's t–test). Furthermore, there was no correlation between tumor diameter and length of surgery ($p > 0.05$, Student's t–test).

Arterial hypertension was found in 53 (79.1%) of the treated patients. Arterial hypertension in the analyzed group was accompanied by DM in 21 (31.3%) cases. Immediately after surgery most patients required either a reduction of antihypertensive medicines or their discontinuation. Patient blood pressure after phaeochromocytoma surgery was monitored at three time points. The first assessment took place on the day of hospital discharge or transfer to another hospital department. The second check was performed during an outpatient visit after 3 months,

whereas the third was made 1 year after phaeochromocytoma excision. The results are presented in Table 1. The hypertensive patients were assessed according to the following groups: 1 – no medicines necessary, 2 – reduction of medicines taken, 3 – no reduction of medicines (Table 1).

As one patient from group 1 and three patients from group 3 changed their place of residence, contact with four patients was lost. Another patient died as a result of circulatory failure following two myocardial infarctions 8 months after adrenalectomy; she was amongst patients who required no hypotensive medicines at the time of hospital discharge. Twenty patients were treated with oral hypoglycaemic drugs and one with insulin.

The same diagnostic algorithm as above was applied to the evaluation of outcomes of diabetic treatment dependent on catecholamine overproduction. The results are presented in Table 2. For the diabetic patients, the groups were as follows: 1 – no medicines, 2 – orally administered drugs, 3 – insulin necessary (Table 2).

The concomitant arterial hypertension was cured in nearly 70% of cases and type 2 DM in 90% of post–phaeochromocytoma excision patients (Tables 1, 2). There is also a high rate of patients (17%) in the remaining group with quantitative reduction of antihypertensive medicines. In 69% of patients cured by surgery, blood pressure and glycaemia returned to normal levels within the first three months after adrenalectomy.

**Table 1.** *Monitoring of the blood pressure of the operated patients at follow–up visits*

| Group | Hypotensive medicines | Examination I* /% | Examination II* /% | Examination III* /% |
|---|---|---|---|---|
| 1 | No medicines | 27 (51.9) | 36 (69.2) | 35 (67.3)[b/c] |
| 2 | Medicine reduction | 18 (34.6) | 9 (17.3) | 4 (7.7) |
| 3 | No medicine reduction | 7 (13.5) | 7 (13.5) | 4 (7.7)[c] |
| TOTAL | | 52[a] (100) p>0.05 | 52 (100) p>0.05 | 43 (82.7)[c] p>0.05 |

[a]one perioperative death; [b]one death due to reasons unrelated to surgery; [c]no contact (4 patients), prior to examination III date (4 patients)
*The first assessment (examination I) took place on the day of hospital discharge or transfer to another hospital department. The second check (examination II) was performed during an outpatient visit after 3 months; and the third (examination III) 1 year after phaeochromocytoma excision.
P values were calculated with Mann–Whitney U test.

**Table 2.** *Monitoring of the glyeacemia of the operated patients at follow–up visits*

| Group | Hypoglycaemic drugs | Examination I* /% | Examination II* /% | Examination III* /% |
|---|---|---|---|---|
| 1 | No medicines | 15 (71.4) | 19 (90.4) | 19 (90.4)[a] |
| 2 | Oral medicines | 5 (23.8) | 1 (4.8) | – |
| 3 | Insulin | 1 (4.8) | 1 (4.8) | 1 (4.8) |
| TOTAL | | 21 (100) p>0.05 | 21 (100) p>0.05 | 20 (95.2) p>0.05 |

[a]one death due to reasons unrelated to surgery
*The first assessment (examination I) took place on the day of hospital discharge or transfer to another hospital department. The second check (examination II) was performed during an outpatient visit after 3 months; and the third one (examination III) after 1 year past phaeochromocytoma excision. P values were calculated with Mann-Whitney U test.

## DISCUSSION

Arterial hypertension and its paroxysmal nature are the most dangerous concomitant features of phaeochromocytoma. Cardiovascular symptoms in particular, mainly in the form of all types of cardiac rhythm disturbances, inclusive of Takotsubo, constitute a genuine threat to the lives of these patients. The symptoms are observed in nearly 20% of patients [14].

On the other hand, approximately 30% of phaeochromocytomas may be asymptomatic [15, 16]. Nevertheless, some stressful situations, such as surgery or pregnancy, may actually activate them [17]. Quite a typical feature of paroxysmal hypertension associated with phaeochromocytoma is secondary hypotonia and orthostatic hypotonia occurring mainly in children, immediately after excision of the affected adrenal gland.

In the large body of literature available, different authors report that significant improvement or complete recovery from hypertension and diabetes mellitus following surgical removal of phaeochromocytoma of up to 75–100% is observed in the majority of patients [6, 18–21]. In the case of arterial hypertension, the underlying issue is follow–up, as in some patients hyperadrenalinemia overlaps primary hypertension.

A Hong Kong study reports that one year after surgery blood pressure was normalised in two–thirds of patients [6]. Others recognised persistent hypertension in 4 out of 19 patients included in the follow–up period lasting 30 months on average, with 63% of patients reporting for follow–up visits [22]. A decisively lower rate of persistent hypertension after surgical treatment of phaeochromocytoma was noted by Kazic, et al. [23]. According to the author, persistent hypertension was found only in 10 (6.9%) out of the total 145 patients who underwent adrenalectomy due to phaeochromocytoma [23].

A little over 50% of patients in the study group were able to discontinue the use of all hypertensive medications. In just under 35%, either doses or quantity

of medicines maintaining adequate arterial blood pressure levels were reduced. Postoperative hypotension is observed due to an abrupt fall in circulating catecholamines after removal of the phaeochromocytoma [14]. In our paper, hypotonia was not considered to be a major problem in the group of younger patients, in contrast to elderly people >70 years old, in whom dangerous postoperative hypotension was observed in some cases. The key observation regards the period of the first three months following adrenalectomy; it is because during this period approximately 20% of patients were able to reduce or discontinue the use of antihypertensive medications. In the period between the third month and first year following the operation, we recorded no significant changes of arterial pressure parameters – the analysis included nearly 83% of patients. As a result, arterial hypertension associated with phaeochromocytoma was cured in more than 67% of surgically–treated patients within one year of the intervention. In less than 8% of operated patients the quantity of antihypertensive medications used decreased; whereas, a similar rate of patients revealed no effect on arterial pressure. Hypertensive treatment in those patients was similar to that from before surgery.

Due to mechanisms causing glucose intolerance and diabetes mellitus associated with phaeochromocytomas, one should expect that when hyperadrenalinemia subsides, glucose intolerance symptoms ought to subside as well, and this is the case in most patients [11, 23, 24, 25]. Still, it is common knowledge that an alpha–blocker is administered to patients preparing for surgery, which deactivates one or more mechanisms underlying glucose intolerance. Thus, glucose intolerance in the analyzed period may be less pronounced [10].

Our studies regarding glucose intolerance in the postoperative period demonstrate that hypoglycaemic drugs were discontinued in more than 70% of patients immediately after adrenalectomy. The risk of hypoglycaemia is related to rebound hyperinsulinaemia due to the recovery of insulin release after removal of the tumor [26]. More importantly, in the study no cases of rapid hypoglycaemia were observed postoperatively. Over 20% of those treated surgically achieved normoglycaemia within 2 weeks to 3 months following intervention. One patient still used insulin, which was administered to her preoperatively, too. In total, normoglycaemia was recorded in over 90% of patients during the one–year long adrenalectomy follow–up period.

Laparoscopic adrenalectomy has recently become the method of choice in surgical treatment of various adrenal gland pathologies, including but not limited to phaeochromocytomas [27, 28]. According to different authors, one should expect a somewhat higher, though still acceptable, rate of complications and conversion to the open method in the case of phaeochromocytoma surgeries [29, 30, 31].

There were several causes for the relatively high percentage of open (classical) adrenalectomies (more than 28%). First of all, it was a period in our centre of transition from the classical approach to laparoscopy of adrenal gland. Some other reasons included the presence of extra–adrenal phaeochromocytomas, large tumors with intratumor bleeding, large fibrous lesions in the adrenal region indicative of a cancerous process, and anaesthesiological contraindications, mainly regarding the respiratory system and patients with respiratory failure.

## CONCLUSIONS

In the majority of patients, surgical treatment of symptomatic phaeochromocytomas leads to a regression of arterial hypertension, or a reduction of the number or doses of medicines taken in one's treatment, as well as glucose–intolerance symptoms.

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