Metastases but not cardiovascular mortality reduces life expectancy following surgical resection of apparently benign pheochromocytoma

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Abstract

The treatment of choice for non-metastatic pheochromocytoma is surgical resection. Its goals are to abolish catecholamine hypersecretion, normalize blood pressure, and prevent further tumor growth or progression to metastatic disease. Data on long-term mortality and morbidity after pheochromocytoma surgery are limited. We here report a retrospective study on the long-term outcome after surgery for apparently benign pheochromocytoma at the Radboud University Nijmegen Medical Centre. Data on clinical presentation, treatment, post-surgical blood pressure and recurrence, metastasis and death were collected of 69 consecutive patients (January 1966–December 2000; follow-up: until death or January 2006). Survival was compared with survival of a matched reference population. Two patients died of surgical complications. All ten patients with metastatic disease (including three diagnosed at first surgery) died. At follow-up, 40 patients were alive and recurrence free and three patients were lost to follow up. Two patients experienced a benign recurrence. Mean±s.d. follow-up was 10.2±7.5 (median 9, range 1–38) years. Kaplan–Meier estimates for 5- and 10-year survival since surgery were 85.8% (95% CI: 77.2–94.4%) and 74.2% (95% CI: 62.0–86.4%) for patients versus 95.5 and 89.4% in the reference population ($P<0.05$). Sixty-four percent of all patients with hypertension prior to surgery showed a significant decrease in blood pressure, but remained hypertensive after surgery. In conclusion, compared with the general population patients have a reduced life expectancy following pheochromocytoma surgery, due to their risk of developing metastatic disease. Only one-third becomes normotensive without antihypertensive medication. Therefore, lifelong follow-up is warranted.

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Introduction

Pheochromocytoma (PHEO) is a rare catecholamine producing tumor that derives from chromaffin cells of the adrenal medulla or extra-adrenal abdominal and thoracic paraganglia (DeLellis *et al*. 2004, Lenders *et al*. 2005, Pacak *et al*. 2005). Symptoms, signs and complications of PHEO are mainly related to hypersecretion of catecholamines. These include headache, palpitations, diaphoresis, and hypertension. Once the biochemical diagnosis of PHEO is established by plasma and/or urine measurements of catecholamines and their metabolites (Lenders *et al*. 2002), tumors are localized by anatomical or functional imaging, such as ^{123}I-MIBG scintigraphy (Ilias *et al*. 2005).

Treatment of non-metastatic PHEO consists of surgical resection following preoperative pharmacological sympathetic blockade (van der Horst-Schrivers et al. 2006). The aims of surgery are abolishment of catecholamine hypersecretion, normalization of blood pressure, and prevention of further tumor growth and progression to metastatic disease. The long-term outcome of patients after PHEO surgery has been addressed in a limited number of studies. Estimates of benign and malignant recurrence rate after surgery vary between 6 and 23% (Modlin et al. 1979, Scott & Halter 1984, van Heerden et al. 1990, Pruszczyk et al. 1991, Plouin et al. 1997). Conflicting results of previous cohort studies suggest that the life expectancy after PHEO surgery is either normal (Stenstrom et al. 1988) or decreased (Khorram-Manesh et al. 2005) when compared with the general population. Furthermore, though PHEO is generally considered to be a surgically curable cause of secondary hypertension, blood pressure remains elevated after surgery in a considerable number of patients without recurrent disease (Plouin et al. 1997, Khorram-Manesh et al. 2005).

The aim of this study was to investigate the long-term follow-up of patients after surgery for apparently benign PHEO. Survival was compared with results obtained from a period-, age-, and gender-matched Dutch reference population.

Methods

Patients

To evaluate long-term outcome, the study was restricted to patients diagnosed with PHEO before January 2001. From January 1966 until December 2000, 71 patients with a histologically confirmed diagnosis of PHEO were evaluated at the departments of General Internal Medicine and Endocrinology at the Radboud University Nijmegen Medical Centre. In all but four patients, initial PHEO surgery was performed at our centre. Two patients were excluded from the study: one patient was referred to our center because of metastases and in a female patient who died during Caesarian section the PHEO was found at autopsy. This left 69 patients (44 females, 25 males) for evaluation of follow-up after surgery for apparently benign PHEO.

Initial work up, surgery, and follow-up

For the biochemical diagnosis of PHEO, plasma and 24-h urine were assayed by HPLC for concentrations of catecholamines (plasma $n=59$, urine $n=38$) and urine fractionated metanephrines ($n=12$), according to previously described procedures (Willemsen et al. 1995, 2003). CT ($n=57$), MRI ($n=4$), abdominal ultrasound ($n=36$) and ^{123}I-MIBG scintigraphy ($n=42$) were employed to localize the tumor(s). Except for three laparoscopic adrenalectomies, tumors were resected by open procedures (including four that initially started laparoscopically). Five patients with bilateral tumors underwent staged open surgery. Surgery was performed before 1990 in 43 per cent (29 out of the 68) of patients. Plasma and urine concentrations of catecholamines and metanephrines were reassessed after a minimum of 1 month post-surgery.

Data collection

Data on clinical presentation, biochemical, radiological and histological diagnosis, and surgical and pharmacological treatment were retrospectively collected from the patients' medical files in a standardized fashion. Post-surgery follow-up data, including blood pressure values, were collected until the end of December 2005. In patients whose most recent visit to our clinic took place before January 2005, information on the current health status, blood pressure, and antihypertensive treatment was updated by telephone interviews of the patients and their primary physicians.

Definitions

Hypersecretion of (nor)epinephrine was defined as elevation of plasma and/or urine levels of (nor)epinephrine and/or its metabolite (nor)metanephrine above the upper range of normal. Malignancy was defined as histological evidence of tumor cells at sites where chromaffin tissue is normally absent and/or by evidence of distant metastases documented by imaging studies (Linnoila et al. 1990). Recurrence was defined as the reappearance of the disease as documented at reintervention or by combined biochemical and imaging tests, after complete eradication of the tumor. Hypertension was defined as repeated office readings of systolic and/or diastolic blood pressure exceeding 140/90 mmHg and/or the use of antihypertensive medication.

Data analysis and statistics

Survival of patients who underwent successful resection of apparently benign PHEO was estimated using the Kaplan–Meier method and compared with the life expectancy of a Dutch reference population that was matched for age, sex, and period. Demographic data

were obtained from Statistics Netherlands (Centraal Bureau voor de Statistiek). The analysis was also performed for a subgroup of patients with metastatic PHEO. Pre- and post-surgery blood pressure values were compared using paired sample *t*-test. Baseline characteristics were compared between patients with metastatic and non-metastatic PHEO, using unpaired *t*-test, Wilcoxon rank sum test, and Fisher exact test, when appropriate. Results are presented as mean±s.d. unless mentioned otherwise. Statistical analysis was performed using Statistical Package for the Social Sciences (for Windows 12.0; SPSS, Chicago, IL, USA).

Results

Clinical presentation and diagnosis

Signs and symptoms at presentation are summarized in Table 1. Symptoms occurred episodically in 82% (55out of the 67) of patients, with a frequency of at least daily in 42% (23 out of the 55). In two patients, an adrenal tumor was found incidentally during work up of colon carcinoma and chest pain respectively. Seventy-seven percent (54 out of the 70) of patients had hypertension. Apart from pre-surgical α- and β-blockade, 64% (43 out of the 67) were on antihypertensive drugs. Age at initial diagnosis of PHEO was 46.1±15.6 (range 21–78) years. Hypersecretion of norepinephrine only occurred in 35% (20 out of 57), epinephrine only in 7% (4 out of the 57), and both epinephrine and norepinephrine in 58% (33 out of the 57) of patients. PHEOs were located as follows: left adrenal ($n=22$), right adrenal ($n=33$), bilateral adrenal ($n=6$), and extra-adrenal ($n=8$: 5 retroperitoneal, three in the bladder). Ninety-three percent (43 out of the 46) of tumors detected by anatomical imaging (CT, MRI, and ultrasound) were positive on ^{123}I-MIBG scintigraphy. Histological findings in all

tumors were consistent with PHEO. Fourteen patients had an underlying familial tumor syndrome: five neurofibromatosis, eight multiple endocrine neoplasia (MEN) type 2A, and one MEN type 2B.

Follow-up

Of the 69 patients, two died within 4 weeks after surgery (Table 2). In three patients, metastatic lesions were detected intra-operatively. The remaining 64 patients were included in the follow-up analysis. Follow-up of these patients was 11.0±7.4 (median 9, range 1–38) years. In 20 patients, the most recent clinical visit took place more than one 1 year before the final analysis (median 5, range 1–7 years). Three patients were lost to follow-up at 2, 8, and 27 years after surgery.

Two patients experienced a benign recurrence (one with MEN 2B). In one patient, initial surgery was incomplete, and plasma catecholamines only normalized after resection of the rest tumor.

Seven additional patients developed metastases, within 1–14 years after the initial diagnosis (Table 3). There were no significant differences between patients with metastatic and non-metastatic PHEO with respect to sex, age at diagnosis, pre-surgical plasma catecholamine levels, and extra-adrenal tumor location (Table 4). All patients with metastases died. Survival since the diagnosis of metastases was 2.6±0.8 (range 0–6) years. Twelve additional patients died during follow-up, all of whom were considered disease free although the cause of death is unknown in 5 out of these 12 patients (Table 3).

Survival

For the 64 patients who underwent successful surgery for non-metastatic PHEO, Kaplan–Meier estimates showed 5- and 10-year survival rates of 85.8% (95% CI:

Table 1 Symptoms and signs at initial presentation

Symptoms and signs	Frequency (*n*)	
	Observed	**Reported** [a]
Headache	77% (40/52)	60–90%
Palpitations	72% (39/54)	50–70%
Diaphoresis	87% (47/54)	55–75%
Pallor	57% (27/47)	40–45%
Nausea	70% (35/50)	20–40%
Flushing	33% (14/43)	10–20%
Tiredness	68% (39/57)	25–40%
Anxiety/panic attacks	65% (24/37)	20–40%
Weight loss	44% (27/61)	20–40%
Hypertension	77% (54/70)	50–60%

[a]Lenders *et al.* 2005.

Table 2 Follow-up

Patients with PHEO, first evaluation between January 1966–December 2000 (*n*=71)
  Excluded:
  Referred for metastatic PHEO, died (*n*=1)
  Heart failure during Caesarian section, post-mortem diagnosis (*n*=1)
Patients undergoing PHEO surgery (*n*=69)
  Intra- and post-operative findings:
  Metastases apparent at surgery (*n*=3)
  Post-surgical mortality <4 weeks (*n*=2, both non-metastatic)
  Post-surgical follow-up of patients with apparently benign PHEO (*n*=64)
    Lost to follow-up (*n*=3)
    Benign recurrence (*n*=2)
    Metastases, died (*n*=7)
    Died, recurrence and metastases free (*n*=12)
    Alive, recurrence and metastases free (*n*=40)

Table 3 Mortality

Sex/age at diagnosis	Year of surgery	Syndrome	Primary tumor location	Metastases-free survival (y)	Post-surgery/ metastases survival (y)	Cause of death
Non-metastatic PHEO						
F50	1984	–	R adrenal	–	0	Post-surgery sepsis
M47	1977	MEN2A	L adrenal	–	0	Post-surgery pulmonary embolism
M54	1995	MEN2A	L+R adrenal	–	1	Car accident
F63	1998	–	R adrenal	–	2	Unknown
F30	1988	MEN2B	L+R adrenal	–	3	Unknown
F48	1966	–	Extra-adrenal	–	3	Sub-arachnoid hemorrhage
F52	1974	NF	L adrenal	–	4	Unknown
F62	1977	–	R adrenal	–	5	Metastatic colon carcinoma
F54	1990	NF	R adrenal	–	7	Mesenteric sarcoma
M73	1989	MEN2A	L+R adrenal	–	10	Gastric bleeding
F60	1993	–	L adrenal	–	11	Unknown
M67	1987	–	R adrenal	–	13	Cardiac
F64	1972	NF	R adrenal	–	14	Unknown
F51	1972	–	L adrenal	–	21	Myocardial infarction
Metastatic PHEO						
F45	1989	–	L adrenal	0	0/0	Multi organ failure post-PHEO surgery
M46	1972	–	L adrenal	0	0/0	Cachexia post-PHEO surgery
M78	1998	–	R adrenal	1	2/1	Suicide
M66	1974	–	R adrenal	0	4/4	Complication of metastatic PHEO
F32	1985	–	L adrenal	3	5/2	Ruptured aortic aneurysm
F32	1988	–	L adrenal	3	6/3	Unknown
M52	1974	–	R adrenal	0	6/0	Unknown
M71	1992	–	L adrenal	7	10/3	Pneumonia, metastatic PHEO
F30	1984	–	Extra-adrenal	5	10/5	Septic shock post-bowel surgery
M75	1989	–	L adrenal	14	16/2	Complication of abdominal metastases

77.2–94.4%) and 74.2% (95% CI: 62.0–86.4%) versus 95.5 and 89.4% in the reference population respectively ($P < 0.05$, Fig. 1). The post-surgical survival of a subgroup of patients who (eventually) developed metastatic PHEO was well below that of a matched reference population (Fig. 2). The survival of patients with really benign PHEO (no metastases during follow-up) was not significantly different from the reference population (Fig. 3): 5- and 10-year survival rates 89.3% (95% CI: 81.3–97.4%) and 84.1% (95% CI: 73.6–94.5%) versus 96.2 and 90.9% in the reference population (ns).

Blood pressure and catecholamines

In patients with a post-surgical follow-up of at least 1 year, 67% (35 out of the 62) were hypertensive. Of 47 patients with hypertension prior to surgery, 17 (36%) became and remained normotensive. Of the 30 recurrence-free patients with hypertension both before surgery

and at most recent post-surgical follow-up, mean blood pressure had decreased from $164 \pm 28/95 \pm 12$ to $143 \pm 21/87 \pm 11$ mmHg ($P < 0.001$ for systolic and diastolic blood pressure).

Plasma catecholamine levels normalized after surgery, except in three patients with slightly elevated levels, despite lack of recurrence on imaging studies.

Discussion

The main finding of our study is that patients undergoing successful surgery for apparently benign PHEO have a reduced life expectancy when compared with a sex, age, and period-matched reference population. This can be ascribed fully to the patients who developed metastatic disease while survival was not reduced in the really benign patients. We also show that only one-third of recurrence-free patients become and remain normotensive on the long-term following surgery.

Table 4 Benign versus malignant PHEO

	Benign PHEO	Malignant PHEO
N	59	10
Sex (M/F)	19/40	6/4
Age at diagnosis (y)	45.2±15.3	51.1±16.3
Pre-surgery E/(E+NE) ratio	0.21±0.22 (n=43)	0.14±0.24 (n=10)
Extra-adrenal tumor	12% (7/59)	10% (1/10)

Benign: no metastatic lesions during follow-up. Malignant: metastatic lesions during follow-up. M, male; F, female; E, epinephrine; NE, norepinephrine.

Only a limited number of publications of the past 10 years provided long-term follow-up data on morbidity and mortality after PHEO surgery (Plouin *et al*. 1997, Goldstein *et al*. 1999, Amar *et al*. 2005, Khorram-Manesh *et al*. 2005). Differences in study population, length of follow-up, definitions of recurrent and malignant disease, and analysis methods hamper comparison of theses studies. The rates of benign recurrence after successful surgery of non-metastatic PHEO ranged from 3.3 to 6.1% (Plouin *et al*. 1997, Amar *et al*. 2005, Khorram-Manesh *et al*. 2005), versus 3% in the present study. The prevalence of malignant disease, ranged from 6.6 to 16% (Plouin *et al*. 1997, Goldstein *et al*. 1999, Amar *et al*. 2005; Khorram-Manesh *et al*. 2005), versus 14% in the present study. Our observation of a 5-year metastases-free survival of 88% after successful surgery for really benign PHEO is
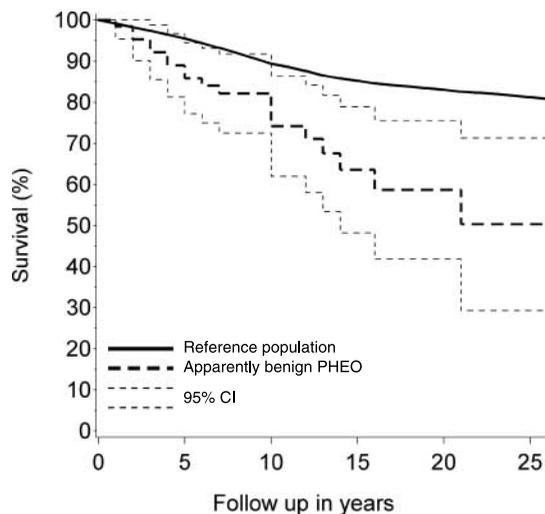

Figure 2 Kaplan–Meier curve of survival after pheochromocytoma surgery of ten patients (eventually) diagnosed with metastatic disease compared with the Kaplan–Meier survival curve of a matched reference population.

comparable with that of 92–94% found in these studies (Plouin *et al*. 1997, Amar *et al*. 2005).

Since there are no established pathology criteria to distinguish benign from malignant PHEO, clinical, biochemical, and temporal characteristics have been evaluated as surrogate predictors of malignant recurrence. Features that were implied to be associated with shorter PHEO-free survival after surgery include extra-adrenal tumor location, low epinephrine/epinephrine+norepinephrine ratio (Plouin *et al*. 1997, Amar *et al*. 2005,

Figure 1 Kaplan–Meier curve of survival after pheochromocytoma surgery of 64 patients with apparently benign disease compared with the Kaplan–Meier survival curve of a matched reference population.
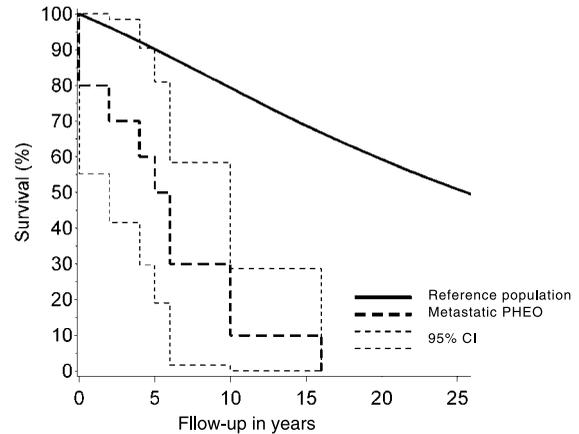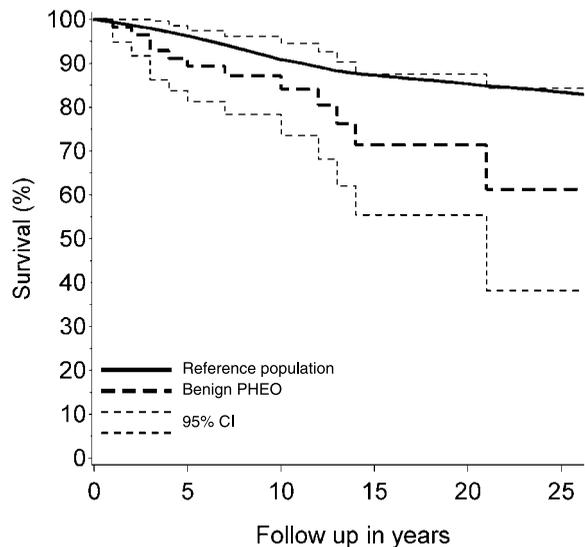

Figure 3 Kaplan–Meier curve of survival after pheochromocytoma surgery of 57 patients with benign disease compared with the Kaplan–Meier survival curve of a matched reference population.

Khorram-Manesh *et al.* 2005, Plouin & Gimenez-Roqueplo 2006) and familial disease, especially SDHB-related PHEO (Neumann *et al.* 2004, Benn *et al.* 2006). In the present study, no predictors of malignant recurrence were identified. However, the lack of significant differences between patients with benign and malignant PHEO may be related to a limited sample size.

Survival after uncomplicated PHEO surgery was lower than in a Dutch reference population. In two previous studies, the survival after PHEO surgery was compared with the expected life expectancy of a general reference population (Stenstrom *et al.* 1988, Khorram-Manesh *et al.* 2005). In a Swedish cohort of 121 patients, 42 patients died during the observation period versus 23.1 expected deaths in the control population ($P < 0.001$; Khorram-Manesh *et al.* 2005). In a prior study performed at the same centre, however, the observed and expected mortality were similar (Stenstrom *et al.* 1988). Our study confirms that patients with successfully resected PHEO still have a reduced life expectancy. This excess mortality is explained by the development of fatal metastatic disease in 11% of patients. In patients with benign PHEO, longstanding hypertension and catecholamine excess prior to surgery can induce (partially) irreversible structural vascular changes (Plouin *et al.* 1997, Khorram-Manesh *et al.* 2005), which might result in increased cardiovascular mortality. The latter was not confirmed by our study, although our study sample does not allow for a comparison of cardiovascular morbidity to that of the general population.

Our findings reinstate that despite radical surgery, a substantial portion of recurrence-free patients remains hypertensive. Although this refutes the original notion, that PHEO is a surgically curable cause of hypertension, blood pressure values of patients with persistent hypertension were significantly lower post- than pre-surgery. Two-thirds of patients with hypertension at presentation were also hypertensive at most recent follow. In previous studies, this frequency ranged from 38–71% (Pruszczyk *et al.* 1991, Plouin *et al.* 1997, Khorram-Manesh *et al.* 2005). Age, familial hypertension, and the presence of hypertension at 1 year after surgery were identified as predictors of hypertension on the long term (Plouin *et al.* 1997). This persistence of hypertension is probably due to structural and functional vascular abnormalities that may be induced by the longstanding antecedent hypertension.

There are two issues that have to be kept in mind when interpreting the Nijmegen cohort. The most important of these is that outcome has been shown to be better in PHEO patients that were diagnosed more recently than in those diagnosed (many) years earlier. This is attributed to the improvement of diagnostic, surgical (laparoscopic surgery has replaced open resection), and anesthetic techniques (Amar *et al.* 2005, Plouin & Gimenez-Roqueplo 2006). All our patients were operated before 2001, mainly through open procedures. Secondly, the prognosis of patients with PHEO is largely determined by the underlying genotype. Genetic testing was not systematically performed in all patients, partly due to the fact that comprehensive genetic testing, including *SDHB* mutations, became available after 2001. The observed prevalence of disease-causing mutations of 20% might, in fact, be an underestimation, and the results may theoretically be influenced by the portion of unrevealed mutations.

In conclusion, patients who undergo successful surgery for apparently benign PHEO have a reduced life expectancy when compared with the general population. The excess mortality is explained by the development of metastatic disease during post-surgical follow-up in some of the patients. By contrast, the survival of patients who do not develop metastatic disease is not different from that of the general population. Hypertension persists in two-thirds of recurrence-free patients. Lifelong follow-up of patients who had surgery for PHEO is warranted.

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