Subtotal Adrenalectomy for Phaeochromocytoma in Multiple Endocrine Neoplasia Type 2A
Abstract

Objective: To describe our surgical technique for, and results of, subtotal adrenalectomy for phaeochromocytoma in multiple endocrine neoplasia (MEN) type 2A.

Design: Retrospective study

Setting: University Hospital.

Subjects: 6 patients (4 women and 2 men, mean age 35 years, range 31-46) with MEN type 2 who presented between 1993 and 1996.

Interventions: Cortical sparing adrenalectomy (n=4) together with contralateral total adrenalectomy in bilateral disease.

Main outcome measures: Morbidity, mortality, adrenal function postoperatively, and recurrence.

Results: Cortical-sparing adrenalectomy leaving adequate adrenal reserve was possible in all cases. There was no operative morbidity or mortality. Mean follow-up was 40 months (range 13-47). One patient developed a recurrent phaeochromocytoma 24 months after subtotal adrenalectomy.

Conclusion: Subtotal adrenalectomy with preservation of adequate adrenal cortical reserve was feasible in all cases. Long-term follow-up is necessary to establish its definitive place in the treatment of familial phaeochromocytoma.

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Introduction

Phaeochromocytoma will develop in 30%-50% of patients with multiple endocrine neoplasia (MEN) type 2A. Nowadays, screening of such patients is provided by a combination of DNA analysis, yearly screening for excess catecholamines and the outstanding localization techniques that are available. Phaeochromocytomas in these particular patients are therefore often asymptomatic and small at the time of diagnosis. Although they are asymptomatic, it can be argued that these tumours should be removed because of the potential danger of a catecholamine crisis. To prevent the risk of recurrence these patients are traditionally treated in many centres by total bilateral adrenalectomy, even when only a unilateral tumour has been found, because adrenal medullary disease in these patients is usually diffuse and bilateral at cellular level. This approach necessitates long-term corticosteroid replacement associated with the risk of an Addisonian crisis, the risks of osteoporosis, and the social implications of complete dependence on lifelong substitution. Because the disease is hereditary most patients are familiar with the complications of inadequate replacement. In our experience, this knowledge makes these patients whose disease is often asymptomatic, hard to motivate to have a total adrenalectomy and they therefore sometimes delay or even refuse operation. For these reasons we have started to treat selected patients with MEN type 2A with cortical-sparing subtotal adrenalectomy. Here we present our surgical technique for, and the results of subtotal adrenalectomy for phaeochromocytoma associated with MEN type 2A.

Patients and Methods

Between 1993 and 1996, six patients with MEN type 2A underwent laparotomy at the University Hospital Utrecht, The Netherlands; our intention was to do a cortical-sparing subtotal adrenalectomy for phaeochromocytoma. MEN type 2A was diagnosed from the family history, or DNA analysis, or both. The mutation in the RET-gene was T 2548 C in four patients and C 2550 G in two patients, resulting in replacement of cysteine by arginine or cysteine by tryptophan, respectively. Pre-operative concentrations of urinary catecholamine metabolites (vanillilmandelic acid, metanephrines, and normetanephrines) and catecholamines (adrenaline and noradrenaline) were measured in all patients as part of an annual screening examination and the adrenal glands were visualised by magnetic resonance imaging (MRI).

Operative Technique

The affected adrenal gland was exposed by an open anterior approach. Adequate venous drainage of the remaining adrenal tissue was obtained by identification and preservation of the adrenal vein. The arterial supply of the diseased part of the adrenal
gland was divided with special attention to the arterial blood supply of the remaining glandular tissue. If venous and arterial preservation of the remaining tissue was feasible, the tumour was resected with a rim of macroscopic normal adrenal tissue. Argon coagulation was used for resection and haemostasis. Final haemostasis was provided by fibrin adhesive after completion of the subtotal adrenalectomy. Follow-up in these patients included interval physical examinations and measurement of 24-hour urinary catecholamines and catecholamine metabolites. Postoperative adrenal function was evaluated in all patients by measuring the plasma cortisol concentration and by stimulation with a synthetic analogue of ACTH, tetracosactrin (cosyntropin). All resected specimens were examined histologically. Medical records of these patients were reviewed to obtain details of operation, perioperative morbidity and mortality, postoperative adrenal function, and recurrence of phaeochromocytomas.

RESULTS

The mean age at operation of the four women and two men was 35 years (range 31-46). Phaeochromocytoma was presymptomatic at the time of screening for adrenal involvement and operation in four patients. The other two had mild paroxysmal symptoms, possibly related to excess catecholamines. In four patients the diagnosis of phaeochromocytoma was confirmed by increased excretion of urinary catecholamines. In all patients MRI showed small adrenal tumours, unilateral (left) in four and bilateral in two. Two patients had had previous unilateral total adrenalectomy for phaeochromocytoma two and four years before a metachronous tumour developed on the other side. Cortical sparing adrenalectomy was technically feasible in all patients and in bilateral involvement (n=2) it was combined with total adrenalectomy on the other side. Histopathological examination of all specimens showed phaeochromocytoma with a mean tumour size of 1.7cm (range 1.3-2.2). Mean duration of hospital stay was 8 days (range 7-9). There was no peri-operative mortality or morbidity. Mean follow-up was 40 months (range 13-47). During follow-up no patients had signs or symptoms of adrenal insufficiency and all had normal plasma cortisol concentrations. All patients made an adequate response to tetracosactrin stimulation, indicating sufficient adrenal cortical reserve.

One patient (RET mutation T 2548 C) developed clinical symptoms possibly related to a phaeochromocytoma without biochemical evidence of a recurrent tumour, 24 months after subtotal left-sided adrenalectomy. MRI showed a small tumour of the partly resected adrenal gland. After total adrenalectomy, histopathological examination showed recurrent phaeochromocytoma of the left adrenal gland. The other five patients had no clinical or biochemical evidence of recurrent phaeochromocytoma during follow-up.
DISCUSSION

We have shown that subtotal adrenalectomy with preservation of adrenocortical function is feasible in patients with MEN type 2A and asymptomatic phaeochromocytoma. The risk of recurrence of the phaeochromocytoma in these patients must be weighed against the risk of producing a permanent Addisonian state by bilateral total adrenalectomy. Bilateral total adrenalectomy has been advocated because it minimises the risk of tumour recurrence or distant metastases and eliminates the risk of a catecholamine crisis\(^1\). Complications associated with the lifelong substitution needed after this operation seem to be a high price to be paid by these patients with asymptomatic disease. Phaeochromocytomas in MEN type 2A are rarely malignant and even in recurrent disease, morbidity or mortality can be minimised by annual screening and early treatment\(^4,8,14\). No deaths of catecholamine crisis have been reported in patients with MEN type 2 treated with less than total adrenalectomy, but at least two deaths have been reported after inadequate supplementation after bilateral adrenalectomy\(^12,17\). Only a few studies have attempted to estimate the complications associated with bilateral adrenalectomy in MEN type 2 patients and they are not conclusive\(^8,12,17\). Because the disease is hereditary, most patients are familiar with the social and medical disadvantages of the substitution needed after bilateral total adrenalectomy. In our experience these patients most of whom have no symptoms, often refuse an operation that will lead to total dependence on medical substitution. For these reasons we have started to treat selected patients with MEN type 2A with cortical-sparing subtotal adrenalectomy. Our selection criteria are: the technical feasibility of subtotal adrenalectomy as dictated by tumour size, the absence of family history or RET gene mutation indicating aggressive and recurrent adrenal medullary disease and complete understanding by the patient of the possible risk of recurrence after subtotal adrenalectomy.

Subtotal adrenalectomy has been described for MEN type 2-related phaeochromocytomas in a few previous reports\(^1,2,7,9,10,15\). Adequate postoperative adrenocortical function could not be obtained in all reported patients, in contrast to our results. Most of these reports described timing and techniques of subtotal adrenalectomy that are different from ours. During operation we meticulously preserve the adrenal vein. Other techniques presented preserve only the arterial supply of the remaining adrenal gland and divide the adrenal vein\(^2\). Early surgery after screening for phaeochromocytoma offers favourable conditions for a subtotal adrenalectomy. Resection of the tumour with a rim of macroscopically normal adrenal tissue was therefore feasible in all patients without compromising venous drainage, and leaving an adequate portion of vascularised adrenal tissue behind. We think that preservation of the venous drainage is essential to obtain sufficient postoperative adrenocortical function.
reserve. This was proved in all our patients by their adequate response to stimulation with tetracosactrin.

In two patients with unilateral phaeochromocytomas we did a unilateral subtotal adrenalectomy leaving the macroscopically normal adrenal gland in place. This approach is in accordance with our previous policy at least to postpone supplementation by doing a unilateral adrenalectomy for patients with unilateral phaeochromocytoma. One patient had a recurrent phaeochromocytoma two years after subtotal adrenalectomy. Because of the relatively short follow-up time (mean 3.3 years) no conclusion can be made about the definitive recurrence rate after subtotal adrenalectomy in our series. Lee et al. found a recurrence rate of 21% after a median follow-up of 11.5 years in 14 patients treated by bilateral subtotal adrenalectomy. They state that this recurrence rate is lower when compared with that of contralateral recurrence rate after unilateral adrenalectomy for clinical unilateral involvement (42%) 8. No hypertensive crisis or metastatic disease as a result of recurrent phaeochromocytoma has been reported in patients who underwent unilateral or subtotal adrenalectomy. All those who developed recurrent disease were treated successfully because of the slow progression of the disease and the available highly sensitive screening techniques. This is illustrated by our patient whose recurrence was diagnosed by MRI during follow-up before abnormal biochemical activity was noted. Although it has not yet been reported we expect that cortical-sparing subtotal adrenalectomy might be possible by a minimally invasive approach in the near future 16,19.

In conclusion, subtotal adrenalectomy in selected patients by our technique is feasible with preservation of adequate adrenal cortical reserve. Long time follow-up is necessary to establish the definitive place of this cortical-sparing approach in patients with familial phaeochromocytoma.
REFERENCES


