Modern Surgical Management of Familial and Sporadic Parathyroid and Adrenal Disorders

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Moderne Chirurgische Behandeling van Familiale en Sporadische Aandoeningen van Bijschildklier en Bijnier

(met een samenvatting in het Nederlands)

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aan mijn sterren

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Chapter 1

General Introduction

Surgical endocrinology or endocrine surgical oncology is an important component of general surgery. As reported in Richard Welbourne's book *History of Endocrine Surgery*, the term "endocrine" is from the Greek *endo*, meaning "within", and *kipiveiv*, meaning "separate", documenting the relationship of endocrine surgery and general surgery.

Endocrine glands and tumors often make and secrete hormones; "hormone" is a term derived from the Greek word "to excite".[1] Examples of such glands are the thyroid gland, the parathyroid glands, the pancreatic gland, and the adrenal glands. Endocrine tumors of these glands can occur sporadically or develop as part of familial syndromes. The most common familial syndromes known to cause endocrine tumors are multiple endocrine neoplasia (MEN) syndromes type 1 and 2.

Multiple Endocrine Neoplasia

Multiple endocrine neoplasia type 1 (MEN1) was first recognized in 1903 by Erdheim, and further described as 'endocrine adenomatosis' by Wermer in 1954.[2] MEN1 is a rare autosomal dominant inherited disorder caused by a germline mutation in the MEN1 gene on chromosome 11. The prevalence is estimated to be two to three per hundred-thousand.[3] Patients with MEN1 are prone to developing primary hyperparathyroidism (pHPT), pancreatic endocrine tumors, and pituitary adenomas. Other less frequent manifestations are adrenocortical adenomas and neuroendocrine tumors of the stomach, thymus, and bronchus.[4]

Multiple endocrine neoplasia type 2 (MEN2) was initially introduced in 1961, as Sipple's syndrome, in a patient with bilateral pheochromocytoma, thyroid cancer and parathyroid enlargement. In 1968, Steiner further described this syndrome as MEN2, a similar but separate entity from MEN1. Later, Williams divided MEN2 into two distinct clinical syndromes: MEN2A and MEN2B.[5] Both are autosomal dominant inherited disorders caused by mutations in the *RET* proto-oncogene on chromosome 10.[6]

Virtually all patients with MEN2A develop medullary thyroid carcinoma. Therefore, affected patients should undergo prophylactic total thyroidectomy according to their *RET* proto-oncogene mutation as recommended by current guidelines. Half of MEN2A patients develop pheochromocytomas, and 20% to 30% develop pHPT in the course of the disease.[5] MEN2B is more aggressive and less prevalent compared with MEN2A. It is associated with medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas, intenstinal ganglioneuromas, and a marfanoid habitus.[7]

This thesis provides up-to-date information on the management of patients with familial and sporadic endocrine tumors of the parathyroid gland and the adrenal gland.

Parathyroid Glands

The parathyroid glands were first discovered in the Indian rhinoceros by Owen in 1850.[8] In 1877, the glands were first discovered in humans by Sandström, a Swedish medical student.[9]

Humans usually have four parathyroid glands, which are generally located on the rear surface of the thyroid gland, or, in rare cases, within the thyroid gland itself or in the chest near the thymus. The parathyroid glands produce parathyroid hormone (PTH), which controls the amount of calcium in the blood and within the bones.[10]

Primary Hyperparathyroidism

Primary hyperparathyroidism was first recognized in the United States in the late 1920s, by Barr, Bulger and Dixon at the University of Washington, as a severe bone disease with significant morbidity.[10] With improvements in biochemical screening, pHPT has become a common disease affecting approximately one in every 500 women older than 40 years and one in every 2000 men. Patients with pHPT have an increased plasma calcium and an increased or unsuppressed PTH level.[1]

PHPT can be caused by adenoma (80% to 90%), hyperplasia, and rarely by carcinoma or cyst. In most cases adenomas develop in a single gland. Hyperplasia of the parathyroid glands develops in multiple glands without a known stimulus for PTH secretion.[11]

The etiology of pHPT is most frequently sporadic and nonfamilial. A significant proportion of patients, however, develop pHPT as part of MEN1 or MEN2A.[12] Signs and symptoms are those of hypercalcemia. They are classically summarized by the mnemonic "stones, bones, abdominal groans, and psychiatric moans" and may consist of nephrolithiasis, bone abnormalities, constipation, mental changes, and weakness.[13]

In all cases of pHPT, parathyroidectomy is the only curative treatment that resolves symptoms and metabolic complications and thus improves quality of life, in both symptomatic and asymptomatic patients. The goals for surgery are restoring calcium levels to normal permanently, while preventing hypoparathyroidism (hypocalcemia) and recurrent laryngeal nerve injury and minimizing the number of reoperations because of recurrence.[13] Acute hypoparathyroidism may cause mild to severe neuromuscular symptoms ranging from neuromuscular irritability to seizures. Unilateral recurrent laryngeal nerve injury leads to hoarseness, bilateral injury results in breathing difficulties and aphonia.

The first successful parathyroidectomy was performed by Olch in 1928.[14] Since 1931, the standard operative procedure for pHPT consisted of bilateral neck exploration to localize all parathyroid glands, including supernumerary and ectopic glands. Subsequently, all pathologically enlarged parathyroid tissue was removed.[14] Improvements in preoperative imaging and intraoperative care have led to a more conservative approach with selective, or minimally invasive techniques, including minimally invasive parathyroidectomy in case of solitary parathyroid disease. A less invasive method could spare the patient an unnecessary bilateral neck exploration, thus saving time and rendering future surgical procedures in the neck less

problematic. Success rates up to 95% for less invasive procedures have been reported.[15,16]

Sporadic versus Multiple Endocrine Neoplasia-Related Primary Hyperparathyroidism
Clinical features that differentiate patients with sporadic pHPT from patients with MEN-related pHPT are: age of onset, female to male ratio, severity of bone involvement, family history and associated endocrine neoplasias.[17,18]

Sporadic pHPT usually presents in the fifth to seventh decade of life and is almost three times more common in women than in men. It is most commonly caused by a single adenoma due to a clonal mutation. Conventional neck exploration with resection of enlarged parathyroid tissue has been replaced by minimally invasive procedures as treatment of choice for patients with sporadic pHPT.

In MEN1, pHPT occurs in 78% to 90% of patients[4] and is often the first presentation of the syndrome.[3] Most commonly, pHPT presents during the second and third decade.[3,13] MEN1-related pHPT usually manifests as multiglandular disease.[19] Controversy exists regarding the optimal surgical strategy for pHPT in MEN1 patients. Most authors have advocated subtotal parathyroidectomy (resection of 3–3½ parathyroid glands) or total parathyroidectomy (resection of 4 glands) with autotransplantation.[13,20,21] Success rates after surgical intervention are usually not as high as for sporadic pHPT, even after extensive surgery. Extensive surgery leads to an increased risk of permanent hypoparathyroidism and recurrent laryngeal nerve injury. However, less extensive surgery yields a higher risk of recurrent disease requiring reintervention, which increases the risk of complications even more.[20,21]

In MEN2A, pHPT is less common than in MEN1 and generally less aggressive with a more variable incidence of multiglandular disease.[5] Controversy remains on its optimal surgical management as well. Some authors advocate total parathyroidectomy combined with autotransplantation of parathyroid tissue.[22] Others favor only selective resection of the enlarged parathyroid gland(s).[23-25]

Most of the current literature analyzes data on surgical treatment of pHPT without making a distinction in the difference in etiology.[17,18] Furthermore, for MEN1 and MEN2, contradictory results have been published on the optimal surgical treatment of pHPT. Some studies are noncomparative with respect to different treatment regimes and study groups are small due to rarity of the disease.

We strongly believe that, sporadic, MEN1-related, and MEN2-related pHPT are very distinct and different entities, requiring a different approach. In *Chapters 2 and 3*, we aimed to determine the optimal surgical strategy for pHPT in MEN1 and MEN2A, respectively. For MEN1, we performed a cohort study and a meta-analysis to determine the optimal surgical therapy. For MEN2A, we performed a relatively large cohort study and a literature review. In *Chapter 4*, we compared sporadic, MEN1-related and MEN2A-related pHPT with respect to the frequency and causes of pHPT, as well as the differences in their clinical presentation, preoperative workup, and operative strategies and outcome in a population based cohort of patients treated for pHPT.

Intraoperative Parathyroid Hormone Measurement

Originally approved for myocardial perfusion imaging, technetium-99m-sestamibi scintigraphy is now the standard method used for preoperative imaging of the parathyroid glands. It can be used in combination with ultrasonography of the neck.[26] Intraoperative PTH (IOPTH) measurement was first described by Irvin in 1988. Since then, it has been refined to a quick and less expensive measurement with results available in less than 20 minutes.[27] It is recommended for minimal invasive procedures in combination with preoperative localization examination to increase the success rate of parathyroidectomy. The Miami criteria, which stipulate that the IOPTH level must fall by 50% from highest preexcision value of PTH at 10 minutes postexcision, are generally applied.[28]

Several prior studies have investigated the impact of ethnicity and geography on the clinical presentation of pHPT.[29-31] Few studies, however, have investigated pHPT in African American patients, specifically the impact of African American race on IOPTH kinetics. The studies that do exist, suggest that African American patients present with more advanced disease with regard to laboratory and pathologic findings.[29,30] The investigators cite racerelated disparities in health care[32] and intrinsic biochemical differences[33] as potential causative factors. Based on our awareness of these data, we hypothesized that race would impact IOPTH kinetics and might affect the optimal interpretation of IOPTH values. In *Chapter 5*, we evaluate this hypothesis in a large cohort of patients undergoing parathyroidectomy for pHPT.

Adrenal Glands

In 1552, Eustachius first depicted the adrenal glands as *glandulae renis incumbents* (glands lying on the kidney).[34] Brown-Séquard showed that the adrenal glands are essential to life (*essentials à la vie*) after he had performed the first adrenalectomies on animals in 1856.[35]

Anatomically, the adrenal glands are located bilaterally, in the retroperitoneum superior to the kidneys. In 1845, Huschke, anatomist and embryonologist at Jena, first used the terms cortex and medulla, to describe the two component parts of the adrenal gland. The cortex is responsible for the production of mineralocorticoids (aldosterone, responsible for the long-term regulation of blood pressure), glucocorticoids (cortisol, responsible for an increase in blood glucose level in response to stress), and androgens (androstenedione and dehydroepiandosterone [DHEA], precursors of testosterone and estrogen). The adrenal medulla comprises chromaffin cells that secrete catecholamines: norepinephrine (noradrenalin) and epinephrine (adrenalin). Both act as stress hormones; when secreted they mainly lead to an increased heart rate and increased blood pressure by increasing vascular tone through α-adrenergic receptor activation.[36]

Due to its elaborate function, the adrenal gland can consequently produce a variety of benign and malignant tumors. Example are, aldosteronoma, Cushing's adenoma, virilizing tumors, pheochromocytoma, and nonfunctioning adenoma. Also, tumors outside the adrenal gland can metastasize to the adrenal gland.

Surgical Management of Adrenal Gland Tumors

In 1889, Thornton performed the first transabdominal adrenalectomy on humans.[37] Over one hundred years later, the laparoscopic adrenalectomy via the lateral transabdominal approach was introduced by Gagner.[38] Since its introduction, laparoscopic adrenalectomy has evolved to become the procedure of choice for most surgical adrenal diseases.[38-40] Indications for laparoscopic adrenalectomy include various endocrine pathologies, such as aldosteronoma, pheochromocytoma, Cushing's syndrome, adrenal metastasis, and nonfunctional adenoma, along with less common conditions such as myelolipomas or cysts.[41]

Adrenalectomy is associated with complication rates ranging from 4% to 20%,[42] and mortality is generally less than 1.5%.[43] There is still much debate in literature regarding the suitable tumor size for laparoscopic adrenal surgery and whether tumor size affects surgical morbidity.[44,45] Besides presenting contradicting results, most of the published literature includes a relatively small number of patients. Also, most authors disregard adrenal disease diagnosis as a potential confounder. Whereas most are uniform that patients with aldosteronoma can be operated on in a relatively safe and uncomplicated manner, it has been shown that a diagnosis of hypercortisolism, pheochromocytoma or adrenal malignancy can influence surgical morbidity in patients undergoing adrenalectomy.[46,47] Most of the previous studies on adrenal disease diagnosis included only a small number of patients or did not have statistical analysis, therefore the reported effect of diagnosis on outcome varied widely, and few studies reported how size of tumor influences outcome. Therefore, in *Chapter 6*, we evaluated the impact of both adrenal tumor size and adrenal disease diagnosis on the short-term operative outcomes of laparoscopic adrenalectomy in a large series of adrenalectomies.

A safe laparoscopic adrenalectomy requires a thorough knowledge of the usual anatomy of the adrenal gland, as well as its unusual anatomic variations. There are generally three arteries that supply each adrenal gland: the superior adrenal artery is provided by the inferior phrenic artery, the middle adrenal artery is provided by the aorta, and the inferior adrenal artery is provided by the renal artery.[48] Basically, adrenal arteries tend to be small and indistinct. They usually can be easily cauterized, except for occasional large inferior arteries that need to be ligated with clips.[49]

Identification and control of the adrenal vein are critical steps in laparoscopic adrenalectomy. The venous drainage from each adrenal gland, is usually via a single vein emptying directly into the inferior vena cava on the right side, and joining with the inferior phrenic vein and then draining into the left renal vein on the left.[48] Variations to this pattern have been documented mostly in cadaver studies.[50-52] These cadaver studies reported on the anatomy of nondiseased adrenal glands. Adrenal pathology, possibly through angiogenesis or vasodilation of preexisting small collateral vessels may increase both the variation of venous drainage and the number of periadrenal vessels. Parnaby et al[53] studied the venous anatomy

encountered in 162 laparoscopic adrenalectomies for adrenal pathology. They found variant venous anatomy in five adrenal glands: four in patients with pheochromocytoma and one in a patient with adrenal cortical cancer. The ability to anticipate variant adrenal venous anatomy is important to prevent excessive bleeding from the adrenal and accessory veins during laparoscopic adrenalectomy. We therefore studied a large series of consecutive laparoscopic adrenalectomies to establish details of the primary venous drainage of the adrenal gland and any variant venous anatomy (*Chapter 7*). In addition, we sought to determine a relationship between variant adrenal venous anatomy and tumor size or pathologic disease.

Pheochromocytoma

Pheochromocytomas are rare neuroendocrine catecholamine-secreting tumors.[54,55] In 1912, Pick introduced the term “pheochromocytoma”, derived from the Greek words *phaios* (dark), *chromo* (color), and *kytos* (cell). It refers to the histologic color change that characterizes most such tumors. Pheochromocytoma can occur in the adrenal gland or extra-adrenal. Extra-adrenal pheochromocytomas, also paragangliomas, are spread throughout the sympathic neuroendocrine system along the paravertebral and para-aortic axis.[1]

Pheochromocytomas have an estimated incidence of two to eight per million per year. They have an equal distribution in sex and occur at any age, but are most common in the fourth and fifth decade.[56] Pheochromocytomas can present as symptomatic tumors or incidentalomas, or can be diagnosed during screening for familial syndromes. Familial syndromes associated with pheochromocytoma are MEN2, von Hippel-Lindau syndrome and neurofibromatosis. The classic presentation of pheochromocytoma consists of paroxysmal hypertension, headaches, palpitations, and diaphoresis. A feared and possibly fatal presentation of pheochromocytoma is pheochromocytoma crisis.[57] Historically, pheochromocytoma has been called the ‘10% tumor’: 10% is malignant, 10% is multiple, 10% is extra-adrenal, and 10% is bilateral.

Surgical resection is the treatment of choice for pheochromocytoma. The first successful resections were performed in 1926, by Roux in Switzerland, and by Mayo at the Mayo Clinic. The surgical procedure itself, however, can be life threatening due to hypertensive crises and multiorgan failure or profound hypotension after tumor resection.[58,59] Preoperative treatment with α-, β-, and/or calcium channel blockers is assumed to lower the risk of intraoperative hemodynamic instability, although randomized, controlled trials are lacking.[60,61]

Pheochromocytoma Crisis

The clinical picture of pheochromocytoma crisis ranges from severe hypertension to circulatory failure and shock with subsequent involvement of multiple organ systems, including the cardiovascular, pulmonary, neurological, gastrointestinal, renal, hepatic and metabolic systems. Pheochromocytoma crisis can be associated with high mortality rates.[62]

The timing of surgery for pheochromocytoma patients presenting with crisis is controversial. Some have argued that these patients need emergency resection, even in the absence of preoperative α-blockade.[62-64] In contrast, other studies have reported favorable results for patients with pheochromocytoma crisis who underwent intensive medical stabilization prior to surgical resection.[65,66]

In *Chapter 8*, we characterize our approach to preoperative medical management and the appropriate timing of surgery in patients presenting with pheochromocytoma crisis. In addition, we performed a literature review to provide data on appropriate timing for adrenalectomy, i.e. is emergency surgery without adequate α-blockade superior to delaying surgery until medical stabilization and adequate α-blockade is achieved.

Pheochromocytoma in Multiple Endocrine Neoplasia

Pheochromocytomas in MEN2 occur in half of the patients, are frequently bilateral and are less frequent malignant compared with sporadic cases. All known MEN2 patients should be screened once yearly for the presence of pheochromocytoma to prevent a potentially life-threatening pheochromocytoma crisis.[7,67,68]

Preoperative medication and improvements in surgical and anesthetic techniques have nearly diminished the risk of perioperative mortality associated with pheochromocytoma resection.[69] However, intraoperative hemodynamic fluctuations can lead to serious morbidity.[70]

Literature on perioperative care of patients undergoing adrenalectomy for pheochromocytoma is often outdated and historical, not taken into account the improvements in peri-anesthetic care.[71] Moreover, the perioperative course concerning hemodynamic data of MEN2 patients with pheochromocytomas has typically been reported only in conjunction with sporadic cases and patients with other familial syndromes or has included only small numbers of patients.[60,72,73] In 2010, high plasma norepinephrine concentration, tumor size larger than 4 cm, high mean arterial blood pressure at presentation and after α-blockade, and more profound postural blood pressure fall after α-blockade were identified as risk factors for hemodynamic instability during surgery of pheochromocytomas.[74] Because of their early identification through the annual screening of mutation carriers, there is reason to think that MEN2-related pheochromocytomas are associated with less hemodynamic instability during pheochromocytoma resection. In *Chapter 9*, we assessed differences in intraoperative hemodynamic data between MEN and non-MEN patients in a large cohort. In addition, we sought to identify risk factors for intraoperative hemodynamic instability.

Since bilateral pheochromocytomas occur frequently in MEN2 patients, theoretically, the ideal operation for a pheochromocytoma in a patient with MEN2 would be to remove the pheochromocytoma and all of the medulla while saving the adrenal cortex to preserve ipsilateral adrenocortical steroid production.

From the mid-1980s through the mid-1990s, total bilateral adrenalectomy has been advocated in patients with MEN2 to prevent the risk of recurrence.[67,75,76]

Because it necessitates lifelong gluco- and mineralocorticoid replacement therapy this method has been disputed. Complete steroid-dependency carries great social implications and the risk of a, potentially life-threatening, Addisonian crisis.[77,78] In addition, corticosteroid replacement therapy is a continuous challenge with possible chronic overreplacement leading to the risk of impaired glucose tolerance, obesity, and osteoporosis and underreplacement with the risk of incipient crises and severe impairment of well being.[79,80]

Fortunately, improvements in imaging techniques – demonstrating a normal contralateral adrenal gland – and better pathophysiological insight, allowed the introduction of more conservative surgical strategies, including the unilateral adrenalectomy. Subsequently, minimally invasive approaches were introduced, and cortical sparing approaches have been used both for initial operations and for reoperations.[81-83] However, because of the rarity of the disease, only scarce data are available on unilateral subtotal adrenalectomy in MEN2 patients. We therefore sought to determine the feasibility of subtotal adrenalectomy as a primary surgical strategy for pheochromocytoma in MEN2 patients in a large cohort study with a long-term follow-up (*Chapter 10*).

References

1. Clark OH, Duh QY, Perrier ND, Jahan TM (eds). *Endocrine tumors.* Atlas of Clinical Oncology. Hamilton, BC Decker, 2003.
2. Wermer P. Genetic aspects of adenomatosis of endocrine glands. *Am J Med* 1954; 16(3):363–371.
3. Pieterman CR, Schreinemakers JM, Koppeschaar HP, et al. Multiple endocrine neoplasia type 1 (MEN1): its manifestations and effect of genetic screening on clinical outcome. *Clin Endocrinol (Oxf)* 2009; 70(4):575–581.
4. Carty SE, Helm AK, Amico JA, et al. The variable penetrance and spectrum of manifestations of multiple endocrine neoplasia type 1. *Surgery* 1998; 124(6):1106–1113, discussion 1113–1114.
5. Steiner AL, Goodman AD, Powers SR. Study of a kindred with pheochromocytoma, medullary thyroid carcinoma, hyperparathyroidism and Cushing's disease: multiple endocrine neoplasia type 2. *Medicine* 1968; 47(5):371-409.
6. Lips CJ, Landsvater RM, Höppener JW, et al. Clinical screening as compared with DNA analysis in families with multiple endocrine neoplasia type 2A. *N Engl J Med* 1994; 331(13):828-835.
7. Carney JA, Go VL, Sizemore GW, et al. Alimentary-tract ganglioneuromatosis. A major component of the syndrome of multiple endocrine neoplasia, type 2b. *N Engl J Med* 1976; 295(23):1287–1291.
8. Cave AJE. Richard Owen and the discovery of the parathyroid glands. In: Underwood EA (ed). *Science medicine and history*. New York, Arno Press, 1975; 217–222.
9. Eknoyan G. A history of the parathyroid glands. *Am J Kidney Dis* 1995; 26(5):801-807.
10. Seipel CM. Ivar Sandström 1852-1890 by A. Hammar (English translation). In: Peters CH, Fulton JF (eds). *On a new gland in man and several mammals (glandulae parathyreoideae).* Baltimore, The Johns Hopkins Press, 1938; 3–13.
11. Clark OH, Duh QY, Kebebew EK (eds). *Textbook of Endocrine Surgery.* Philadelphia, Elsevier Saunders, 2005; 384-392.
12. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001; 86(12):5658-5671.
13. Malone JP, Srivastava A, Khardori R. Hyperparathyroidism and multiple endocrine neoplasia. *Otolaryngol Clin North Am* 2004; 37(4):715–736.
14. Dubose J, Ragsdale T, Morvant J. “Bodies so tiny”: the history of parathyroid surgery. *Curr surg* 2005; 62(1):91-95.
15. Smit PC, Borel Rinkes IHM, van Dalen A, van Vroonhoven TJ. Direct, minimally invasive adenomectomy for primary hyperparathyroidism: An alternative to conventional neck exploration? *Ann Surg* 2000; 231(4):559-565.
16. Kebebew E, Hwang J, Reiff E, et al. Predictors of single-gland versus multigland parathyroid disease in primary hyperparathyroidism: a simple and accurate scoring model. *Arch surg* 2006; 141(8):777-782, discussion 782.
17. Eller-Vainicher C, Chiodini I, Battista C, et al. Sporadic and MEN1-related primary hyperparathyroidism: differences in clinical expression and severity. *J Bone Miner Res* 2009; 24(8):1404-1410.
18. Katai M, Sakurai A, Ikeo Y, Hashizume K. Primary hyperparathyroidism in patients with multiple endocrine neoplasia type 1: comparison with sporadic parathyroid adenomas. *Horm Metab Res* 2001; 33(8):499-503.
19. Doherty GM, Lairmore TC, DeBenedetti MK. Multiple endocrine neoplasia type 1 parathyroid adenoma development over time. *World J Surg* 2004; 28(11):1139–1142.

20. Burgess JR, David R, Parameswaran V, et al. The outcome of subtotal parathyroidectomy for the treatment of hyperparathyroidism in multiple endocrine neoplasia type 1. *Arch Surg* 1998; 133(2):126–129.
21. Tonelli F, Marcucci T, Fratini G, et al. Is total parathyroidectomy the treatment of choice for hyperparathyroidism in multiple endocrine neoplasia type 1? *Ann Surg* 2007; 246(6):1075–1082.
22. Herfarth KK, Bartsch D, Doherty GM, Wells SA Jr, Lairmore TC. Surgical management of hyperparathyroidism in patients with multiple endocrine neoplasia type 2A. *Surgery* 1996; 120(6):966-973.
23. Raue F, Kraimps JL, Dralle H, et al. Primary hyperparathyroidism in multiple endocrine neoplasia type 2A. *J Intern Med* 1995; 238(4):369-373.
24. Dotzenrath C, Cupisti K, Goretzki PE, et al. Long-term biochemical results after operative treatment of primary hyperparathyroidism associated with multiple endocrine neoplasia types I and IIa: Is a more or less extended operation essential? *Eur J Surg* 2001; 167(3):173-178.
25. Dralle H, Scheumann GFW. How to handle the parathyroid glands in multiple endocrine neoplasia type I (MEN I) and type II (MEN II)? Surgical approach to uniglandular versus multiglandular disease in hereditary primary hyperparathyroidism. *Acta Chir Austriaca* 1994; 26:35-38.
26. Mullan BP. Nuclear medicine imaging of the parathyroid. *Otolaryngol Clin North Am* 2004; 37(4):909-939.
27. Irvin GL 3rd, Prudhomme DL, Deriso GT, Stakianakis G, Chandarlapathy SK. A new approach to parathyroidectomy. *Ann Surg* 1994; 219(5):574-581.
28. Molinari AS, Irvin GL 3rd, Deriso GT, Bott L. Incidence of multiglandular disease in primary hyperparathyroidism determined by parathyroid hormone secretion. *Surgery* 1996; 120(6):934-936, discussion 936-937.
29. Bilezikian JP, Meng X, Shi Y, Silverberg SJ. Primary hyperparathyroidism in women: a tale of two cities – New York and Beijing. *Int J Fertil Womens Med* 2000; 45(2):158-165.
30. Kandil E, Tsai HL, Somervell H, et al. African Americans present with more severe primary hyperparathyroidism than non-African Americans. *Surgery* 2008; 144(6):1023-1026, discussion 1026-1027.
31. Mishra SK, Agarwal G, Kar DK, Gupta SK, Mithal A, Rastad J. Unique clinical characteristics of primary hyperparathyroidism in India. *Br J Surg* 2001; 88(5):708-714.
32. Cohen JJ. Disparities in health care: an overview. *Acad Emerg Med* 2003; 10(11):1155-1160.
33. Cosman F, Morgan DC, Nieves JW, et al. Resistance to bone resorbing effects of PTH in black women. *J Bone Miner Res* 1997; 12(6):958-966.
34. Eustachius B. Tabulae Anatomicae Clarissimi Viri Bartholomaei. In: Harrison TS, Gann DS, Edis AJ, Egdahl RH (eds). *Surgical Disorders of the Adrenal Gland.* New York, Grune and Stratton, 1975; 1-2.
35. Brown-Sequard C. Recherches experimentales sur la physiologie et la pathologie des capsules surrenales. *Arch Gen Med* 1856; 8:395-401.
36. Linos DA, van Heerden JA (eds). *Adrenal Glands: Diagnostic Aspects and Surgical Therapy.* Berlin, Heidelberg, New York, Springer-Verlag, 2005.
37. Thornton J. Abdominal nephrectomy for large sarcoma of the left suprarenal capsule: Recovery. *Trans Clin Soc London* 1890; 23:150-153.
38. Gagner M, Lacroix A, Bolté E. Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma. *N Engl J Med* 1992; 327(14):1033.

39. Gagner M, Pomp A, Heniford BT, Pharand D, Lacroix A. Laparoscopic adrenalectomy: Lessons learned from 100 consecutive procedures. *Ann Surg* 1997; 226(3):238–246.
40. Lal G, Duh Q. Laparoscopic adrenalectomy: Indications and technique. *Surg Oncol* 2003; 12(2):105–123.
41. Gill IS. The case for laparoscopic adrenalectomy. *J Urol* 2001; 166(2):429–436.
42. Lee J, El-Tamer M, Schifftner T, et al. Open and laparoscopic adrenalectomy: analysis of the National Surgical Quality Improvement Program. *J Am Coll Surg* 2008; 206(5):953–959.
43. Brunt LM. The positive impact of laparoscopic adrenalectomy on complications of adrenal surgery. *Surg Endosc* 2002; 16(2):252–257.
44. Castillo OA, Vitagliano G, Secin FP, Kerkebe M, Arellano L. Laparoscopic adrenalectomy for adrenal masses: does size matter? *Urology* 2008; 71(6):1138-1141.
45. Kazaryan AM, Mala T, Edwin B. Does tumor size influence the outcome of laparoscopic adrenalectomy? *J Laparoendosc Adv Surg Tech A* 2001; 11(1):1-4.
46. Poulin E, Schlachta CM, Burpee SE. Laparoscopic adrenalectomy: pathologic features determine outcome. *Can J Surg* 2003; 46(5):340–344.
47. Fernández-Cruz L, Sáenz A, Benarroch G, Sabater L, Taurá P. Does hormonal function of the tumor influence the outcome of laparoscopic adrenalectomy? *Surg Endosc* 1996; 10(11):1088-1091.
48. Standring S. Suprarenal (adrenal) gland. In: Standring S (ed). *Gray's Anatomy*. London, Elsevier, 2005; 1245–1249.
49. Joel AB, Rubenstein JN, Arredondo S, Meng MV, Duh QY, Stoller ML. Laparoscopic appreciation of the adrenal artery: fact or fiction? *J Endourol* 2005; 19(7):793-796.
50. Anson BJ, Caudwell EW. The anatomy of the para-renal system of veins, with comments on the renal arteries. *J Urol* 1948; 60(5):714-737.
51. Johnstone FR. The suprarenal veins. *Am J Surg* 1957; 94(4):615–620.
52. Clark K. The blood vessels of the adrenal gland. *J R Coll Surg Edinb* 1959; 4(3):257–262.
53. Parnaby CN, Galbraith N, O'Dwyer PJ. Experience in identifying the venous drainage of the adrenal gland during laparoscopic adrenalectomy. *Clin Anat* 2008; 21(7):660–665.
54. Desmonts JM, Marty J. Anaesthetic management of patients with phaeochromocytoma. *Br J Anaesth* 1984; 56(7):781-789
55. Bravo EL, Gifford RW. Current concepts. Pheochromocytoma: diagnosis, localization and management. *N Engl J Med* 1984; 311(20):1298–1303.
56. Reisch N, Peczkowska M, Januszewicz A, Neumann HP. Pheochromocytoma: presentation, diagnosis and treatment. *J Hypertens* 2006; 24(12):2331-2339.
57. Guerrero MA, Schreinemakers JM, Vriens MR, et al. Clinical spectrum of pheochromocytoma. *J Am Coll Surg* 2009; 209(6):727-732.
58. Lo CY, Lam KY, Wat MS, Lam KS. Adrenal pheochromocytoma remains a frequently overlooked diagnosis. *Am J Surg* 2000; 179(3):212–215.
59. Apgar V, Papper EM. Pheochromocytoma: anesthetic management during surgical treatment. *Arch of Surg* 1951; 62(5):634–648.
60. Kinney MA, Narr BJ, Warner MA. Perioperative management of pheochromocytoma. *J Cardiothor Vasc Anesth* 2002; 16(3):359–369.
61. Miura Y, Yoshinaga K. Doxazosin: a newly developed, selective alpha 1-inhibitor in the management of patients with pheochromocytoma. *Am Heart J* 1988; 116(6 Pt 2):1785–1789.
62. Newell, KA, Prinz RA, Pickleman J, et al. Phaeochromocytoma multisystem crisis. A surgical emergency. *Arch Surg* 1988; 123(8):956-959.

63. Bos JC, Toorians AW, van Mourik JC, van Schijndel RJ. Emergency resection of an extra-adrenal phaeochromocytoma: wrong or right? A case report and a review of literature. *Neth J Med* 2003; 61(8):258-625.
64. Uchida N, Ishiguro K, Suda T, Nishimura M. Pheochromocytoma multisystem crisis successfully treated by emergency surgery: report of a case. *Surg Today* 2010; 40(10):990-996.
65. Kolhe N, Stoves J, Richardson D, Davison AM, Gilbey S. Hypertension due to phaeochromocytoma – an unusual cause of multiorgan failure. *Nephrol Dial Transplant* 2001; 16(10):2001-2004.
66. Imperato-McGinley J, Gautier T, Ehlers K, Zullo MA, Goldstein DS, Vaughan ED Jr. Reversibility of catecholamine-induced dilated cardiomyopathy in a child with a pheochromocytoma. *N Engl J Med* 1987; 316(13):793-797.
67. Lips KJ, Van der Sluys Veer J, Struyvenberg A, et al. Bilateral occurrence of pheochromocytoma in patients with the multiple endocrine neoplasia syndrome type 2A (Sipple's syndrome). *Am J Med* 1981; 70(5):1051–1060.
68. Raue F, Frank-Raue K. Update multiple endocrine neoplasia type 2. *Fam Cancer* 2010; 9(3):449–457.
69. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. *Lancet* 2005; 366(9486):665–675.
70. Shupak RC. Difficult anesthetic management during pheochromocytoma surgery. *J Clin Anesth* 1999; 11(3):247–250.
71. Goldstein RE, O'Neill JA Jr, Holcomb GW 3rd, et al. Clinical experience over 48 years with pheochromocytoma. *Ann Surg* 1999; 229(6):755–764, discussion 764–766.
72. Luo A, Guo X, Yi J, Ren H, Huang Y, Ye T. Clinical features of pheochromocytoma and perioperative anesthetic management. *Chin Med J* 2003; 116(10):1527–1531.
73. Van Heerden JA, Sheps SG, Hamberger B, Sheedy PF, Poston JG, ReMine WH. Pheochromocytoma: current status and changing trends. *Surgery* 1982; 91(4):367–373.
74. Bruynzeel H, Feelders RA, Groenland TH, et al. Risk factors for hemodynamic instability during surgery for pheochromocytoma. *J Clin Endocrinol Metab* 2010; 95(2):678–685.
75. van Heerden JA, Sizemore GW, Carney JA, et al. Surgical management of the adrenal glands in the multiple endocrine neoplasia type 2 syndrome. *World J Surg* 1984; 8(4):612.
76. Modigliani E, Vasen HM, Raue K, et al. Pheochromocytoma in multiple endocrine neoplasia type 2: European Study. *J Intern Med* 1995; 238(4):236–237.
77. de Graaf JS, Dullaart RP, Zwierstra RP. Complications after bilateral adrenalectomy for phaeochromocytoma in multiple endocrine neoplasia type 2 – a plea to conserve adrenal function. *Eur J Surg* 1999; 165(9):843–846.
78. Telenius-Berg M, Ponder MA, Berg B, et al. Quality of life after bilateral adrenalectomy in MEN2. *Henry Ford Hosp Med J* 1989; 37(3-4):160–163.
79. Reisch N, Arlt W. Fine tuning for quality of life: 21st century approach to treatment of Addison's disease. *Endocrinol Metab Clin N Am* 2009; 38(2):407–418.
80. Hahner S, Allolio B. Therapeutic management of adrenal insufficiency. *Best Pract Res Clin Endocrinol Metabol* 2009; 23(2):167–179.
81. Lee JE, Curley SA, Gagel RF, et al. Cortical-sparing adrenalectomy for patients with bilateral pheochromocytoma. *Surgery* 1996; 120(6):1064–1070, discussion 1070–1071.
82. Iihara M, Suzuki R, Kawamata A, et al. Adrenal-preserving laparoscopic surgery in selected patients with bilateral adrenal tumors. *Surgery* 2003; 134(6):1066–1072, discussion 1072–1073.

83. Asari R, Scheuba C, Kaczirek K, et al. Estimated risk of pheochromocytoma recurrence after adrenal-sparing surgery in patients with multiple endocrine neoplasia type 2A. *Arch Surg* 2006; 141(12):1199–1205.

Part 1
Parathyroid Glands

Chapter 2

The Optimal Surgical Treatment for Primary Hyperparathyroidism in Multiple Endocrine Neoplasia Type 1,
A Systematic Review

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Abstract

Objective The optimal surgical approach for patients with primary hyperparathyroidism (pHPT) and multiple endocrine neoplasia type 1 (MEN1) is controversial. We sought to determine the best type of surgery for pHPT in MEN1.

Methods We collected data on clinical presentation, surgery and follow-up for MEN1 patients with pHPT at the University Medical Center Utrecht, The Netherlands and affiliated hospitals between 1967 and 2008. Furthermore, we performed a systematic review of the literature and meta-analysis. Surgical procedures were classified into less than subtotal (<SPTX) versus subtotal (SPTX) and total parathyroidectomy (TPTX).

Results Fifty-two patients underwent primary surgery for pHPT, of which 29 had <SPTX, 17 SPTX, and 6 TPTX. Recurrent pHPT was most frequent after SPTX (65%) followed by <SPTX (59%). Persistent disease was most frequent after <SPTX (31%). Time to recurrence was 61 months longer after SPTX than after <SPTX. Although recurrent pHPT was not seen after TPTX, permanent hypoparathyroidism developed in 67% of the patients. The meta-analysis showed that after SPTX and TPTX, patients had the lowest risk of persistent and recurrent PHPT. TPTX had the highest risk of permanent hypoparathyroidism. Large noncomparative studies showed a low recurrence rate after SPTX and TPTX.

Conclusion We believe that SPTX is the best surgical therapy for pHPT in MEN1. MEN1 patients with pHPT should not be treated with <SPTX because of the unacceptable high rates of recurrent and persistent pHPT. Additionally, a thymectomy should routinely be performed in these patients.

Introduction

Multiple endocrine neoplasia syndrome type 1 (MEN1) is a rare autosomal dominant inherited disorder. MEN1 is caused by a germline mutation in the *MEN1* gene on chromosome 11. The prevalence is estimated to be two to three per hundred-thousand.[1] Patients with MEN1 are prone to developing endocrinopathies. These endocrinopathies are primary hyperparathyroidism (pHPT), pancreatic endocrine tumors, and pituitary adenomas. Other less frequent manifestations are adrenocortical adenomas and neuroendocrine tumors of the stomach, thymus, and bronchus. Hyperparathyroidism is the most prevalent manifestation, occurring in 78% to 90% of MEN1 patients.[2,3] It is often the first presentation of MEN1 syndrome.[1] These patients tend to be younger than patients with sporadic pHPT. Most commonly, pHPT presents during the second and third decade.[1,4] pHPT can be both asymptomatic and symptomatic. Signs and symptoms may consist of bone abnormalities, mental changes, weakness, nephrolithiasis, and marked hypercalcemia.[4] MEN1-related pHPT tends to be more aggressive than sporadic pHPT and usually manifests as multiglandular disease.[5]

The treatment of pHPT is primarily surgical. The goals for surgery are restoring calcium levels to normal permanently, while preventing hypoparathyroidism and minimizing the number of reoperations.[4,6] Parathyroidectomy reduces the risk of nephrolithiasis, fractures (improved bone mineral density), and potential cardiovascular morbidity. It may also improve quality of life. In MEN1 patients who also have a gastrinoma, parathyroidectomy may reduce gastrin production.[7] Controversy exists on the optimal surgical strategy. Most authors have advocated subtotal (SPTX) or total parathyroidectomy (TPTX) with autotransplantation.[4,8,9] There is a high risk of recurrence after surgical intervention, even after extensive surgery. The downside of extensive surgery is the increased risk of permanent hypoparathyroidism (hypocalcemia) and recurrent laryngeal nerve injury. Acute hypoparathyroidism may cause mild to severe neuromuscular symptoms ranging from neuromuscular irritability to seizures. Yet, less extensive surgery yields a higher risk of recurrent disease requiring reintervention, which increases the risk of complications even more.

To the best of our knowledge, there is no published systematic review with a meta-analysis of the results reported in the current available literature that compares different surgical therapies with respect to recurrent and persistent pHPT and permanent hypoparathyroidism in MEN1 patients. The aim of this study was to determine the optimal surgical therapy for pHPT in patients with MEN1. To this end, we evaluated our experience with surgical treatment in these patients and carried out a meta-analysis.

Materials and Methods

From the MEN1 database at the University Medical Center Utrecht, The Netherlands, patients diagnosed with pHPT between 1967 and 2008 were selected. Patients were included in the MEN1 database if they had genetically proven MEN1 or three of five manifestations of MEN1 or one of five manifestations and a first-degree family

member with MEN1. The medical records of these patients were reviewed. Since the University Medical Center Utrecht is a tertiary referral center, patients who were initially treated at other institutions and later referred to our institution were included.

The diagnosis of pHPT was confirmed when serum calcium or ionized calcium levels were elevated in combination with elevated or inadequately suppressed parathyroid hormone (PTH) levels (normal reference value: 1.0 to 7.0 mmol/L). We have chosen to use ionized calcium levels (normal reference value: 1.15 to 1.32 mmol/L) in our analysis, as this became the standard parameter measured routinely since 1993 in our hospital. Before 1993, we used the serum calcium levels to diagnose hyperparathyroidism.

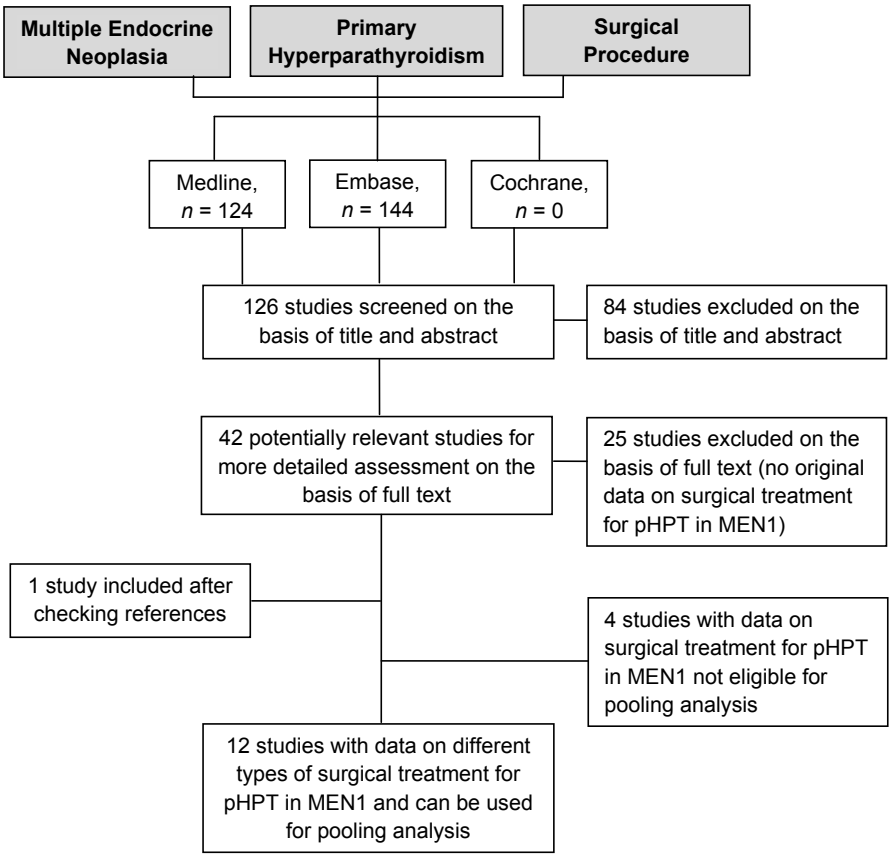
Operative Technique

Throughout the years, our operative strategy has evolved. In the past, only subtotal or total parathyroidectomy with autotransplantation were performed. In SPTX, 3–3½ parathyroid glands were resected during a bilateral cervical exploration after identification of all parathyroid glands. In TPTX, 4 glands were resected and one (partial) gland was used as a graft for autotransplantation into the brachioradial muscle of the nondominant forearm. The autotransplantation was performed during the same operation, using fresh parathyroid tissue. The resected gland with the least abnormal macroscopic appearance (size, color, and vascularization) was used for the transplant. The gland was cut into multiple small fragments a millimeter in size. Minimally invasive parathyroidectomy (MIP) has been performed in selected cases in order to reduce the morbidity of surgery and postpone more radical surgery. A MIP would be performed only if the affected parathyroid gland could be localized preoperatively with identical location of an enlarged gland on both ultrasound and sestamibi scan. During the procedure, intraoperative PTH measurement was carried out after the affected parathyroid gland was resected to determine if PTH levels had decreased at least 50% as a measure of success. If PTH levels did not decrease sufficiently, conversion to a bilateral cervical exploration would follow.

We did not routinely perform a thymectomy. Our standard policy was to perform a thymectomy only if uncertainty remained about whether the inferior parathyroid glands had been completely removed. We classified the surgical strategy based on operation reports and medical records.

Surgical outcome was defined as initial success after surgery, persistence and recurrence rates, and complications, particularly permanent hypoparathyroidism. Surgical cure was defined as normalization of serum (ionized) calcium and PTH levels for a period of at least six months after the surgical procedure. If not, it was classified as persistent pHPT. Permanent hypoparathyroidism was defined as hypocalcemia persisting beyond the first six months after surgery and requiring supplementation with calcium and an active form of vitamin D. Both duration of follow-up and time to recurrence were calculated in months. The duration of follow-up was defined as the time between the first surgical procedure and the date of final contact with the patient.

Figure 1. Article Selection on Surgery for Primary Hyperparathyroidism in MEN1.



Abbreviations: MEN1, multiple endocrine neoplasia type 1; pHPT, primary hyperparathyroidism.

Meta-Analysis and Systematic Review

We searched Medline (1966 to 2008), Embase (1980 to 2008), and the Cochrane database of systematic reviews and the Cochrane Central Controlled Trials Register (2008) using predefined search terms (Appendix A). On the basis of title and abstract, we selected 126 studies. Only studies that compared different surgical treatments of pHPT were included (*n* = 12) (Figure 1). We also included the results of the present study.

Pooling was done for the following groups: patients who underwent resection of fewer than 3 parathyroid glands (<SPTX), 3-3½ parathyroid glands (SPTX), or all parathyroid glands (TPTX) including autotransplantation. We studied outcome of surgery between different groups. Outcome was defined as the risk of persistent pHPT, recurrent pHPT, and permanent hypoparathyroidism. To determine the risk of recurrent pHPT, patients who had persistent pHPT were excluded. We performed a

two-step meta-analysis. First, we studied if fewer than 3 parathyroid glands resected (<SPTX) or 3 or more glands resected (SPTX and TPTX) had a better outcome. Secondly, we compared SPTX with TPTX. The odds-ratio (OR), the 95% confidence interval (95% CI), and *P* value were calculated. The I^2 test was used to check for quantitative heterogeneity. This test measures the proportion of inconsistency between studies that cannot be explained by chance alone. Additionally, we included the results of the noncomparative studies, which could not be used in the meta-analysis, in the Results section.

Statistical Analysis

SPSS version 16.0 (SPSS, Inc., Chicago, IL) was used for statistical analysis. Review manager 5.0 (Cochrane Collaboration) was used for the meta-analysis. Depending on distribution, numerical data are depicted as mean ± standard deviation or median with its interquartile range. Presented percentages are calculated on the basis of the available data. When appropriate, the χ^2 test was used for statistical analysis of the data. To determine if the surgical procedure was associated with recurrent disease, univariate analysis was performed. For this purpose, patients were divided into three groups; <SPTX (fewer than 3 glands resected), SPTX (3–3½ glands resected), and TPTX (4 glands resected).

Results

From the MEN1 database at our institution, 54 patients with pHPT were identified. Twenty-one were men (39%). Ten patients were asymptomatic. Forty-one patients (76%) had one or more of the following symptoms: nephrolithiasis, mood disorders, fatigue, and gastrointestinal complaints. Baseline characteristics are given in Table 1.

Fifty-two patients underwent primary surgery either at our hospital (*n* = 36) or at another hospital (*n* = 16). Two other patients did not undergo surgical treatment. Eight patients underwent a MIP, 21 underwent <SPTX, 17 SPTX, and 6 TPTX. Three times, during an initial MIP, PTH levels remained elevated and the surgical procedure was converted to a conventional or bilateral neck exploration with a TPTX either in the same session or a (few) day(s) later due to logistical reasons.

Table 1. Characteristics of Primary Hyperparathyroidism in MEN1 Patients

Characteristics	Type of Surgery				*P* Value
	<SPTX, *n* = 29	SPTX, *n* = 17	TPTX, *n* = 6	Overall, *n* = 52	
Age at surgery, y, mean ± SD	35 ± 12	32 ± 11	29 ± 8	34 ± 11	NS
Preoperative ionized calcium level, mmol/L, mean ± SD	1.40 ± 0.07	1.39 ± 0.08	1.45 ± 0.07	1.40 ± 0.07	NS
Preoperative parathyroid hormone level, mmol/L, mean ± SD	8.60 ± 4.18	7.60 ± 3.28	9.16 ± 4.14	8.40 ± 3.90	NS

Abbreviations: MEN1, multiple endocrine neoplasia type 1; SD, standard deviation; <SPTX, fewer than 3 parathyroid glands resected; SPTX, subtotal parathyroidectomy with 3–3½ parathyroid glands resected; TPTX, total parathyroidectomy; NS, not significant.

An overview of the surgical procedures is given in Table 2. After the primary surgery, 10 patients (19%) developed permanent hypoparathyroidism. In most cases, this occurred after total parathyroidectomy. One patient had a transient recurrent laryngeal nerve injury and another patient had laryngeal nerve injury of an unknown duration.

Eleven patients (21%) developed hypercalcemia within six months, indicating persistent disease. Twenty-eight patients (54%) developed a recurrence after a median of 121 months (range 47 to 201). Time to recurrence was 61 months shorter in patients who underwent <SPTX (93 months) than in patients who underwent SPTX (154 months), although this was not significant. Outcomes of surgical treatment for persistent and recurrent disease in follow-up are given in Table 3.

Thirty-one percent of the patients with <SPTX had persistent disease. Additionally, 59% of patients with <SPTX developed recurrent disease. After SPTX, one patient had persistent PHPT, but 65% developed recurrent disease after a median of 13 years. Although none of the six patients who had TPTX developed recurrent pHPT, one patient had persistent pHPT. Patients who had TPTX had the highest risk of permanent hypoparathyroidism (67%) compared with those who had <SPTX (7%) and SPTX (25%) (*P* = 0.003) (Table 2).

Table 2. Outcome of Primary Surgery for Primary Hyperparathyroidism in MEN1

Characteristics	<SPTX, *n* = 29[a]	SPTX, *n* = 17[b]	TPTX, *n* = 6	Overall, *n* = 52	*P* Value
Postoperative ionized calcium level, mmol/L, mean ± SD	1.25 ± 0.12	1.13 ± 0.13	1.07 ± 0.76	1.19 ± 0.14[c]	0.011
Postoperative parathyroid hormone level, mmol/L, mean ± SD	5.70 ± 4.26	2.97 ± 1.72	2.35 ± 2.99	4.42 ± 3.70[d]	0.070
Complications, n					
Hypoparathyroidism					0.003
Transient	0	3 (18%)[f]	1 (17%)	4 (8%)	
Permanent[e]	2 (7%)[f]	4 (24%)[f]	4 (67%)	10 (19%)	
Unknown duration	1 (3%)[f]	0	0	1 (2%)	
Recurrent laryngeal nerve injury					NS
Transient	1 (3%)	1 (6%)	0	2 (4%)	
Permanent	0	1 (6%)	0	1 (2%)	

Abbreviations: MEN1, multiple endocrine neoplasia type 1; SD, standard deviation; <SPTX, fewer than 3 parathyroid glands resected; SPTX, subtotal parathyroidectomy with 3–3½ parathyroid glands resected; TPTX, total parathyroidectomy; NS, not significant.

[a] Eight of the 29 in the <SPTX group underwent minimally invasive parathyroidectomy. Two patients underwent delayed conversion to a conventional neck exploration.

[b] One patient in the SPTX group underwent a minimally invasive parathyroidectomy, but the procedure was immediately converted to a SPTX because of an insufficient drop in parathyroid hormone level of less than 50%.

[c] Overall, preoperative ionized calcium levels were significantly higher than postoperative ionized calcium levels, *P* = 0.0001.

[d] Overall, preoperative parathyroid hormone levels were significantly higher than postoperative parathyroid hormone levels, *P* = 0.002.

[e] Permanent hypoparathyroidism is defined as a duration of hypoparathyroidism of six months or longer.

[f] Of the patients with hypoparathyroidism, three of four after <SPTX developed recurrent pHPT, and four of six after SPTX developed recurrent disease.

Table 3. Outcome of Surgery for Primary Hyperparathyroidism in MEN1

Characteristics	<SPTX, *n* = 29	SPTX, *n* = 17	TPTX, *n* = 6	Overall, *n* = 52	*P* Value
Follow-up, mo, median (range)	99 (44 to 162)	144 (71 to 207)	16 (4 to 236)	121 (47 to 201)	NS
Cure, n	20 (69%)	13 (93%)	5 (83%)	38 (73%)	NS
Persistent primary hyperparathyroidism,[a] n	9 (31%)	1 (7%)	1 (17%)	11 (22%)	NS
Recurrent primary hyperparathyroidism, n	17 (59%)[b]	11 (65%)	0	28 (54%)	0.010
Time to recurrence, mo, median (range)	93 (44 to 164)	154 (46 to 207)	-	127 (34 to 194)	0.088
Reintervention, n	16 (55%)	8 (47%)	1 (17%)		
Reintervention number, n				25 (48%)	NS
One				16 (31%)	
Two				3 (6%)	
Three				5 (9%)	
Seven				1 (2%)	
Second reoperation, n					
Number of glands resected					
0	2 (7%)	1 (6%)	0		
1	7 (24%)	6 (36%)	1 (17%)		
2	5 (17%)	0	0		
3	1 (3%)	0	0		
Autotransplantation	7 (24%)	4 (24%)	-		
Unknown	1 (3%)	1 (6%)	-		
Final TPTX status	6 (21%)	6 (36%)	-		
Complications					
Permanent hypoparathyroidism	2 (7%)	2 (12%)	0		
Recurrent primary hyperparathyroidism	5 (17%)	5 (30%)	0		

Abbreviations: <SPTX, fewer than 3 parathyroid glands resected; SPTX, subtotal parathyroidectomy with 3–3½ parathyroid glands resected; TPTX, total parathyroidectomy; NS, not significant.

[a] Persistent pHPT is defined as hypercalcemia within six months after surgery.

[b] All eight patients who underwent minimally invasive parathyroidectomy developed recurrent pHPT.

We performed 25 reoperations for persistent or recurrent pHPT. The number of reoperations per patient ranged from one to seven. During the second operation, 1 parathyroid gland was resected in 14 patients, 2 glands in five patients, and 3 glands in one patient. No parathyroid glands could be identified in three patients. After secondary surgery, calcium levels initially normalized in 19 patients (76%). Three patients developed hypoparathyroidism, two of whom had permanent hypoparathyroidism. None of the patients who developed hypoparathyroidism after the first operation or after reoperation has had a reautotransplantation.

No reintervention was performed in the 13 patients with persistent or recurrent disease. The patient who developed eight episodes of recurrence, underwent seven reinterventions in both the cervical region and the arm where the autotransplant graft was located. She now suffers from a permanent unilateral laryngeal nerve injury. She was the only patient in our series who had supernumerary glands. Median follow-up was 121 months (range 47 to 201). At the end of follow-up, nine patients had died, six because of metastasized neuroendocrine tumors, one because of metastasized melanoma and two of an unknown cause.

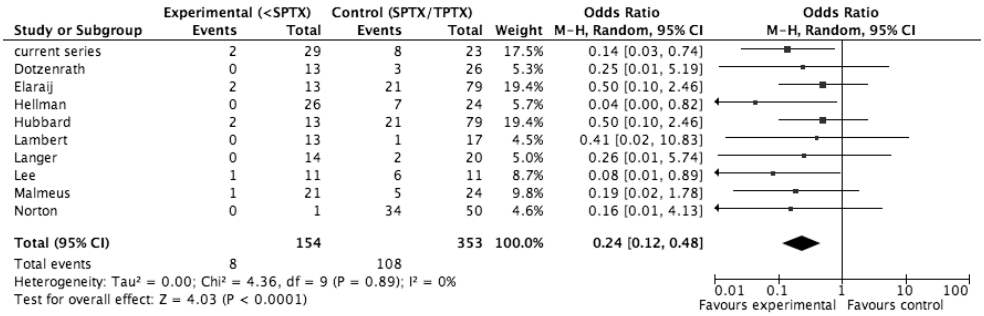
Meta-Analysis and Systematic Review

Twelve studies were included in our meta-analysis. First, we compared patients who had undergone <SPTX with patients who had undergone SPTX or TPTX. After <SPTX, patients had a significantly higher risk of developing recurrent and persistent pHPT than did patients with SPTX or TPTX. The odds-ratio for recurrent PHPT was 3.11 (95% CI = 2.00 to 4.84) for patients who underwent <SPTX (Figure 2). Patients with <SPTX had a significantly lower risk of developing permanent hypoparathyroidism (OR = 0.24, 95% CI = 0.24 to 0.48) (Figure 3) and a higher risk of persistent pHPT (Appendix C). Second, we compared patients who had SPTX with patients who had TPTX. Patients with SPTX did not have a significantly higher risk of developing recurrent pHPT than patients with TPTX (OR = 2.15, 95% CI = 0.82 to 5.61, P = 0.12) (Figure 4). Neither did they have a higher risk of developing persistent pHPT (Appendix D). After SPTX, patients had a significantly lower risk of permanent hypoparathyroidism than after TPTX (OR = 0.25, 95% CI = 0.11 to 0.54, P = 0.0004) (Figure 5). The I^2 test revealed moderate heterogeneity between the study outcomes on recurrent pHPT (percentage of total variation across the studies not due to chance alone was 38% and 46%).

There was no heterogeneity for study outcomes with respect to permanent hypoparathyroidism. An overview of the surgical outcomes from studies that were included and those that couldn't be included in meta-analysis is given in Appendix B.

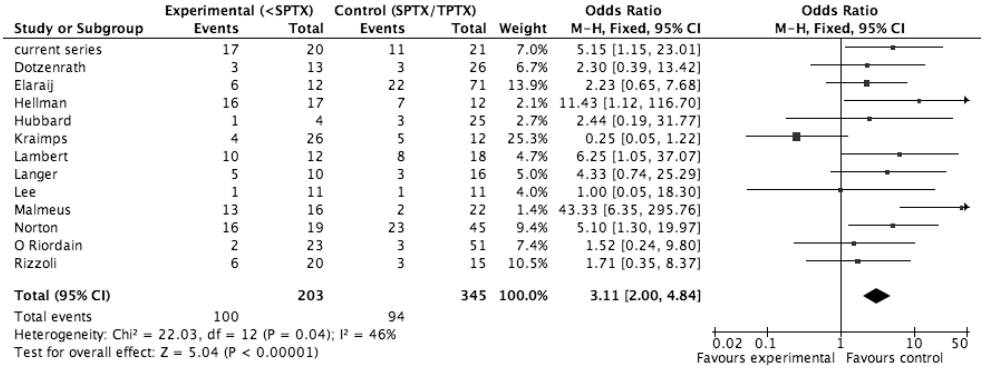
Most noncomparative studies had large study populations.[8-12] The overall recurrence rates are difficult to compare because of different techniques used in the studies. One series showed an overall recurrence rate of 7.6% after SPTX (n = 66) with bilateral thymectomy and <SPTX.[10] Another series of 100 patients had a failure rate of 26% after <SPTX (n = 37) and a combined failure rate of 11% after SPTX (n = 43) and TPTX (n = 11) after a follow-up period of 4.6 years.[11]

Figure 2. <SPTX versus SPTX and TPTX on Recurrent Primary Hyperparathyroidism in MEN1.



Abbreviations: <SPTX, fewer than 3 parathyroid glands resected; SPTX, 3-3½ parathyroid glands resected; TPTX, total parathyroidectomy with autotransplantation; MEN1, multiple endocrine neoplasia type 1.
SPTX and TPTX were analyzed together.
After <SPTX, patients are 3.11 times more likely to develop recurrent disease than after SPTX and TPTX (95% CI = 2.00 to 4.84, *P* < 0.0001). Patients who had persistent pHPT were excluded from analysis.

Figure 3. <SPTX versus SPTX and TPTX on Permanent Hypoparathyroidism in MEN1.

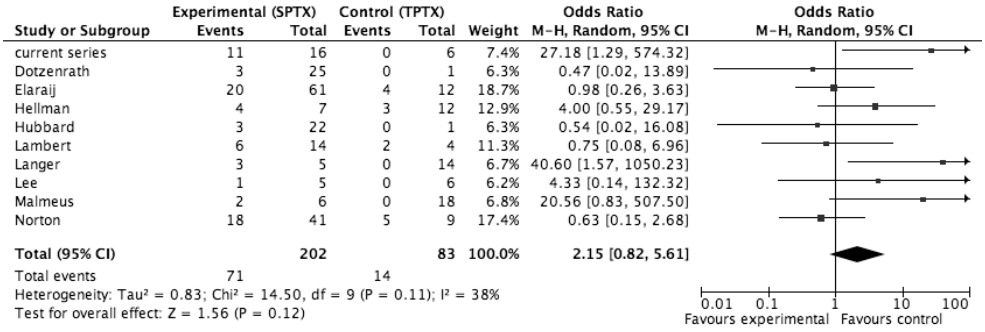


Abbreviations: <SPTX, fewer than 3 parathyroid glands resected; SPTX, 3-3½ parathyroid glands resected; TPTX, total parathyroidectomy with autotransplantation; MEN1, multiple endocrine neoplasia type 1.
SPTX and TPTX were analyzed together.
After <SPTX, patients have a significantly lower risk of developing permanent hypoparathyroidism than after SPTX and TPTX (OR = 0.24, 95% CI = 0.12 to 0.48, *P* < 0.0001).

A series of 51 patients who underwent 45 TPTX with thymectomy, had only five recurrences; all in the autografts after 6.7 years of follow-up. The rate of permanent hypoparathyroidism in that series was 22%.

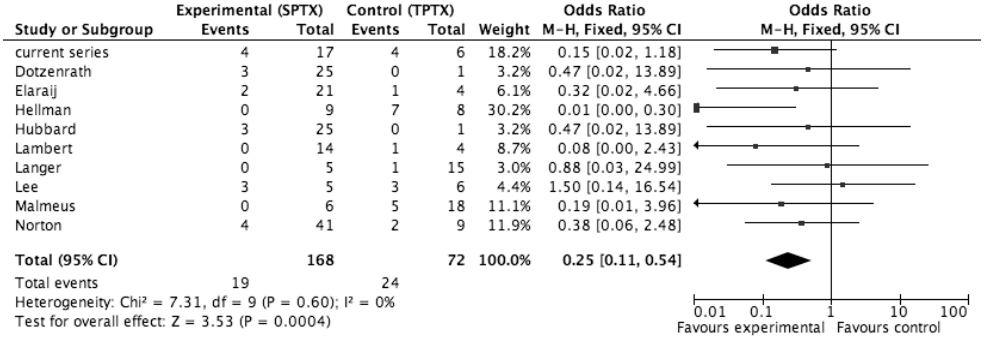
One large series of only patients who underwent reoperations for pHPT in MEN1 had a recurrence rate of 27% after 72 months; only two of 75 patients (3%) had permanent recurrent laryngeal nerve injury after their reoperation.[12]

Figure 4. SPTX versus TPTX on Recurrent Primary Hyperparathyroidism in MEN1.



Abbreviations: SPTX, 3-3½ parathyroid glands resected; TPTX, total parathyroidectomy with autotransplantation; MEN1, multiple endocrine neoplasia type 1.
After SPTX, patients do not have a significantly higher risk of developing recurrent pHPT than after TPTX (OR = 2.15, 95% CI = 0.82 to 5.61, *P* = 0.12). Patients who had persistent pHPT were excluded from analysis.

Figure 5. SPTX versus TPTX on Permanent Hypoparathyroidism in MEN1.



Abbreviations: SPTX, 3-3½ parathyroid glands resected; TPTX, total parathyroidectomy with autotransplantation; MEN1, multiple endocrine neoplasia type 1.
After SPTX, patients have a significantly lower risk of developing permanent hypoparathyroidism than after TPTX (OR = 0.25, 95% CI = 0.11 to 0.54, *P* = 0.0004).

Discussion

This study confirms the difficulties of managing primary hyperparathyroidism in MEN1 patients. Contradictory findings on surgical treatment have been reported. In our study, recurrent pHPT was most frequently seen after SPTX, yet the follow-up was long compared with other series (Appendix B). Even though none of the patients developed recurrent pHPT after TPTX, the majority developed permanent hypoparathyroidism (67%). Persistent disease was most frequently seen after <SPTX. These results and those of the meta-analysis and systematic review confirm that <SPTX should not be performed, because it has the highest risk of persistent

and recurrent disease. We propose that subtotal parathyroidectomy (SPTX) is the preferred treatment for pHPT in MEN1.

Some caution must be taken when interpreting the data presented here. There were no randomized controlled trials and most series were retrospective. Furthermore, the duration of follow-up was different in the studies. To evaluate permanent hypoparathyroidism only a few studies were available. The main limitation of our study is its retrospective nature. Some data were unavailable and there may have been confounding by indication for the type of surgery. Unfortunately, the results of the large noncomparative studies could not be included; they could have had a significant effect in the meta-analysis. An international randomized controlled trial with a long-term follow-up is necessary to answer some of the remaining questions. Nonetheless, such a study design would be very problematic to accomplish in view of the rarity of this disease.

Most authors agree that pHPT in MEN1 is caused by multiglandular disease.[6,9,12-15] The theory that MEN1-related pHPT develops asymmetrically and in time all parathyroid glands can become hyperplastic or develop adenomas, is based on the observation that there is a high risk of developing recurrent pHPT when limited resections are performed.[5,6] Even parathyroid glands that appear normal can have a diffuse positive staining reaction for parathyroid hormone.[16] Most authors therefore recommend SPTX or TPTX.[5,8,13,15,17,18] SPTX is generally considered to be superior to TPTX because the risk of permanent hypoparathyroidism is much lower. However, there might be an increased risk of recurrence compared with TPTX since some parathyroid tissue remains in situ. The controlled-cohort studies and case series that we identified in our systematic review of the literature showed the recurrence rate of pHPT was high after SPTX (3-3½ glands resected), ranging from 12% up to 67% after eight years of follow-up (Appendix B). The noncontrolled series had large study populations and more favorable outcomes with respect to recurrence rates for SPTX and TPTX, but follow-up rates were shorter than in our series. In our series, the recurrence rate was 65% after a long median follow-up of 12 years. This risk of recurrence increases with time and does not seem to reach a plateau phase.[8] After total parathyroidectomy with autotransplantation, recurrence rates of 4% to 55% have been reported.[8,15,17-20] The higher recurrence rate after SPTX in our series may be explained by the longer follow-up period than in other (noncomparative) series and the fact that in our series a cervical thymectomy was seldom performed.

The risk of severe and permanent hypoparathyroidism is highest after TPTX with autotransplantation. It ranges from 13% to 47% in the literature and was 67% in our series. After subtotal parathyroidectomy this risk ranges from 0% to 22%.[15,18] Patients with <SPTX are the least likely to develop permanent hypoparathyroidism.[13] These findings are confirmed by our meta-analysis. If patients with permanent hypocalcemia require lifelong vitamin D and calcium supplements, this may well affect their quality of life. If left untreated, longstanding hypoparathyroidism may lead to extrapyramidal disorders (Parkinson's disease and dementia), skin disorders, and cataracts. These risks have to be balanced against the benefits of curing the patient by performing extensive parathyroid resections, especially since the time to develop

recurrent disease after SPTX is long and a reoperation is often required only after several years.

Some authors have found uniglandular disease in MEN1.[21,22] In a small number of our patients, we had performed MIP to reduce complications and mainly at the patient's request. This practice has been abandoned after the poor results. In our and others' experience, the recurrence rate after MIP is unacceptably high: 100%.[6,23]Additionally, there is a higher risk of persistent disease after <SPTX, which was 31% in our series.[13] However, some authors have had better results with <SPTX, with cure rates of approximately 70% after 48 months[21] and 100% after five years.[22]

The possibility of supernumerary parathyroid glands should also be considered in the surgical treatment of pHPT in patients with MEN1.[24,25] Although some authors have not found supernumerary glands,[9] these may occur in up to 30% of MEN1 patients (Appendix B). The superior parathyroid glands are frequently located within the fascial sheath of the thyroid. Therefore, this fascia should be removed to localize the parathyroid glands. If the fascial sheath is not removed, subcapsular parathyroid glands may be overlooked.[26] Not only supernumerary glands can be found, but ectopic ones as well can be found, in up to 33% of cases.[27] These ectopic glands most often are located in the thymus.[9] Some authors advocate that during cervical exploration in these patients, a routine thymectomy should be performed to search for supernumerary and ectopic glands.[3,5,6,9,10,13,17,28] After SPTX with thymectomy, calcium levels return to normal more often (84.1%) than after SPTX without transcervical thymectomy (57.6%, $P = 0.0001$).[29] In our series, thymectomy was rarely performed. Some authors even recommend removal of the fatty tissue in the central compartment to remove all (ectopic) parathyroid tissue.[18]

Finally, one large case series that studied reoperations for pHPT in MEN1 found a recurrent laryngeal nerve injury rate of 2% and a permanent hypoparathyroidism rate of 16%.[12] In our series only one patient, who had undergone seven reoperations, developed permanent recurrent laryngeal nerve injury.

Conclusion

Given the currently available evidence, limited resections of fewer than 3 glands should not be part of a primary operation for pHPT in MEN1 patients since the persistence and recurrence rates are too high. SPTX might be the best surgical treatment for patients who have MEN1 and pHPT, despite the higher risk of recurrent pHPT. In addition, a thymectomy should routinely be performed in these patients.

Appendix A

Predefined Search Terms

Multiple endocrine neoplasia type 1

“Multiple endocrine neoplasia type 1” OR “multiple endocrine neoplasia type I” OR “multiple endocrine neoplasia syndrome type 1” OR “multiple endocrine neoplasia syndrome type I” OR “MEN 1” OR “MEN1” OR “MENI” OR “MEN I”.

Primary hyperparathyroidism

"Hyperparathyroidism, Primary"[Mesh] OR "Parathyroid Neoplasms"[Mesh] OR “primary hyperparathyroidism” OR “hyperparathyroidism” OR “HPT” OR “parathyroid adenoma*” OR “parathyroid hyperplasia”.

Surgical procedure

"Parathyroidectomy"[Mesh] OR “parathyroid surgery” OR “parathyroidectomy” OR “total parathyroidectomy” OR “subtotal parathyroidectomy” OR “conventional neck exploration” OR “unilateral neck exploration” OR “minimally invasive adenomectomy”.

Appendix B

Table 4.

Appendix C

Figure 6.

Appendix D

Figure 7.

Table 4. Outcome of Primary Surgery for Primary Hyperparathyroidism in MEN1 in Literature

Author, y Study Type Number of Patients with MEN1-pHPT	Number of Patients, Type of Surgery	Outcome of Surgery, n			Duration of Follow-up[a]	Comments
		Persistent pHPT	Recurrent pHPT	Permanent Hypopara-thyroidism		
Included in pooling analysis						
Rizzoli, 1985[20] Retrospective cohort study *n* = 61	41 <SPTX 20 SPTX/TPTX	21 (51%) 2 (10%)	7 (41%) 3 (15%)	0 0	7.8 y (1.3 to 12) overall	-
Malmeus, 1986[19] Retrospective cohort study *n* = 30	21 <SPTX 6 SPTX 3 TPTX	5 (24%) 0 0	13 (62%) 2 (33%) 0	1 (5%) 0 3 (100%)	6.5 y (1 to 14) overall	-
Kraimps, 1992[27] Retrospective case series *n* = 36 MEN1 *n* = 4 MEN2A	26 <SPTX 14 SPTX	0 2 (14%)	4 (15%) 5 (36%)	4 (10%) overall	8 y (1 to 46) overall	MEN1 and MEN2 analyzed together. None of the 4 MEN2 patients had recurrent pHPT 5 (13%) supernumerary glands 13 (33%) ectopic glands
O'Riordain, 1992[25] Retrospective cohort study *n* = 84	30 <SPTX 54 SPTX	5 (17%) 0	2 (7%) 3 (56%)	7 (8%) overall	6.7 y (2.5 to 11.1) overall	6 (7%) supernumerary glands
Hellman, 1998[13] Retrospective cohort study *n* = 50	26 <SPTX 9 SPTX 15 TPTX	9 (35%) 2 (22%) 0	16 (62%) 4 (44%) 3 (20%)	0 0 15 (100%)[c]	8.2 y ± 3.9 9.1 y ± 3.9 5.2 y ± 2.8	-
Dotzenrath, 2001[17] Retrospective cohort study *n* = 38	13 <SPTX 25 SPTX	0 0	3 (23%) 3 (12%)	2 (15%) 3 (12%)	54 mo (12 to 180) overall	2 (5%) supernumerary glands

Elaraj, 2003[15]	13 <SPTX	0	6 (46%)	2 (15%)	5.3 y	79 (86%) thymectomy
Retrospective cohort study	63 SPTX	0	20 (32%)	16 (26%)	6.1 y	Significant difference in time to recurrence between <SPTX and SPTX/TPTX
n = 92	16 TPTX	0	4 (25%)	7 (46%)	6.1 y	
Langer, 2004[24]	14 <SPTX	0	0	0	132 mo (6 to 240)	2 (6%) supernumerary glands
Cohort study	5 SPTX	0	0	0	151 mo (84 to 264)	2 (6%) ectopic glands
n = 34	15 TPTX	0	0	0	36 mo (6 to 192)	
Lambert, 2005[6]	16 <SPTX (+ 4 thymectomy)	0	12 (75%)	1 (6%)	4 y (*n* = 13)	1 (3%) supernumerary glands 8 (22%) ectopic glands
Retrospective cohort study						
n = 37	16 SPTX (+ 5 thymectomy)	0	6 (38%)	0	4.6 y (*n* = 14)	
	5 TPTX (+ 3 thymectomy)	0	2 (40%)	0	4.6 y (*n* = 4)	
Lee, 2005[22]	11 <SPTX	0	0	1 (9%)	7.0 y (0.5 to 19.5)	-
Retrospective cohort study	5 SPTX	0	1 (20%)	3 (60%)	6.9 y (1.5 to 15.5)	
n = 22	6 TPTX	0	0	3 (50%)	7.7 y (2 to 11.5)	
Hubbard, 2006[14]	4 <SPTX	0	1 (25%)	0	152 mo (8 to 285)	-
Retrospective cohort study	21 SPTX	0	1 (5%)	2(10%)	62 mo (8 to 192)	
n = 29	4 TPTX	0	2 (50%)	1 (25%)	167 mo (18 to 226)	
Norton, 2008[7]	35 <SPTX	15 (43%)	16 (46%)	1 (3%)	20.7 y ± 1.9	Patients have also have Zollinger-Ellison syndrome
Prospective cohort study	40 SPTX	5 (13%)	18 (45%)	4 (10%)	14.5 y ± 1.5	
n = 84	9 TPTX	0	5 (56%)	2 (22%)	9.9 y ± 1.5	
Not included in pooling analysis						
Cougard, 1994[11]	37 <SPTX	0	10 (26%)	0	4.6 y overall	41 (45%) thymectomy
Retrospective case series	43 SPTX	0	6 (11% SPTX/ TPTX)	0		28 (31%) ectopic glands
n = 91	11 TPTX	0		0		
			20 (22%) overall			

Burgess, 1998[8] Retrospective case series *n* = 37	37 SPTX	3 (8%)	7 (19%)	9 (24%)	8 y	-
Kivlen, 2001[12] Retrospective case series *n* = 75 with recurrent pHPT and reoperation	94 Reoperation 79 Neck exploration 3 Median sternotomy 12 Autograft resection 39 Operations for persistent pHPT 55 Operations for recurrent pHPT	0	58 of 64 (91%) cure or permanent hypopara-thyroidism 17 of 64 (27%) recurrent pHPT	310 (16%) overall	72 mo overall	9 (12%) overall complication rate Recurrent laryngeal nerve injury < 1982: 2 (3%) (permanent) > 1982: 0 Mediastinal exploration 1 (1%) Horner's syndrome 1 (1%) bleeding 2 (3%) chylus fistula 1 (1%) postoperative arrhythmia
Arnalsteen, 2002[10b] Retrospective cohort study *n* = 79	13 <SPTX 66 SPTX (+ 55 thymectomy)	0 0	4 (31%) 5 (7.6%)[b]	11 (13%) overall	37 mo ± 34 50 mo ± 54	24 (30%) supernumerary glands No significant differences in follow-up
Tonelli, 2007[9] Retrospective case series *n* = 45	45 TPTX (+ 45 thymectomy)	0	5 (11%) autograft	10 (22%)	80 mo ± 62	-

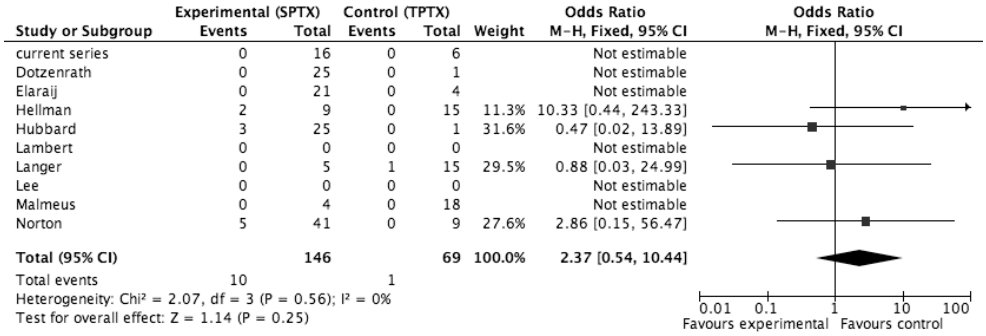
Abbreviations: MEN1, multiple endocrine neoplasia type 1; pHPT, primary hyperparathyroidism; <SPTX, fewer than 3 glands resected; SPTX, subtotal parathyroidectomy, TPTX, total parathyroidectomy.

[a] Duration of follow-up is reported in mean ± standard deviation or median (range) in months or years.

[b] Excluded from pooling analysis because of the unclear recurrence rate.

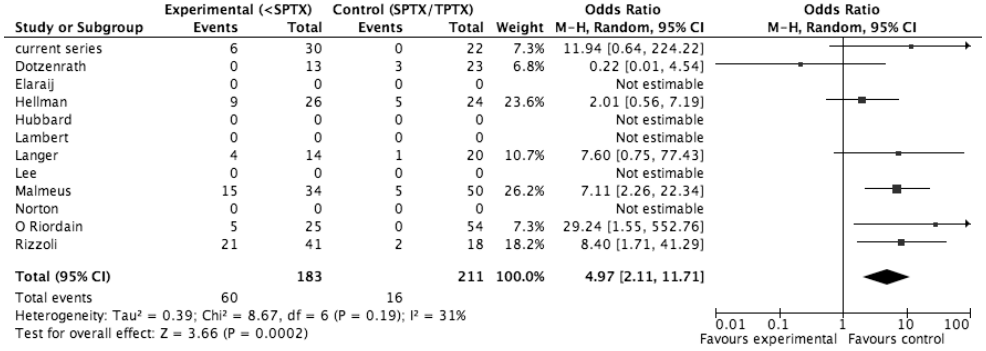
[c] Pemanent hypoparathyroidism, but recovery after one to seven years.

Figure 6. <SPTX versus SPTX and TPTX on Persistent Primary Hyperparathyroidism in MEN1.



Abbreviations: <SPTX, fewer than 3 parathyroid glands resected; SPTX, 3-3½ parathyroid glands resected; TPTX, total parathyroidectomy with autotransplantation; MEN1, multiple endocrine neoplasia type 1.
SPTX and TPTX are analyzed together. After <SPTX, patients are more likely to develop persistent primary hyperparathyroidism than after SPTX and TPTX (OR = 4.97, 95% CI = 2.11 to 11.71, *P* = 0.0002).

Figure 7. SPTX versus TPTX on Persistent Primary Hyperparathyroidism in MEN1.



Abbreviations: SPTX, 3-3½ parathyroid glands resected; TPTX, total parathyroidectomy with autotransplantation; MEN1, multiple endocrine neoplasia type 1.
After SPTX, patients do not have a significantly higher risk of developing persistent primary hyperparathyroidism than after TPTX (OR = 2.37, 95% CI = 0.54 to 10.44, *P* = 0.25).

References

1. Pieterman CR, Schreinemakers JM, Koppeschaar HP, et al. Multiple endocrine neoplasia type 1 (MEN1): its manifestations and effect of genetic screening on clinical outcome. *Clin Endocrinol (Oxf)* 2009; 70(4):575-581.
2. Carty SE, Helm AK, Amico JA, et al. The variable penetrance and spectrum of manifestations of multiple endocrine neoplasia type 1. *Surgery* 1998; 124(6):1106-1113, discussion 1113-1114.
3. Akerstrom G, Juhlin C, Skogseid B. Surgical treatment of multiple endocrine neoplasia type 1 (MEN I) associated parathyroid hyperplasia. *Acta Chir Austriaca* 1994; 26:30-32.
4. Malone JP, Srivastava A, Khardori R. Hyperparathyroidism and multiple endocrine neoplasia. *Otolaryngol Clin North Am* 2004; 37(4):715-736.
5. Doherty GM, Lairmore TC, DeBenedetti MK. Multiple endocrine neoplasia type 1 parathyroid adenoma development over time. *World J Surg* 2004; 28(11):1139-1142.
6. Lambert LA, Shapiro SE, Lee JE, et al. Surgical treatment of hyperparathyroidism in patients with multiple endocrine neoplasia type 1. *Arch Surg* 2005; 140(4):374-382.
7. Norton JA, Venzon DJ, Berna MJ, et al. Prospective study of surgery for primary hyperparathyroidism (HPT) in multiple endocrine neoplasia-type 1 and Zollinger-Ellison syndrome: long-term outcome of a more virulent form of HPT. *Ann Surg* 2008; 247(3):501-510.
8. Burgess JR, David R, Parameswaran V, et al. The outcome of subtotal parathyroidectomy for the treatment of hyperparathyroidism in multiple endocrine neoplasia type 1. *Arch Surg* 1998; 133(2):126-129.
9. Tonelli F, Marcucci T, Fratini G, et al. Is total parathyroidectomy the treatment of choice for hyperparathyroidism in multiple endocrine neoplasia type 1? *Ann Surg* 2007; 246(6):1075-1082.
10. Arnalsteen LC, Alesina PF, Quiereux JL, et al. Long-term results of less than total parathyroidectomy for hyperparathyroidism in multiple endocrine neoplasia type 1. *Surgery* 2002; 132(6):1119-1124, discussion 1124-1115.
11. Cougard P, Proye C. Hyperparathyroidism and multiple endocrine neoplasia type I (MENI). *Acta Chir Austriaca* 1994; 26:32-35.
12. Kivlen MH, Bartlett DL, Libutti SK, et al. Reoperation for hyperparathyroidism in multiple endocrine neoplasia type 1. *Surgery* 2001; 130(6):991-998.
13. Hellman P, Skogseid B, Oberg K, et al. Primary and reoperative parathyroid operations in hyperparathyroidism of multiple endocrine neoplasia type 1. *Surgery* 1998; 124(6):993-999.
14. Hubbard JG, Sebag F, Maweja S, et al. Subtotal parathyroidectomy as an adequate treatment for primary hyperparathyroidism in multiple endocrine neoplasia type 1. *Arch Surg* 2006; 141(8):235-239.
15. Elaraj DM, Skarulis MC, Libutti SK, et al. Results of initial operation for hyperparathyroidism in patients with multiple endocrine neoplasia type 1. *Surgery* 2003; 134(6):858-864, discussion 864-865.
16. Harach HR, Jasani B. Parathyroid hyperplasia in multiple endocrine neoplasia type 1: a pathological and immunohistochemical reappraisal. *Histopathology* 1992; 20(4):305-313.
17. Dotzenrath C, Cupisti K, Goretzki PE, et al. Long-term biochemical results after operative treatment of primary hyperparathyroidism associated with multiple endocrine neoplasia types I and IIa: is a more or less extended operation essential? *Eur J Surg* 2001; 167(3):173-178.

18. Hubbard JG, Sebag F, Maweja S, et al. Primary hyperparathyroidism in MEN 1 - how radical should surgery be? *Langenbecks Arch Surg* 2002; 386(8):553-557.
19. Malmaeus J, Benson L, Johansson H. Parathyroid surgery in the multiple endocrine neoplasia type I syndrome: Choice of surgical procedure. *World J Surg* 1986; 10(4):668-672.
20. Rizzoli R, Green J 3rd, Marx SJ. Primary hyperparathyroidism in familial multiple endocrine neoplasia type I. Long-term follow-up of serum calcium levels after parathyroidectomy. *Am J Med* 1985; 78(3):467-474.
21. Dralle H, Scheumann GFW. How to handle the parathyroid glands in multiple endocrine neoplasia type I (MEN I) and type II (MEN II)? Surgical approach to uniglandular versus multiglandular disease in hereditary primary hyperparathyroidism. *Acta Chir Austriaca* 1994; 26:35-38.
22. Lee CH, Tseng LM, Chen JY, et al. Primary hyperparathyroidism in multiple endocrine neoplasia type 1: individualized management with low recurrence rates. *Ann Surg Oncol* 2006; 13(1):103-109.
23. Jansson S, Tisell LE. Total parathyroidectomy and parathyroid transplantation into subcutaneous fat tissue in the treatment of hyperparathyroidism in multiple endocrine neoplasia type I (MEN I). *Acta Chir Austriaca* 1994; 26:23-26.
24. Langer P, Wild A, Schilling T, et al. Multiple endocrine neoplasia type 1. Surgical therapy of primary hyperparathyroidism. *Chirurg* 2004; 75(9):900-906.
25. O'Riordain DS, O'Brien T, Grant CS, et al. Surgical management of primary hyperparathyroidism in multiple endocrine neoplasia types 1 and 2. *Surgery* 1993; 114(6):1031-1037, discussion 1037-1039.
26. Bonjer HJ. Technique of parathyroidectomy. In: Clark OH (ed). *Textbook of Endocrine Surgery.* Philadelphia, Elsevier Saunders, 2003.
27. Kraimps JL, Duh QY, Demeure M, et al. Hyperparathyroidism in multiple endocrine neoplasia syndrome. *Surgery* 1992; 112(6):1080-1086, discussion 1086-1088.
28. Gauger PG, Thompson NW. Early surgical intervention and strategy in patients with multiple endocrine neoplasia type I. *Best Pract Res Clin Endocrinol Metab* 2001; 15(2):213-223.
29. Goudet P, Cougard P, Verges B, et al. Hyperparathyroidism in multiple endocrine neoplasia type I: surgical trends and results of a 256-patient series from Groupe D'etude des Neoplasies Endocriniennes Multiples Study Group. *World J Surg* 2001; 25(7):886-890.

Chapter 3

Evolution of Surgical Treatment of Primary Hyperparathyroidism in Multiple Endocrine Neoplasia Type 2A

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Abstract

Objective To determine the best surgical strategy for patients with multiple endocrine neoplasia type 2A (MEN2A) who have primary hyperparathyroidism (pHPT).

Methods We performed a systematic literature review and conducted a retrospective cohort study that included patients with pHPT identified from the MEN2A database at the University Medical Center Utrecht, The Netherlands, between 1979 and 2009.

Results The review describes the course of worldwide surgical management in MEN2A-related pHPT over the past 75 years, which has evolved from aggressive parathyroid resections to minimally invasive parathyroidectomy (MIP). The study cohort included 20 patients. Primary surgery for parathyroid disease in patients with MEN2A patients (*n* = 16) included MIP (*n* = 6), conventional neck exploration with resection of enlarged parathyroid gland(s) (*n* = 4), and resection of one or more enlarged gland(s) during total thyroidectomy (*n* = 6). Thirteen patients were initially cured after the primary operation. Five patients experienced persistent or recurrent pHPT. After MIP, one patient had persistent pHPT, but no patient developed recurrent pHPT during five years of follow-up. Five patients had hypoparathyroidism after subtotal or total parathyroidectomy with autotransplantation, but only one patient had transient hypoparathyroidism after MIP. One patient had a transient recurrent laryngeal nerve injury after MIP.

Conclusion Surgery for pHPT in patients with MEN2A has evolved from aggressive conventional exploration of all four glands to focused MIP, which appears to be a feasible approach. MIP has low rates of persistent and recurrent pHPT, and the complications are minimal.

Introduction

Multiple endocrine neoplasia syndrome type 2A (MEN2A) is an autosomal dominant inherited disorder caused by mutations in the *RET* proto-oncogene on chromosome 10. This disorder can be diagnosed by genetic screening before manifestations exist.[1] Virtually all patients with the syndrome develop medullary thyroid carcinoma (MTC). Therefore, affected patients should undergo prophylactic total thyroidectomy according to their *RET* proto-oncogene mutation as recommended by current guidelines. Thirty to forty percent of persons with a *RET* proto-oncogene mutation develop pheochromocytomas, and 20% to 30% develop primary hyperparathyroidism (pHPT) in the course of the disease.[2] The latter is in contrast to patients with multiple endocrine neoplasia syndrome type 1 (MEN1), who have a 78% to 100% risk of developing pHPT at a relatively young age.[3,4] PHPT in MEN2A generally presents after the third decade of life.[5]

PHPT as part of MEN2A has a diverse clinical spectrum. First, parathyroid gland disease can be diagnosed in the laboratory at an early age if parathyroid glands are resected during (prophylactic) total thyroidectomy for C-cell hyperplasia or MTC. Histologic examination of these parathyroid glands may show hyperplasia or adenoma. Second, pHPT can be diagnosed during routine biochemical screening (elevated serum calcium level in combination with an inadequately nonsuppressed or elevated parathyroid hormone [PTH] level) for follow-up of MEN2A. Finally, patients can present with signs and symptoms of pHPT, i.e. nephrolithiasis or bone disease.[6]

Several factors hinder choosing the right treatment of pHPT in MEN2A patients. First, MEN2A is a very rare disease, and the associated pHPT has a different course than that of pHPT associated with MEN1. Second, the incidence of multiglandular disease is variable in pHPT associated with MEN2A. Furthermore, supernumerary glands may be present and affected. Hence, recommendations on surgical therapy in MEN2A-related pHPT are contradictive. Some authors advocate total parathyroidectomy combined with autotransplantation of parathyroid tissue.[7] Others favor only selective resection of the enlarged parathyroid gland(s).[6,8-11] Previous reports have included relatively few patients with MEN2A and pHPT.[6,8,9,11-13] In most reports, outcome of surgical treatment was analyzed in conjunction with outcome in patients with MEN1.[8-12]

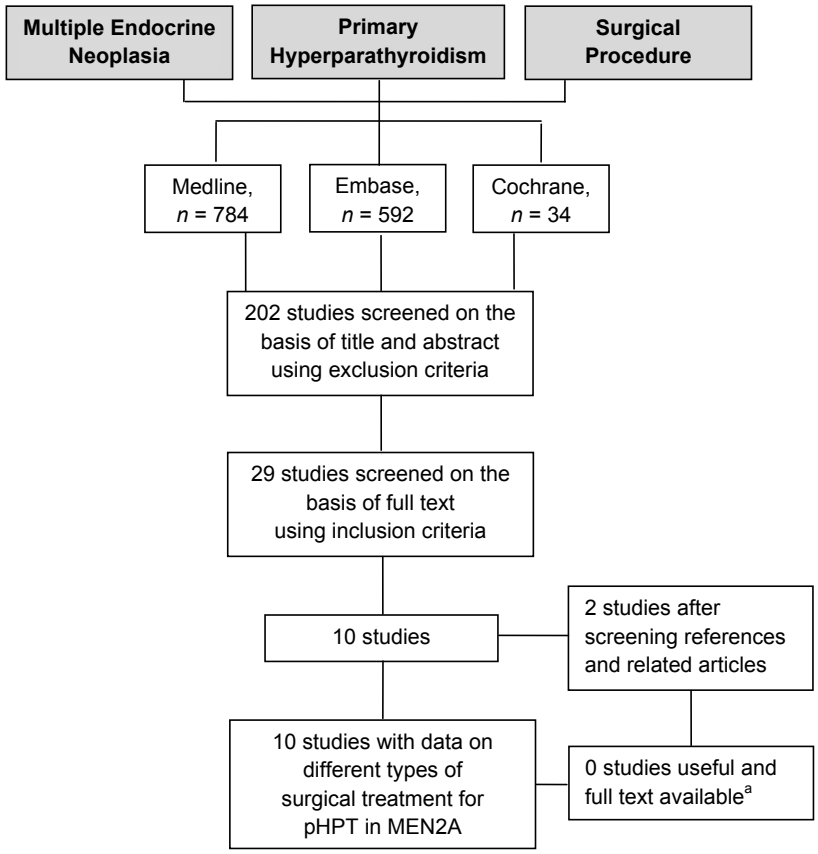
The purpose of this study was to evaluate the outcome of surgical treatment of pHPT in a large cohort of patients with MEN2A treated at the University Medical Center Utrecht, The Netherlands, during long-term follow-up. Our outcome of surgical treatment of pHPT in MEN2A was compared with the available literature in a review of the evolution of parathyroid surgery in patients with MEN2A over the last 75 years.

Materials and Methods

Literature Review

We searched Medline (1966 to 2010), Embase (1980 to 2010), and the Cochrane database of systematic reviews (2010) using predefined search terms (Appendix A). On the basis of title and abstract, we selected 29 studies using predetermined exclusion criteria (Appendix A). Applying inclusion criteria (Appendix A) to the full text

Figure 1. Article Selection on Surgery for Primary Hyperparathyroidism in MEN2A.



Abbreviations: MEN2A, multiple endocrine neoplasia type 2A.
Search date: September 4, 2010.
[a] Full text was unavailable for the following citations: Block MA, Frame B, Jackson CE. The efficacy of subtotal parathyroidectomy for primary hyperparathyroidism due to multiple gland involvement. *Surg Gynaecol Obstet* 1978; 147(1):1-5; Edis AJ, van Heerden JA, Scholz DA. Results of subtotal parathyroidectomy for primary chief cell hyperplasia. *Surgery* 1979; 86(3):462-466.

resulted in 10 studies with original data on surgery for MEN2A-related pHPT (Figure 1). We also included the results of our cohort study. Analyzed outcomes included persistent pHPT, recurrent pHPT, and permanent hypoparathyroidism.

Cohort Study

This retrospective cohort study includes patients with pHPT identified from the MEN2A database at the University Medical Center Utrecht, The Netherlands between 1979 and 2009.

We defined MEN2A as the presence of two or more manifestations of the syndrome (MTC, pheochromocytoma, pHPT) or a *RET* proto-oncogene mutation.

Patients with MEN2A were included if they had either biochemical evidence of pHPT (elevated serum calcium level in combination with an inadequately nonsuppressed or elevated PTH level) or enlarged parathyroid glands during total thyroidectomy. In the regular management and surveillance of the MEN2A population, patients are screened annually for the presence of biochemical evidence of pHPT. Data on patient characteristics at baseline, *RET* proto-oncogene mutation, surgical treatment, and outcome were collected. Surgical cure was defined as a return to normal serum calcium levels for at least six months after operation. Recurrence was defined as a return of documented hypercalcemia after surgical cure. Persistence was defined as hypercalcemia that remained after surgery or returned within six months after surgery. Hypoparathyroidism and nerve damage were considered complications of surgery. Hypoparathyroidism was defined as a serum ionized calcium level less than 4.60 mg/dL or total calcium level less than 8.8 mg/dL and/or the use of calcium and/or vitamin D supplements. Hypoparathyroidism was considered permanent if it persisted for more than six months after surgery. Injury of the recurrent laryngeal nerve was based on clinical diagnosis and confirmation by postoperative laryngoscopy in case of clinical hoarseness. Damage was considered to be permanent if it was still present at final follow-up (at least 5 years).

Patients were treated by minimally invasive parathyroidectomy (MIP), conventional neck exploration (CNE) combined with excision of enlarged glands, or resection of only the enlarged gland(s) during total thyroidectomy. The MIP technique used at our institution is performed in selected cases if a parathyroid adenoma has been localized in the same location on sestamibi scan and ultrasonography preoperatively. Intraoperative PTH measurements are routinely performed whenever a MIP is performed. A significant drop of more than 50% of the intraoperative PTH level compared with the most recent preoperative level is considered successful.[14]

We defined the histopathologic diagnosis of the resected glands as adenoma or hyperplasia of the parathyroid glands. The finding of a rim of normal tissue surrounding enlarged parathyroid tissue makes the diagnosis adenoma more likely. The absence of this rim of normal tissue or the presence of two or more enlarged parathyroid glands during the same operation makes hyperplasia more likely.[15]

The duration of follow-up was defined as the interval between the date of primary surgery and the date of last contact or the last measured serum calcium level.

Statistical Analysis

We used SPSS version 16.0 (SPSS, Inc., Chicago, IL), to describe the population. Data are shown as mean or median based on their distribution. For the description and analysis of the patients who underwent surgery, we excluded those who did not undergo surgery. Analysis of variance was applied to calculate the statistical difference in mean follow-up between intervention groups.

Table 1. Outcome of Primary Surgery for Primary Hyperparathyroidism in MEN2A in Literature

Author, y	Clinic	Study Period	Study Type	Level of Evidence[a]	Preoperative Imaging, IOPTH	Initial Approach	Number of Patients, Type of Surgery	Persistent pHPT, n	Recurrent pHPT, n	Permanent Hypoparathyroidism, n	Follow-up,[b] y
Van Heerden, 1983[11]	Mayo Clinic, Rochester, Minnesota	1960 to 1980	Retrospective case series	3b	-, -	CNE, TT, cryopreservation	9 overall	1 (12%)	1 (12%)	0	3.6
							3 selective TT	1 (33%)	0	1 (33%)	4.1
							6 subtotal TT	ND	ND	ND	3.3
Cance, 1985[17]	University of Washington	ND	Retrospective cohort series	2b	-, -	CNE, 18 of 36 (50%) TT	36 overall	6 (17%)	1 (3%)	ND	ND
							28 selective	ND	ND	ND	
							8 total	ND	ND	1 (13%)	
Kraimps, 1992[12]	University of California, San Francisco	1935 to 1988	Retrospective case series	4	-, -	CNE, TT, cryopreservation, thymectomy, biopsy nonenlarged glands	4 selective	0	0	1 (25%)	8
O'Riordain, 1993[13]	Mayo Clinic, Rochester, Minnesota	1970 to 1991	Retrospective cohort series	2b	-, -	CNE, TT	18 overall	0	0	4 (22%)	5.8
							9 selective TT	0	0	ND	
							7 subtotal TT	0	0	ND	
							2 total TT	0	0	2 (100%)	
Dotzenrath, 1994[9]	Dusseldorf	1986 to 1993	Retrospective case series	4	-, -	CNE, thymectomy	3 overall	0	0	0	ND
							1 selective	0	0	0	
							1 subtotal	0	0	0	4
							1 total + autoTx	0	0	0	
Dralle, 1994[10]	Medical School Hannover	1976 to 1992	Retrospective case series	4	-, -	CNE, 12 of 15 (80%) TT, thymectomy, excision one nonenlarged gland	15 overall	90 (6%)	ND	4 (27%)	8 and 5.5
							11 selective TT	0	ND	0	
							2 selective	0	1 (50%)	1 (50%)	
							1 subtotal	1 (100%)	ND	ND	
							1 total	0	ND	ND	

Raue, 1995[6]	Euromen study group, Europe	1972 to 1993	Retrospective cohort study	2b	-, -	CNE, 50 of 67 (75%) TT	67 overall 28 selective 21 subtotal 11 total	2 (3%) 0 2 (11%) 0	8 (12%) 4 (14%) 2 (11%) 2 (18%)	9 (13%) 4 (14%) 4 (19%) 1 (9%)	8
Herfarth, 1996[7]	University of Washington	1963 to 1989	Retrospective cohort study	2b	-, -	CNE, 31 of 35 (89%) TT, thymectomy	35 overall 21 selective 8 subtotal 5 total + autoTx 1 total	3 (9%) 3 (14%) 0 0 0	5 (14%) 3 (14%) 2 (25%) 0 0	8 (23%) 4 (19%) 1 (13%) 1 (20%) 1 (100%)	14.7 14.4 14.4 16.3
Kraimps, 1996[5]	Multicentral, France	1969 to 1994	Retrospective cohort study	2b	-, -	52 of 56 (93%) CNE	54 overall 29 selective 12 subtotal 11 total	6 (11%) 2 (7%) 2 (17%) 1 (9%)	5 (9%) 4 (14%) 1 (8%) 0	12 (22%) 3 (10%) 6 (50%) 2 (19%)	6.4
Dotzenrath, 2001[8]	Germany	1968 to 1998	Retrospective case series	4	-, -	CNE, TT	7 overall 5 selective 1 subtotal 1 total	0 0 0 0	2 (29%) 2 (40%) 0 0	1 (14%) 0 1 (100%) 0	3.5
Scholten, 2011 (current study)	University Medical Center Utrecht	1979 to 2009	Retrospective cohort study	2b	US, MIBI, IOPTH	CNE, MIP, TT	16 overall 6 MIP 4 subtotal 6 selective TT	3 (19%) 1 (17%) 1 (25%) 1 (17%)	2 (13%) 0 1 (25%) 1 (17%)	5 (31%) 0 0 3 (31%)	9.6 5.0 7.8 16.1

Abbreviations: ND, not described; IOPTH, intraoperative parathyroid hormone measurement; US, ultrasonography; MIBI, technetium-99m-sestamibi scintigraphy; CNE, conventional neck exploration; TT, during total thyroidectomy; autoTx, autotransplantation; MIP, minimal invasive parathyroidectomy with resection of a single parathyroid gland.

[a] Levels of evidence are based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence, 2001.[16]

[b] Duration of follow-up is reported in mean or median.

Results

Literature Review

Since 1931, the standard operative procedure for sporadic pHPT consisted of bilateral neck exploration to localize all parathyroid glands, including supernumerary and ectopic glands. Subsequently, all pathologically enlarged parathyroid tissue was removed. Improvements in preoperative imaging and intraoperative care have led to a more conservative approach with minimally invasive techniques, including MIP in case of solitary parathyroid disease.

Results of surgery to treat pHPT in patients with MEN2A cover a study period of 75 years (1935 to 2010) (Table 1). As for sporadic pHPT, subtotal or selective parathyroidectomy of enlarged glands after bilateral neck exploration and identification of all four parathyroid glands was initially considered the best surgical strategy in these patients.[6,8,11-13] Occasionally, this was performed during total thyroidectomy for MTC. Additional procedures advised in the past include cryopreservation of parathyroid tissue in case of late-onset postoperative hypoparathyroidism,[11,12] biopsy of nonenlarged glands,[12,17] and bilateral cervical thymectomy with resection of surrounding fatty tissue.[7,10,12] Herfarth et al[7] preferred total parathyroidectomy in all patients with MEN2A, and Cance and Wells[17] preferred total parathyroidectomy in all patients with MEN2A with more than one enlarged gland. Dralle and Scheumann[10] advised resection of one or two macroscopically enlarged parathyroid glands during total thyroidectomy even in normoparathyroid patients with MEN2A.

More recently, selective resection of enlarged parathyroid glands without routine thymectomy became generally accepted in patients with MEN2A and pHPT and was associated with good results.[5,9,13] The results of our study (see following text) agree with this approach. An overview of the results of primary surgery in MEN2A-related pHPT obtained in worldwide studies is given in Table 1.

Successful selective resection of enlarged parathyroid glands by MIP is moderated by preoperative imaging and intraoperative PTH determination. These techniques aid in the differentiation between uniglandular and multiglandular disease. In the past, this differentiation was mostly based on surgical and pathological expertise, which often led to misdiagnosis of adenomatous disease rather than hyperplasia or vice versa with inadequate, or too extensive, resections. Also, ectopic or supernumerary glands can be easily missed.[14]

Originally approved for myocardial perfusion imaging, technetium-99m-sestamibi scintigraphy is now the standard method used for preoperative imaging of the parathyroid glands.[18,19] It can be used in combination with ultrasonography of the neck. Intraoperative PTH measurement was first described by George Irvin in 1988. Since then, it has been refined to a quick and less expensive measurement with results available in less than 20 minutes.[20,21] In none of the previously reported studies did patients with MEN2A undergo preoperative localization imaging or have intraoperative PTH determination.

Cohort Study

From our MEN2A database, 130 patients with MEN2A were identified, 23 (18%) of whom had pHPT. Three patients had insufficient information available, and they were hence excluded from the study. As a result, the study population consisted of 20 patients. Patient characteristics are given in Table 2.

In our cohort, 16 patients underwent primary surgery for parathyroid disease between 1979 and 2009 (Table 3). Two patients had mild and asymptomatic hypercalcemia and were treated conservatively, and two patients are awaiting surgery. Operations were performed at the University Medical Center Utrecht, a tertiary referral center in 11 cases and in community hospitals in five cases. Six patients underwent MIP, four patients underwent a CNE combined with excision of one or two enlarged gland(s), and six patients underwent selective resection of the enlarged gland(s) during total thyroidectomy (Table 3). As previously stated, intraoperative PTH measurement is currently routinely performed whenever MIP is performed. Due to logistic reasons, this was only done in two of six patients. The mean overall follow-up after the primary surgery was 9.1 years (range 0.5 to 26.7), with significant differences between surgical groups (P = 0.04) (Table 4).

Table 2. Characteristics of Primary Hyperparathyroidism in MEN2A Patients

Characteristics	Data
Patient characteristics	
Female, n	9 (45%)
Age at diagnosis of primary hyperparathyroidism, y, median (range)	39 (20 to 66)
RET proto-oncogene mutation, n	
Cys634Arg	10 (50%)
Cys634Tyr	3 (15%)
Cys634Trp	1 (5%)
Codon 618	1 (5%)
Unknown	5 (25%)
Symptoms and diagnostic characteristics, n	8 (40%)
Fatigue	4 (20%)
Nephrolithiasis	3 (15%)
Bone pain or osteopenia	4 (20%)
Muscle weakness	1 (5%)
Preoperative ionized calcium level,[a] mg/dL, median (range)	5.44 (5.32 to 5.68)
Preoperative parathyroid hormone level,[b] pg/mL, median (range)	89.0 (52.6 to 248.9)
Other MEN2A-associated features, n	
Medullary thyroid carcinoma, total thyroidectomy	19 (95%)
Pheochromocytoma, adrenalectomy	17 (85%)
Pruritus	1 (5%)
Cutaneous lichen amyloid	2 (10%)
Lipoma	1 (5%)
Angiolipoma	1 (5%)
Age at total thyroidectomy, y, mean (range)	32 (9 to 65)

Abbreviations: MEN2A, multiple endocrine neoplasia type 2A.

[a] Reference range 4.60 to 5.28 mg/dL (1.15 to 1.32 mmol/L).

[b] Reference range < 67 pg/mL (< 7.0 pmol/L).

Overall, 13 patients (81%) were cured, with the highest cure rate obtained after MIP (5 of 6 [83%]). Three patients had persistent pHPT, one after MIP, one after CNE (one gland resected) and one after total thyroidectomy (no enlarged glands resected, because none were found). Two patients developed recurrent disease, one of whom developed recurrence 10.3 years after removal of one gland during total thyroidectomy. In the other patient, recurrence occurred 11.2 years after removal of one gland by CNE.

Complications of nerve injury and hypoparathyroidism following primary surgery are listed in Table 4. One patient had immediate postoperative failure (PTH levels remained elevated) and underwent successful reexploration one week later, with removal of a second adenoma. Three patients underwent reoperation for persistent or recurrent pHPT. After a mean follow-up of 8.9 years (range 3.3 to 12.8), one patient was cured, another had persistent pHPT and the third developed recurrent pHPT 2.0 years after the reoperation. Four patients died during follow-up, two patients died of non-MEN2A-related malignancy and two died of unknown causes.

Discussion

Review of the literature on pHPT in MEN2A shows an evolving preference for minimal resection of parathyroid glands. In addition, from the data of our cohort study, we conclude that MIP may be considered the initial procedure of choice for patients with MEN2A at our institution. Our series is one of the largest series to report results of surgical therapy for pHPT in patients with MEN2A with a long follow-up.

MIP has a minimal risk of damage to surrounding tissues. Furthermore, MIP provides better cosmetic results, patient comfort and a shorter duration of hospital stay.[14] The MIP technique has become the standard of care for sporadic pHPT in institutions with substantial experience with the procedure. Its role in the setting of familial pHPT is evolving. MIP can be performed if preoperative imaging studies are concordant. In the current time of genetic screening and prophylactic total thyroidectomy at a young age, almost all patients with MEN2A will undergo some form of neck surgery for MTC before the presentation of and surgery to treat pHPT. This was the case in all patients in our series who underwent a MIP. Taking the postoperative fibrosis and scarring after neck surgery into account, an image-guided minimally invasive procedure is preferred over more invasive approaches. For example, the risk of recurrent laryngeal nerve injury is minimized, as is the chance of permanent hypoparathyroidism, which can have a dramatic impact on the quality of life.

Our results suggest that pHPT in MEN2A is generally not an aggressive disease. Hypercalcemia was commonly mild. pHPT was asymptomatic in 60% of patients in our series and 42% to 84% of patients in retrospective studies.[5-7,11-13] PHPT is rarely the first diagnosed endocrinopathy in MEN2A (15% in our series). In most affected patients in our series, MEN2A-related pHPT was present in the third and fourth decade, which was also seen in other series.[6,9,12,13]

Table 3. Operative Findings of Primary Surgery for Primary Hyperparathyroidism in MEN2A

Type of Surgery	Number of Patients	Number of Glands Resected	Pathology			Localisation of Glands
			Adenoma	Hyperplasia	None	
Minimally invasive parathyroidectomy	6	1 gland (*n* = 6)	5	1	0	Adenoma: right cranial (*n* = 2), left caudal (*n* = 3) Hyperplasia: left caudal
Conventional neck exploration with resection of enlarged glands	4	1 gland (*n* = 3) 2 glands (*n* = 1)	1	3	0	Adenoma: left caudal Hyperplasia: left cranial, right cranial, right cranial + caudal, right paratracheal
Resection of glands during total thyroidectomy	6	0 glands (*n* = 1)[a] 1 gland (*n* = 4) 2 glands (*n* = 1)	1	4	1	Adenoma: left caudal Hyperplasia: left caudal, right cranial, left + right cranial

[a] No glands found.

Table 4. Outcome of Primary Surgery for Primary Hyperparathyroidism in MEN2A

Type of Surgery	Number of Patients	Number of Patients					
		Cure	Recurrent pHPT	Persistent pHPT	Hypocalcemia (Transient, Permanent)	Recurrent Laryngeal Nerve Injury (Transient, Permanent)	Follow-up,[a] y, mean ± SD
Minimally invasive parathyroidectomy	6	5	0	1	1 (transient)	1 (transient)	5.0 ± 5.8
Conventional neck exploration with resection of enlarged glands	4	2	1	1	2 (1 unknown, 1 transient)	1 (transient) 1 phrenic (permanent)	7.8 ± 6.2
Resection of glands during total thyroidectomy	6	4	1	1	2 (permanent)	0	16.1 ± 6.2

Abbreviations: pHPT, primary hyperparathyroidism; SD, standard deviation.
[a] Mean follow-up between the different surgical groups was significantly different, $P = 0.04$.

We found relatively low rates of persistent and recurrent pHPT after selective gland resection during a long follow-up period. This supports our belief that patients with MEN2A-related pHPT often have uniglandular, rather than multiglandular, disease. We propose that a more conservative approach with selective resection of enlarged glands is justified rather than a subtotal or total parathyroidectomy. This is in line with most reports on pHPT in MEN2A (Table 1).

Three patients had persistent pHPT, and two patients developed recurrent hypercalcemia. The somewhat unfavorable results of persistent pHPT after surgery may be related to the fact that some patients underwent operation at the beginning of the 1980s, a time when MEN diseases were less well appreciated, and at hospitals with less experience in operating on multiglandular disease. Unfortunately, the latter is not always preventable because the syndrome is so rare. This emphasizes, however, the importance of recognizing MEN2A and appropriately referring affected patients to tertiary referral centers.

We also found a high rate of postoperative hypoparathyroidism in patients with MEN2A (31%). In two patients, hypoparathyroidism was transient. Permanent hypoparathyroidism after neck exploration most likely reflects inadvertent parathyroid injury during operation. Because permanent hypoparathyroidism developed in two patients who had their parathyroid glands resected during total thyroidectomy, the hypoparathyroidism could also be the result of damage to the glands during thyroidectomy. The histopathologic diagnosis of the resected parathyroid glands may be under influence of selection bias of the operating procedure. If more than one or two glands are found and affected, it is often regarded as hyperplasia. During MIP however, only one gland is removed, which is often considered to be an adenoma.

Although this is one of the largest studies on surgery in MEN2A-related pHPT, the number of patients per group was small and patients could not be randomized. In addition, there was a relatively small number of patients with pHPT among the total group of 130 patients with MEN2A. MIP at our institution is considered only if imaging studies are concordant. In our series, the results may therefore show confounding by indication. In addition, follow-up after MIP was significant shorter than after other procedures. Nonetheless, we advocate MIP as an adequate surgical procedure for patients with MEN2A who have pHPT.

Conclusion

Surgery for pHPT in patients with MEN2A has evolved from aggressive, conventional exploration of all four glands to focused MIP, which appears to be a feasible and safe approach. MIP has low persistence and recurrence rates, and complications are minimal.

Appendix A

Predefined Search Terms

Multiple endocrine neoplasia type 2A

“Multiple endocrine neoplasia type II*” OR “Multiple endocrine neoplasia syndrome type II*” OR “Multiple endocrine neoplasia type 2*” OR “Multiple endocrine neoplasia syndrome type 2*” OR “Sipple’s syndrome” OR “MEN 2*” OR “MEN2*” OR “MENII*” OR “MEN II*”

Primary hyperparathyroidism

"Hyperparathyroidism, Primary"[Mesh] OR "Parathyroid Neoplasms"[Mesh] OR “hyperparathyroidism” OR “HPT” OR “PHPT” OR “parathyroid adenoma*” OR “parathyroid hyperplasia” OR “parathyroid neoplasm*”

Surgical procedure

"Parathyroidectomy"[Mesh] OR “parathyroid surgery” OR “parathyroidectomy” OR “neck exploration” OR “minimally invasive adenomectomy” OR “adenomectomy”

Exclusion Criteria

Animal studies
Diagnostic, prognostic, etiologic studies
Case reports, systematic reviews
Sporadic primary hyperparathyroidism
Secondary and tertiary hyperparathyroidism

Inclusion Criteria

Human studies
Therapeutic studies on original data
Randomized controlled trials
Retrospective or prospective case series or cohort studies
Primary hyperparathyroidism
Multiple endocrine neoplasia type 2A
Parathyroidectomy, minimally invasive or selective versus subtotal versus total
English, Dutch studies

References

1. Lips CJ, Landsvater RM, Hoppener JW, et al. Clinical screening as compared with DNA analysis in families with multiple endocrine neoplasia type 2A. *N Engl J Med* 1994; 331(13):828-835.
2. Steiner AL, Goodman AD, Powers SR. Study of a kindred with pheochromocytoma, medullary thyroid carcinoma, hyperparathyroidism and Cushing's disease: multiple endocrine neoplasia, type 2. *Medicine (Baltimore)* 1968; 47(5):371-409.
3. Carty SE, Helm AK, Amico JA, et al. The variable penetrance and spectrum of manifestations of multiple endocrine neoplasia type 1. *Surgery* 1998; 124(6):1106-1113, discussion 1113-1114.
4. Pieterman CR, Schreinemakers JM, Koppeschaar HP, et al. Multiple endocrine neoplasia type 1 (MEN1): its manifestations and effect of genetic screening on clinical outcome. *Clin Endocrinol (Oxf)* 2009; 70(4):575-581.
5. Kraimps JL, Denizot A, Carnaille B, et al. Primary hyperparathyroidism in multiple endocrine neoplasia type IIa: retrospective French multicentric study. Groupe d'Etude des Tumeurs a Calcitonine (GETC, French Calcitonin Tumors Study Group), French Association of Endocrine Surgeons. *World J Surg* 1996; 20(7):808-812, discussion 812-813.
6. Raue F, Kraimps JL, Dralle H, et al. Primary hyperparathyroidism in multiple endocrine neoplasia type 2A. *J Intern Med* 1995; 238(4):369-373.
7. Herfarth KK, Bartsch D, Doherty GM, Wells SA Jr, Lairmore TC. Surgical management of hyperparathyroidism in patients with multiple endocrine neoplasia type 2A. *Surgery* 1996; 120(6):966-973.
8. Dotzenrath C, Cupisti K, Goretzki PE, et al. Long-term biochemical results after operative treatment of primary hyperparathyroidism associated with multiple endocrine neoplasia types I and IIa: is a more or less extended operation essential? *Eur J Surg* 2001; 167(3):173-178.
9. Dotzenrath C, Goretzki PE, Roher HD. Surgery of primary hyperparathyroidism in patients with multiple gland disease: The Dusseldorf experience. *Acta Chir Austriaca* 1994; 26:47-49.
10. Dralle H, Scheumann GFW. How to handle the parathyroid glands in multiple endocrine neoplasia type I (MEN I) and type II (MEN II)? Surgical approach to uniglandular versus multiglandular disease in hereditary primary hyperparathyroidism. *Acta Chir Austriaca* 1994; 26:35-38.
11. van Heerden JA, Kent RB 3rd, Sizemore GW, Grant CS, ReMine WH. Primary hyperparathyroidism in patients with multiple endocrine neoplasia syndromes. Surgical experience. *Arch Surg* 1983; 118(5):533-536.
12. Kraimps JL, Duh QY, Demeure M, Clark OH. Hyperparathyroidism in multiple endocrine neoplasia syndrome. *Surgery* 1992; 112(6):1080-1086, discussion 1086-1088.
13. O'Riordain DS, O'Brien T, Grant CS, Weaver A, Gharib H, van Heerden JA. Surgical management of primary hyperparathyroidism in multiple endocrine neoplasia types 1 and 2. *Surgery* 1993; 114(6):1031-1037, discussion 1037-1039
14. Smit PC, Borel Rinkes IHM, van Dalen A, van Vroonhoven TJ. Direct, minimally invasive adenomectomy for primary hyperparathyroidism: An alternative to conventional neck exploration? *Ann Surg* 2000; 231(4):559-565.
15. Lewis PD. Surgical pathology of the parathyroids in primary and secondary hyperparathyroidism. In: Lynn J, Bloom SR (eds). *Surgical Endocrinology*. Oxford, Butterworth-Heineman Ltd, 1993; 331-393.

16. Oxford Centre for Evidence-based Medicine Levels of Evidence, 2001. Available at: http://www.cebm.net/index.aspx?o=1047. Accessed April 10, 2010.
17. Cance WG, Wells SA Jr. Multiple endocrine neoplasia. Type IIa. *Curr Probl Surg* 1985; 22(5):1-56.
18. Norman J. Recent trends becoming standard of care yielding smaller, more successful operations at a lower cost. *Otolaryngol Clin North Am* 2004; 37(4):683-688.
19. Mullan BP. Nuclear medicine imaging of the parathyroid. *Otolaryngol Clin North Am* 2004; 37(4):909-939.
20. Irvin GL 3rd, Prudhomme DL, Deriso GT, Stakianakis G, Chandarlapathy SK. A new approach to parathyroidectomy. *Ann Surg* 1994; 219(5):574-581.
21. Shindo M. Intraoperative rapid parathyroid hormone monitoring in parathyroid surgery. *Otolaryngol Clin North Am* 2004; 37(4):779-787.

Chapter 4

Differences Between Sporadic and Multiple Endocrine Neoplasia-Related Primary Hyperparathyroidism; Clinical Expression, Preoperative Workup, Operative Strategy and Follow-up

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Abstract

Background Primary hyperparathyroidism (pHPT) is most commonly sporadic (spHPT). However, sometimes pHPT develops as part of multiple endocrine neoplasia (MEN) type 1 or 2A. In all cases, parathyroidectomy is the only curative treatment. Nevertheless, there are important differences in clinical expression and treatment.

Methods We analyzed a consecutive cohort of patients treated for sporadic, MEN1-related, and MEN2A-related pHPT and compared them regarding clinical and biochemical parameters, differences in preoperative workup, operative strategies, findings, and outcome.

Results A total of 467 patients with spHPT, 52 with MEN1-related and 16 with MEN2A-related pHPT were analyzed. Patients with spHPT were older, more often female, and had higher preoperative calcium and parathyroid hormone (PTH) levels compared with MEN1 and MEN2A patients. Minimally invasive parathyroidectomy (MIP) was performed in 367 of 467 spHPT patients (79%). One abnormal parathyroid was found in 426 patients (91%). Two or more in 35 patients (7%). In six patients (1%) no abnormal parathyroid gland was retrieved. Of 52 MEN1 patients, eight (15%) underwent a MIP and 44 (85%) underwent conventional neck exploration (CNE); with resection of fewer than 3 enlarged glands in 21 patients (40%), subtotal parathyroidectomy (SPTX, 3-3½ glands) in 17 (33%) and total parathyroidectomy with autotransplantation (TPTX) in six (12%). Eleven patients (21%) had persistent disease, 29 (56%) recurrent pHPT and nine (17%) permanent hypoparathyroidism, mostly after TPTX. Of 16 MEN2A patients, six (38%) underwent MIP, four (25%) CNE and six (38%) selective resection of the enlarged gland(s) during total thyroidectomy. Three patients (19%) suffered from persistent pHPT and two (13%) developed recurrent disease.

Conclusion Sporadic pHPT, MEN1-, and MEN2A-related pHPT are three distinct entities as is reflected preoperatively by differences in sex, age at diagnosis, and calcium and PTH levels. MEN2A patients are very similar to spHPT with respect to operative approach and findings. MIP is the treatment of choice for both. MIP has low rates of persistent and recurrent pHPT and a low complication rate. The percentage of multiglandular disease and recurrences are significantly higher in MEN1 patients, demonstrating the need for a different approach. We advocate treating all these patients with CNE and SPTX.

Introduction

The etiology of primary hyperparathyroidism (pHPT), a common endocrine disease, is most frequently sporadic and nonfamilial (spHPT).[1] A significant proportion of patients, however, develop pHPT as part of the familial syndromes multiple endocrine neoplasia (MEN) type 1 or 2A.[2,3] Major features of MEN1 are endocrine tumors of the parathyroid, pituitary, and pancreas. Minor features consists of bronchial and thymic tumors.[4,5] MEN2A is associated with medullary thyroid cancer, pHPT, and pheochromocytoma.[6] In all cases of pHPT, parathyroidectomy is the only curative treatment that resolves symptoms and metabolic complications and thus improves quality of life, in both symptomatic and asymptomatic patients.

Clinical features that differentiate between patients with sporadic pHPT and MEN-related pHPT are: age of onset, female to male ratio, severity of bone involvement, family history, and related endocrine neoplasias.[7-9] Once pHPT and its setting are diagnosed, the course of the disease and its treatment will change the perspective for both surgeon and patient considerably.

However, most of the current literature analyzes data on surgical management of pHPT without making any such distinction to this profound difference in etiology.[9-11] Although hypercalcemia might be the first clinical parameter to be discovered in all three, we strongly believe, these are very distinct and different entities, requiring a different approach.

In a population based cohort of patients treated for pHPT, we evaluated the frequency and causes (number of affected glands) of sporadic, MEN1- and MEN2A-related pHPT, as well as the differences in their clinical presentation, preoperative workup and operative strategies, findings and outcome. We sought to determine whether, with optimal surgical strategies for each subgroup, a comparable outcome regarding persistent and recurrence rates, with equally low complication rates (hypoparathyroidism and recurrent laryngeal nerve injury) could be obtained.

Materials and Methods

We retrospectively analyzed the records of a consecutive cohort of patients treated for spHPT in one geographical region of The Netherlands between 1994 and 2009, comprising one academic center and three affiliated hospitals. All patients were symptomatic. The diagnosis pHPT was established biochemically by a serum calcium level greater than 10.20 mg/dL (> 2.55 mmol/L) and/or a serum ionized calcium level greater than 5.28 mg/dL (> 1.32 mmol/L) combined with an increased, greater than 65 pg/mL (> 6.5 pmol/L), or nonsuppressed plasma parathyroid hormone (PTH) level. In a few patients calcium levels were normal, but an increased renal calcium excretion combined with an elevated PTH level was affirmative for pHPT.[12-14]

In addition, all patients with pHPT from the MEN1 and MEN2 database at the University Medical Center Utrecht, The Netherlands were analyzed. The MEN1 database includes patients diagnosed with pHPT between 1967 and 2009. Patients were included in the MEN1 database if they had genetically proven MEN1, or three of five manifestations of MEN1 or one of five manifestations and a first-degree family member with MEN1. Gene testing (mutation analysis) was performed in very young

patients with pHPT, pHPT in combination with possible MEN1 manifestations, or a MEN-positive family history.[15]

From the MEN2 database, patients diagnosed with pHPT between 1979 and 2009 were selected. MEN2A was defined in case of a MEN2A germline mutation. Patients with MEN1 and MEN2A were included if they had biochemical evidence of pHPT as stated above or enlarged parathyroid glands while undergoing a total thyroidectomy. Since the University Medical Center Utrecht is a tertiary referral center, also patients who were initially treated at another institution and later referred to our institution were included.

Preoperative localizing studies were used in spHPT and MEN2A patients and included ultrasonography, computed tomography and/or technetium-99m-sestamibi scintigraphy (MIBI). The preoperative diagnostic workup differed between hospitals and evaluated over time. Presently, our preferential preoperative workup consists of MIBI and ultrasonography. Depending on the results of the preoperative localization studies, spHPT and MEN2A patients were subsequently operated in a preferentially minimally invasive approach.[16] Minimally invasive parathyroidectomy (MIP) was defined as a small (3 cm) incision over the suspected adenoma as guided by preoperative localization (two concordant preoperative imaging techniques), whereas an unilateral approach involves a larger incision and larger exposure plus systematic exploration of the entire area of interest on one side (based on one positive preoperative imaging). Both inferior and superior parathyroid glands will have to be identified using this approach. In case of no visualization of an enlarged gland or discordant imaging techniques a convention neck exploration (CNE) was performed. Preoperative imaging for MEN1 patients is not part of our policy, although many patients underwent preoperative imaging studies prior to referral to our surgical department. In subtotal parathyroidectomy (SPTX), 3–3½ parathyroid glands were resected during a CNE after identification of all parathyroid glands. In total parathyroidectomy (TPTX), 4 glands were resected and 1 (partial) gland was used as a graft for autotransplantation into the brachioradial muscle of the nondominant forearm. The autotransplantation was performed during the same operation, using fresh parathyroid tissue.

Intraoperative PTH (IOPTH) measurements and/or intraoperative frozen section analysis, to verify removal of aberrant parathyroid tissue, were carried out in a routine fashion whenever a MIP was performed. A significant drop of more than 50% from the highest of either preoperative baseline or preexcision level at 10 minutes after hyperfunctioning parathyroid gland(s) excision, indicates surgical cure and predicts postoperative normocalcemia.[17,18]

Surgical cure was defined as normalization of serum (ionized) calcium and PTH levels for a period of at least six months after the surgical procedure. Persisting hypercalcemia or renewed hypercalcemia within the first six months after surgery was considered indicative of surgical failure. Hypercalcemia after a period of six month of postoperative normocalcemia was defined as recurrent disease. The findings of all operations necessary to achieve normocalcemia were taken into account when determining the cause of pHPT. Extirpation of a single enlarged

parathyroid gland with subsequent normalization of serum calcium was defined as single gland disease. Retrieval of more than one enlarged parathyroid gland leading to normocalcemia was defined as multiglandular disease. Multiglandular hyperplasia was defined as the situation when all four glands appeared abnormal. Hypoparathyroidism and nerve damage were considered complications of surgery. Permanent hypoparathyroidism was defined as a serum ionized calcium level of less than 4.60 mg/dL (< 1.15 mmol/L) and/or total calcium level of less than 8.5 mg/dL (< 2.12 mmol/L), persisting beyond the first six months after surgery and requiring substitution with calcium and an active form of vitamin D.

To get insight into pHPT in MEN1 and MEN2A and their difference with respect to spHPT, we evaluated clinical and biochemical parameters, differences in preoperative workup, operative strategies, and findings.

Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL). All continuous variables were reported as median (range). Mann-Whitney *U* test and *t* test were used for two-group comparison of continuous variables and χ^2 test for analysis of categorical data. Statistical significance was established at $P < 0.05$.

Results

A total of 535 patients were analyzed. The cohort consists of 467 patients with spHPT, 52 with MEN1- and 16 with MEN2A-related pHPT. Patient characteristics are summarized in Table 1. Sex, age, preoperative calcium and PTH levels were significantly different among groups. In the spHPT group, there were more females, patients were older and preoperative calcium and PTH levels were higher compared with the MEN1 and MEN2A patients ($P < 0.001$, χ^2, $P < 0.001$, *t* test and $P = 0.012$, *U* test, respectively). Clinical complaints as lethargy and renal stones were not significantly different between spHPT patients and MEN1 and MEN2A patients ($P = 0.184$ and $P = 0.06$ versus $P = 0.22$ χ^2 and $P = 0.59$ χ^2, respectively).

The average number of preoperative imaging was similar in the spHPT and MEN2A group (mean number of used imaging modalities 1.97 and 1.63 respectively), but higher when compared with MEN1 patients (mean number of used imaging modalities 1.06).

The operative findings and postoperative course, as well as the complications for each group are given in Table 2 and Table 3.

Sporadic Primary Hyperparathyroidism

Of 467 patients with spHPT, treated at the University Medical Center Utrecht or in one of three regional teaching hospitals, 367 patients (79%) were scheduled for a MIP. The remaining 100 patients underwent a planned CNE. In 39 patients (8%) a MIP procedure was intraoperatively converted to a CNE. In 18 of these patients, the minimal invasive approach provided insufficient exposure to enucleate a correctly localized adenoma. In one patient the adenoma was not found. In the other 20 patients, the preoperative imaging was not consistent with the intraoperative findings.

Table 1. Characteristics of Primary Hyperparathyroidism in Sporadic, MEN1 and MEN2A Patients

Characteristics	Sporadic pHPT, *n* = 467	MEN1-pHPT, *n* = 52	MEN2A-pHPT, *n* = 16
Patient characteristics			
Female, n	357 (76%)	33 (63%)	9 (56%)
Age, y, median (range)	63 (20 to 88)	33 (11 to 62)	39 (20 to 66)
Symptoms at first presentation, n	467 (100%)	42 (81%)	12 (75%)
Fatigue	188 (40%)	16 (31%)	4 (25%)
Nephrolithiasis	115 (25%)	14 (27%)	3 (19%)
Osteoporosis	73 (16%)	0	4 (25%)
Gastrointestinal symptoms	67 (14%)	7 (14%)	0
Neuropsychiatric symptoms	42 (9%)	7 (14%)	1 (6%)
Preoperative serum level, mean (range)			
Ionized calcium, mg/dL	6.76 (4.60 to 7.40)	5.56 (4.44 to 6.44)	5.4 (5.32 to 5.68)
Calcium, mg/dL	11.56 (10.12 to 22.20)	-	-
Parathyroid hormone, pg/mL	219 (10 to 3097)	78 (16 to 191)	89 (52 to 249)
Imaging modality, n			
Ultrasonography	399 (85%)	30 (57%)	10 (63%)
Computed tomography	317 (68%)	13 (25%)	8 (50%)
Technetium-99m-sestamibi scintigraphy	206 (44%)	12 (23%)	8 (50%)
Number of used imaging modalities, mean	1.97	1.06	1.63

Abbreviations: pHPT, primary hyperparathyroidism; MEN1, multiple endocrine neoplasia type 1; MEN2A, multiple endocrine neoplasia type 2A.

The surgical success rate after primary surgery was 93% (*n* = 436). Hypercalcemia persisted after the primary surgery in 31 patients (7%). The persistence rate in patients with IOPTH measurement was 4%. The cumulative surgical success rate, including an early second operative procedure, was 99% (*n* = 461). Normocalcemia resulted from removing one abnormal parathyroid gland in 426 patients (91%). Two or more abnormal glands were removed in 35 patients (7%), while four gland hyperplasia was the observed cause of pHPT in one patient. In six patients (1%) no abnormal parathyroid gland was retrieved and thus hypercalcemia persisted. Four patients developed recurrent hypercalcemia. Parathyroid carcinoma was diagnosed in four patients. The median follow-up was two years (range 1 to 15). Three patients sustained permanent recurrent laryngeal nerve damage and one patient became permanent hypocalcemic.

Multiple Endocrine Neoplasia Type 1-Related Primary Hyperparathyroidism

Fifty-two patients underwent primary surgery for pHPT, either at the University Medical Center Utrecht (*n* = 36) or another affiliated hospital (*n* = 16). Eight patients underwent a MIP, 21 underwent less than SPTX (<SPTX), 17 underwent SPTX, and six underwent TPTX. In three patients a MIP procedure was intraoperatively converted to a CNE with TPTX due to inadequate drop of IOPTH levels.

Eleven patients (21%) had persistent disease: nine patients (31%) after <SPTX, one (7%) after SPTX and one (17%) after TPTX. Twenty-eight patients (54%) developed recurrent pHPT; after a median time of 8.0 years after <SPTX (56%), and after a median time of 13.0 years after SPTX (65%). None of the patients who underwent TPTX had recurrence. After primary surgery, 10 patients (19%) developed permanent hypoparathyroidism: two (7%) after <SPTX, four (25%) after SPTX, and four of the patients (67%) who underwent TPTX. One patient had a permanent recurrent laryngeal nerve injury after multiple operations for persistent and recurrent pHPT.

Multiple Endocrine Neoplasia Type 2A-Related Primary Hyperparathyroidism

Sixteen MEN2A patients underwent primary surgery for parathyroid disease between 1979 and 2010. Eleven operations were carried out at the University Medical Center Utrecht and five in affiliated hospitals. Ten patients were operated in varying years after a previous total thyroidectomy. Six patients of these underwent MIP and four patients underwent CNE combined with excision of one (*n* = 3) or two (*n* = 1) enlarged glands. In the other six patients, selective resection of the enlarged gland(s) was performed during a total thyroidectomy for medullary thyroid carcinoma (no glands resected because none were found *n* = 1, one gland resected *n* = 4, two glands resected *n* = 1). None of our MEN2 patients underwent a parathyroidectomy before they underwent a thyroidectomy.

Thirteen patients were initially cured after the primary operation. Three patients suffered from persistent pHPT, two patients developed recurrent disease. The mean overall follow-up after primary surgery was 9 years (range 5 to 27). After MIP, one patient had persistent pHPT, but no one developed recurrent pHPT during

Table 2. Surgery for Primary Hyperparathyroidism in Sporadic, MEN1 and MEN2A

Characteristics	Sporadic pHPT, *n* = 467	MEN1-pHPT, *n* = 52	MEN2A-pHPT, *n* = 16
Initial operation, n			
Minimally invasive parathyroidectomy	328 (70%)	5 (10%)	6 (38%)
Minimally invasive parathyroidectomy converted to conventional neck exploration	39 (8%)	3 (6%)	0
Conventional neck exploration	100 (21%)	44 (84%)	10 (62%)
Subtotal parathyroidectomy, n	-	38 (73%)	-
Total parathyroidectomy, n	-	6 (12%)	-
Number of operations, n			
One procedure	435 (93%)	26 (50%)	13 (81%)
Two procedures	31 (7%)	17 (33%)	1 (6%)
Three or more procedures	1 (<1%)	9 (17%)	2 (13%)
Number of operations, mean	1.07	1.85	1.29
Cumulative operative findings, n			
No adenoma found	6 (1%)	0	1 (6%)
1 enlarged gland	426 (91%)	17 (33%)	13 (81%)
Solitary (adenoma, hyperplasia)	422 (90%)	17 (33%)	13 (81%)
Carcinoma	4 (1%)	0	0
> 1 enlarged gland	35 (7%)	35 (56%)	2 (13%)
2 enlarged glands	26 (6%)	12 (23%)	2 (13%)
3 enlarged glands	8 (2%)	17 (33%)	0
> 3 enlarged glands or hyperplasia	1 (<1%)	6 (12%)	0

Abbreviations: pHPT, primary hyperparathyroidism; MEN1, multiple endocrine neoplasia type 1; MEN2A, multiple endocrine neoplasia type 2A.

five years of follow-up. Five patients had hypoparathyroidism, due to inadvertent damage to parathyroid glands during total thyroidectomy.

The percentage of operations started as a minimally invasive operation was higher in the spHPT group compared with the MEN populations ($P < 0.001$, χ^2). The mean number of operations was higher in MEN patients compared with the spHPT population ($P < 0.001$, χ^2); between MEN1 and MEN2A we could not demonstrate a significant difference. The number of patients with multiglandular disease was the highest in the MEN1 group ($P < 0.001$, χ^2).

Discussion

According to our study and previous literature, sporadic, MEN1-related and MEN2A-related pHPT are three distinct entities, as is reflected preoperatively by differences in sex, age at diagnosis, and preoperative calcium and PTH levels.[7-9] Clearly this leads to a distinct algorithm regarding the preoperative workup and operative strategy (Figure 1). We found no difference in the prevalence of clinical symptoms, in agreement with previous studies.[9,19]

As others have demonstrated, operative findings may be a function of the operative approach; a CNE leads to removal of more parathyroid glands and thus a

Table 3. Outcome of Surgery for Primary Hyperparathyroidism in Sporadic, MEN1 and MEN2A

Characteristics	Sporadic pHPT, *n* = 467	MEN1-pHPT, *n* = 52	MEN2A-pHPT, *n* = 16
Persistent disease, n			
After first procedure	31 (7%)	11 (21%)	3 (19%)
After second procedure	6 (1%)	4 (8%)	1 (6%)
Recurrent disease, n			
After first procedure	3 (<1%)	28 (54%)	2 (13%)
After second procedure	0	12 (24%)	1 (6%)
Complications, n			
Recurrent laryngeal nerve injury	3 (<1%)	1 (2%)	1 (6%)
Hypocalcemia	1 (<1%)	10 (19%)	2 (13%)

Abbreviations: pHPT, primary hyperparathyroidism; MEN1, multiple endocrine neoplasia type 1; MEN2A, multiple endocrine neoplasia type 2A.

higher percentage of multiglandular disease.[20,21] In our series, the frequency of solitary adenomas observed is higher than historically reported.[22] The extent of the preoperative workup influences the number of observed solitary adenomas. In case of two concordant imaging studies we advocate to perform a MIP, if there is only one positive study an unilateral exploration and if all imaging studies are negative or contradictive an upfront CNE. The use of IOPTH remains controversial and we advise not to use it in a routine fashion.[23-29] Others, however, do report benefits of IOPTH measurement.[30-32] Especially, in patients with recurrent disease, in patients with proven or suspected multiglandular disease, as well as in patients with inconsistent preoperative imaging, IOPTH can add to decision making and improve outcome.[33--35]

We included some patients with a normal calcium level. One might argue whether in these patients pHPT can be diagnosed. However, pathologic examination confirmed the diagnosis. Part of these patients might only be intermittent normocalcemic or become asymptomatic patients later. Furthermore, there is some evidence for a generalized target-tissue resistance to PTH and as a result a renal tubular resistance to the action of PTH and thus increased renal calcium excretion.[12,14]

The percentage of multiglandular disease is significantly higher in MEN1 patients, this demonstrates the need for a different approach in this category of patients. Ninety-five percent of MEN1 patients were treated with a CNE. Some advocate to perform a TPTX.[36-38] Based on the data presented by the DutchMEN1 Study Group, who reported a genotype-phenotype correlation in MEN1-related pHPT, we have changed our surgical strategy over the last years. Part of the patients in the present study was included in the patient cohort of a previous study. Recurrence after <SPTX, in this cohort, was significantly lower in patients with nonsense or frameshift mutations in exon 2, 9, and 10. This indicates that cure depends primarily on the amount of parathyroid tissue removed. As these results

have to be confirmed in an independent patient population, we have not repeated this analysis in the present cohort.[5] Because TPTX frequently results in hypoparathyroidism,[38-45] SPTX combined with bilateral transcervical thymectomy is now the preferred procedure in our institution, providing the best balance between cure and postoperative hypoparathyroidism.[5,46]

When taken the high number of CNE into account, we found the number of used imaging modalities in the MEN1 group rather high. A plausible cause might be the unawareness of referring physicians with the possibility of MEN-related pHPT and the inability to localize a solitary gland at first presentation causing more extensive preoperative imaging.

Despite different patient characteristics, MEN2A patients are very similar to patients with spHPT with respect to their operative approach and intraoperative findings. A focused MIP is therefore the treatment of choice for pHPT in MEN2A patients.[47] MIP has low rates of persistent and recurrent pHPT and the complications are minimal. Especially patients treated in more recent years have equal rates of solitary and multiglandular disease.

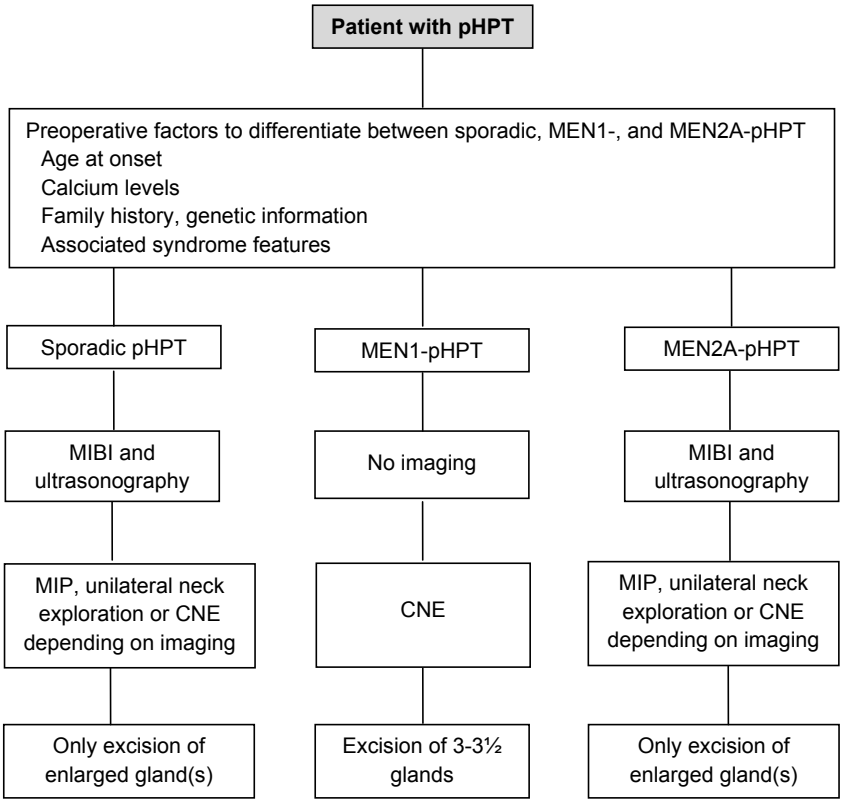
Weaknesses of our study are the fairly large differences in the number of sporadic, MEN1- and MEN2A-related pHPT patients and the time period in which they were treated. Unfortunately, due to the rarity of MEN syndromes these differences are inevitable. Furthermore, treatment of all three categories has gradually changed over the years due to more refined preoperative localization techniques, IOPTH measurement, and the growing awareness and understanding of their differences in pathophysiology and genotype. This implies a heterogeneous case mix. On the other hand, this does reflect the clinical practice over the past decades in many hospitals and countries. A potential confounding factor is the location of treatment. The majority of MEN patients were treated in a tertiary referral center, whereas half of the spHPT patients were treated in an affiliated hospital. However, preoperative imaging and a preferentially minimally invasive approach was the standard of care in all four hospitals.

Many studies have focused on patients with sporadic and MEN-related pHPT separately. The strength of this study is the description of both phenotype, preoperative workup and surgical strategy in all three categories, offering a complete overview and a treatment algorithm.

Conclusion

We performed a descriptive case-control study in which the different outcomes for sporadic, MEN1-related and MEN2A-related pHPT were assessed and possible contributing confounding factors were analyzed. In light of our findings in these three categories of patients; i.e. the significant higher number of multiglandular disease, reoperation rate, and percentage of recurrent disease in MEN1 patients, we advocate the treatment algorithm as outlined in Figure 1. In our opinion, these findings are a corroboration to concentrate and treat MEN patients in a tertiary referral center.

Figure 1. Approach to Preoperative Workup and Surgery for Primary Hyperparathyroidism in Sporadic, MEN1 and MEN2A.



Abbreviations: MEN1, multiple endocrine neoplasia type 1; MEN2A, multiple endocrine neoplasia type 2A; pHPT, primary hyperparathyroidism; MIBI, technetium-99m-sestamibi scintigraphy; MIP, minimally invasive parathyroidectomy; CNE, conventional neck exploration.

References

1. Melton LJ 3rd. Epidemiology of primary hyperparathyroidism. *J Bone Miner Res* 1991; 6(Suppl 2):S25-S30, discussion S31-32.
2. Takami H, Shirahama S, Ikeda Y, et al. Familial hyperparathyroidism. *Biomed Pharmacother* 2000; 54(Suppl 1):21s-24s.
3. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 2001; 86(12):5658-5671.
4. Carty SE, Helm AK, Amico JA, et al. The variable penetrance and spectrum of manifestations of multiple endocrine neoplasia type 1. *Surgery* 1998; 124(6):1106-1113, discussion 1113-1114.
5. Pieterman CR, van Hulsteijn LT, den Heijer M, et al. Primary hyperparathyroidism in MEN1 patients: a cohort study with longterm follow-up on preferred surgical procedure and the relation with genotype. *Ann Surg* 2012; 255(6):1171-1178.
6. Lips CJ, Landsvater RM, Hoppener JW, et al. Clinical screening as compared with DNA analysis in families with multiple endocrine neoplasia type 2A. *N Engl J Med* 1994; 331(13):828-835.
7. Marx SJ, Simonds WF, Agarwal SK, et al. Hyperparathyroidism in hereditary syndromes: special expressions and special managements. *J Bone Miner Res* 2002; 17(Suppl 2):N37-N43.
8. Lourenco DM Jr, Coutinho FL, Toledo RA, Montenegro FL, Correia-Deur JE, Toledo SP. Early-onset, progressive, frequent, extensive, and severe bone mineral and renal complications in multiple endocrine neoplasia type 1-associated primary hyperparathyroidism. *J Bone Miner Res* 2010; 25(11):2382-2391.
9. Eller-Vainicher C, Chiodini I, Battista C, et al. Sporadic and MEN1-related primary hyperparathyroidism: differences in clinical expression and severity. *J Bone Miner Res* 2009; 24(8):1404-1410.
10. Katai M, Sakurai A, Ikeo Y, Hashizume K. Primary hyperparathyroidism in patients with multiple endocrine neoplasia type 1: comparison with sporadic parathyroid adenomas. *Horm Metab Res* 2001; 33(8):499-503.
11. Sato M, Miyauchi A, Takahara J. Clinical aspects of hyperparathyroidism in Japanese multiple endocrine neoplasia type 1. *Biomed Pharmacother* 2000; 54(Suppl 1):86s-89s.
12. Bilezikian JP, Silverberg SJ. Normocalcemic primary hyperparathyroidism. *Arq Bras Endocrinol Metabol* 2010; 54(2):106-109.
13. Gardin JP, Paillard M. Normocalcemic primary hyperparathyroidism: resistance to PTH effect on tubular reabsorption of calcium. *Miner Electrolyte Metab* 1984; 10(5):301-308.
14. Maruani G, Hertig A, Paillard M, Houillier P. Normocalcemic primary hyperparathyroidism: evidence for a generalized target-tissue resistance to parathyroid hormone. *J Clin Endocrinol Metab* 2003; 88(10):4641-4648.
15. de Laat JM, Tham E, Pieterman CR, et al. Predicting the risk of multiple endocrine neoplasia type 1 for patients with commonly occurring endocrine tumors. *Eur J Endocrinol* 2012; 167(2):181–187.
16. Smit PC, Borel Rinkes IHM, van Dalen A, van Vroonhoven TJ. Direct, minimally invasive adenomectomy for primary hyperparathyroidism: An alternative to conventional neck exploration? *Ann Surg* 2000; 231(4):559-565.
17. Barczynski M, Konturek A, Hubalewska-Dydejczyk A, Cichon S, Nowak W. Evaluation of Halle, Miami, Rome, and Vienna intraoperative iPTH assay criteria in guiding minimally invasive parathyroidectomy. *Langenbecks Arch Surg* 2009; 394(4):843-849.

18. Carneiro DM, Solorzano CC, Nader MC, Ramirez M, Irvin GL 3rd. Comparison of intraoperative iPTH assay (QPTH) criteria in guiding parathyroidectomy: which criterion is the most accurate? *Surgery* 2003; 134(6):973-979, discussion 979-981.
19. Lamers CB, Froeling PG. Clinical significance of hyperparathyroidism in familial multiple endocrine adenomatosis type I (MEA I). *Am J Med* 1979; 66(3):422-424.
20. Genc H, Morita E, Perrier ND, et al. Differing histologic findings after bilateral and focused parathyroidectomy. *J Am Coll Surg* 2003; 196(4):535-540.
21. Lee NC, Norton JA. Multiple-gland disease in primary hyperparathyroidism: a function of operative approach? *Arch Surg* 2002; 137(8):896-869, discussion 899-900.
22. Twigt BA, Vollebregt AM, van Dalen T, et al. Shifting incidence of solitary adenomas in the era of minimally invasive parathyroidectomy. A multi-institutional study. *Ann Surg Oncol* 2011; 18(4):1041-2046.
23. Gil-Cardenas A, Gamino R, Reza A, Pantoja JP, Herrera MF. Is intraoperative parathyroid hormone assay mandatory for the success of targeted parathyroidectomy? *J Am Coll Surg* 2007; 204(2):286-290.
24. Jacobson SR, van Heerden JA, Farley DR, et al. Focused cervical exploration for primary hyperparathyroidism without intraoperative parathyroid hormone monitoring or use of the gamma probe. *World J Surg* 2004; 28(11):1127-1131.
25. Mihai R, Palazzo FF, Gleeson FV, Sadler GP. Minimally invasive parathyroidectomy without intraoperative parathyroid hormone monitoring in patients with primary hyperparathyroidism. *Br J Surg* 2007; 94(1):42-47.
26. Ollila DW, Caudle AS, Cance WG, et al. Successful minimally invasive parathyroidectomy for primary hyperparathyroidism without using intraoperative parathyroid hormone assays. *Am J Surg* 2006; 191(1):52-56.
27. Pang T, Stalberg P, Sidhu S, et al. Minimally invasive parathyroidectomy using the lateral focused mini-incision technique without intraoperative parathyroid hormone monitoring. *Br J Surg* 2007; 94(3):315-319.
28. Stalberg P, Sidhu S, Sywak M, Robinson B, Wilkinson M, Delbridge L. Intraoperative parathyroid hormone measurement during minimally invasive parathyroidectomy: does it "value-add" to decision-making? *J Am Coll Surg* 2006; 203(1):1-6.
29. Twigt BA, van Dalen T, Vollebregt AM, Kortlandt W, Vriens MR, Borel Rinkes IHM. The additional value of intraoperative parathyroid hormone assessment is marginal in patients with nonfamilial primary hyperparathyroidism: a prospective cohort study. *Am J Surg* 2012; 204(1):1-6.
30. Chen H, Pruhs Z, Starling JR, Mack E. Intraoperative parathyroid hormone testing improves cure rates in patients undergoing minimally invasive parathyroidectomy. *Surgery* 2005; 138(4):583-587, discussion 587-590.
31. Inabnet WB 3rd, Dakin GF, Haber RS, Rubino F, Diamond EJ, Gagner M. Targeted parathyroidectomy in the era of intraoperative parathormone monitoring. *World J Surg* 2002; 26(8):921-925.
32. Irvin GL 3rd, Solorzano CC, Carneiro DM. Quick intraoperative parathyroid hormone assay: surgical adjunct to allow limited parathyroidectomy, improve success rate, and predict outcome. *World J Surg* 2004; 28(12):1287-1292.
33. Barczynski M, Konturek A, Cichon S, Hubalewska-Dydejczyk A, Golkowski F, Huszno B. Intraoperative parathyroid hormone assay improves outcomes of minimally invasive parathyroidectomy mainly in patients with a presumed solitary parathyroid adenoma and missing concordance of preoperative imaging. *Clin Endocrinol (Oxf)* 2007; 66(6):878-885.

34. Bergson EJ, Sznyter LA, Dubner S, Palestro CJ, Heller KS. Sestamibi scans and intraoperative parathyroid hormone measurement in the treatment of primary hyperparathyroidism. *Arch Otolaryngol Head Neck Surg* 2004; 130(1):87-91.
35. Irvin GL 3rd, Molinari AS, Figueroa C, Carneiro DM. Improved success rate in reoperative parathyroidectomy with intraoperative PTH assay. *Ann Surg* 1999; 229(6):874-878.
36. Burgess JR, David R, Parameswaran V, Greenaway TM, Shepherd JJ. The outcome of subtotal parathyroidectomy for the treatment of hyperparathyroidism in multiple endocrine neoplasia type 1. *Arch Surg* 1998; 133(2):126-129.
37. Malone JP, Srivastava A, Khardori R. Hyperparathyroidism and multiple endocrine neoplasia. *Otolaryngol Clin North Am* 2004; 37(4):715-736.
38. Tonelli F, Marcucci T, Fratini G, Tommasi MS, Falchetti A, Brandi ML. Is total parathyroidectomy the treatment of choice for hyperparathyroidism in multiple endocrine neoplasia type 1? *Ann Surg* 2007; 246(6):1075-1082.
39. Elaraj DM, Skarulis MC, Libutti SK, et al. Results of initial operation for hyperparathyroidism in patients with multiple endocrine neoplasia type 1. *Surgery* 2003; 134(6):858-864, discussion 879-9.
40. Hellman P, Skogseid B, Juhlin C, Akerstrom G, Rastad J. Findings and long-term results of parathyroid surgery in multiple endocrine neoplasia type 1. *World J Surg* 1992; 16(4):718-722, discussion 722-723.
41. Hellman P, Skogseid B, Oberg K, Juhlin C, Akerstrom G, Rastad J. Primary and reoperative parathyroid operations in hyperparathyroidism of multiple endocrine neoplasia type 1. *Surgery* 1998; 124(6):993-999.
42. Hubbard JG, Sebag F, Maweja S, Henry JF. Subtotal parathyroidectomy as an adequate treatment for primary hyperparathyroidism in multiple endocrine neoplasia type 1. *Arch Surg* 2006; 141(8):235-239.
43. Lambert LA, Shapiro SE, Lee JE, et al. Surgical treatment of hyperparathyroidism in patients with multiple endocrine neoplasia type 1. *Arch Surg* 2005; 140(4):374-382.
44. Lee CH, Tseng LM, Chen JY, Hsiao HY, Yang AH. Primary hyperparathyroidism in multiple endocrine neoplasia type 1: individualized management with low recurrence rates. *Ann Surg Oncol* 2006; 13(1):103-109.
45. Malmaeus J, Benson L, Johansson H et al. Parathyroid surgery in the multiple endocrine neoplasia type I syndrome: choice of surgical procedure. *World J Surg* 1986; 10(4):668-672.
46. Schreinemakers JM, Pieterman CR, Scholten A, Vriens MR, Valk GD, Rinkes IH. The optimal surgical treatment for primary hyperparathyroidism in MEN1 patients: a systematic review. *World J Surg* 2011; 35(9):1993-2005.
47. Scholten A, Schreinemakers JM, Pieterman CR, Valk GD, Vriens MR, Borel Rinkes IHM. Evolution of surgical treatment of primary hyperparathyroidism in patients with multiple endocrine neoplasia type 2A. *Endocr Pract* 2011; 17(1):7-15.

Chapter 5

The Impact of Race on Intraoperative Parathyroid Hormone Kinetics,

An Analysis of 910 Patients Undergoing Parathyroidectomy for Primary Hyperparathyroidism

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Abstract

Background Prior studies suggest that African American patients with primary hyperparathyroidism (pHPT) present with more severe biochemical and symptomatic disease than non-African American patients. However, the impact of race on intraoperative parathyroid hormone (IOPTH) measurements has not been determined.

Hypothesis African American patients exhibit different IOPTH profiles than non-African Americans.

Design Retrospective review.

Setting University medical center.

Patients Nine-hundred-ten patients who underwent parathyroidectomy for pHPT between July 2005 and August 2010.

Interventions All patients underwent preoperative imaging with ultrasonography and sestamibi; operative exploration; and IOPTH measurement at two points preexcision and 5 and 10 minutes postexcision.

Main Outcome Measures Preexcision and postexcision IOPTH measurements.

Results Of the 910 patients, 734 (81%) self-reported their race as white, 91 (10%) reported Latino/other, 56 (6%) reported Asian, and 28 (3%) reported African American. African American patients had significantly higher initial preexcision IOPTH levels compared with white patients (348 versus 203 pg/mL, $P = 0.048$), and significantly higher 5-minute postexcision IOPTH levels (151 versus 80 pg/mL, $P = 0.01$). The 10-minute postexcision IOPTH levels were similar between the two groups (52 versus 50 pg/mL, $P = 0.85$). A similar percentage of white and African American patients had a 50% drop in IOPTH at 10 minutes postexcision. No differences in IOPTH kinetics were observed in the other racial groups examined.

Conclusion African American patients with pHPT exhibit significantly higher preincision and 5-minute postexcision IOPTH values compared with white patients. The 10-minute postexcision IOPTH values did not differ between races. The altered IOPTH kinetics identified in African American patients may reflect the severity of biochemical disease, but may also be related to genetically predetermined differences in parathyroid hormone metabolism.

Introduction

Primary hyperparathyroidism (pHPT) is a common disease affecting approximately one in every 500 women and one in every 2000 men older than 40 years.[1] Several prior studies have investigated the impact of ethnicity and geography on the clinical presentation of pHPT.[2-5] In 2000, Bilezikian et al[3] investigated the presentation of pHPT among women in China. They found that Chinese women presented at a younger age than their American counterparts and manifested more severe biochemical and clinical disease, including more advanced bone disease. In 2001, Mishra et al[4] published similar findings regarding the presentation of young patients with pHPT in India. Few studies, however, have investigated pHPT in African American patients, and to our knowledge, there are no existing data regarding the impact of African American race on intraoperative parathyroid hormone (IOPTH) kinetics. The studies that do exist, suggest that African American patients present with more advanced disease with regard to laboratory and pathologic findings.[2,4] The investigators cite race-related disparities in health care[6,7] and intrinsic biochemical differences[8] as potential causative factors. However, available data are limited, and, to our knowledge, there are no population-based studies to describe clinical presentation, outcomes, or even incidence of pHPT among African American individuals.

A separate and more comprehensive body of literature describes metabolic and endocrine differences between African American and non-African American individuals with regard to calcium metabolism and bone turnover.[8-11] These studies focus on differences in renal calcium absorption, bone density and skeletal sensitivity to parathyroid hormone (PTH).[12] They do not typically include patients with pHPT. Based on our awareness of these data, we hypothesized that race would impact IOPTH kinetics and might affect the optimal interpretation of IOPTH values.

Materials and Methods

Creation of Database

A retrospective database was created with approval of the University of California, San Francisco Institutional Review Board, including all patients who underwent parathyroidectomy for pHPT by one of four endocrine surgeons at the University of California, San Francisco between July 2005 and August 2010. Diagnosis of pHPT was based on an inappropriately elevated PTH level in a patient with hypercalcemia and a normal serum creatinine level.

Patient characteristics collected included age, sex, race, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), family history of pHPT, and history of nephrolithiasis or osteoporosis. Classification of race was based on the patient's self-identification at the time of initial clinic visit. Laboratory data included serum calcium level, ionized calcium level, 24-hour urine calcium excretion, intact PTH level, 25-hydroxyvitamin D level, alkaline phosphatase level, and creatinine level. Details of the preoperative evaluation were collected, including results of ultrasonography and sestamibi scan and concordance (or lack thereof) of preoperative study results. Intraoperative and postoperative variables

examined included IOPTH level, focused versus bilateral exploration, findings of single or double adenoma versus four-gland hyperplasia, postoperative calcium level, and presence of persistent or recurrent disease.

Protocol for Intraoperative Parathyroid Hormone Measurement

During parathyroidectomy, PTH level was measured at four points. The first time was following induction of anesthesia but before incision. The second was preexcision, typically upon identification of an abnormal-appearing gland. Times three and four were at 5 and 10 minutes postexcision, respectively. The Siemens ADVIA Centaur immunoassay was used, with the assay performed outside of the operating room within 10 minutes of the blood draw. The Miami criteria, which stipulate that IOPTH must fall by 50% from highest preexcision value at 10 minutes postexcision, was used to assess adequacy of resection.[13]

Reference Values

Reference ranges for key values at our institution include serum calcium, 8.8 to 10.3 mg/dL (to convert to milllimoles per liter, multiple by 0.25); 24-urine calcium, 50 to 300 mg per 24 hour; intact PTH, 12 to 65 pg/mL (to convert to nanograms per liter, multiple by 1); alkaline phosphatase, 42 to 141 U/L (to convert to microkatels per liter, multiply by 0.0167); creatinine, 0.5 to 1.3 mg/dL (to convert to micromoles per liter, multiply by 88.4); and 25-hydroxyvitamin D, 30 to 100 ng/mL (to convert to nanomoles per liter, multiply by 2.496).

Statistical Analysis

Comparison of binary variables was by χ^2 test. Comparison of continuous variables was by *t* test. Descriptive statistics were calculated for all variables. Simple linear regression was used to evaluate correlation between two continuous variables. A multivariate analysis including IOPTH as dependent variable and age, sex, race, and BMI as independent variables was performed using JMP 9 (SAS, Inc., Cary, NC).

Results

Of the 910 patients who underwent surgery for pHPT between July 2005 and August 2010, 734 (81%) self-reported their race as white, 91 (10%) reported Latino/other, 56 (6%) reported Asian, and 28 (3%) reported African American.

Compared with white patients, African American patients presented with a significantly higher serum calcium level (11.4 versus 10.9 mg/dL, $P < 0.001$), but lower mean 24-hour urine calcium level (192 versus 336 mg per 24 hour, $P = 0.007$). African American and white patients did not differ significantly in mean level of 25-hydroxyvitamin D (24.8 versus 30.5 pg/mL, $P = 0.28$); however, the percentage of African American patients presenting with vitamin D deficiency (defined as 25-hydroxyvitamin D level < 20 ng/mL) was significantly higher (56% versus 26%, $P = 0.02$). African American patients also showed a trend towards higher BMI (30.6 versus 27.6, $P = 0.06$).

Fewer African American patients than white patients carried a diagnosis of osteoporosis (4% versus 19%, *P* = 0.03); however, fewer African American patients had undergone formal preoperative bone density testing. Seven percent of African American and 18% of white patients (*P* = 0.20) had a history of nephrolithiasis. There was no significant difference between the two groups in age, sex, serum alkaline phosphatase level, or serum creatinine level. Comparison of preoperative patient characteristics is summarized in Table 1. Although there was no significant difference between rate of either abnormal sestamibi scan or ultrasonography between races, African American patients were significantly more likely to have concordant preoperative studies (Table 2).

During surgery, African American patients had higher initial IOPTH measurements than white patients (348 versus 202 pg/mL, *P* = 0.048). Measurements at 5 minutes postexcision were also higher (151 versus 80 pg/mL, *P* = 0.01); however, IOPTH level at 10 minutes postexcision was nearly identical between the two groups (52 versus 50 pg/mL, *P* = 0.85). No significant differences in IOPTH kinetics were observed among the other races examined (Table 3). Rates of multiglandular disease were similar between African American and white patients (11% versus 13%, *P* = 0.97). A similar percentage of white and African American patients had a 50% drop in IOPTH level during surgery.

Table 1. Characteristics of Primary Hyperparathyroidism in African American versus White Patients

Characteristics	Patients		*P* Value
	African American, *n* = 28	White, *n* = 734	
Patient characteristics			
Female, n	24 (86%)	535 (73%)	0.21
Age, yr, mean	61.5	61.0	0.84
Body mass index, kg/m^2, mean	30.6	27.6	0.06
Body mass index > 30, n	12 (43%)	220 (30%)	0.11
Symptoms and diagnostic characteristics			
Nephrolithiasis, n	2 (7%)	132 (18%)	0.20
Osteoporosis, n	1 (4%)	139 (19%)	0.03
Vitamin D deficiency (< 20 ng/mL), n	16 (57%)	191 (26%)	0.02
Initial serum calcium level, mg/dL, mean	11.4	10.9	<0.001
24-urine calcium level, mg, mean	192	336	0.007
Parathyroid hormone level (outpatient), pg/mL, mean	157	124	0.08
25-hydroxyvitamin D level, ng/mL, mean	24.8	30.5	0.28
Alkaline phosphatase level, U/L, mean	87.8	92.6	0.80
Creatinine level, mg/dL, mean	1.02	0.97	0.70

Body mass index is calculated as weight in kilograms divided by height in meters squared.

SI conversion factor: To convert serum calcium level to millimoles per liter, multiply by 0.25; parathyroid hormone level to nanograms per liter, multiply by 1; 25-hydroxyvitamin D level to nanomoles per liter, multiply by 2.496; alkaline phosphatase level to microkatals per liter, multiply by 0.0167; and creatinine level to micromoles per liter, multiply by 88.4.

Table 2. Preoperative Imaging Studies of African American versus White Patients Undergoing Surgery for Primary Hyperparathyroidism

Characteristics	Patients		*P* Value
	African American, *n* = 28	White, *n* = 734	
Abnormal ultrasonography, n	25 (89%)	579 (79%)	0.24
Abnormal sestamibi scan, n	27 (96%)	667 (91%)	0.50
Concordant study results, n	24 (86%)	545 (62%)	0.01

However, 11% of African American patients versus 4% of white patients went on to have persistent disease despite a 50% drop in IOPTH level (not significant). In contrast, when criteria were expanded to also require a drop of IOPTH into the normal range, none of the African American patients had persistent disease. Comparison of intraoperative and postoperative variables by race is summarized in Table 3. Simple linear regression was used to evaluate correlation between initial IOPTH measurement and individual continuous variables that might account for racial differences. Variables evaluated in this manner include age, BMI, serum creatinine level, and 25-hydroxyvitamin D level (data not shown). Of these variables, only BMI reached significance (P = 0.005). Graphs of IOPTH curves by race and BMI are shown in Figure 1.

A multivariate analysis was then performed evaluating the association between age, sex, race, and BMI and initial IOPTH measurement. In this analysis, BMI remained a significant predictor (P = 0.006), while African American race did not quite reach significance (P = 0.08). This suggests that differences in BMI explain at least part of the racial difference seen in our initial comparison of means.

Discussion

To our knowledge, only two previous studies have investigated differences between African American and non-African American patients undergoing parathyroidectomy for pHPT.[2,4] In 2004, Barker et al[2] conducted a case-control comparison of 36 African American and 36 white patients with pHPT. The authors reported that preoperative serum calcium was equivalent for the two groups, but that African American patients had a higher preoperative intact PTH level. African American and white patients had equivalent rates of “objective symptoms” including osteoporosis, nephrolithiasis, pancreatitis, and mental status changes, leading Barker et al to conclude that the PTH level differences might be clinically insignificant and attributable to biochemical racial differences such as decreased skeletal sensitivity to PTH.[2] Subsequently, in 2008, Kandil et al[4] evaluated the clinical presentation of 113 African American and 475 non-African American patients with pHPT. African American patients had significantly higher serum calcium and PTH levels at presentation, as well as higher parathyroid adenoma weight on pathologic analysis. Kandil et al identified vitamin D deficiency and increased BMI as potential contributors. However, they concluded that African American patients presented with more severe disease, and that late

presentation due to disparities in access to health care should be considered a likely explanation. More recently, Jabiev et al[12] reported higher serum calcium and PTH levels at presentation among underinsured and uninsured patients with pHPT, although they did not evaluate the potential contribution of race to these trends.

Our data confirm higher serum calcium and higher initial IOPTH levels in African American patients. However, we, like Barker et al,[2] did not observe higher rates of either osteoporosis or nephrolithiasis, raising the issue of whether African American patients truly present with more severe disease. Current guidelines for patient selection for parathyroidectomy rely heavily on presence of clinical manifestations of the disease, so it is not clear that African American patients in this study had a delay in operative intervention.[14] However, our data are potentially biased by the lower index of suspicion for osteoporosis among clinicians evaluating African American patients, as these patients had lower rates of bone density testing. We can only truly conclude that African American patients have lower rates of hyperparathyroidism-related renal disease. Further investigation will be needed to clarify whether they have lower rates of hyperparathyroidism-related osteoporosis as well. Other important limitations of our data include the absence of information on insurance status or preoperative neuropsychological symptoms.

The finding of decreased 24-hour urine calcium excretion was unexpected and raised concern for familial hypocalciuric hypercalcemia. However, on review of the available data, this finding in African American individuals has previously been described.[15-17] Very recently, Taha et al[17] reported that a low urine calcium is frequently seen in African American patients with pHPT, even in the setting of significant hypercalcemia. Racial differences in renal calcium resorption provide one possible explanation. Race-associated polymorphisms in the calcium sensing receptor may offer a clue to the underlying etiology.[10] Among the African American patients in our database, six (21%) had urine calcium less than 200 mg per 24 hour. However, all six patients had durable resolution of hypercalcemia with parathyroidectomy, in five cases after single-gland excision.

To our knowledge, this is the first report demonstrating a difference in IOPTH kinetics between African American and white patients with pHPT. We found that African American patients undergoing surgery for pHPT had elevated levels of initial IOPTH and IOPTH at 5 minutes postexcision but an equivalent level of IOPTH at 10 minutes postexcision. However, a similar percentage of African American and white patients had an adequate drop in IOPTH level by the Miami criteria. We did observe a trend towards a higher rate of persistent disease among African American patients when Miami criteria alone were applied (11% versus 4%), although this did not reach significance. This effect was abrogated when IOPTH level was required to drop into the normal range. It seems plausible that given the higher starting IOPTH level among African American patients, a drop of more than 50% should be expected. However, additional studies with larger numbers of patients will be necessary to determine whether this is the case, and if so, what percentage drop should be required.

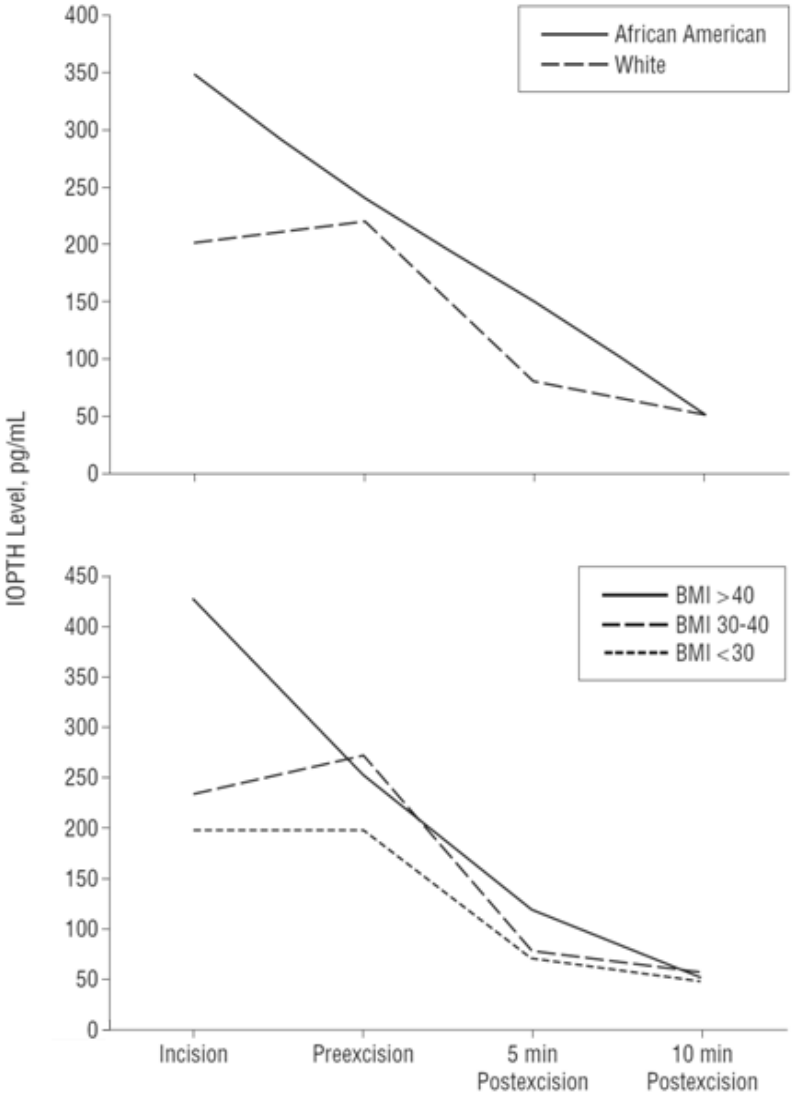
Table 3. Intraoperative and Postoperative Parathyroid Hormone Measures, by Race, for Patients Undergoing Surgery for Primary Hyperparathyroidism

Characteristics	White Patients, *n* = 734	African American Patients, *n* = 28	*P* Value[a]	Asian Patients, *n* = 56	*P* Value[a]	Latino/Other Patients, *n* = 91	*P* Value[a]
Intraoperative parathyroid hormone level, pg/mL, mean							
Incision	202	348	0.048	254	0.28	272	0.19
Preexcision	220	240	0.87	226	0.94	195	0.76
5 minutes postexcision	80	151	0.01	79	0.96	85	0.82
10 minutes postexcision	50	52	0.85	50	0.99	45	0.49
Multiglandular disease, n	95 (13%)	3 (11%)	0.97	6 (11%)	0.83	12 (13%)	0.99
50% Drop in parathyroid hormone level at 10 minutes, n	683 (93%)	25 (88%)	0.33	54 (96%)	0.76	91 (100%)	0.16
50% Drop in parathyroid hormone level but persistent disease, n	29 (4%)	3 (11%)	0.11	0	0.24	2 (2%)	0.90
50% Drop in parathyroid hormone level and into normal range at 10 min, n	580 (79%)	20 (71%)	0.36	43 (77%)	0.68	71 (78%)	0.83
50% Drop in parathyroid hormone level and into normal range but persistent disease, n	15 (2%)	0	0.99	0	0.99	2 (2%)	0.99

SI conversion factor: To convert parathyroid hormone to nanograms per liter, multiply by 1.

[a] *P* value reflects comparison with white patients.

Figure 1. Intraoperative Parathyroid Hormone Curves, by Race and Body Mass Index, for Patients Undergoing Surgery for Primary Hyperparathyroidism



Abbreviations: IOPTH, intraoperative parathyroid hormone; BMI, body mass index.
BMI is calculated as weight in kilograms divided by height in meters squared.
SI conversion factor: To convert IOPTH level to nanograms per liter, multiply by 1.

Although no previous studies have evaluated the impact of race on IOPTH level, several authors have investigated other patient characteristics that may impact presentation of pHPT and IOPTH kinetics. Untch et al[18] describe a characteristic trend of perioperative PTH levels in patients with vitamin D deficiency. Their vitamin D-deficient patients had an elevated initial IOPTH level but equivalent postexcision values, closely mirroring the pattern of IOPTH level in the African American patients in our study. Similar findings are reported by Adler et al,[19] who emphasize that IOPTH is as predictive of cure in vitamin D-deficient patients as in nondeficient patients.[20] Although we found that African American patients had a higher rate of vitamin D deficiency, vitamin D level did not significantly correlate with initial IOPTH measurement in our linear regression analysis. The study by Adam et al,[20] describing a higher preoperative PTH in obese patients with pHPT, prompted us to consider BMI as a possible contributor to the racial differences we noted. In fact, we found that BMI was not only correlated with higher initial IOPTH level in single-variable linear regression, but remained the only significant predictor in multivariate analysis after controlling for age, sex, and race.

Conclusion

African American patients with pHPT show significant differences in preoperative laboratory values and IOPTH curves compared with white patients. However, these findings do not appear to be associated with more severe clinical manifestations of pHPT. African American race may be associated with lower sensitivity of the Miami Criteria in detection of multiglandular disease during parathyroidectomy. Further investigation is needed to clarify this. Additional investigation is also needed into the contribution of other variables such as vitamin D deficiency and BMI to the racial differences we observed.

References

1. Lal G. Diagnosis of primary hyperparathyroidism and indications for parathyroidectomy. In: Clark OH, Duh QY, Kebebew E (eds). *Textbook of Endocrine Surgery*. Philadelphia, Elsevier Saunders, 2005; 384-392.
2. Barker H, Caldwell L, Lovato J, Woods KF, Perrier ND. Is there a racial difference in presentation of primary hyperparathyroidism? *Am Surg* 2004; 70(6):504-506.
3. Bilezikian JP, Meng X, Shi Y, Silverberg SJ. Primary hyperparathyroidism in women: a tale of two cities - New York and Beijing. *Int J Fertil Womens Med* 2000; 45(2):158-165.
4. Kandil E, Tsal HL, Somervell H, et al. African Americans present with more severe primary hyperparathyroidism than non-African Americans. *Surgery* 2008; 144(6):1023-1026.
5. Mishra SK, Agarwal G, Kar DK, Gupta SK, Mithal A, Rastad J. Unique clinical characteristics of primary hyperparathyroidism in India. *Br J Surg* 2001; 88(5):708-714.
6. Cohen JJ. Disparities in health care: an overview. *Acad Emerg Med* 2003; 10(11):1155-1160.
7. Zuvekas SH, GS Taliaferro. Pathways to access: health insurance, the health care delivery system, and racial/ethnic disparities, 1996-1999. *Health Aff (Millwood)* 2003; 22(2):139-153.
8. Cosman F, Morgan DC, Nieves JW, et al. Resistance to bone resorbing effects of PTH in black women. *J Bone Miner Res* 1997; 12(6):958-966.
9. Bell NH, Greene A, Epstein S, Oexmann MJ, Shaw S, Shary J. Evidence for alteration of the vitamin D-endocrine system in blacks. *J Clin Invest* 1985; 76(2):470-473.
10. Jung J, Foroud TM, Eckert GJ, et al. Association of the calcium-sensing receptor gene with blood pressure and urinary calcium in African-Americans. *J Clin Endocrinol Metab* 2009; 94(3):1042-1048.
11. Perry HM 3rd, Horowitz M, Morley JE, et al. Aging and bone metabolism in African American and Caucasian women. *J Clin Endocrinol Metab* 1996; 81(3):1108-1117.
12. Jabiev AA, Lew JI, Garb JL, Sanchez YM, Solorzano CC. Primary hyperparathyroidism in the underinsured: A study of 493 patients. *Surgery* 2012; 151(3):471-476.
13. Molinari AS, Irvin GL 3rd, Deriso GT, Bott L. Incidence of multiglandular disease in primary hyperparathyroidism determined by parathyroid hormone secretion. *Surgery* 1996; 120(6): 934-936.
14. Bilezikian JP, Khan AA, Potts JT Jr. Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. *J Clin Endocrinol Metab* 2009; 94(2):335-339.
15. Bell NH, Williamson BT, Hollis BW, Riggs BL. Effects of race on diurnal patterns of renal conservation of calcium and bone resorption in premenopausal women. *Osteoporos Int* 2001; 12(1):43-48.
16. Bell NH, Yergey AL, Vieira NE, Oexmann MJ, Shary JR. Demonstration of a difference in urinary calcium, not calcium absorption, in black and white adolescents. *J Bone Miner Res* 1993; 8(9):1111-1115.
17. Taha W, Singh N, Flack JM, Abou-Samra AB. Low urine calcium excretion in african american patients with primary hyperparathyroidism. *Endocr Pract* 2011; 17(6):867-872.
18. Untch BR, Barfield, Dar M, Dixit D, Leight GS Jr, Olson JA Jr. Impact of 25-hydroxyvitamin D deficiency on perioperative parathyroid hormone kinetics and results in patients with primary hyperparathyroidism. *Surgery* 2007; 142(6):1022-1026.

19. Adler JT, RS Sippel, Chen H. 25-hydroxyvitamin D status does not affect intraoperative parathyroid hormone dynamics in patients with primary hyperparathyroidism. *Ann Surg Oncol* 2010; 17(11): 2958-2962.
20. Adam MA, Untch BR, Danko ME, et al. Severe obesity is associated with symptomatic presentation, higher parathyroid hormone levels, and increased gland weight in primary hyperparathyroidism. *J Clin Endocrinol Metab* 2010; 95(11):4917-4924.

Part 2

Adrenal Glands

Chapter 6

Tumor Size is the Most Significant Predictor of Short-Term Surgical Outcome: Analysis of 523 Patients Undergoing Laparoscopic Adrenalectomy

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Abstract

Objective To evaluate the effect of tumor size and diagnosis on the surgical outcome of laparoscopic adrenalectomy.

Background There is much debate in literature regarding the effect of tumor size and diagnosis on the short-term outcome of adrenal surgery.

Methods We retrospectively reviewed the records of 523 consecutive patients who underwent 563 laparoscopic adrenalectomies performed at the University of California, San Francisco, by one surgeon between April 1993 and October 2011. Outcomes measured included operation time, conversion rate, estimated blood loss, rate of intraoperative and postoperative complications (including transfusion and mortality), and duration of postoperative hospital stay. We conducted a multivariate analysis including patient characteristics, diagnosis, and tumor size to determine factors influencing surgical outcome.

Results There were 218 right, 265 left, and 40 bilateral adrenalectomies. Multivariate analysis showed tumor size (≥ 3 cm versus < 3 cm) to have a significant independent effect on surgical outcome ($P < 0.0001$). In addition, multivariate analysis showed patients with adrenal metastasis, hypercortisolism and pheochromocytoma to have significantly more blood loss than patients with aldosteronoma ($P < 0.001$, $P = 0.014$, and $P = 0.013$, respectively), while operation time for patients with pheochromocytoma and adrenal metastasis was longer ($P = 0.001$).

Conclusion Although short-term operative outcome is influenced by disease process (patients with pheochromocytoma, hypercortisolism and adrenal metastasis fared slightly worse than patients with aldosteronoma), multivariate analysis demonstrates that tumor size is the strongest independent predictor of outcome of laparoscopic adrenalectomy.

Introduction

Laparoscopic adrenalectomy has evolved to become the procedure of choice for most surgical adrenal diseases.[1-3] Indications for laparoscopic adrenalectomy include various endocrine pathologies, such as aldosteronoma, pheochromocytoma, Cushing's syndrome, and nonfunctional adenoma, along with less common conditions such as myelolipoma or cysts.[4] Recently, laparoscopic surgery has gained acceptance as treatment for adrenal metastasis and adrenocortical cancer confined to the adrenal gland.[5,6]

Adrenalectomy is associated with complication rates ranging from 3.6% to 20%[7,8] and mortality is generally low (less than 1.5%).[9] Adrenalectomy outcomes have been explored with respect to the patient's sex[10,11] and body mass index (BMI),[11,12] tumor size[10,13-24] and side,[10] hormone production,[25-29] and surgeon characteristics.[32-33]

There is still much debate in literature regarding the suitable tumor size for laparoscopic adrenal surgery and whether tumor size affects surgical morbidity. Some believe a larger tumor size leads to a longer operation time,[10,13-16] a higher conversion rate,[14,17,18] more blood loss,[13,14,16,19] and a longer postoperative hospital stay.[13]

On the other hand, there are studies that suggest that laparoscopy can also be used for larger adrenal masses, because the large masses in their series seemed to have a similar operation time,[19-24] rate of conversion[16,19,20,24] and complications,[13,14,16,19,20] estimated blood loss,[15,19,23] and duration of postoperative hospital stay[15,16,19,23,24] in comparison with the smaller masses.

Most of these conflicting studies include a relatively small number of patients or disregard adrenal disease diagnosis as a potential confounder. Most studies agree that patients with aldosteronoma can be operated on in a relatively safe and uncomplicated manner. However, it has been shown that a diagnosis of hypercortisolism, pheochromocytoma or adrenal malignancy can influence surgical morbidity in patients undergoing adrenalectomy.

Most studies on pheochromocytomas reported higher surgical morbidity in terms of operation time,[9,10,25-28] rate of conversion,[17] estimated blood loss,[9,25,26,27] complications,[29] and duration of postoperative hospital stay[9,21,25,26,28] in patients with pheochromocytoma compared with patients with other diagnosis. However, Chan et al[21] and Kalady et al[30] found no differences between patients operated for pheochromocytoma and patients with non-pheochromocytoma regarding these outcomes.

Studies reporting on surgical outcome in patients with hypercortisolism, compared patients undergoing total bilateral adrenalectomy for Cushing's syndrome with other groups undergoing unilateral adrenalectomy and found a longer operation time,[25,31] more estimated blood loss,[25,31] more complications,[21] and a longer hospital stay.[21,22,25,31]

Regarding malignant tumors, a longer operation time,[15] a higher conversion rate,[17], and higher surgical mortality[34] compared with nonmalignant adrenal tumors have been reported.

Most of these previous studies included only a small number of patients or did not have statistical analysis, therefore the reported effect of diagnosis on outcome varied widely, and few studies reported how size of tumor influences outcome. We therefore sought to evaluate the impact of both adrenal tumor size and adrenal disease diagnosis on the operative outcomes of laparoscopic adrenalectomy in a large series of adrenalectomies performed by one surgeon.

Materials and Methods

We retrospectively reviewed the records of 523 consecutive patients who underwent 563 laparoscopic adrenalectomies at the University of California, San Francisco and the San Francisco Veterans Affairs Medical Center between April 1993 and October 2011. All patients were operated by one surgeon (QYD).

Indications for adrenal surgery included primary aldosteronism, pheochromocytoma, hypercortisolism, adrenal metastasis, benign nonfunctioning adrenal tumors, virilizing tumors, and adrenal cortical cancer. Patients operated for extra-adrenal tumors were excluded.

Incidentaloma was defined as an adrenal tumor initially discovered by diagnostic imaging for a clinical condition not related to, or suspicious for, adrenal disease. On the basis of their clinical and pathological diagnosis, patients were divided in five diagnosis groups: aldosteronism, hypercortisolism, pheochromocytoma, adrenal metastasis, and others.

Primary aldosteronism was diagnosed by a plasma aldosterone concentration (ng/dL) to plasma renin activity (ng/mL per hour) ratio higher than 20. The diagnosis of pheochromocytoma and adrenal metastasis was confirmed by pathology. Hypercortisolism was diagnosed by an elevated 24-hour urinary cortisol level or an elevated cortisol level higher than 5.0 mg/dL after an overnight 1 mg dexamethasone suppression test. The group of patients with hypercortisolism included those with primary adrenal tumors and clinical or subclinical Cushing's adenoma, hyperplasia, or carcinoma, and those who underwent bilateral adrenalectomy because of failed pituitary operation for Cushing's disease or ectopic adrenocorticotropic hormone production. The group with other diagnose included patients with nonfunctional benign adrenal tumors, virilizing tumors, and adrenocortical cancer. All patients had preoperative imaging, by computed tomography or magnetic resonance imaging.

Preoperative patient variables analyzed included age, sex, pregnancy status, medical and surgical history, BMI, and American Society of Anesthesiologists physical status. Disease related variables included disease presentation, tumor size on imaging, and pathologic diagnosis. Outcomes measured included operation time, conversion rate, estimated blood loss, rate of intra- and postoperative complications (including transfusion and mortality), and duration of postoperative hospital stay. Operation time was calculated as the time between skin incision and skin closure. Surgical mortality was defined as death occurring within 30 days after surgery or during the same hospital stay.

Follow-up information included complications, persistent or recurrent disease, and nonsurgical mortality.

Statistical Analysis

Patients with tumors 3 cm or larger were compared with patients with tumors smaller than 3 cm regarding surgical outcome measurements. This was done for all patients together as a group and for all diagnostic groups separately.

In addition, we conducted a multivariate analysis including patient characteristics (age, sex, BMI, and comorbidity), diagnosis, and tumor size to determine factors influencing surgical outcome. Patients with aldosteronoma were used as baseline group in comparison with other adrenal disease diagnosis.

SAS version 9.1 (SAS Institute, Cary, NC) was used for statistical analysis. Comparison of binary variables was by χ^2 test. Comparison of continuous values was by unpaired *t* test. Descriptive statistics were calculated for all variables. $P < 0.05$ was considered statistically significant.

Results

Between 1993 and 2011, 523 patients underwent 218 right, 265 left and 40 bilateral laparoscopic adrenalectomies for various indications. Patient characteristics, average tumor size, and type of surgery for the total group of patients and by adrenal disease diagnosis are listed in Table 1.

The average tumor size for the total group was 3.5 cm (range 0.4 to 15.0). Patients with pheochromocytoma had the largest tumors (mean of 4.7 cm). Bilateral procedures were performed for patients with hypercortisolism (*n* = 35) and pheochromocytoma (*n* = 5).

Surgical outcomes by tumor size are listed in Table 2. Sufficient information on tumor size was available for 470 patients; patients with normal adrenal glands on imaging were excluded from analysis. All aldosteronomas, except four (*n* = 158) were smaller than 3 cm. Patients with tumors 3 cm or larger (≥ 3 cm) fared worse on all surgical outcomes than patients with tumors smaller than 3 cm.

Blood transfusion was necessary in 11 patients (2%); eight patients with pheochromocytoma, two with adrenal metastases, and one with hypercortisolism. Half of the complications (26 of 49 [53%]) in the pheochromocytoma group were related to hemodynamic difficulties during or after tumor resection.

No patients died during surgery. Two patients died in the postoperative period. One patient with aldosteronoma and renal cell carcinoma underwent a left adrenalectomy and nephrectomy, had an uneventful postoperative stay, was discharged on day six postoperatively and died 13 days after surgery. Another patient was discharged home two days after adrenalectomy and died 14 days later due to metastatic melanoma disease spread to the duodenum. Long-term mortality occurred in 14 patients (aldosteronoma *n* = 4, hypercortisolism *n* = 1, pheochromocytoma *n* = 2, adrenal metastases *n* = 6, and nonfunctioning adenoma *n* = 1).

An outline of the clinicopathological diagnosis is presented in Table 3. There were nine patients with two different tumors in the same adrenal gland (Table 4).

Twenty-three patients (4%) had recurrent or persistent disease after a mean follow-up of 22 months (aldosteronoma *n* = 4, hypercortisolism *n* = 1, pheochromocytoma *n* = 9, metastases *n* = 6, adrenocortical cancer *n* = 1, and adrenal cyst *n* = 1).

Table 1. Characteristics of Patients Undergoing Laparoscopic Adrenalectomy

Characteristics	Total, *n* = 523	Aldosteronism, *n* = 180	Hypercortisolism, *n* = 85	Pheochromocytoma, *n* = 123	Metastasis, *n* = 44	Other, *n* = 91
Patient characteristics						
Age, y, mean	50.7	51.1	46.8	47.9	61.0	52.4
Female, n	275 (53%)	84 (47%)	65 (76%)	63 (51%)	15 (34%)	48 (53%)
Comorbidity						
Hypertension, n	329 (63%)	179 (99%)	31 (36%)	68 (55%)	18 (41%)	33 (36%)
Diabetes mellitus, n	91 (17%)	27 (15%)	21 (25%)	20 (16%)	5 (11%)	18 (20%)
ASA physical status, mean	2.5	2.5	2.5	2.5	2.7	2.4
Prior abdominal surgery, n	162 (31%)	486 (27%)	25 (29%)	38 (31%)	18 (41%)	33 (36%)
Prior (extra-)adrenal surgery, n	15 (3%)	0	0	9 (7%)	6 (14%)	0
Body mass index, mean	29.4	30.6	30.8	26.6	26.8	31.7
Symptoms and diagnostic characteristics						
Incidentaloma, n	153 (29%)	11 (6%)	24 (28%)	51 (41%)	2 (5%)	65 (71%)
Signs and symptoms, n	357 (68%)	176 (98%)	73 (86%)	83 (67%)	3 (7%)	22 (24%)
Tumor size, cm, mean (range)	3.5 (0.4 to 15)	1.7 (0.4 to 4)	3.9 (1.2 to 12)	4.7 (1.2 to 13)	4.0 (1.1 to 12)	4.6 (1.2 to 15)
Treatment						
Preoperative admission, n	20 (4%)	0	8 (9%)	9 (7%)	2 (5%)	1 (1%)
Type of adrenalectomy, n						
Left	265 (51%)	112 (62%)	27 (32%)	52 (42%)	20 (45%)	54 (59%)
Right	218 (41%)	68 (38%)	23 (27%)	66 (54%)	24 (55%)	37 (41%)
Bilateral	40 (8%)	0	35 (41%)	5 (4%)	0	0

Abbreviations: ASA, American Society of Anesthesiologists.
Body mass index calculated as weight in kilograms divided by height in meters squared.

Table 2. Outcome of Laparoscopic Adrenalectomy, by Diagnosis and Tumor Size

Group	Operation Time, hr, mean	Conversion, n	Estimated Blood Loss, mL, mean	Complications, n			Duration of Postoperative Stay, d, mean
				Total	Intraoperative	Postoperative	
Total				112 (24%)			
< 3 cm (*n* = 260)	2.29	1 (0.4%)	44		6 (2%)	36 (14%)	1.6
≥ 3 cm (*n* = 210)	3.07	13 (6%)	97		20 (10%)	50 (24%)	2.5
P value[a]	<0.001	0.001	0.006		0.001	0.003	0.001
Aldosteronism[b]				16 (10%)			
< 3 cm (*n* = 158)	2.25	0	25		2 (1%)	14 (9%)	1.6
Hypercortisolism				7 (13%)			
< 3 cm (*n* = 25)	1.88	0	14		0	3 (12%)	1.2
≥ 3 cm (*n* = 31)	2.92	0	48		1 (3%)	3 (10%)	2.8
P value[a]	0.020		0.035		0.365	0.780	0.004
Pheochromocytoma				49 (40%)			
< 3 cm (*n* = 30)	2.56	1 (3%)	113		3 (10%)	7 (23%)	1.4
≥ 3 cm (*n* = 93)	3.20	7 (8%)	129		12 (13%)	27 (29%)	2.5
P value[a]	0.006	0.540	0.884		0.919	0.710	0.001
Metastasis				18 (41%)			
< 3 cm (*n* = 21)	2.67	0	64		0	6 (29%)	2.0
≥ 3 cm (*n* = 23)	3.30	3 (13%)	173		4 (17%)	8 (35%)	4.1
P value[a]	0.051	0.265	0.085		0.021	0.910	0.072
Other				21 (24%)			
< 3 cm (*n* = 25)	2.35	0	89		1 (4%)	6 (24%)	1.6
≥ 3 cm (*n* = 64)	2.88	3 (5%)	46		3 (5%)	12 (18%)	1.6
P value[a]	0.011	0.042	0.282		0.888	0.794	0.380

[a] *P* value reflects < 3 cm versus ≥ 3 cm per group.

[b] Only patients with primary aldosteronism and tumors smaller than 3 cm were included in analyses.

Multivariate Analysis

Multivariate analysis showed tumor size to have a significant independent effect on all measures of surgical outcome (operation time $P < 0.0001$, conversion $P < 0.0001$, estimated blood loss $P < 0.0001$, intraoperative complications $P < 0.0001$, postoperative complications $P = 0.009$, and duration of postoperative hospital stay $P < 0.001$), except surgical mortality ($P = 0.736$). In addition, multivariate analysis showed patients with adrenal metastasis, hypercortisolism, and pheochromocytoma to have significantly more blood loss than patients with aldosteronoma ($P = 0.0004$, $P = 0.01$ and $P = 0.01$, respectively), while operation time for patients with pheochromocytoma was longer than that for patients with aldosteronoma ($P = 0.001$). Patients with adrenal metastasis had a longer duration of postoperative hospital stay compared with patients with aldosteronoma ($P = 0.02$).

Table 3. Clinicopathological Diagnosis

Group	Clinicopathological Diagnosis
Aldosteronism (*n* = 180)	130 adenoma, 30 hyperplasia, 20 adenoma or hyperplasia
Hypercortisolism (*n* = 85)	41 adenoma, 9 hyperplasia, 1 carcinoma, 12 ectopic adrenocorticotropic hormone production, 22 pituitary
Pheochromocytoma (*n* = 123)	97 sporadic (3 malignant) 26 familial 11 multiple endocrine neoplasia type 2A, 1 multiple endocrine neoplasia type 2B, 2 von Hippel-Lindau syndrome, 3 neurofibromatosis, 2 mutation in succinate dehydrogenase subunit B, 1 mutation in succinate dehydrogenase subunit D, 6 familial
Metastasis (*n* = 44)	17 lung, 7 melanoma, 7 renal, 5 gastrointestinal, 8 other (leiomyosarcoma, hepatocellular, breast, thyroid, endometrium, unknown)
Other (*n* = 91)	3 adrenal hemorrhage, 2 angiomyelolipoma, 15 cyst (8 pseudocyst, 4 endothelial, 1 epithelial, 2 not classified or simple), 1 cortical cancer, 3 ganglioneuroma, 5 myelolipoma, 1 neurofibroma, 2 Schwannoma, 3 virilizing tumors (2 adenoma, 1 hyperplasia), 51 nonfunctioning tumors (39 adenoma, 5 hyperplasia, 7 adenoma or hyperplasia), 5 normal adrenal tissue

Table 4. Clinicopathological Diagnosis – Multiple Diagnosis

Primary Diagnosis	Concomitant Diagnosis
Pheochromocytoma (*n* = 2)	1 aldosteronism (adenoma), 1 nonfunctioning adenoma,
Metastasis (*n* = 2)	1 hemorrhagic cyst, 1 pheochromocytoma
Hypercortisolism (carcinoma)	Myelolipoma
Hypercortisolism (hyperplasia)	Neuroendocrine tumor
Pseudocyst	Nonfunctioning hyperplasia
Myelolipoma	Nonfunctioning adenoma
Nonfunctioning adenoma	Ganglion

Discussion

Laparoscopic adrenalectomy is the procedure of choice for most surgical adrenal diseases. There is still much debate in literature regarding the effect of tumor size and diagnosis on the short-term outcomes of adrenal surgery. Therefore, we sought to evaluate the impact of both adrenal tumor size and adrenal disease diagnosis on the operative outcome of laparoscopic adrenalectomy in a large series of consecutive patients. Results from our study indicate that tumor size is the most significant predictor of surgical outcome. In addition, adrenal disease diagnosis affects intraoperative blood loss (adrenal metastasis, hypercortisolism, and pheochromocytoma), operation time (pheochromocytoma) and length of postoperative hospital stay (adrenal metastasis) to a lesser degree than tumor size.

A longer operation time for larger tumors has been described before.[10,14-16] The increase in operation time for large adrenal masses can be explained by several factors. Larger tumors have more surface to dissect and are frequently more vascular. The latter can also explain why larger tumors in our study were associated with more intraoperative blood loss.[14,18]

The morbidity of adrenalectomy in patients with pheochromocytoma is largely related to hypersecretion of catecholamines, preoperative adrenergic blockade and postexcision fluid shifts (53% of the complications in pheochromocytoma patients in our series were related to these factors). To minimize complications, adrenalectomy for pheochromocytoma should be meticulous and deliberate. The procedure is sometimes paused to prevent or to treat blood pressure fluctuations. Pheochromocytomas are larger on average when compared with aldosteronomas and vasculogenesis and angiogenesis make them prone to bleeding during dissection.[18] We observed longer operation time and more estimated blood loss in patients with pheochromocytoma compared with other diagnoses. Prior studies on adrenalectomy for pheochomocytoma also found a longer operation time[28] and a higher rate of conversions to open procedure[21,25] compared with other diagnosis. However, multivariate analysis in Morris' study and in our study showed that it is tumor size and not the diagnosis of pheochromocytoma that significantly predicted the increased conversion rate.[18]

Patients with hypercortisolism tend to have more comorbidities related to the underlying illness. They are frequently hypertensive, obese, weak, and immunosuppressed and have parchment-like skin and poor overall tissue quality. These factors make surgery and postoperative recovery more difficult.[21,25] Those with chronic adrenocorticotropic hormone stimulations may have inflamed and hyperplastic adrenal glands, making their resection more difficult with more associated blood loss and a longer operation time.[25,31] We, therefore, expected patients with hypercortisolism to have more complications and a longer duration of postoperative hospital stay. However, in contrast with previous studies,[21,22,25,31] our multivariate analysis including comorbidity as factors, showed patients with hypercortisolism did not have more complications or a longer postoperative hospital stay than other patients. This discrepancy may be explained by our grouping of very heterogeneous patients ranging from mild subclinical Cushing's syndrome caused by

a small adenoma to severely ill patients with ectopic adrenocorticotropic hormone production. The small number of patients with hypercortisolism made further subgroup analysis not reliable.

Most prior studies including ours have reported excellent locoregional control after laparoscopic adrenalectomy for isolated adrenal metastasis when compared with open adrenalectomy.[6,35,36] The current study showed that short-term morbidity of laparoscopic adrenalectomy for patients with adrenal metastasis involved more estimated blood loss and a longer postoperative hospital stay than patients with aldosteronoma. Adrenal glands containing small metastases are readily operable laparoscopically. Larger ones tend to have significant larger vessels on the surface of the gland, making the dissection more treacherous.

There is no doubt that the clinicopathologic diagnosis of the patients with adrenal diseases predicts long-term outcome. What the current study showed is that the size of adrenal tumor correlates best with short-term surgical outcome of laparoscopic adrenalectomy. If asked, most adrenal surgeons would agree that size matters. Our study provides the data that support this intuitive observation.

Conclusion

Multivariate analysis showed that tumor size is the strongest independent predictor of short-term outcome of laparoscopic adrenalectomy.

References

1. Gagner M, Lacroix A, Bolte E. Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma. *N Engl J Med* 1992; 327(14):1033.
2. Gagner M, Pomp A, Heniford BT. Laparoscopic adrenalectomy: Lessons learned from 100 consecutive procedures. *Ann Surg* 1997; 226(3):238–246.
3. Lal G, Duh Q. Laparoscopic adrenalectomy: Indications and technique. *Surg Oncol* 2003; 12(2):105–123.
4. Gill IS. The case for laparoscopic adrenalectomy. *J Urol* 2001; 166(2):429–436.
5. Sturgeon C, Kebebew E. Laparoscopic adrenalectomy for malignancy. *Surg Clin North Am* 2004; 84(3):755–774.
6. Sarela AI, Murphy I, Coit DG, Conlon KCP. Metastasis to the adrenal gland: the emerging role of laparoscopic surgery. *Ann Surg Oncol* 2003; 10(10):1191–1196.
7. Gonzalez R, Smith CD, McClusky DA 3rd, et al. Laparoscopic approach reduces likelihood of perioperative complications in patients undergoing adrenalectomy. *Am Surg* 2004; 70(8):674-688.
8. Lee J, El-Tamer M, Schifftner T, et al. Open and laparoscopic adrenalectomy: analysis of the National Surgical Quality Improvement Program. *J Am Coll Surg* 2008; 206(5):953–959.
9. Brunt LM. The positive impact of laparoscopic adrenalectomy on complications of adrenal surgery. *Surg Endosc* 2002; 16(2):252–257.
10. Walz MK, Peitgen K, Walz MV, et al. Posterior retroperitoneoscopic adrenalectomy: lessons learned within five years. *World J Surg* 2001; 25(6):728-734.
11. Rutherford JC, Stowasser M, Tunny TJ, Klemm SA, Gordon RD. Laparoscopic adrenalectomy. *World J Surg* 1996; 20(7):758-760, discussion 761.
12. Kazaure HS, Roman SA, Sosa JA. Obesity is a predictor of morbidity in 1,629 patients who underwent adrenalectomy. *World J Surg* 2011; 35(6):1287-1295.
13. Castillo OA, Vitagliano G, Secin FP, Kerkebe M, Arellano L. Laparoscopic adrenalectomy for adrenal masses: does size matter? *Urology* 2008; 71(6):1138-1141.
14. Walz M, Petersenn S, Koch JA, et al. Endoscopic treatment of large primary adrenal tumors. *Br J Surg* 2005; 92(6):719–723.
15. Porpiglia F, Destefanis P, Fiori C, et al. Does adrenal mass size really affect safety and effectiveness of laparoscopic adrenalectomy? *Urology* 2002; 60(5):801-805.
16. Kazaryan AM, Mala T, Edwin B. Does tumor size influence the outcome of laparoscopic adrenalectomy? *J Laparoendosc Adv Surg Tech A* 2001; 11(1):1-4.
17. Shen WT, Kebebew E, Clark OH, Duh QY. Reasons for conversion from laparoscopic to open or hand-assisted adrenalectomy: review of 261 laparoscopic adrenalectomies from 1993; to 2003. *World J Surg* 2004; 28(11):1176-1179.
18. Morris L, Ituarte P, Zarnegar R, et al. Laparoscopic adrenalectomy after prior abdominal surgery. *World J Surg* 2008; 32(5):897-903.
19. Hobart MG, Gill IS, Schweizer D, et al. Laparoscopic adrenalectomy for large-volume (< or >5 cm) adrenal masses. *J Endourol* 2000; 14(2):149-514.
20. Henry JF, Defechereux T, Gramatica L, et al. Should laparoscopic approach be proposed for large and/or potentially malignant adrenal tumors? *Langenbecks Arch Surg* 1999; 384(4):366–369.
21. Chan J, Meneghetti AT, Meloche RM, et al. Prospective comparison of early and late experience with laparoscopic adrenalectomy. *Am J Surg* 2006; 191(5):682–686.
22. Ramacciato G, Paolo M, Pietromaria A, et al. Ten years of laparoscopic adrenalectomy: lesson learned from 104 procedures. *Am Surg* 2005; 71(4):321-325.

23. MacGillivray DC, Whalen GF, Malchoff CD, Oppenheim DS, Shichman SJ. Laparoscopic resection of large adrenal tumors. *Ann Surg Oncol* 2002; 9(5):480-485.
24. Pugliese R, Boniardi M, Sansonna F, et al. Outcomes of laparoscopic adrenalectomy. Clinical experience with 68 patients. *Surg Oncol* 2008; 17(1):49-57.
25. Poulin E, Schlachta CM, Burpee SE. Laparoscopic adrenalectomy: pathologic features determine outcome. *Can J Surg* 2003; 46(5):340–344.
26. Bjornsson B, Birgisson G, Oddsdottir M. Laparoscopic adrenalectomies: A nationwide single-surgeon experience. *Surg Endosc* 2008; 22(3):622-626.
27. Nguyen PH, Keller JE, Novitsky YW, Heniford BT, Kercher KW. Laparoscopic approach to adrenalectomy: review of perioperative outcomes in a single center. *Am Surg* 2011; 77(5):592-596.
28. Kim A, Quiros RM, Maxhimer JB, et al. Outcome of laparoscopic adrenalectomy for pheochromocytomas vs. aldosteronomas. *Arch Surg* 2004; 139(5):526-529, discussion 529-531.
29. Gagner M. Laparoscopic adrenalectomy. *Surg Clin North Am* 1996; 76(3):523-537.
30. Kalady MF, McKinlay R, Olson JA Jr, et al. Laparoscopic adrenalectomy for pheochromocytoma. A comparison to aldosteronoma and incidentaloma. *Surg Endosc* 2004; 18(4):621-625.
31. Fernández-Cruz L, Sáenz A, Benarroch G, Sabater L, Taurá P. Does hormonal function of the tumor influence the outcome of laparoscopic adrenalectomy? *Surg Endosc* 1996; 10(11):1088-1091.
32. Park HS, Roman SA, Sosa JA. Outcomes from 3144 adrenalectomies in the United States: which matters more, surgeon volume or specialty? *Arch Surg* 2009; 144(11):1060–1067.
33. Guerrieri M, Campagnacci R, De Sanctis A, et al. The learning curve in laparoscopic adrenalectomy. *J Endocrinol Invest* 2008; 31(6):531–536.
34. Lo CY, van Heerden JA, Grant CS, Söreide JA, Warner MA, Ilstrup DM. Adrenal surgery in the elderly: too risky? *World J Surg* 1996; 20(3):368-373, discussion 374.
35. Kebebew E, Siperstein AE, Clark OH, Duh QY. Results of laparoscopic adrenalectomy for suspected and unsuspected malignant adrenal neoplasms. *Arch Surg* 2002; 137(8):948–951, discussion 952–953.
36. Henriford BT, Arca MJ, Walsh RM, Gill IS. Laparoscopic adrenalectomy for cancer. *Semin Surg Oncol* 1999; 16(4):293–306.

Chapter 7

Variant Adrenal Venous Anatomy in 546 Laparoscopic Adrenalectomies

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Abstract

Importance Knowing the types and frequency of adrenal vein variants would help surgeons identify and control the adrenal vein during laparoscopic adrenalectomy.

Objective To establish the surgical anatomy of the main adrenal vein and its variants for laparoscopic adrenalectomy and to analyze the relationship between variant adrenal venous anatomy and tumor size, pathologic diagnosis, and operative outcomes.

Design, Setting, and Patients In a retrospective review of patients at a tertiary referral hospital, 506 patients underwent 546 consecutive laparoscopic adrenalectomies between April 1993 and October 2011. Patients with variant adrenal venous anatomy were compared with patients with normal adrenal venous anatomy regarding preoperative variables (patient and tumor characteristics [size and location] and clinical diagnosis), intraoperative variables (details on the main adrenal venous drainage, any variant venous anatomy, operation time, rate of conversion to hand-assisted or open procedure, and estimated blood loss), and postoperative variables (transfusion requirement, reoperation for bleeding, duration of hospital stay, and histologic diagnosis).

Intervention Laparoscopic adrenalectomy.

Main Outcome Measures Prevalence of variant adrenal venous anatomy and its relationship to tumor characteristics, pathologic diagnosis, and operative outcomes.

Results Variant venous anatomy was encountered in 70 of 546 (13%) adrenalectomies. Variants included no main adrenal vein identifiable (n = 18), 1 main adrenal vein with additional small veins (n = 11), 2 adrenal veins (n = 20), more than 2 (n = 14) adrenal veins, and variants of the adrenal vein drainage to the inferior vena cava and hepatic vein or with the inferior phrenic vein (n = 7). Variants occurred more often on the right side than on the left side (42 of 250 [17%] versus 28 of 296 [9%] glands, P = 0.015). Patients with variant anatomy compared with those with normal anatomy had larger tumors (5.1 versus 3.3 cm, P < 0.001), more pheochromocytomas (24 of 70 [35%] versus 100 of 476 [21%], P = 0.020), and more estimated blood loss (134 versus 67 mL, P = 0.014). For patients with variant anatomy versus those with normal anatomy, the rates of transfusion requirement (2 of 70 [3%] versus 10 of 476 [2%], P = 0.687) and reoperation for bleeding (1 of 70 [1%] versus 3 of 476 [1%], P = 0.465) were similar.

Conclusion Understanding variant adrenal venous anatomy is important to avoid bleeding during laparoscopic adrenalectomy, particularly in patients with large tumors or pheochromocytomas. Surgeons should anticipate a higher probability of adrenal variants when operating on pheochromocytomas and larger adrenal tumors.

Introduction

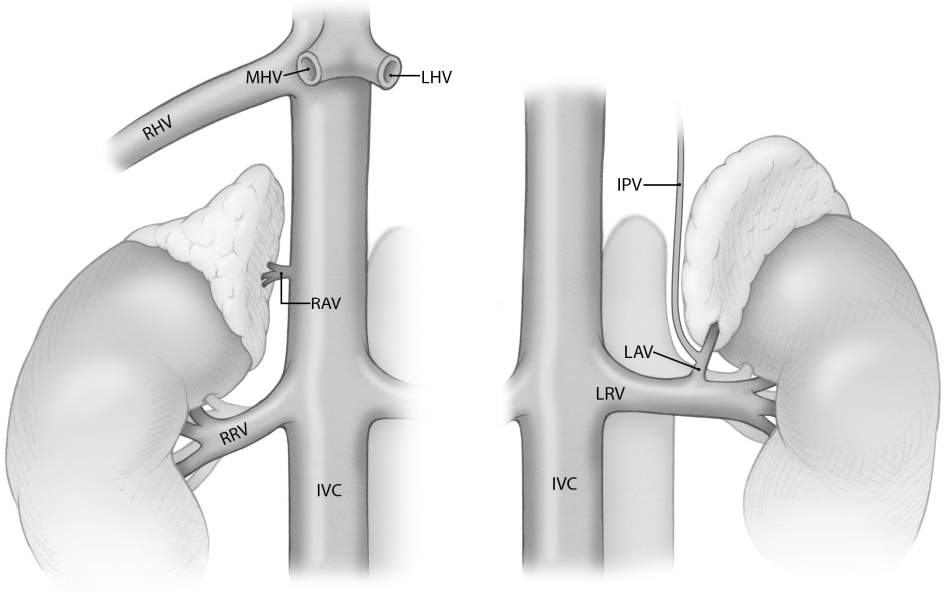
Laparoscopic adrenalectomy has evolved to become the procedure of choice for most surgically treated adrenal diseases.[1-3] A safe laparoscopic adrenalectomy requires a thorough knowledge of the usual anatomy of the adrenal gland as well as its unusual anatomical variations.

The venous drainage from each adrenal gland, described in standard anatomical texts, is usually via a single vein emptying directly into the inferior vena cava on the right side and joining with the inferior phrenic vein and then draining into the left renal vein on the left (Figure 1 and Figure 2).[4] Variations to this pattern have been documented in cadaver studies,[5-11] a clinical study,[12] and a few case reports.[13,14]

Anson and Caudwell[5] studied the venous drainage of the adrenal glands in 450 cadavers. They confirmed the constancy of conventional venous drainage anatomy, with only one variant identified in 900 adrenals. Subsequent cadaver studies described more variations in the adrenal veins, mainly on the right side.[6-11] These cadaver studies reported the anatomy of nondiseased adrenal glands.

Figure 1. Normal Adrenal Venous Anatomy on the Right Side.

Figure 2. Normal Adrenal Venous Anatomy on the Left Side.



Abbreviations: RHV, right hepatic vein; MHV, middle hepatic vein; LHV, left hepatic vein; RAV, right adrenal vein; RRV, right renal vein; IVC, inferior vena cava; IPV, inferior phrenic vein; LAV, left adrenal vein; LRV, left renal vein.

Adrenal pathology, possibly through angiogenesis or vasodilation of preexisting small collateral vessels, may increase both the variation of venous drainage and the number of periadrenal vessels. Parnaby et al[12] studied the venous anatomy encountered in 162 laparoscopic adrenalectomies for adrenal pathology. They found variant venous anatomy in five adrenal glands: four in patients with pheochromocytoma and one in a patient with adrenal cortical cancer. In addition, MacGillivray et al[13] reported confluence of the right adrenal vein with the accessory right hepatic vein in a patient with primary aldosteronism, and Stack et al[14] described an anomalous left adrenal vein draining directly into the inferior vena cava in a patient with primary aldosteronism.

The ability to anticipate variant adrenal venous anatomy is important to prevent excessive bleeding from the adrenal and accessory veins during laparoscopic adrenalectomy. We therefore studied 546 consecutive laparoscopic adrenalectomies to establish details of the primary venous drainage and any variant venous anatomy. In addition, we compared patients with variant adrenal venous anatomy with patients with normal adrenal venous anatomy.

Materials and Methods

With approval of the University of California, San Francisco Institutional Review Board, we retrospectively reviewed the records of all patients (*n* = 523) who underwent consecutive laparoscopic adrenalectomy performed by a single surgeon at the University of California, San Francisco and the San Francisco Veterans Affairs Medical Center between April 1993 and October 2011.

With the exception of 19 cases performed via a retroperitoneal approach, all operations were performed via the lateral transperitoneal approach.

Adrenal vascular anatomy was routinely recorded prospectively by the attending surgeon in the operative findings part of the detailed operative report. Only patients with such a report describing the venous anatomy were included. We reviewed these operative notes to assess variant adrenal venous anatomy. Sufficient information was available for 506 patients. Forty of these patients underwent bilateral adrenalectomy, yielding a total of 546 procedures evaluable for adrenal venous anatomy.

Preoperative data included patient and tumor characteristics (size and location) and clinical diagnosis. Intraoperative data included the details on the main adrenal venous drainage, any variant venous anatomy, operation time, rate of conversion to hand-assisted or open procedure, and estimated blood loss. Postoperative data included transfusion requirement, reoperation for bleeding, duration of hospital stay, and histologic diagnosis.

Statistical Analysis

Patients with variant adrenal venous anatomy were compared with patients with normal adrenal venous anatomy regarding the various preoperative, intraoperative, and postoperative variables.

Table 1. Variant Adrenal Venous Anatomy, by Number

Variant	Number of Patients, *n* = 63
No central adrenal vein identified (with multiple small veins)	18 (7)
1 central adrenal vein with multiple small veins	11
2 adrenal veins (with multiple small veins)	20 (2)
> 2 adrenal veins (with multiple small veins)	14 (1)

Table 2. Variant Adrenal Venous Anatomy, by Location

Side	Variant, *n* = 7
Left	Central adrenal vein, 2 branches
	Central adrenal vein draining into left renal vein, branch to inferior phrenic vein
	Central adrenal vein, inferior phrenic vein draining separately into left renal vein (*n* = 2)
Right	Central adrenal vein draining into right hepatic vein
	Central adrenal vein draining into right hepatic vein, multiple small veins draining into inferior vena cava
	Central adrenal vein draining into inferior vena cava, accessory adrenal vein draining into right hepatic vein

All data were analyzed with SPSS version 17.0 (SPSS, Inc., Chicago, IL). Comparison of binary variables was by χ^2 test. Comparison of continuous values was by unpaired *t* test. Descriptive statistics were calculated for all variables. Statistical significance was shown at $P < 0.05$.

Results

In 70 of the 546 (13%) evaluable procedures (250 [46%] right-sided procedures and 296 [54%] left-sided procedures), there was a variant adrenal venous anatomy (Table 1, Table 2, Figure 3, and Figure 4). Variants can be related to the number of veins and/or the location of the adrenal vein. Eighteen patients had no single adrenal vein identifiable, 11 had 1 central adrenal vein with additional but significant small veins, 20 had 2 adrenal veins, and 14 had more than 2 adrenal veins. Seven patients had a variant of the adrenal vein in relation to the hepatic vein and inferior vena cava or to the inferior phrenic vein. Venous variants occurred more often on the right side than on the left side (42 of 250 [17%] versus 28 of 296 [9%], $P = 0.015$).

Patients with variant venous anatomy compared with those with normal venous anatomy had larger tumors (5.1 versus 3.3 cm, $P < 0.001$), more pheochromocytomas (24 of 70 [35%] versus 100 of 476 [21%], $P = 0.020$), and more bilateral adrenalectomies (13 of 70 [19%] versus 27 of 476 [6%], $P < 0.001$) (Table 3). The mean operation time was longer for the variant group than for the group with normal venous anatomy (right side: 2.62 versus 2.32 hours, $P = 0.028$, left side: 2.99 versus 2.50 hours, $P = 0.007$).

Table 3. Normal versus Variant Adrenal Venous Anatomy

Characteristics	Adrenal Venous Anatomy		*P* Value
	Normal, *n* = 476	Variant, *n* = 70	
Patient characteristics			
Age at surgery, y, mean	49.9	50.0	0.489
Female, n	266 (56%)	35 (50%)	0.427
Diagnosis, n			
Primary aldosteronism	162 (34%)	8 (12%)	<0.001
Pheochromocytoma	100 (21%)	24 (35%)	0.012
Metastasis	38 (8%)	5 (7%)	0.853
Hypercortisolism	101 (21%)	17[a] (25%)	0.670
Cortical cancer	1 (0.2%)	0	0.701
Other	77 (16%)	14[b] (21%)	0.188
Tumor size, cm, mean	3.3	5.1	<0.001
Adrenalectomy, n			0.015
Right	208 (44%)	42 (60%)	
Left	268 (56%)	28 (40%)	
Perioperative outcome			
Operation time, hr, mean			
Right	2.32	2.62	0.028
Left	2.50	2.99	0.007
Intraoperative bleeding complications, n	2 (0.4%)	1 (1%)	0.842
Conversion, n	11 (2%)	3 (4%)	0.568
Estimated blood loss, mL, mean	67	134	0.014
Transfusion, n	10 (2%)	2 (3%)	0.687
Reoperation for bleeding, n	3 (1%)	1 (1%)	0.465
Duration of hospital stay, d, mean	2.0	2.6	0.044

[a] One cortisol producing carcinoma.

[b] Nonfunctioning adenoma or hyperplasia (*n* = 10), cyst (*n* = 3), myelolipoma (*n* = 1), angiomyelolipoma (*n* = 1), and neurofibroma (*n* = 1).

The group with variant anatomy compared with those with normal anatomy had more intraoperative estimated blood loss (134 versus 67 mL, *P* = 0.014), although the transfusion rate was similar (2 of 70 [3%] versus 10 of 476 [2%], *P* = 0.687). Reoperation for bleeding was required in one patient (1%) with variant anatomy and three patients (1%) with normal anatomy (*P* = 0.465). In the variant group, one patient with adrenal metastases required conversion to an open procedure due to adhesion of the tumor to the inferior vena cava and bleeding from parasitic vessels. One patient had conversion to an open procedure owing to adhesions and one patient had conversion to a hand-assisted procedure owing to large tumor size and adhesions. In the group with normal venous anatomy, there were 11 (2%) conversions. These were due to tumor adhesion to or invasion in surrounding tissue (*n* = 7), bleeding (*n* = 2), and tumor size (*n* = 2).

Sixteen variants (3 left-sided, 13 right-sided) occurred in patients with bilateral disease; two of 21 patients with bilateral pheochromocytoma and 14 of 17 patients with bilateral hypercortisolism. Three patients had bilateral variant venous anatomy. These included no adrenal vein identified bilaterally, bilateral duplication of the

adrenal vein, and duplication of the left adrenal vein and triplication of the right adrenal vein. Two of these patients had bilateral cortical hyperplasia due to ectopic corticotropin production and one had pituitary Cushing's syndrome.

In the variant group, two patients histologically had two separate tumors in a single adrenal gland. There was one case of Cushing's carcinoma with a myelolipoma and one case of a cortical adenoma with a myelolipoma.

Patients with variant anatomy and hypercortisolism most often had either no single adrenal vein identifiable (n = 9) or duplication of the adrenal vein (n = 6) as the variant identified in their adrenal venous anatomy. Most of these patients also had enlarged, inflamed atrophic, or, rarely, hypoplastic glands found during operation.

Patients with variant anatomy and pheochromocytoma had either duplication (n = 5) or triplication (n = 6) of their adrenal vein or had multiple small adrenal veins instead of (n = 2) or in addition to (n = 9) a single adrenal vein. One patient had 4 adrenal veins and one patient had more than 5 adrenal veins, draining into the inferior vena cava, the lumbar veins, and the hepatic veins.

Variants in patients with primary aldosteronism occurred in three left and five right adrenal glands. These variants included duplication (n = 4) and triplication (n = 1) of the adrenal vein, and variants involving the hepatic vein (n = 2) or inferior phrenic vein (n = 1).

We also performed a subgroup analysis excluding the 19 patients who underwent laparoscopic adrenalectomy performed via a retroperitoneal approach. This analysis showed no differences in results (data not shown).

Discussion

Each adrenal gland is typically drained by a single vein emptying directly into the inferior vena cava on the right side and joining with the inferior phrenic vein and then draining into the left renal vein on the left.[4] Identification and control of the adrenal vein are critical steps in laparoscopic adrenalectomy. However, few clinical studies report data on variants in the adrenal venous anatomy. There are also no clinical studies reporting the relationship between variant adrenal venous anatomy and tumor size or pathologic disease. To our knowledge, this is the first report of data on variant adrenal venous anatomy in a large series of laparoscopic adrenalectomies showing an association of variant adrenal venous anatomy versus tumor size and pathology. We found variants of the adrenal venous anatomy in a significant percentage of patients (13%), particularly in patients with pheochromocytomas and large tumors.

Most previous reports on adrenal venous drainage are cadaver studies (Table 4). Anson and Caudwelll[5] studied 450 cadavers and found variant anatomy in only one patient (where the left adrenal vein joined the right renal vein). However, they did not specify whether they had dissected the adrenal vein in all cadavers. They also did not comment on the presence or absence of multiple small veins surrounding the adrenal gland. Other, smaller cadaver studies on adrenal venous anatomy have found higher rates of variation of the adrenal venous anatomy.[6-11]

Figure 3. Variant Adrenal Venous Anatomy on the Right Side.

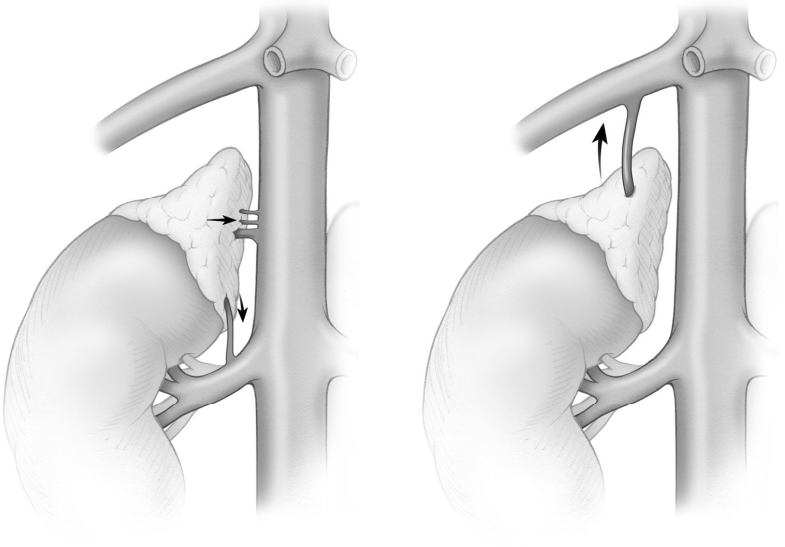
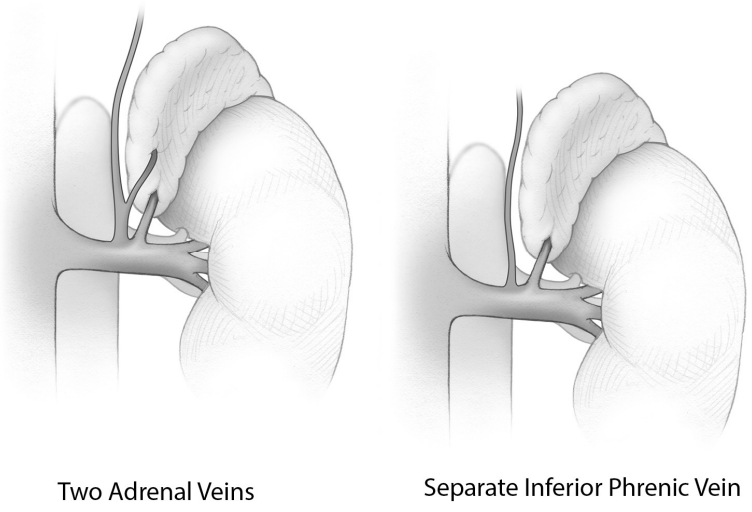


Figure 4. Variant Adrenal Venous Anatomy on the Left Side.



Variants in these studies included both the number of veins draining the adrenal gland as well as the location of the adrenal vein in relation to the hepatic vein or inferior phrenic vein.

These autopsy studies, however, were performed on normal adrenal glands and not pathologic adrenal glands. Parnaby et al[12] studied adrenal vein anatomy in 162 pathologic adrenal glands. They found that only five patients (3%) had adrenal vein variants. These variants included duplication of the right (*n* = 2) and left (*n* = 3) adrenal veins and were present in patients with pheochromocytoma (*n* = 4) or adrenocortical carcinoma (*n* = 1). They also found that patients with pheochromocytoma had increased numbers of periadrenal vessels. Although this was a small series, it demonstrated a higher rate of adrenal vein variants in patients with pheochromocytoma ($P = 0.014$).[12] We confirmed this finding, with variants occurring more often in patients with pheochromocytoma compared with other diagnoses. Twenty-four of the 124 patients (19%) with pheochromocytoma had variant adrenal venous anatomy. This may be explained by an increase in angiogenesis and vasculogenesis in pheochromocytoma.[15]

Table 4. Variant Adrenal Venous Anatomy in Literature

Author, y	Number of Adrenals, n		Variant Venous Anatomy, n	
	Right	Left	Right	Left
Anson, 1948[5a]	450	450	0	1 (0.1%)
Johnstone, 1957[6a]	10	10	5 (50%)	1 (10%)
Clark, 1959[7a]	16	16	10 (62%)	5 (31%)
Davidson, 1975[8a]	50	50	2 (1%)	4 (2%)
Nakamura, 1981[9a]	83	83	11 (13%)	0
El-Sherief, 1982[10a]	20	20	11 (55%)	0
Monkhouse, 1986[11a]	45	57	18 (40%)	0
MacGillivray, 1996[13a]	1	0	1	-
Stack, 2001[14]	1	0	-	1
Parnaby, 2008[12]	79	83	2 (1%)	3 (2%)
Scholten, 2012 (current study)	250	296	42 (8%)	26 (5%)

[a] Cadaver study

We had a subgroup of patients with no single identifiable adrenal vein. Their tumors obviously still had blood drainage, just from multiple small vessels. For this study, we defined “veins” operationally by their surgical significance for the conduct of the operation. What constitutes a vein is decided by the surgeon at the time of operation. In general, we cauterize small arteries or veins, and we clip sizable veins. Veins in this study are usually at least 2 to 3 mm wide and are distinct.

We showed that some patients had multiple small veins draining into the inferior vena cava or renal vein, in addition to or instead of a main adrenal vein. Some even had multiple small veins in addition to 2 or 3 main adrenal veins. Small periadrenal veins may be collateral venous drainage pathways. The presence of

multiple periadrenal veins has been reported before by others.[6,12] More collateral veins may become apparent as the tumor grows. This is consistent with our finding of larger tumors in patients with variant adrenal venous anatomy.

In our study and in previous studies,[6,7,10,11] variation in adrenal venous drainage occurred more often on the right side than on the left side. Previously reported variants of the left adrenal vein include duplication, with both the left adrenal vein and the inferior phrenic vein draining into the renal vein (n = 8)[7,12] or with one adrenal vein draining into the renal vein and one adrenal vein draining into the left lumbar vein (n = 1).[6]

We found three patients with variant anatomy of the right adrenal vein joining an (accessory) hepatic vein. This has been described in one case report by MacGillivray et al[13] and three cases reported by Johnstone[6] and was commented on in an editorial on minimal-access versus open adrenalectomy.[16] In a study focused on the anatomy of the hepatic veins and the vena cava, Nakamura and Tsuzuki[9] found that in eight of 83 cadavers (10%), the right adrenal vein joined an accessory hepatic vein. We found one case of a duplicate right adrenal vein, one that drained into the vena cava and another that joined an accessory hepatic vein. This was also found in one patient in the study by Nakamura and Tsuzuki. These data show that drainage of the right adrenal vein into an (accessory) hepatic vein may be a more common occurrence than is generally appreciated.

Laparoscopic right adrenalectomy, especially for larger tumors, requires extensive mobilization and medial retraction of the right lobe of the liver to expose the inferior vena cava and right adrenal vein. In patients with variant venous anatomy of the right adrenal gland, excessive retraction of the liver or rough dissection along the retrohepatic vena cava may injure a variant vein. Extra attention to the venous anatomy is advised during right adrenalectomy, especially for large tumors and pheochromocytoma.

We have addressed only the adrenal venous anatomy in this study. The adrenal arterial anatomy has been addressed in our prior study.[17] Adrenal arteries tend to be small and indistinct. They usually can be easily cauterized, except for occasional large inferior arteries that need to be ligated with clips.

This study showed that the adrenal venous drainage including anatomical variants can be defined clearly during laparoscopic adrenalectomy. Because of magnification, laparoscopy provides better visualization of the adrenal anatomy. We show a similar rate of (bleeding) complications between patients with normal venous anatomy and those with variant venous adrenal anatomy. Only one patient with variant anatomy in our study needed conversion to an open procedure owing to invasion of the tumor into the inferior vena cava and bleeding from numerous parasitic veins. None of the five patients with variant adrenal venous anatomy in the study by Parnaby et al[12] had bleeding complications due to failure to identify or ligate the adrenal vein variants, and conversion was necessary in only one of their patients because of concern of invasion to the adjacent structure. Laparoscopic adrenalectomy is a safe procedure if the surgeon is aware of the possible anatomical venous variants.

We found no venous variants in 19 retroperitoneal adrenalectomies. It is possible that the adrenal venous anatomy is not seen as well during a retroperitoneal approach, but we do not have sufficient retroperitoneal cases to make a firm conclusion. Subgroup analysis excluding these 19 cases, however, did not change our overall findings and conclusions.

Conclusion

Variants in adrenal venous anatomy are commonly found during laparoscopic adrenalectomy. Understanding these variants is important to prevent bleeding from the adrenal and accessory veins during surgery, particularly in patients with large tumors or pheochromocytoma.

References

1. Gagner M, Lacroix A, Bolte E. Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma. *N Engl J Med* 1992; 327(14):1033.
2. Gagner M, Pomp A, Heniford BT, Pharand D, Lacroix A. Laparoscopic adrenalectomy: Lessons learned from 100 consecutive procedures. *Ann Surg* 1997; 226(3):238-247.
3. Lal G, Duh Q. Laparoscopic adrenalectomy: Indications and technique. *Surg Oncol* 2003; 12(2):105-123.
4. Standring S. Suprarenal (adrenal) gland. In: Standring S (ed). *Gray's Anatomy*. London, Elsevier, 2005; 1245-1249.
5. Anson BJ, Caudwell EW. The anatomy of the para-renal system of veins, with comments on the renal arteries. *J Urol* 1948; 60(5):714-737.
6. Johnstone FR. The suprarenal veins. *Am J Surg* 1957; 94(4):615-620.
7. Clark K. The blood vessels of the adrenal gland. *J R Coll Surg Edinb* 1959; 4(3):257-262.
8. Davidson JK, Morley P, Hurley GD, Holford NG. Adrenal venography and ultrasound in the investigation of the adrenal gland: an analysis of 58 cases. *Br J Radiol* 1975; 48(570):435-450.
9. Nakamura S, Tsuzuki T. Surgical anatomy of the hepatic veins and the inferior vena cava. *Surg Gynecol Obstet* 1981; 152(1):43-50.
10. El-Sherief MA. Adrenal vein catheterization. Anatomic considerations. *Acta Radiol Diagn (Stockh)* 1982; 23(4):345-360.
11. Monkhouse WS, Khalique A. The adrenal and renal veins of man and their connections with azygos and lumbar veins. *J Anat* 1986; 146:105-115.
12. Parnaby CN, Galbraith N, O'Dwyer PJ. Experience in identifying the venous drainage of the adrenal gland during laparoscopic adrenalectomy. *Clin Anat* 2008; 21(7):660-665.
13. MacGillivray DC, Khwaja K, Shickman SJ. Confluence of the right adrenal vein with the accessory right hepatic veins. A potential hazard in laparoscopic right adrenalectomy. *Surg Endosc* 1996; 10(11):1095-1096.
14. Stack SP, Rösch J, Cook DM, Sheppard BC, Keller FS. Anomalous left adrenal venous drainage directly into the inferior vena cava. *J Vasc Interv Radiol* 2001; 12(3):385-387.
15. Zielke A, Middeke M, Hoffmann S, et al. VEGF-mediated angiogenesis of human pheochromocytomas is associated to malignancy and inhibited by anti-VEGF antibodies in experimental tumors. *Surgery* 2002; 132(6):1056-1063.
16. Pertsemlidis D. Minimal-access versus open adrenalectomy. *Surg Endosc* 1995; 9(4):384-386.
17. Joel AB, Rubenstein JN, Arredondo S, Meng MV, Duh QY, Stoller ML. Laparoscopic appreciation of the adrenal artery: fact or fiction? *J Endourol* 2005; 19(7):793-796.

Chapter 8

Pheochromocytoma Crisis Is Not a Surgical Emergency

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Abstract

Context Pheochromocytoma crisis is a feared and potentially lethal complication of pheochromocytoma.

Objective We sought to determine the best treatment strategy for pheochromocytoma crisis patients and hypothesized that emergency resection is not indicated.

Design Retrospective cohort study (1993 to 2011); literature review (1944 to 2011).

Setting Tertiary referral center.

Patients There were 137 pheochromocytoma patients from our center and 97 pheochromocytoma crisis patients who underwent adrenalectomy from the literature.

Intervention Medical management of pheochromocytoma crisis; adrenalectomy.

Main Outcome Measures Perioperative complications, conversion, and mortality.

Results In our database, 25 patients (18%) presented with crisis. After medical stabilization and α-blockade, 15 patients were discharged and readmitted for elective surgery and 10 patients were operated on urgently during the same hospitalization. None underwent emergency surgery. Postoperatively, patients who underwent elective surgery had shorter hospital stays (1.7 versus 5.7 days, $P = 0.001$) and fewer postoperative complications (1 of 15 [7%] versus 5 of 10 [50%], $P = 0.045$) and were less often admitted to the intensive care unit (1 of 15 [7%] versus 5 of 10 [50%], $P = 0.045$) in comparison with urgently operated patients. There was no mortality. Review of the literature showed that crisis patients who underwent elective or urgent surgery versus emergency surgery had less intraoperative (13 of 31 [42%] versus 20 of 25 [80%], $P < 0.001$) and postoperative complications (15 of 45 [33%] versus 15 of 21 [71%], $P = 0.047$) and a lower mortality (0 of 64 versus 6 of 33 [18%], $P = 0.002$).

Conclusion Management of patients presenting with pheochromocytoma crisis should include initial stabilization of the acute crisis followed by sufficient α-blockade before surgery. Emergency resection of pheochromocytoma is associated with high surgical morbidity and mortality.

Introduction

Pheochromocytomas are rare catecholamine-secreting tumors with an estimated incidence of two to eight per million per year.[1] Pheochromocytomas can present as symptomatic tumors or incidentalomas, or can be diagnosed during screening for familial syndromes. The classic presentation consists of paroxysmal hypertension, headaches, palpitations, and diaphoresis. A feared and possibly fatal presentation of pheochromocytoma is pheochromocytoma crisis.[2]

The clinical picture of pheochromocytoma crisis ranges from severe hypertension to circulatory failure and shock with subsequent involvement of multiple organ systems, including the cardiovascular, pulmonary, neurological, gastrointestinal, renal, hepatic, and metabolic systems. Cardiac manifestations include myocardial infarction (MI), arrhythmia, myocarditis, cardiomyopathy, and cardiogenic shock.[3,4] Pulmonary features include acute pulmonary edema (PE) and adult respiratory distress syndrome (ARDS).[5] Neurological crises include cerebrovascular accident (CVA) (ischemia or hemorrhage), encephalopathy, and seizures.[6] Paralytic ileus[7] and bowel ischemia are some of the gastrointestinal manifestations.[8] Renal failure and hepatic failure are generally part of multisystem failure.[9] Vascular complications include peripheral thrombosis and embolism and vasospasm.[10] Finally, diabetic ketoacidosis and lactic acidosis can occur.[11] Pheochromocytoma multisystem crisis is an unusual presentation of pheochromocytoma and consists of hypertension and/or hypotension, hyperthermia, encephalopathy, and multiorgan failure. Pheochromocytoma crisis can be associated with high mortality rates.[12]

Pheochromocytoma crisis can occur spontaneously or can be precipitated by manipulation of the tumor, trauma, certain medications (corticosteroids, β-blockers, metoclopramide, and anesthetic agents), or stress from nonadrenal surgery.[4,13-17]

Surgical resection is the treatment of choice for pheochromocytoma. It is generally accepted that nonemergent surgery should be preceded by one to two weeks of α-blockade and, if necessary, followed by β-blockade to treat tachycardia.[18] Surgery in unprepared patients is associated with high morbidity and mortality rates due to intraoperative hypertensive crises and profound hypotension after tumor resection.[19]

The timing of surgery for pheochromocytoma patients presenting with crisis is controversial. Some have argued that these patients need emergency resection, even in the absence of preoperative α-blockade.[12,20-24] For example, in patients with shock due to hemorrhagic necrosis or rupture of a pheochromocytoma, progressive multiorgan failure may leave emergency tumor resection as the only option.[20,22,24]

In contrast, other studies have reported favorable results for patients with pheochromocytoma crisis who underwent intensive medical stabilization prior to surgical resection.[25,26]

Although the presentations of pheochromocytoma crisis are well described in numerous case reports, data on the perioperative management of patients presenting with pheochromocytoma crisis are lacking. More specifically, data on appropriate timing for adrenalectomy are sparse, i.e. is emergency surgery without

adequate α-blockade superior to delaying surgery until medical stabilization and adequate α-blockade are achieved.

We therefore reviewed the records of patients with pheochromocytoma crisis treated at our institution, to characterize our approach to preoperative medical management and the appropriate timing of surgery. Additionally, we performed a literature review and compared perioperative outcomes of the patients who underwent surgery after medical stabilization and preoperative α-blockade with those who underwent emergency surgery.

Materials and Methods

Between March 1993 and October 2011, 557 patients underwent adrenalectomy performed by one surgeon at the University of California, San Francisco and the San Francisco Veterans Affairs Medical Center. From this operative database, we searched for patients with pheochromocytoma or paraganglioma on the final pathology and reviewed their records. We analyzed how the patients presented for care with special attention to crisis. Data collected included patient demographics, presentation, preoperative catecholamine levels, radiographic tumor size (computed tomography or magnetic resonance imaging), medical and surgical treatment, and outcomes.

Pheochromocytoma crisis was defined as severe hypertension and/or hypotension resulting in end organ damage (cardiovascular decompensation, MI, PE, ARDS, CVA, renal failure, or liver failure). Patients with pheochromocytoma crisis were analyzed separately from the patients without pheochromocytoma crisis.

Patients who undergo surgery for pheochromocytoma or paraganglioma at our hospitals are routinely treated with phenoxybenzamine for at least 10 days preoperatively. In general, the dose of phenoxybenzamine is titrated to keep blood pressure between 100 to 140 mmHg systolic and 50 to 90 mmHg diastolic. A β-blocker (metoprolol or atenolol) is added after appropriate α-blockade in cases of tachycardia (heart rate above 90 beats per minute).

For those patients who initially presented with crisis, we define the timing of surgery as elective if operation occurred after initial hospital discharge and adequate α-blockade, and urgent if operation took place after adequate α-blockade but during the same hospitalization for crisis.

Intraoperative complications included damage to adjacent organs, bleeding, hyper- or hypotension during surgery, and respiratory insufficiency. Conversion to open or hand-assisted operation and transfusion requirement were considered separately. Postoperative complications were defined as adverse events occurring within 30 days postoperatively or during the same hospitalization. Mortality was defined as death within 30 days of surgery or during the same hospitalization.

Literature Review

In addition to the patients in our series, we reviewed all cases of patients with pheochromocytoma crisis who underwent surgery, published in the English-language literature. We searched Medline (1944 to 2011) and Embase (1980 to 2011) using

predefined search terms (Appendix A). On the basis of full text, we selected studies using predetermined inclusion and exclusion criteria (Appendix A). In addition, we screened references and related articles. Only studies with original information on patients with pheochromocytoma crisis, as defined above, who underwent surgery for their pheochromocytoma were included. Patients were classified into groups according to the timing of surgery; i.e. elective if operation occurred after initial hospital discharge and stabilization, urgent if operation took place after stabilization and during the same hospitalization, and emergent if operation took place immediately after crisis presentation or because of clinical deterioration without appropriate blockade or preoperative management.

Statistical Analysis

We compared patient demographics, presentation, medical management modalities, and perioperative outcomes in two groups of patients: patients with pheochromocytoma crisis and patients with pheochromocytoma but without crisis presentation. In addition, we compared the same parameters in two subgroups of patients with pheochromocytoma crisis: patients who underwent elective surgery and patients who underwent urgent surgery. Finally, we compared the crisis patients from the literature who underwent elective and urgent surgery with the crisis patients who underwent emergency surgery.

All data were analyzed with SPSS version 17.0 (SPSS, Inc., Chicago, IL). Comparison of binary variables was by χ^2 test or Fisher's exact test. Comparison of continuous values was by unpaired *t* test. Descriptive statistics were calculated for all variables. Statistical significance was defined at $P < 0.05$.

Results

From 1993 to 2011, 137 patients were operated on for pheochromocytoma (128 of 137 [93%]) and functional paraganglioma (9 of 137 [7%]) at our hospital. Of these, 25 (18%; 23 pheochromocytoma, 2 paraganglioma) presented with crisis.

Pheochromocytoma Crisis Patients

Each of the 25 crisis patients was hospitalized, including 14 admissions to the intensive care unit (ICU). Twenty-two (88%) were first hospitalized elsewhere and transferred to our hospitals. The clinical presentations and outcomes of the crisis patients are detailed in Table 1 and summarized in Table 2.

Nine of the 25 patients had prior symptoms and five patients had prior pheochromocytoma crises before their current presentation. Four of these patients had a diagnosis of pheochromocytoma established before their current crisis.

Precipitating causes were nonadrenal surgery (n = 7), lithotripsy (n = 1), glucocorticoid therapy (n = 2), and unknown or other (n = 15).

Severe hypertension occurred in 23 patients, and seven of these patients also had severe hypotension. Cardiac crises occurred in 22 patients. The cardiac crises were severe and included MI in 13 patients (four underwent cardiac catheterization) and cardiomyopathy or cardiogenic shock in 13 patients (four required intra-aortic

Table 1. Pheochromocytoma Crisis Patients

Sex, Age, y	Precipitating Cause	Severe Hypertension[b]	Severe Hypotension	Crisis				
				Cardiac	Pulmonary	Neurologic	Multiorgan	Other
F, 36	Unknown	Yes	-	Cardiomyopathy (EF 45%), MI	-	-	-	-
F, 38	Ventral hernia repair surgery	Yes	-	Cardiomyopathy	-	-	-	-
M, 72	Knee surgery	Yes	-	Cardiomyopathy (EF 25%), MI (catheterization)	-	-	-	-
M, 49	Unknown	Yes, 280/100	-	MI (catheterization)	-	-	-	-
M, 60	Unknown	Yes	-	Cardiomyopathy (EF 30%), MI, arrhythmia	ARDS	-	-	-
M, 32	Unknown	Yes, 230/180	Yes	Cardiogenic shock (IABP)	Edema	Encephalopathy	Renal, Liver	-
M, 23	Unknown	Yes, 230/110	-	MI	-	-	-	-
M, 39	Hand surgery	Yes, 250/140	Yes	Cardiogenic shock (IABP), LVH, valve insufficiency	Edema	-	Liver	-
F, 61	Travel	Yes, 220/100	-	MI (EF 65%)	-	-	-	-
M, 56	Unknown	Yes	Yes	Cardiomyopathy (EF 15%, IABP), MI (catheterization), valve insufficiency	ARDS	-	Renal	Fever
M, 45	Lithotripsy	Yes, 220/170	-	MI	Edema	-	-	-
F, 71	Nissen fundoplication	Yes	-	MI, arrhythmia	-	-	-	-
M, 64[a]	Unknown	Yes	-	MI, arrhythmia	-	-	-	-
F, 54	Unknown	Yes	-	MI	-	-	-	-
M, 35	Unknown	Yes	-	Cardiomyopathy (EF 35%), coronary vasospasms (catheterization)	-	-	-	Lower extremity thrombosis (amputation)
M, 53	Unknown	Yes	Yes	Cardiogenic shock (IABP, cardioversion), MI	Edema	-	Liver	-

M, 50	Travel, urination	Yes, 220/110	-	MI (catheterization), palpitations, recurrent syncope	Dyspnea	-	-	-
M, 28	Knee surgery	Yes, 250/150	Yes	Cardiogenic shock	-	-	Renal, Liver	Fever
F, 51	Unknown	Yes	-	-	-	CVA	-	-
M, 53	Inguinal hernia repair surgery	Yes, 250/140	Yes	Cardiogenic shock	Edema	-	-	-
M, 37	Inhalation steroids	Unknown	-	Cardiomyopathy (EF 75%), cardiac thrombus	-	CVA	-	-
F, 65	Nissen fundoplication	Yes, 200/110	-	Cardiomyopathy (EF 15%)	-	CVA, seizure	-	-
M, 34	Unknown	Unknown	-	-	-	CVA	-	-
F, 27	Unknown	Yes	-	(EF 75%)	-	-	-	Paralytic ileus
M, 20	Marijuana, infection, dexamethasone	Yes, 230/115	Yes	Arrhythmia, cardiac arrest (resuscitation)	-	GCS 14, CVA (hemangio-blastoma), hydrocephalus	-	-
Total	-	23	7	22	8	6	5	4

Abbreviations: EF, ejection fraction; MI, myocardial infarction; ARDS, adult respiratory distress syndrome; IABP, intra-aortic balloon pump; CVA, cerebrovascular accident; GCS, Glasgow Coma Scale.

[a] Thought to have primary aldosteronism.

[b] If available, blood pressure in mmHg.

balloon pump [IABP]). One patient suffered cardiac arrest with arrhythmia and was successfully resuscitated. Three other patients had arrhythmias. Pulmonary crises occurred in eight patients (PE in five and ARDS in two) and neurologic crises occurred in six patients (CVA in five and encephalopathy in one). Five patients had multiorgan crises.

All but one patient had elevated levels of catecholamines and their metabolites (22.8 [range 3.5 to 546.6] and 11.6 [range 1.9 to 511.0] median times the highest reference value, respectively) (Table 3). The one patient with normal catecholamines and metabolites presented with severe hypertension, MI, and arrhythmia; evaluation suggested primary aldosteronism.

If not already initiated at the referring hospital, phenoxybenzamine was started and titrated to control blood pressure after initial stabilization. All patients, except the patient who was thought to have primary aldosteronism, were treated pharmacologically for at least 10 days before operation. This patient was medically stabilized but not α-blocked, because the diagnosis of pheochromocytoma was not made preoperatively.

One patient with multiple endocrine neoplasia type 2B underwent open surgery because of severe bowel distention and bilateral large pheochromocytomas; the others underwent laparoscopic surgery.

Despite the fact that most our patients were critically ill at presentation, there was no mortality, and only one patient had a minor intraoperative complication. Postoperative complications occurred in six patients (24%) and were transient in five (Table 2).

Pheochromocytoma Crisis versus Pheochromocytoma Noncrisis Patients

We compared the patients presenting with pheochromocytoma crisis with the noncrisis patients (Table 3). The crisis patients were more often men (17 of 25 [68%] versus 49 of 112 [44%], $P = 0.048$), with larger tumors (5.4 versus 4.5 cm, $P = 0.045$), and a higher American Society of Anesthesiologists physical status (3.0 versus 2.5, $P < 0.001$). The crisis patients had markedly higher levels of both catecholamines (22.8 [range 3.5 to 645.6] versus 3.7 [range 0 to 54.0] median times the highest reference value, $P = 0.071$) and metabolites (11.6 [range 1.9 to 511.0] versus 6.3 [range 0 to 90.1], $P = 0.007$) than the noncrisis patients. There was no mortality in either group with similar doses and duration of phenoxybenzamine preparation. The groups had similar perioperative outcomes, however the crisis patients had longer postoperative hospital stays (3.4 versus 2.4 days, $P = 0.047$) compared with the noncrisis patients.

Elective versus Urgent Surgery Pheochromocytoma Crisis Patients

All 25 crisis patients were hospitalized for their crisis (Table 4). After medical stabilization and α-blockade, it was determined that 15 patients were sufficiently stable to be discharged and subsequently readmitted for elective surgery, including one patient who initially presented with multiorgan crisis.

Table 2. Characteristics of Pheochromocytoma Crisis Patients

Characteristics	Data
Prior pheochromocytoma symptoms, n	9 (36%)
Time from pheochromocytoma symptoms to crisis, mo, median (range)	12 (8.4 to 25)
Prior pheochromocytoma crisis, n	
Multiple periods of severe hypertension with angina	2
Multiple intensive care unit admissions with hemodynamic instability, myocardial infarction and arrhythmia	1
Severe hypertension with pulmonary edema	1
Cardiac emboli and lower extremity emboli	1
Time of most recent prior crisis to current crisis, mo, median (range)	12 (8.0 to 16.6)
Crisis manifestations, n	
Severe hypertension	23 (92%)
Severe hypotension	7 (28%)
Cardiac crisis	22 (88%)
Pulmonary crisis	8 (32%)
Neurologic crisis	6 (24%)
Multiorgan crisis	5 (20%)
Other (fever, ileus, peripheral thrombosis)	4 (16%)
Ejection fraction, %, mean (range)	
During crisis (*n* = 11)	46 (15 to 75)
After preoperative treatment (*n* = 6)	61 (45 to 75)
Treatment	
Intra-aortic balloon pump, n	4 (16%)
Hospital admission for crisis, in intensive care unit, n	25 (100%), 14 (56%)
Duration of preoperative admission in referral hospital, d, mean	12
Duration of preoperative admission in our hospital, d, mean	12
Discharged to home before surgery, n	15 (60%)
Time from current crisis to surgery, d, median (range)	57 (11 to 536)
Perioperative outcome, n	
Intraoperative ST segment depression and hypertension	1
Postoperative complications (all requiring intensive care unit admission)	
Hypoglycemia	1
Hypertension	1
Hypotension	2
Resuscitation due to profound hypotension	1
Respiratory distress due to pulmonary embolism, brainstem stroke requiring tracheostomy	1
Mortality	0

Table 3. Pheochromocytoma Crisis versus Pheochomocytoma Noncrisis Patients

Characteristics	Patients		*P* Value
	Crisis, *n* = 25	Noncrisis, *n* = 112	
Patient characteristics			
Female, n	8 (32%)	63 (56%)	0.048
Age at surgery, y, mean	46.1	47.2	0.376
Pregnant at diagnosis, at surgery, n	0, 0	3, 1 (4%)	0.943
ASA physical status, mean	3.0	2.5	<0.001
Diabetes mellitus, n	7 (28%)	16 (14%)	0.173
History of prior adrenal surgery, n	0	17 (15%)	0.081
History of familial syndrome, n	4 (16%)	24 (21%)	0.738
Symptoms and diagnostic characteristics			
Incidentaloma, n	5 (20%)	50 (45%)	0.041
Pheochromocytoma symptoms, n	9 (36%)	71 (63%)	0.022
Hypertension, n	23 (92%)	53 (47%)	<0.001
Tumor size on imaging, cm, mean	5.4	4.5	0.045
Highest catecholamine ratio,[a] median (range)	22.8 (3.5 to 645.6)	3.7 (0.0 to 54.0)	0.071
Highest metabolite ratio,[a] median (range)	11.6 (1.9 to 511.0)	6.3 (0.0 to 90.1)	0.007
Treatment			
Preoperative hospitalization, n, location	10 (40%), ICU	3 (3%), ward	<0.001
Duration, d, mean	24	6	<0.001
Preoperative α-blockade, n	24 (96%)	111 (99%)	0.803
Daily doses, mg, median (range)	40 (20 to 210)	40 (20 to 160)	0.160
Duration, d, median (range)	27 (10 to 125)	28 (10 to 480)	0.395
Type of surgery, n			
Laparoscopic	24 (96%)	106 (95%)	0.781
Bilateral	2 (8%)	4 (4%)	0.662
Extra-adrenal	2 (8%)	7 (6%)	0.750
Perioperative outcome			
Operation time, hr, mean	3.65	3.11	0.110
Conversion to open or hand-assisted operation, n	3 (12%)	6 (5%)	0.444
Estimated blood loss, mL, mean	227	321	0.291
Transfusion, n	2 (8%)	11 (10%)	0.779
Intraoperative complications, n	1 (4%)	11 (10%)	0.590
Postoperative complications, n	6 (24%)	22 (20%)	0.830
Postoperative intensive care unit admission, n	6 (24%)	12 (11%)	0.147
Duration, d, mean	2.7	2.0	0.181
Duration of postoperative hospital stay, d, mean	3.4	2.4	0.047
Mortality, n	0	0	-
Hemorrhage or necrosis on pathology, n	3 (12%)	1 (1%)	0.020
Malignancy, n	2 (8%)	7 (6%)	0.750
Recurrent disease, n	3 (12%)	10 (10%)	0.923

Abbreviations: ASA, American Society of Anesthesiologists.

[a] Multiplication of reference value.

Table 4. Elective versus Urgent Surgery for Pheochromocytoma Crisis

Characteristics	Patients		*P* Value
	Elective Surgery, *n* = 15	Urgent Surgery, *n* = 10	
Patient characteristics			
Female, n	7 (46%)	1 (10%)	0.086
Age at surgery, y, mean	54.4	38.2	0.014
Crisis manifestations, n			
Severe hypertension	14 (93%)	9 (90%)	0.736
Severe hypotension	2 (14%)	5 (50%)	0.075
Cardiac crisis	11 (73%)	9 (90%)	0.610
Pulmonary crisis	3 (20%)	5 (50%)	0.255
Neurologic crisis	3 (20%)	3 (30%)	0.924
Multiorgan crisis	1 (7%)	4 (40%)	0.126
Other (fever, ileus, peripheral thrombosis)	1 (7%)	3 (30%)	0.267
Diagnostic characteristics			
Tumor size on imaging, cm, mean	4.1	7.2	0.001
Highest catecholamine ratio,[a] median (range)	22.6 (3.5 to 29.8)	75.3 (3.9 to 645.6)	0.098
Highest metabolite ratio,[a] median (range)	13.1 (1.9 to 75.4)	11.4 (4.7 to 511.0)	0.195
Treatment			
Cardiac catheterization, n	3 (20%)	2 (20%)	0.945
Intra-aortic balloon pump, n	0	4 (40%)	0.034
Intensive care unit admission for crisis, n	4 (27%)	10 (100%)	0.001
Time from current crisis to surgery, d, median ± SD	91 ± 158	24 ± 76	0.027
Type of surgery, n			
Laparoscopic	15 (100%)	9 (90%)	0.835
Bilateral	1 (7%)	1 (10%)	0.763
Extra-adrenal	2 (14%)	0	0.652
Perioperative outcome			
Operation time, hr, mean	3.10	4.48	0.053
Conversion to open or hand-assisted operation, n	0	3 (30%)	0.102
Estimated blood loss, mL, mean	228	225	0.496
Transfusion, n	1 (7%)	1 (10%)	0.763
Intraoperative complications, n	1 (7%)	0	0.405
Postoperative complications, n	1 (7%)	5 (50%)	0.045
Postoperative intensive care unit admission, n	1 (7%)	5 (50%)	0.045
Duration of postoperative hospital stay, d, mean	1.7	5.7	0.001
Mortality	0	0	-

Abbreviations: SD, standard deviation.

[a] Multiplication of reference value.

Ten patients were operated on urgently during the same hospitalization, as judged on clinical grounds and social factors which include our clinical assessment that the patients could not be safely discharged because of other medical issues, insurance policy and restriction, travel distance, patient compliance, patient preference, and referral physicians' preference.

Patients who underwent elective surgery had smaller tumors (4.1 versus 7.2 cm, $P = 0.001$), did not need IABP (0 of 15 versus 4 of 10 [40%], $P = 0.034$), and had fewer ICU admissions for their crisis presentation (4 of 15 [27%] versus 10 of 10 [100%], $P = 0.001$), in comparison with patients who underwent urgent surgery. Although the frequency of individual crisis manifestation was similar between groups, fewer patients who underwent elective surgery presented with multiorgan failure (1 of 15 [7%] versus 4 of 10 [40%], $P = 0.126$). This group of patients also had a trend of lower catecholamines levels ($P = 0.098$). Postoperatively, patients who underwent elective surgery had shorter hospital stays (1.7 versus 5.7 days, $P = 0.001$), fewer postoperative complications (1 of 15 [7%] versus 5 of 10 [50%], $P = 0.045$), and were less often admitted to the ICU (1 of 15 [7%] versus 5 of 10 [50%], $P = 0.045$) in comparison with patients who underwent urgent surgery. There was no mortality in either group.

Literature Review

From the English literature, we identified 97 patients who presented with pheochromocytoma crisis and subsequently underwent pheochromocytoma resection (Appendix B). For these patients, the mean age at presentation was 42 years (range 13 to 77). There was a slight female predominance (49 of 97 [53%]). The mean tumor size was 7.0 cm (range 2 to 25).

Ten patients underwent elective surgery during subsequent admission, 54 patients underwent urgent surgery during the same hospitalization, and 33 patients underwent emergency surgery. Results comparing crisis patients who underwent elective or urgent surgery with crisis patients who underwent emergency surgery are given in Table 5. Patients who underwent elective or urgent surgery had smaller tumors (6.0 versus 8.6 cm, $P = 0.006$) and less often presented with ruptured or hemorrhagic pheochromocytoma (12 of 64 [19%] versus 14 of 33 [42%], $P = 0.024$), but had similar crisis manifestations in comparison with patients who underwent emergency surgery. Eight patients (8% of total group, 80% of elective group) in the electively operated group had laparoscopic resection. None of the patients operated emergently underwent laparoscopic surgery. Patients who underwent elective or urgent surgery had less intraoperative (13 of 31 [42%] versus 20 of 25 [80%], $P < 0.001$) and postoperative (13 of 40 [33%] versus 15 of 22 [71%], $P = 0.047$) complications in comparison with patients who underwent emergency surgery. Six of 33 patients operated on emergently died, in comparison with none of the 64 urgently or electively operated patients ($P = 0.002$).

To further evaluate whether less advanced surgical and anesthetic techniques in the earlier years may have contributed to the perioperative complications and mortality in those who underwent surgery emergently, we divided the 65 years of

literature review into two different eras, i.e. the earlier era from 1944 to 1990 and the later era from 1991 to 2011. The latter approximated the time period in our series. We then compared the complication and mortality rates between the two eras, as well as the complication and mortality rates between the elective and urgent surgery group versus the emergency surgery group in each era (Table 6, Table 7, and Table 8). Timing of operation was similar between the two eras. Complication rates were high, greater than 50%, in both the elective and urgent group and the emergency group prior to 1990. There was a trend towards increased mortality in the emergency group versus the elective or urgent group (5 of 15 [33%] versus 0 of 23, *P* = 0.052).

Table 5. Elective and Urgent versus Emergency Surgery for Pheochromocytoma Crisis in Literature

Characteristics	Patients		*P* Value
	Elective and Urgent Surgery, *n* = 64	Emergency Surgery, *n* = 33	
Patient characteristics			
Female, n	33 (51%)	16 of 32 (49%)	0.942
Age at surgery, y, mean	41	43	0.347
Crisis manifestations, n			
Severe hypertension	45 (70%)	23 (70%)	0.950
Severe hypotension	28 (44%)	20 (61%)	0.174
Cardiac crisis	48 (75%)	20 (61%)	0.218
Pulmonary crisis	37 (58%)	14 (42%)	0.221
Neurologic crisis	14 (22%)	6 (18%)	0.872
Multiorgan crisis	16 (25%)	10 (30%)	0.751
Pheochromocytoma multisystem crisis	13 (20%)	11 (33%)	0.246
Other[a]	24 (38%)	19 (58%)	0.095
Tumor size on imaging, cm, mean	6.0	8.6	0.006
Preoperative diagnosis of pheochromocytoma, n	64 (100%)	24 (73%)	<0.001
Hemorrhage or rupture of pheochromocytoma, n	12 (19%)	14 (42%)	0.024
Treatment			
Preoperative α-blockade, n	50 of 58 (86%)	17 of 33 (52%)	<0.001
Duration, d, median (range)	26 (1 to 50)	4 (1 to 10)	0.013
Elective surgery, n	10 (16%)	-	-
Urgent surgery, n	54 (84%)	-	-
Time from crisis to surgery, d, median (range)	42 (3 to 290)	3 (0 to 20)	<0.001
Laparoscopic surgery, n	8 of 59 (14%)	0	0.002
Perioperative outcome			
Intraoperative complications, n	13 of 31 (42%)	20 of 25 (80%)	<0.001
Postoperative complications, n	13 of 40 (33%)	15 of 2 (71%)	0.047
Duration of postoperative hospital stay, d, mean	15	25	0.135
Mortality, n	0	6 (18%)	0.002

[a] Including fever, ileus, acute abdomen, bowel ischemia, pancreatitis, acidosis, peripheral thrombosis, skin infarction, diffuse intravascular coagulation, exanthema, and rhabdomyolysis.

After 1990, even with anticipated better techniques and more advanced technology, complication rates remained high in the emergency group: 77% intraoperative complications and 70% postoperative complications versus 23% and 20% respectively, in the elective and urgent group (P = 0.019 and P = 0.014, respectively). There was one death in the emergency group and none in the elective or urgent group; the difference did not reach statistical significance (P = 0.310).

Discussion

We present the largest series to date of patients with pheochromocytoma crisis. We analyzed the medical and surgical treatment strategies and outcome, both in our series and in the literature. We identified three surgical treatment strategies: elective, urgent, and emergency resection of the pheochromocytoma.

None of the patients in our series underwent emergency pheochromocytoma resection without medical stabilization. All but one patient with crisis in our series were first stabilized and treated with α-blockade prior to surgery. Fifteen patients were discharged from hospital and underwent elective surgery at a later time. There was no mortality in our series, and all but one patient underwent laparoscopic resection.

In our series, the decision regarding elective or urgent surgery was usually based on clinical presentation and clinical judgment, as well as social factors, without predetermined criteria in this retrospective review. All patients were stabilized and adequately α-blocked prior to surgery. Although we did not have an objective measure for severity of illness, the urgently operated group appeared to have a higher level of illnesses with more ICU admissions and more IABP use, and tended to have multiorgan involvement. This higher level of crisis presentation may explain more postoperative complications and longer postoperative hospital stay in this group compared with the elective group. Although the urgently operated group might be sicker with more severe crisis complications, there was no significant correlation with the catecholamines and metabolites levels, which were similar in both groups. This lack of correlation may be due to small numbers presented in each group. On the other hand, there were higher catecholamines and metabolites levels in the crisis group in comparison with the noncrisis group. Others have demonstrated that higher hormone levels correlate with high blood pressure at presentation and hemodynamic instability during pheochromocytoma resection.[27]

Although preoperative medications and improved surgical and anesthetic technique have largely improved the perioperative mortality associated with resection of pheochromocytoma; surgery in poorly prepared patients can lead to serious morbidity and mortality.[8] While our own series did not have patients who were operated emergently, our findings from our literature review support this conclusion. Even in the later era with more refined surgical and anesthetic techniques, there were more intraoperative and postoperative complications in the group that was operated on emergently. Although it was not statistically different, either due to under reporting of deaths or type 2 error, there was one death in the emergency group versus no death in the elective and urgent group.

We had no mortality in our series; the elective and urgent group from the literature review also had no deaths, even prior to 1990. It is interesting to note that during the later era from 1991 to 2011, the time period approximating that of our series, the elective and urgent group from the literature review had a postoperative complication rate of 20%, quite similar to ours of 24%. The intraoperative complication rate was 23% versus 4% in our series. The lower intraoperative complication rate in our series is perhaps due to the use of laparoscopic surgery. These numbers are in contrast to the emergency group who had significantly higher rates of complications. Our findings suggest that pheochromocytoma crisis should not be treated as a surgical emergency.

Table 6. Outcome of Surgery for Pheochromocytoma Crisis in Literature Before versus After 1990

Characteristics	Surgery		*P* Value
	Before 1990, *n* = 38	After 1990, *n* = 59	
Type of surgery			
Elective, n	1 (3%)	9 (15%)	0.083
Urgent, n	22 (58%)	32 (54%)	0.885
Emergency, n	15 (39%)	18 (31%)	0.490
Perioperative outcome, n			
Intraoperative complications	20 of 30 (67%)	13 of 27 (48%)	0.252
Postoperative complications	15 of 26 (58%)	13 of 33 (39%)	0.256
Mortality	5 (13%)	1 (2%)	0.064

Table 7. Outcome of Elective and Urgent versus Emergency Surgery for Pheochromocytoma Crisis in Literature Before 1990

Characteristics	Patients		*P* Value
	Elective and Urgent Surgery, *n* = 23	Emergency Surgery, *n* = 15	
Intraoperative complications, n	10 of 18 (56%)	10 of 12 (84%)	0.236
Postoperative complications, n	9 of 17 (53%)	6 of 9 (67%)	0.797
Mortality, n	0	5 (33%)	0.052

Table 8. Outcome of Elective and Urgent versus Emergency Surgery for Pheochromocytoma Crisis in Literature After 1990

Characteristics	Patients		*P* Value
	Elective and Urgent Surgery, *n* = 40	Emergency Surgery, *n* = 18	
Intraoperative complications, n	3 of 13 (23%)	10 of 13 (77%)	0.019
Postoperative complications, n	4 of 20 (20%)	9 of 13 (70%)	0.014
Mortality, n	0	1 (6%)	0.310

It may seem intuitive that removing the source of the crisis presentation, i.e. pheochromocytoma, will most quickly resolve or improve the crisis, however, this approach may increase mortality and morbidity. Studies by Brown et al[28] and Kobayashi et al[29] demonstrated high mortality associated with emergency surgery in patients with ruptured pheochromocytoma or pheochromocytoma hemorrhage. The prognosis is already grim in those patients, and massive catecholamine release may occur during surgical manipulation of the tumor when abdominal exploration is made to stop bleeding, leading to significant hemodynamic instability.

While our approach to pheochromocytoma crisis is always medical stabilization and adequate α-blockade prior to surgery, the median time from onset of pheochromocytoma crisis to surgery of 57 days (range 11 to 536) is longer than what we would prefer. We typically recommend surgery within one month of hospital discharge. One patient with neurofibromatosis type 1 and bilateral pheochromocytoma did not want to be operated and was maintained on phenoxybenzamine. She consented to surgery after 1.5 years of her crisis presentation. Operative timing also depended on insurance and social factors, which we could not control. Nevertheless, the 15 patients who were operated electively were stable on α-blockade without recurrent pheochromocytoma crisis, and nobody died while waiting to have surgery. This finding suggests that for some patients who present with pheochromocytoma crisis, it is safe to discharge them and to perform surgery at a later time.

Medical stabilization for pheochromocytoma crisis requires an individualized approach depending on clinical presentation. Extraordinary efforts may be needed to initially stabilize the patient. In our study, four crisis patients with significant cardiomyopathy or cardiogenic shock were successfully treated with IABP. Others have also reported successful use of IABP to treat and stabilize pheochromocytoma-induced cardiogenic shock.[5,6,11,14,22,24,30] Huang et al[31] and Suh et al[32] reported the use of extracorporeal membrane oxygenation (ECMO) in treating cardiogenic shock.

We routinely use phenoxybenzamine, a noncompetitive α-blocker, as the preoperative α-blockade agent for at least 10 days prior to surgery. We add atenolol or metoprolol to control tachycardia after adequate α-blockade. Most patients who were well prepared in this manner did not have intraoperative complications in our series. Others have reported successful use of selective nonspecific α-blockers – such as prazosin, doxazosin, and terazosin[33,34] – as well as calcium channel blockers.[35] However, there have been no randomized controlled trials comparing these agents to determine the best antihypertensive or blockade agent for preoperative preparation.

It is important to note that hyperglycemia can be a complication of pheochromocytoma and hypoglycemia can rarely present as a postoperative complication (one patient in the crisis group, no patients in the noncrisis group). In our series, 28% of patients in the crisis group versus 14% in the noncrisis group had diabetes mellitus. Higher levels of catecholamines and metabolites in the crisis patients may increase the risk of abnormal carbohydrate metabolism.[36] Postoperative glucose monitoring is important in patients who developed hyperglycemia due to

pheochromocytoma, to identify potentially life-threatening hypoglycemia.

Laparoscopic removal of pheochromocytomas and paragangliomas is now the preferred surgical technique because it reduces postoperative morbidity, hospital stay, and expense in comparison with laparotomy.[37,38] We demonstrate that laparoscopy can also be performed safely in patients presenting with pheochromocytoma crisis after medical stabilization and α-blockade. Twenty-four (96%) of our pheochromocytoma crisis patients were operated upon laparoscopically, with three (12%) conversions to open or hand-assisted operation. Conversion to open operation was required in one case because of tumor size (12 cm). Conversion to hand-assisted operation was necessary in two patients due to adhesion of the tumor to surrounding tissue (one case of malignancy). The conversion rate in our crisis patients is similar to the conversion rate in our noncrisis patients (P = 0.174), although the overall numbers are small.

One major limitation of our study is its retrospective design, resulting in bias in patient selection with respect to mortality, treatment strategies, and timing of surgery. Some patients might have died prior to transfer to our institution for tertiary care. Patients with pheochromocytoma crisis were gravely ill and already at a high risk for mortality, and some might not have benefitted from any treatment strategy. Pheochromocytoma crisis is rare and a prospective randomized study is unlikely. Although we frequently received requests for emergency resection for those patients transferred to our institution, our approach has been medical stabilization followed by adequate α-blockade prior to surgery. This study demonstrates that this strategy is safe and effective.

In conclusion, we present the largest series of pheochromocytoma crisis to date. We analyzed our series and the cases in the literature and found that emergency surgery may carry higher perioperative complications and mortality. Medical stabilization followed by appropriate α-blockade is safe and effective and pheochromocytoma crisis should be treated as a medical emergency rather than a surgical emergency. We acknowledge that an emergency resection may be required in cases of tumor rupture and uncontrolled bleeding, but it should be the exception rather than the rule.

Conclusion

Management of patients with pheochromocytoma crisis depends on the clinical presentation; however, it should always include initial stabilization and subsequent α- and, if necessary, β-blockade in combination with elective or urgent surgery. Emergency resection of pheochromocytoma is associated with high surgical morbidity and mortality and should be avoided.

Appendix A

Predefined Search Terms

Pheochromocytoma

Pheochromocytoma [Mesh] OR phaeochromocytoma OR paraganglioma [Mesh] OR "*epinephrine-producing tumor" OR "catecholamine-producing tumor" OR "*adrenaline-producing tumor" OR "*epinephrine-secreting tumor" OR "catecholamine-secreting tumor" OR "*adrenaline-secreting tumor" OR "chromaffin* tumor".

Crisis

Crisis OR shock OR decompensation OR emergency OR "myocardial infarction" OR "heart infarction" OR cardiomyopath* OR "cardiac failure" OR "pulmonary edema" OR ARDS OR "acute respiratory distress syndrome" OR "adult respiratory distress syndrome" OR "cerebrovascular event" OR "cerebrovascular accident" OR seizure* OR "renal failure" OR "kidney failure" OR "liver failure" OR "hepatic failure".

Exclusion Criteria

Animal studies
Systematic reviews
Death prior to surgery, no surgery
Not a pheochromocytoma crisis[a]
Not full text available

Inclusion Criteria

Human studies
English studies
Original data
Pheochromocytoma crisis[a]
Adrenalectomy or pheochromocytoma resection, paraganglioma resection

[a] Pheochromocytoma crisis is defined as severe hypertension and/or severe hypotension, with end organ damage (cardiovascular decompensation, myocardial infarction, pulmonary edema, adult respiratory distress syndrome, cerebrovascular accident, renal failure, or liver failure).

Appendix B

Table 9.

Table 9. Pheochromocytoma Crisis Patients in Literature

Author, y	Sex, Age, y	Manifestation	Tumor Size, cm	α-Blockade	Time to Surgery, d	Type of Surgery[a]		Complications		Admission ICU, Ward, d
								Intraoperative	Postoperative	
Cahill, 1944	F, 53	Shock, syncope	ND	-	0	Emergency	Open	Death	-	-
McFarland, 1951[b]	F, 54	Shock, HTN, acute abdomen	4 (IOF)	-	0	Emergency	Open	Hypotension	Hypotension, hypoxemia, abdominal distention	ND, 13
Gilliland, 1951[b]	M, 29	Cardiogenic shock, PE, acute abdomen	13 (path)	-	0	Emergency	Open	Death	-	-
Terry, 1958	F, 18	HTN-hypotension, cardiogenic shock, fever	3	+	3	Urgent	Open	Hypotension	Hypotension	ND
French, 1961	F, 53	HTN, cardiogenic shock, MI, arrhythmia, ileus	7 (path)	+	9	Urgent	Open	HD instable	Hypotension	ND, 14
Mattman, 1961	M, 45	HTN, MI	10 (IOF)	-	26	Urgent	Open	HD instable	Hypotension	3, ND
Ramsay, 1962	M, 52	HTN-hypotension, angina, arrhythmia, peripheral thrombosis	5 (IOF)	-	50	Urgent	Open	HD instable	Hypotension	0, > 21
Hamrin, 1962	F, 42	Hypotensive shock, encephalopathy, fever	200 g	+	> 61	Urgent	Open	ND	Orthostatic hypotension	ND
Leather, 1962	M, 15	HTN, arrhythmia, CVA, seizures	35 g	-	> 10	Urgent	Open	ND	Hypotension	ND, > 14
Huston, 1965[b]	F, 20	Hypotensive shock, acute abdomen, ileus	13 (IOF)	-	0	Emergency	Open	Hypotension	Hypotension, transfusion	ND, 15
Engelman, 1968 (intrathoracic)	M, 59	Hypotension, cardiogenic shock, arrhythmia, CVA	6 (IOF)	+	290	Urgent	Open	Hypotensive shock, bleeding, arrhythmia (VF, asystole), coma	None	ND, 92
Page, 1969	M, 39	HTN, cardiomyopathy, MI, arrhythmia, PE	3 (IOF)	-	26	Urgent	Open	HD instable, arrhythmia	None	ND

Delaney, 1969	F, 32	HTN, hypotensive shock, syncope	6 (IOF)	+ (1 d)	14	Urgent	Open	None	None	ND
Armstrong, 1972	F, 47	Cardiomyopathy, arrhythmia, PE	86 g	+ (5 d)	> 5	Urgent	Open	Arrhythmia, HD instable	Cardiogenic shock, arrhythmia (AV-block), PE	0, 14
Radtke, 1975	F, 59	HTN, MI, CVA, encephalopathy	5	+	22	Urgent	Open	None	None	ND
Radtke, 1975	F, 41	Syncope, fever, peripheral skin infarction (spasm)	12 (IOF)	+	24	Urgent	Open	ND	None	ND
Van Way, 1976	F, 76	Shock, HTN	5	+ (1 d)	1	Emergency	Open	Hypotension, transfusion	Circulatory overload	ND, 10
Atuk, 1977	M, 15	HTN-hypotension, cardio-myopathy, MI, PE, RF	3 (IOF)	+	41	Urgent	Open	ND	ND	0, 6
Munk, 1977	F, 28	HTN, cardiomyopathy, PE	317 g	+ (7 d)	19	Urgent	Open	HTN	ND	ND
Freier, 1980	ND	'Crisis', RF	ND	+	ND	Emergency	Open	ND	Hypotension, RF, death	-
Greatorex, 1984	M, 46	Shock, HTN, angina	ND	-	0	Emergency	Open	None	None	ND, 10
Suzuki, 1984	F, 40	Shock, HTN	7	-	92	Urgent	Open	None	ND	ND
Jones, 1985	M, 55	Shock, HTN, cardiomyo-pathy, acute abdomen	22	-	0	Emergency	Open	PE	Death	-
Jones, 1985[b]	F, 77	Shock, HTN, arrhythmia, acute abdomen	3 (path)	-	0	Emergency	Open	ND	Cardiac failure, hypotension, death	-
Stenström, 1985	F, 39	HTN, arrhythmia (AF), PE, CVA	20 g	+ (17 d)	> 61	Urgent	Open	None	None	ND
Scully, 1986	M, 34	HTN, PE, CVA, encephalopathy, RF, fever	8	+ (10 d)	20	Emergency	Open	Brief asystole	None	ND
Friedman, 1986	M, 14	HTN, cardiomyopathy, MI, arrhythmia	6	+	21	Urgent	Open	ND	None	ND
Shaw, 1987	M, 41	Cardiogenic shock, MI, PE	3	-	> 42	Elective	Open	HTN	Transient agitation and aggression	ND
Blom, 1987	M, 43	Shock, HTN, PE	ND	+	ND	Urgent	Open	None	ND	ND
Schorr, 1987	M, 60	HTN, arrhythmia	5	+ (14 d)	> 54	Urgent	Open	None	Arrhythmia	2, ND

Newell, 1988	F, 62	HTN, hypotensive shock, cardiorespiratory failure, MI, encephalopathy, RF, DIC, fever, acidosis	10	+	4	Emergency	Open	ND	Quadriparese, dysarthry	ND
Newell, 1988	F, 50	HTN-hypotension, respiratory failure, encephalopathy, RF, rhabdomyolysis, fever, acidosis	7	+	7	Emergency	Open	ND	ND	ND
Scully, 1988	F, 26	Hypotension, cardiomyo-pathy, MI, CVA, DIC, fever	6.5	+	> 8	Urgent	Open	HTN	ND	ND
Scully, 1989	F, 48	Hypotension, MI, ARDS, fever	12	+ (6 d)	25	Urgent	Open	None	ND	ND
Greaves, 1989[b]	M, 22	Shock, ARDS, acute abdomen	10 (IOF)	-	0	Emergency	Open	HD instable, MI, PE	ND	ND
Terai, 1989	F, 63	HTN-hypotension, cardiogenic shock, MI, PE, acidosis	6	-	33	Urgent	Open	None	None	ND
Sue-Ling, 1989[c]	M, 55	HTN, hypotensive shock, acute abdomen	6 (IOF)	+	ND	Emergency	Open	None	None	ND
Sue-Ling, 1989[b]	M, 63	Hypotensive shock, acute abdomen, ileus	13 (IOF)	-	0	Emergency	Open	Hypotension	Persistent intra-abdominal bleeding (reoperation), bowel ischemia	ND
Nirgiotis, 1990	F, 14	HTN-hypotension, MI, syncope	4	+	ND	Urgent	Open	ND	None	ND, 5
Shemin, 1990	F, 29	HTN, PE, RF, fever	6	+	> 40	Urgent	Open	ND	ND	ND
Salathe, 1992	M, 42	HTN, cardiomyopathy, MI, PE	5.5	+	23	Urgent	Open	None	None	ND
McNeill, 1992	M, 49	HTN, MI, arrhythmia (AF, VES, VF)	4	+ (84 d)	105	Urgent	Open	ND	Hypotension	ND, 42

Hamada, 1993[d]	M, 54	HTN, cardiomyopathy, cardiac arrest, arrhythmia, PE, RF, acidosis, fever	5.9 (IOF)	+	25	Urgent	Open	ND	HTN	4, > 2
Spencer, 1993[b]	M, 45	Hypotensive shock, PE, DIC, acidosis	6 (IOF)	-	0	Emergency	Open	Hypotension	Hypotension	8, 11
Lorz, 1993	F, 65	Hypotension, cardiomyopathy, arrhythmia (VF, VT, AF, atrial flutter), PE, CVA, encephalopathy, RF, LF, DIC, fever, exanthema	4	+ (21 d)	46	Urgent	Open	ND	None	ND
Joshi, 1993	F, 36	HTN, PE, RF	5.5	+ (10 d)	20	Urgent	Open	None	Hypoglycemia	ND, 7
Elian, 1993	M, 41	HTN, cardiomyopathy, cardiac thrombus, PE, renal embolism	4 (IOF)	ND	30	Urgent	Open	ND	ND	ND
Yamanaka, 1994	F, 49	Cardiogenic shock, MI	3	ND	77	Urgent	Open	ND	None	ND
Hatada, 1994	F, 45	PE, RF, LF, acute abdomen, ileus, DIC	11 (IOF)	+	60	Urgent	Open	None	None	ND, 3
Ferguson, 1994	M, 35	Hypotension, cardiogenic shock, PE	ND	+ (16 d)	19	Urgent	Open	ND	None	ND, 10
Nanda, 1995	F, 18	HTN, cardiogenic shock, PE	ND	+	19	Urgent	Open	ND	None	ND, 6
Goswami, 1995	M, 18	HTN, cardiomyopathy, CVA, fever	4	+ (7 d)	92	Urgent	Open	ND	ND	ND
Lamberts, 1996	M, 66	Cardiorespiratory failure, RF, fever	5.8	+	ND	Emergency	Open	None	Proximal muscle weakness	ND
Korzets, 1997	M, 53	HTN, PE, encephalopathy, fever	3	+	> 14	Urgent	Open	ND	ND	ND, 14
Ford, 1997[e]	M, 46	Hypotensive shock, ARDS, fever	5	+ (14 d)	28	Urgent	Open	None	None	ND, 10
Del Rosso, 1997	M, 41	HTN, Cardiogenic shock, MI, ARDS, CVA, RF, LF	5	+	14	Urgent	Open	ND	None	ND
Kokkonen, 1997	F, 46	HTN-hypotension, cardiomyopathy, PE	ND	ND	25	Urgent	Open	None	None	ND, 7

Brueckel, 1998	M, 61	HTN-hypotension, cardiomyopathy	6	+	> 3	Urgent	Open	ND	ND	ND
Kothari, 1998	F, 34	Hypotension, cardiomyopathy, MI, respiratory arrest	4.1	+	> 17	Elective	Open	ND	ND	ND
Mishra, 2000	F, 22	HTN, cardiomyopathy	12; 4	+	ND	Emergency; bilateral	Open	Transfusion	None	ND
May, 2000[f]	F, 34	HTN, hypotensive shock, cardiomyopathy, ARDS, acidosis	6	-	0	Emergency	Open	HD instable, respiratory failure	Hypotension, ARDS	92, ND
Takagi, 2000	M, 52	HTN, cardiomyopathy, PE, RF	3.3	-	9	Urgent	ND	ND	ND	ND
Kaye, 2001	M, 39	HTN, cardiogenic shock, MI, PE, CVA, fever, acidosis	6	+	21	Urgent	Open	None	None	ND
Kohle, 2001	F, 42	Hypotensive shock, PE, RF, acidosis	7	+	31	Urgent	Lap	ND	ND	ND
Kohle, 2001	F, 28	Multiple cardiorespiratory arrests, RF	3.7	+	> 30	Urgent	Lap	ND	ND	ND
Mishra, 2001	F, 44	Hypotensive shock, PE, respiratory failure	12.8	+ (10 d)	42	Elective	Lap	Hypotension	None	ND
Van Iperen, 2001	F, 42	HTN, cardiogenic shock, VF, MI, PE	5; 3.5	+	> 6	Urgent, bilateral	Open	None	None	ND
Maxwell, 2001	F, 66	HTN, hypotensive shock, PE, RF, acidosis	4.5	+	122	Elective	ND	ND	ND	ND
Dagartzikas, 2002	M, 13	HTN, cardiogenic shock, cardiac thrombus, CVA, bilateral peripheral emboli	8.5	+(≥ 3 d)	> 6	Urgent	Open	Hypotension	Hypotension	> 2, ND
Sumino, 2002	F, 39	HTN	5 (IOF)	+	0	Emergency	Open	ND	ND	ND
Bos, 2003[b]	F, 31	Hypotensive shock, cardiac arrest, PE, acidosis	5	-	0	Emergency	Open	Hypotension	Respiratory failure	3, ND

Chan, 2003[b]	F, 35	HTN, hypotensive shock, PE, acidosis	25	-	0	Emergency	Open	Hypotension, bradycardia	Hypotension, cardio-respiratory failure, RF, DIC, death	-
James, 2004	F, 27	HTN, cardiomyopathy, MI	10	+	> 10	Emergency	Open	Hypotension	None	2, 10
James, 2004	M, 19	Shock, HTN, cardiomyopathy, PE	7	+	> 7	Emergency	Open	Hypotension	None	ND
James, 2004	M, 13	HTN, encephalopathy	6	+	13	Emergency	Open	None	ND	4, 4
Brown, 2005	F, 44	HTN, hypotensive shock, cardiomyopathy, recurrent MI,	6.2	+ (10 d)	12	Urgent	Open	Bradycardia	None	ND, 3
Farroni, 2005	M, 36	Cardiomyopathy, VF, syncope	6	+	115	Urgent	ND	ND	ND	ND
Moran, 2006	M, 41	HTN, MI, pulmonary arrest, PE, CVA, RF, LF, fever	10	+	ND	Emergency	Open	PE	ND	4, 10
Van Lennep, 2007	M, 43	HTN-hypotension, PE, RF, LF, rhabdomyolysis	9.4	+	31	Urgent	Open	ND	ND	ND, 61
Siddik-Sayyid, 2007	F, 43	HTN-hypotension, cardiomyopathy, PE, RF, LF, pancreatitis, DIC, fever, acidosis	5.8	+ (2 d)	13	Emergency	Open	HD instable	Persisting RF	ND
Eschen, 2007	F, 44	Hypotension, cardiogenic shock, MI,	8.6	+ (26 d)	31	Urgent	ND	None	None	ND
Takizawa, 2007	M, 32	HTN, cardiomyopathy, MI, PE	5	+ (2 d)	3	Emergency	Open	ND	None	ND
Rashid, 2007	M, 58	Shock, HTN, ARDS	10	+	> 3	Urgent	Open	None	None	ND, 10
Solorzano, 2008	M, 61	HTN-hypotension, cardiomyopathy, PE, RF	12	+	6	Emergency	Open	Hypotension	Hypotension	ND, 31
Rosas, 2008	M, 40	HTN, cardiogenic shock, cardiac arrest, encephalo-pathy, RF, LF, fever	5	-	0	Emergency	Open	ND	ND	ND
Rosas, 2008	F, 39	HTN, MI	6.9	+	14	Urgent	Lap	ND	ND	ND

Zegdi, 2008	F, 51	HTN, cardiac arrest, cardiomyopathy, MI, PE, RF, acidosis,	ND	ND	41	Elective	Lap	ND	ND	ND
De Souza, 2008	F, 31	HTN, cardiomyopathy, PE	9.5	+	ND	Urgent	Lap	ND	ND	ND
Maruyama, 2008	M, 58	HTN, PE, ileus	3	+ (71 d)	85	Elective	Lap	ND	ND	ND, 9
Von Bergen, 2009	M, 17	HTN, cardiomyopathy, MI, PE	6.7	+	> 6	Elective	Open	ND	ND	ND
Rashid-Farokhi, 2009	M, 36	HTN, RF, acidosis	2	ND	ND	Elective	ND	ND	ND	ND
Musuraca, 2009	M, 57	HTN-hypotension, cardiomyopathy, MI	8.5 (IOF)	+	20	Urgent	Open	ND	ND	ND
Uchida, 2010	F, 52	HTN, cardiomyopathy, MI, PE, RF, acidosis	6	+	11	Emergency	Open	HD instable	Hypotension, RF	ND, 95
Zaludik, 2010	F, 39	Cardiogenic shock, MI, PE, RF, acidosis	ND	ND	15	Urgent	Open	None	None	ND, 11
Salinas, 2011	M, 31	Cardiogenic shock	6	-	1	Emergency	Open	None	Hypotension	5, ND
Hosseinnezhad, 2011	F, 76	HTN, cardiomyopathy, MI, arrhythmia, respiratory failure, RF, LF encephalopathy	6.5	+	122	Elective	Lap	ND	ND	ND
Hanna, 2011[g]	M, 38	Hypotensive shock, cardiac arrest, bowel ischemia, acidosis	4; 5	+ (150 d)	160	Elective; bilateral	Lap	ND	ND	ND

Abbreviations: ND, not described; HTN, hypertension; IOF, intraoperative finding; PE, pulmonary edema; path, pathology; MI, myocardial infarction; HD, hemodynamic; CVA, cerebrovascular accident; VF, ventricular fibrillation; AV, atrioventricular; RF, renal failure; AF, atrial fibrillation; DIC, diffuse intravascular coagulation; ARDS, adult respiratory distress syndrome; VES, ventricular extrasystoles; VT, ventricular tachycardia; LF, liver failure; lap, laparoscopic; ICU, intensive care unit.

[a] Type of surgery: elective, after initial hospital discharge and stabilization; urgent, after stabilization and during the same hospitalization; emergency, immediately after crisis presentation or because of clinical deterioration without appropriate blockade or preoperative management.

[b] Not known pheochromocytoma prior to surgery.

[c] Patient underwent emergency operation for suspected ruptured aortic aneurysm. Pheochromocytoma was removed during a second operation.

[d] Resuscitated on hospital day 20.

[e] Fine-needle biopsy on hospital day 14 induced recurrent shock.

[f] Underwent coil embolization for active bleeding of the right lumbar artery.

[g] Patient underwent two complicated emergency laparotomies and coil embolization for adrenal hemorrhage. Pheochromocytoma was removed during a third operation.

References

1. Reisch N, Peczkowska M, Januszewicz A, Neumann HP. Pheochromocytoma: presentation, diagnosis and treatment. *J Hypertens* 2006; 24(12):2331-2339.
2. Guerrero MA, Schreinemakers JM, Vriens MR, et al. Clinical spectrum of pheochromocytoma. *J Am Coll Surg* 2009; 209(6):727-732.
3. Van Vliet PD, Burchell HB, Titus JL. Focal myocarditis associated with pheochromocytoma. *N Engl J Med* 1966; 274(20):1102-1108.
4. Ferguson KL. Imipramine-provoked paradoxical pheochromocytoma crisis: a case of cardiogenic shock. *Am J Emerg Med* 1994; 12(2):190-192.
5. May EE, Beal AL, Beilman GJ. Traumatic hemorrhage of occult phaeochromocytoma: a case report and review of the literature. *Am Surg* 2000; 66(8):720-724.
6. Kaye J, Edlin S, Thompson I, Leedma PJ. Pheochromocytoma presenting as life-threatening pulmonary edema. *Endocrine* 2001; 15(2):203-204.
7. Sawaki D, Otani Y, Sekita G, et al. Pheochromocytoma complicated with refractory paralytic ileus dramatically improved with intravenous administration of alpha-adrenergic receptor antagonist, phentolamine. *J Clin Gastroenterol* 2003; 37(2):194.
8. Chan MK, Tse HW, Mok FP. Ruptured phaeochromocytoma lesson in acute abdomen. *Hong Kong Med J* 2003; 9(3):221-223.
9. Raman GV. Phaeochromocytoma presenting with cardiogenic shock and acute renal failure. *J Hum Hypertens* 1987; 1(3):237-238.
10. Tack CJ, Lenders JW. Pheochromocytoma as a cause of blue toes. *Arch Intern Med* 1993; 153(17):2061.
11. Zaludik J, Schuitemaker F, DeWaal R, Veldjuijzen B, Van der Meer N. Severe lactate acidosis and cardiogenic shock: a rare manifestation of a phaeochromocytoma. *Anaesth Intensive Care* 2010; 38(3):593-594.
12. Newell, KA, Prinz RA, Pickleman J, et al. Phaeochromocytoma multisystem crisis. A surgical emergency. *Arch Surg* 1988; 123(8):956-959.
13. Greaves DJ, Barrow PM. Emergency resection of phaeochromocytoma presenting with hyperamylasaemia and pulmonary oedema after abdominal trauma. *Anaesth* 1989; 44(10):841-842.
14. Takagi S, Miyazaki S, Fujii T, et al. Dexamethasone-induced cardiogenic shock rescued by percutaneous cardiopulmonary support (PCPS) in a patient with pheochromocytoma. *Jpn Circ J* 2000; 64(10):785-788.
15. Jones DJ, Durning P. Phaeochromocytoma presenting as an acute abdomen: report of two cases. *Br Med J (Clin Res Ed)* 1985; 291(6504):1267-1268.
16. Plouin PF, Menard J, Corvol P. Hypertensive crisis in patient with phaeochromocytoma given metoclopramide. *Lancet* 1976; 2(7999):1357-1358.
17. Eisenhofer G, Rivers G, Rosas AL, Quezado Z, Manger WM, Pacak K. Adverse drug reactions in patients with phaeochromocytoma: incidence, prevention and management. *Drug Saf* 2007; 30(11):1031-1062
18. Kinney MA, Narr BJ, Warner MA. Perioperative management of pheochromocytoma. *J Cardiothor Vasc Anesth* 2002; 16(6):359-369.
19. Lo CY, Lam KY, Wat MS, Lam KS. Adrenal pheochromocytoma remains a frequently overlooked diagnosis. *Am J Surg* 2000; 179(3):212-215.

20. Bos JC, Toorians AW, van Mourik JC, van Schijndel RJ. Emergency resection of an extra-adrenal phaeochromocytoma: wrong or right? A case report and a review of literature. *Neth J Med* 2003; 61(8):258-265.
21. Solorzano CC. Pheochromocytoma presenting with multiple organ failure. *Am Surg* 2008; 74(11):1119-1121.
22. Uchida N, Ishiguro K, Suda T, Nishimura M. Pheochromocytoma multisystem crisis successfully treated by emergency surgery: report of a case. *Surg Today* 2010; 40(10):990-996.
23. Freier DT, Eckhauser FE, Harrison TS. Pheochromocytoma. A persistently problematic and still potentially lethal disease. *Arch Surg* 1980; 115(4):388-391.
24. Salinas CL, Gómez Beltran OD, Sánchez-Hidalgo JM, Bru RC, Padillo FJ, Rufián S. Emergency adrenalectomy due to acute heart failure secondary to complicated pheochromocytoma: a case report. *World J Surg Oncol* 2011; 9:49.
25. Kolhe N, Stoves J. Richardson D, Davison AM, Gilbey S. Hypertension due to phaeochromocytoma—an unusual cause of multiorgan failure. *Nephrol Dial Transplant* 2001; 16(10):2001-2004.
26. Imperato-McGinley J, Gautier T, Ehlers K, Zullo MA, Goldstein DS, Vaughan ED Jr. Reversibility of catecholamine-induced dilated cardiomyopathy in a child with a pheochromocytoma. *N Engl J Med* 1987; 316(13):793-797.
27. Bruynzeel H, Feelders RA, Groenland TH, et al. Risk factors for hemodynamic instability during surgery for pheochromocytoma. *J Clin Endocrinol Metab* 2010; 95(2):678–685.
28. Brown H, Goldberg PA, Selter JG, et al. Hemorrhagic pheochromocytoma associated with systemic corticosteroid therapy and presenting as myocardial infarction with severe hypertension. *J Clin Endocrinol Metab* 2005; 90(1):563–569.
29. Kobayashi T, Iwai A, Takahashi R, Ide Y, Nishizawa K, Mitsumori K. Spontaneous rupture of adrenal pheochromocytoma: review and analysis of prognostic factors. *J Surg Oncol* 2005; 90(1):31-35.
30. Yamanaka O, Yasumasa F, Nakamura T, et al. "Myocardial stunning"-like phenomenon during a crisis of pheochromocytoma. *Jpn Circ J* 1994; 58(9):737-742.
31. Huang JH, Huang SC, Chou NK. Extracorporeal membrane oxygenation rescue for cardiopulmonary collapse secondary to pheochromocytoma: report of three cases. *Intensive Care Med* 2008; 34(8):1551-1552.
32. Suh IW, Lee CW, Kim YH. Catastrophic catecholamine-induced cardiomyopathy mimicking acute myocardial infarction, rescued by extracorporeal membrane oxygenation (ECMO) in pheochromocytoma. *J Korean Med Sci* 2008; 23(2):350-354.
33. Weingarten TN, Cata JP, O'Hara JF, et al. Comparison of two preoperative medical management strategies for laparoscopic resection of pheochromocytoma. *Urology* 2010; 76(2):508.
34. Prys-Roberts C, Farndon JR. Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. *World J Surg* 2002; 26(8):1037-1042.
35. Lebuffe G, Dosseh ED, Tek G, et al. The effect of calcium channel blockers on outcome following the surgical treatment of phaeochromocytomas and paragangliomas. *Anaesth* 2005; 60(5):439-444.
36. Wiesner TD, Blüher M, Windgassen M, Paschke R. Improvement of insulin sensitivity after adrenalectomy in patients with pheochromocytoma. *J Clin Endocrinol Metab* 2003; 88(8):3632-3636.

37. Shen WT, Grogan R, Vriens M, Clark OH, Duh QY. One hundred two patients with pheochromocytoma treated at a single institution since the introduction of laparoscopic adrenalectomy. *Arch Surg* 2010; 145(9):893-897.
38. Walz MK, Peitgen K, Neumann HP, Janssen OE, Philipp T, Mann K. Endoscopic treatment of solitary, bilateral, multiple, and recurrent pheochromocytomas and paragangliomas. *World J Surg* 2002; 26(8):1005-1012.

References Appendix B

1. Cahill J. Hormonal tumors of the adrenal medulla. *Pa J Med* 1944 47(3):655–667.
2. McFarland GE Jr, Bliss WR. Hemorrhage from spontaneous rupture of a pheochromocytoma of the right adrenal gland; a case report. *Ann Surg* 1951; 133(4):404-407.
3. Gilliland IC, Daniel O. Phaeochromocytoma presenting as an abdominal emergency. *Br Med J* 1951; 2(4726):275-277.
4. Terry RB, Tobin JR Jr, O'Connor RB. Intravenous phentolamine for phaeochromocytoma and adrenaline shock. *Br Med J* 1958; 2(5099):771-772.
5. French C, Campagna FA. Pheochromocytoma with shock, marked leukocytosis, and unusual electrocardiograms. Case report and review of the literature. *Ann Intern Med* 1961; 55:127-134.
6. Mattman PE. Successful removal of a pheochromocytoma four weeks after acute myocardial infarction. *Am J Cardiol* 1961; 8:426-430.
7. Ramsay ID, Langlands JH. Phaeochromocytoma with hypotension and polycythaemia. *Lancet* 1962; 2(7247):126-128.
8. Hamrin B. Sustained hypotension and shock due to an adrenaline-secreting phaeochromocytoma. *Lancet* 1962; 2(7247):123-124.
9. Leather HM, Shaw DB, Cates JE, Walker RM. Six cases of phaeochromocytoma with unusual clinical manifestations. *Br Med J* 1962; 1(5289):1373-1378.
10. Huston JR, Stewart RC. Hemorrhagic phaeochromocytoma with shock and abdominal pain. *Am J Med* 1965; 39:502-504.
11. Engelman K, Hammond WG. Adrenaline production by an intrathoracic phaeochromocytoma. *Lancet* 1968; 1(7543):609-611.
12. Page LB, Raker JW, Berberish FR. Pheochromocytoma with predominant epinephrine secretion. *Am J Med* 1969; 47(4):648-652.
13. Delaney JP, Paritzky AZ. Necrosis of a pheochromocytoma with shock. *N Engl J Med* 1969; 280(25):1394-1395.
14. Armstrong BK, Beahan PG, Leedman RL. Phaeochromocytoma with catecholamine cardiomyopathy successfully treated surgically. *Aust N Z J Med* 1972; 2(4):402-404.
15. Radtke WE, Kazmier FJ, Rutherford BD, Sheps SG. Cardiovascular complications of pheochromocytoma crisis. *Am J Cardiol* 1975; 35(5):701-705.
16. Van Way CW 3rd, Faraci RP, Cleveland HC, Foster JF, Scott HW Jr. Hemorrhagic necrosis of pheochromocytoma associated with phentolamine administration. *Ann Surg* 1976; 184(1):26-30.
17. Atuk NO, Teja K, Mondzelewski P, Turner SM, Selden R. Avascular necrosis of pheochromocytoma followed by spontaneous remission. *Arch Intern Med* 1977; 137(8):1073-1075.
18. Munk Z, Tolis G, Jones W, Fallen E, McLean P. Pheochromocytoma presenting with pulmonary edema and hyperamylasemia. *Can Med Assoc J* 1977; 116(4):357-359.
19. Freier DT, Eckhauser FE, Harrison TS. Pheochromocytoma. A persistently problematic and still potentially lethal disease. *Arch Surg* 1980; 115(4):388-391.
20. Greatorex RA, Raftery A. Intraperitoneal rupture of a phaeochromocytoma. *J R Soc Med* 1984; 77(6):513-514.
21. Suzuki T, Mori C, Asakage H, et al. Pheochromocytoma with remission following phentolamine-induced shock. *Urology* 1984; 23(6):582-524.

22. Jones DJ, Durning P. Phaeochromocytoma presenting as an acute abdomen: report of two cases. *Br Med J (Clin Res Ed)* 1985; 291(6504):1267-1268.
23. Stenström G, Holmberg S. Cardiomyopathy in phaeochromocytoma: report of a case with a 16-year follow-up after surgery and review of the literature. *Eur Heart J* 1985; 6(6):539-544.
24. No authors listed. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 6. A 34-year-old man with hypertension and episodes of flushing, nausea, and vomiting. *N Engl J Med* 1986; 314(7):431-439.
25. Friedman E, Mandel M, Katznelson D, Sack J. Pheochromocytoma and hydralazine-induced myocardial ischaemia in a 14-year-old boy. *Eur J Pediatr* 1986; 145(4):318-320.
26. Shaw TR, Rafferty P, Tait GW. Transient shock and myocardial impairment caused by phaeochromocytoma crisis. *Br Heart J* 1987; 57(2):194-198.
27. Blom HJ, Karsdorp V, Birnie R, Davies G. Phaeochromocytoma as a cause of pulmonary oedema. *Anaesth* 1987; 42(6):646-650.
28. Schorr RT, Rogers SN. Intraoperative cardiovascular crisis caused by glucagon. *Arch Surg* 1987; 122(7):833-834.
29. Newell, KA, Prinz RA, Pickleman J, et al. Phaeochromocytoma multisystem crisis. A surgical emergency. *Arch Surg* 1988; 123(8):956-959.
30. No authors listed. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 15. A 26-year-old woman with cardiomyopathy, multiple strokes, and an adrenal mass. *N Engl J Med* 1988; 318(15):9709-9781.
31. No authors listed. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 45. A 48-year-old woman with acute respiratory failure and a left suprarenal mass. *N Engl J Med* 1989; 321(19):1316-1329.
32. Greaves DJ, Barrow PM. Emergency resection of phaeochromocytoma presenting with hyperamylasaemia and pulmonary oedema after abdominal trauma. *Anaesth* 1989; 44(10):841-842.
33. Sue-Ling HM, Foster ME, Wheeler MH, McMahon MJ. Spontaneous rupture of phaeochromocytoma mimicking leaking aortic aneurysm. *J R Soc Med* 1989; 82(1):53-54.
34. Nirgiotis JG, Andrassy RJ. Pheochromocytoma and acute myocardial infarction. *South Med J* 1990; 83(12):1478-1480.
35. Shemin D, Cohn PS, Zipin SB. Pheochromocytoma presenting as rhabdomyolysis and acute myoglobinuric renal failure. *Arch Intern Med* 1990; 150(11):2384-2385.
36. Salathe M, Weiss P, Ritz R. Rapid reversal of heart failure in a patient with phaeochromocytoma and catecholamine-induced cardiomyopathy who was treated with captopril. *Br Heart J* 1992; 68(5):527-528.
37. McNeill AJ, Adgey AA, Wilson C. Recurrent ventricular arrhythmias complicating myocardial infarction in the presence of phaeochromocytoma. *Br Heart J* 1992; 67(1):97-98.
38. Hamada N, Akamatsu A, Joh T. A case of pheochromocytoma complicated with acute renal failure and cardiomyopathy. *Jpn Circ J* 1993; 57(1):84-90.
39. Spencer E, Pycock C, Lytle J. Phaeochromocytoma presenting as acute circulatory collapse and abdominal pain. *Intensive Care Med* 1993; 19(6):356-357.

40. Lorz W, Cottier C, Imhof E, Gyr N. Multiple organ failure and coma as initial presentation of pheochromocytoma in a patient with multiple endocrine neoplasia (MEN) type II A. *Intensive Care Med* 1993; 19(4):235-238.
41. Joshi R, Manni A. Pheochromocytoma manifested as noncardiogenic pulmonary edema. *South Med J* 1993; 86(7):826-828.
42. Elian D, Harpaz D, Sucher E, Kaplinsky E, Motro M, Vered Z. Reversible catecholamine-induced cardiomyopathy presenting as acute pulmonary edema in a patient with pheochromocytoma. *Cardiology* 1993; 83(1-2):118-120.
43. Yamanaka O, Yasumasa F, Nakamura T, et al. "Myocardial stunning"-like phenomenon during a crisis of pheochromocytoma. *Jpn Circ J* 1994; 58(9):737-742.
44. Hatada T, Nakai T, Aoki I, et al. Acute abdominal symptoms caused by hemorrhagic necrosis of a pheochromocytoma: report of a case. *Surg Today* 1994; 24(4):363–367.
45. Ferguson KL. Imipramine-provoked paradoxical pheochromocytoma crisis: a case of cardiogenic shock. *Am J Emerg Med* 1994; 12(2):190–192.
46. Nanda AS, Feldman A, Liang CS. Acute reversal of pheochromocytoma-induced catecholamine cardiomyopathy. *Clin Cardiol* 1995; 18(7):421-423.
47. Goswami R, Tandon N, Singh B, Kochupillai N. Adrenal tumour, congestive heart failure and hemiparesis in an 18-year-old male. A clinical-pathological conference. *Int J Cardiol* 1995; 49(3):233-238.
48. Lamberts R, Kreuzer H. Pheochromocytoma-induced multiorgan failure. An internal medicine and surgical emergency. *Dtsch Med Wochenschr* 1996; 121(15):479-484.
49. Korzets A, Floro S, Ori Y, Weizer N, Gruzman C. Clomipramine-induced pheochromocytoma crisis: a near fatal complication of a tricyclic antidepressant. *J Clin Psychopharmacol* 1997; 17(5):428-430.
50. Ford J, Rosenberg F, Chan N. Pheochromocytoma manifesting with shock presents a clinical paradox: a case report. *Can Med Ass J* 1997; 157(7):923-925.
51. Del Rosso A, Fradella G, Russo L, et al. Pheochromocytoma crisis caused by contemporary ergotamine, caffeine, and nimesulide administration. *Am J Med Sci* 1997; 314(6):396-398.
52. Kokkonen JO, Lammintausta O, Luomanmäki K. Acute heart failure and transient low voltage in electrocardiogram after massive catecholamine release from a phaeochromocytoma. *Eur Heart J* 1997; 18(8):1357.
53. Brueckel J, Boehm BO. Crisis after angiography. *Lancet* 1998; 352(9136):1278.
54. Kothari SN, Kisken WA. Dexamethasone-induced congestive heart failure in a patient with dilated cardiomyopathy caused by occult pheochromocytoma. *Surgery* 1998; 123(1):102-105.
55. Mishra AK, Agarwal G, Kapoor A, Agarwal A, Bhatia E, Mishra SK. Catecholamine cardiomyopathy in bilateral malignant pheochromocytoma: successful reversal after surgery. *Int J Cardiol* 2000; 76(1):89-90.
56. May EE, Beal AL, Beilman GJ. Traumatic hemorrhage of occult phaeochromocytoma: a case report and review of the literature. *Am Surg* 2000; 66(8):720-724.
57. Takagi S, Miyazaki S, Fujii T, et al. Dexamethasone-induced cardiogenic shock rescued by percutaneous cardiopulmonary support (PCPS) in a patient with pheochromocytoma. *Jpn Circ J* 2000; 64(10):785-788.
58. Kaye J, Edlin S, Thompson I, Leedma PJ. Pheochromocytoma presenting as life-threatening pulmonary edema. *Endocrine* 2001; 15(2):203-204.

59. Kohle N, Stoves J, Richardson D, Davison AM, Gilbey S. Hypertension due to phaeochromocytoma – an unusual cause of multiorgan failure. *Nephrol Dial Transplant* 2001; 16(10):2100-2104.
60. Mishra AK, Agarwal G, Agarwal A, Mishra SK. Cystic phaeochromocytoma presenting as an acute abdomen with shock. *Eur J Surg* 2001; 167(11):863-865.
61. Van Iperen CE, Giezen J, Kramer WL, Lips CJ, Bartelink AK. Acute dyspnoea resulting from pulmonary oedema as the first sign of a phaeochromocytoma. *Respiration* 2001; 68(3):323-326.
62. Maxwell PH, Buckley C, Gleadle JM, Mason PD. Nasty shock after an anti-emetic. *Nephrol Dial Transplant* 2001; 16(5):1069-1072.
63. Dagartzikas MI, Sprague K, Carter G, Tobias JD. Cerebrovascular event, dilated cardiomyopathy, and pheochromocytoma. *Pediatr Emerg Care* 2002; 18(1):33-35.
64. Sumino Y, Tasaki Y, Satoh F, Mimata H, Nomura Y. Spontaneous rupture of adrenal pheochromocytoma. *J Urol* 2002; 168(1):188-189.
65. Bos JC, Toorians AW, van Mourik JC, van Schijndel RJ. Emergency resection of an extra-adrenal phaeochromocytoma: wrong or right? A case report and a review of literature. *Neth J Med* 2003; 61(8):258-265.
66. Chan MK, Tse HW, Mok FP. Ruptured phaeochromocytoma lesson in acute abdomen. *Hong Kong Med J* 2003; 9(3):221–223.
67. James MF, Cronjé L. Pheochromocytoma crisis: the use of magnesium sulfate. *Anesth Analg* 2004; 99(3):680-686.
68. Brown H, Goldberg PA, Selter JG, et al. Hemorrhagic pheochromocytoma associated with systemic corticosteroid therapy and presenting as myocardial infarction with severe hypertension. *J Clin Endocrinol Metab* 2005; 90(1):563-569.
69. Farroni JA. Pheochromocytoma presenting as heart failure. *Prog Cardiovasc Nurs* 2005; 20(3):117-119.
70. Moran ME, Rosenberg DJ, Zornow DH. Pheochromocytoma multisystem crisis. *Urology* 2006; 67(4):846.
71. Van Lennep JR, Romijn JA, Harinck HI. Multi-organ failure after a glucagon test. *Lancet* 2007; 369(9636):798.
72. Siddik-Sayyid SM, Dabbous AS, Shaaban JA, Daaboul DG, Baraka AS. Catastrophic cardiac hypokinesis and multiple-organ failure after surgery in a patient with an undiagnosed pheochromocytoma: emergency excision of the tumor. *J Cardiothorac Vasc Anesth* 2007; 21(6):863-836.
73. Eschen O, Frøbert O, Jensen V, Hvitfeldt Poulsen S. Pheochromocytoma, a rare cause of acute cardiogenic shock. *Clin Res Cardiol* 2007; 96(4):232-235.
74. Takizawa M, Kobayakawa N, Uozumi H, et al. A case of transient left ventricular ballooning with pheochromocytoma, supporting pathogenetic role of catecholamines in stress-induced cardiomyopathy or takotsubo cardiomyopathy. *Int J Cardiol* 2007; 114(1):e15-e17.
75. Rashid Sh, Youssef H, Ali A, Apakama I. Previously clinically "silent" adrenal phaeochromocytoma presenting as hypovolemic shock with paradoxical hypertension. *Libyan J Med* 2007; 2(3):150-151.
76. Solorzano CC. Pheocromocytoma presenting with multiple organ failure. *Am Surg* 2008; 74(11):1119-1121.

77. Rosas AL, Kasperlik-Zaluska AA, Papierska L, Bass BL, Pacak K, Eisenhofer G. Pheochromocytoma crisis induced by glucocorticoids: a report of four cases and review of the literature. *Eur J Endocrinol* 2008; 158(3):423-429.
78. Zegdi R, Parisot C, Sleilaty G, Deloche A, Fabiani JN. Pheochromocytoma-induced inverted Takotsubo cardiomyopathy: a case of patient resuscitation with extracorporeal life support. *J Thorac Cardiovasc Surg* 2008; 35(2):434-435.
79. De Souza F, Altenburg Odebrecht Curi Gismondi R, Henriques Cunha Neto S, de Mattos MA. Tako-tsubo-like cardiomyopathy and extra-adrenal pheochromocytoma: case report and literature review. *Clin Res Cardiol* 2008; 97(6):397-401.
80. Maruyama M, Sato H, Yagame M, Shoji S, Terachi T, Osamura RY. Spontaneous rupture of pheochromocytoma and its clinical features: a case report. *Tokai J Exp Clin Med* 2008; 33(3):110-115.
81. Von Bergen NH, Lyon JK, Edens RE. Takotsubo-like cardiomyopathy in a 17-year-old male with a pheochromocytoma. *Pediatr Cardiol* 2009; 30(2):184-187.
82. Rashid-Farokhi F, Cheraghvandi A, Masjedi MR. Pheochromocytoma crisis due to glucocorticoid administration: a case report and review of the literature. *Arch Iran Med* 2009; 12(2):190-194.
83. Musuraca G, Imperadore F, Terraneo C, et al. Pheochromocytoma mimicking a non-ST elevation acute myocardial infarction. *Cardiol J* 2009; 16(4):355-357.
84. Uchida N, Ishiguro K, Suda T, Nishimura M. Pheochromocytoma multisystem crisis successfully treated by emergency surgery: report of a case. *Surg Today* 2010; 40(10):990-996.
85. Zaludik J, Schuitemaker F, DeWaal R, Veldjuijzen B, Van der Meer N. Severe lactate acidosis and cardiogenic shock: a rare manifestation of a phaeochromocytoma. *Anaesth Intensive Care* 2010; 38(3):593-594.
86. Salinas CL, Gómez Beltran OD, Sánchez-Hidalgo JM, Bru RC, Padillo FJ, Rufián S. Emergency adrenalectomy due to acute heart failure secondary to complicated pheochromocytoma: a case report. *World J Surg Oncol* 2011; 9:49.
87. Hosseinnezhad A, Black RM, Aeddula NR, Adhikari D, Trivedi N. Glucagon-induced pheochromocytoma crisis. *Endocr Pract* 2011; 17(3):51-54.
88. Hanna JS, Spencer PJ, Savopoulou C, Kwasnik E, Askari R. Spontaneous adrenal pheochromocytoma rupture complicated by intraperitoneal hemorrhage and shock. *World J Emerg Surg* 2011; 6(1):27.

Chapter 9

Hemodynamic Instability During Resection of Pheochromocytoma in Multiple Endocrine Neoplasia versus Non-Multiple Endocrine Neoplasia

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Abstract

Objective Hemodynamic (HD) instability still underlies difficulties during pheochromocytoma resection. Little is known about HD instability in patients with multiple endocrine neoplasia (MEN) type 2-related pheochromocytoma. Our aim was to assess differences in HD during pheochromocytoma resection between MEN2 and non-MEN patients. In addition, we sought to identify risk factors for intraoperative HD instability.

Design Retrospective cohort study.

Methods A total of 22 MEN2 and 34 non-MEN patients underwent 61 pheochromocytoma resections at the University Medical Center Utrecht, The Netherlands between 2000 and 2010. All MEN2-related pheochromocytomas were diagnosed by annual screening. HD instability was assessed by measuring the frequency of hypotensive (mean arterial blood pressure [MABP] below 60 mmHg) and/or hypertensive (systolic arterial blood pressure [SABP] above 200 mmHg) episodes.

Results Compared with non-MEN patients, MEN2 patients were younger at diagnosis, had less symptoms, lower hormone levels, and smaller tumors. Intraoperatively, MEN2 patients had a similar frequency of hypertensive episodes (1.3 versus 1.9, P = 0.162, 95% confidence interval (CI): -6.7 to 35.4) and a similar maximum SABP (200 versus 220 mmHg, P = 0.180, 95% CI: -9.7 to 50.5). However, MEN2 patients experienced less frequent (1.04 versus 2.6, P = 0.003, 95% CI: 0.57 to 2.6) and less severe hypotensive episodes after tumor resection (lowest MABP: 52.5 versus 45.6 mmHg, P = 0.015, 95% CI:-12.6 to -1.16). Tumor size was an independent risk factor for HD instability for the total group after multivariate analysis.

Conclusion MEN2 patients with pheochromocytoma, despite their smaller tumors, do not distinguish themselves from non-MEN patients in terms of hypertensive episodes during pheochromocytoma resection. Therefore, pretreatment with α- and β-blockade remains the standard of care in MEN2-related as well as in non-MEN related pheochromocytoma.

Introduction

Pheochromocytomas are rare neuroendocrine catecholamine-secreting tumors, occurring mainly in the adrenal medulla.[1,2] Pheochromocytomas can occur as part of a familial syndrome and are, in that case, often diagnosed by periodic screening of known mutation carriers. Pheochromocytomas can present with symptoms or as an incidental mass on radiologic imaging studies. Symptoms include episodic hypertension, headaches, and palpitations. Hypertensive crisis may develop in some patients that can result in myocardial infarction, adult respiratory distress syndrome, cerebral vascular accident, renal failure, and mortality.[3]

Surgical resection is the treatment of choice for pheochromocytoma, although the surgical procedure itself can be life threatening due to hypertensive crises and multiorgan failure or profound hypotension after tumor resection.[4,5] During induction of anesthesia or surgical manipulation of their tumors, patients with pheochromocytoma may have wide swings in blood pressure (BP) and heart rate (HR).[6] Administration of α-, β-, and/or calcium channel blockers is assumed to lower the risk of intraoperative hemodynamic (HD) instability (including preventing a hypertensive crisis), although randomized, controlled trials are lacking.[2,7,8]

Preoperative medication and improvements in surgical and anesthetic techniques have nearly diminished the risk of perioperative mortality associated with pheochromocytoma resection.[3,6] However, intraoperative HD fluctuations can lead to serious morbidity.[9] Recently, high plasma norepinephrine concentration, tumor size larger than 4 cm, a high mean arterial blood pressure (MABP) at presentation and after α-blockade, and more profound postural BP reduced after α-blockade were identified as risk factors for HD instability during surgery of pheochromocytomas.[10]

Literature on perioperative care of patients undergoing adrenalectomy for pheochromocytoma is often outdated and historical without considering the improvements in perianesthetic care mentioned earlier.[11] Moreover, the perioperative course concerning HD data of multiple endocrine neoplasia (MEN) type 2 patients with pheochromocytomas has typically been reported only in conjunction with sporadic cases and patients with other familial syndromes or has included only small numbers of patients.[7,12-14]

Because of their early identification using the annual screening of mutation carriers, we questioned whether MEN2-related pheochromocytomas are associated with less HD instability during pheochromocytoma resection. Therefore, we assessed differences in intraoperative HD between MEN2 and non-MEN patients in a large cohort. In addition, we sought to identify risk factors for intraoperative HD instability.

Materials and Methods

We took the opportunity of a large database of patients for pheochromocytoma resection, at the University Medical Center Utrecht, The Netherlands from January 2000 to August 2010 following a homogeneous anesthetic and surgical care, to investigate whether patients with MEN have different intraoperative HD compared with non-MEN patients. A total of 56 patients were considered for this investigation after selection from the pathology database in which the pathology results of all

operatively removed tissues are included.

In our institution, the diagnosis of pheochromocytoma is based on the urinary laboratory results of catecholamines and metanephrines and the presence of an (extra-)adrenal tumor on imaging. MEN2 is defined as the presence of a MEN2 mutation in the *RET* proto-oncogene. All pheochromocytomas in MEN2 patients were diagnosed through (annual, biochemical) screening.

α-blockers (doxazosin) are administered to all patients at least two weeks before operation. β-blockers (metoprolol) are administered to a subgroup of patients with a HR above 80 beats per minute after adequate α-blockade. Patients are encouraged to hydrate themselves well and a salty diet is advised. Patients are admitted one week before surgery to maximize the dose of doxazosin and to start saline infusion two days before surgery. Criteria for efficacy include a systolic arterial BP (SABP) below 140 to 160 mmHg and a HR below 80 beats per minute. Anesthetic care includes propofol, rocuronium, sufentanil and/or isoflurane, or enflurane. Intraoperatively, BP and HR values are automatically, continuously, and digitally recorded by invasive measurement through an arterial line in the radial artery. Central venous pressure is measured in all patients. Undesirable elevations in BP or HR during surgery are treated with intravenous doses of nitrates, phentolamine, and/or esmolol. Crystalloids or colloids are infused and (nor)epinephrine, phenylephrine, and/or ephedrine are administered in case of hypotension after tumor removal.

Variables investigated included patient demographics, urinary hormone levels, tumor size on preoperative imaging (computed tomography or magnetic resonance imaging), and preoperative blockade regimes. The outcomes on hormone level were adjusted by generating a ratio of the highest level for that hormone divided by the corresponding upper limit of normal. In addition, maximum and minimum SABP, diastolic arterial BP (DABP) and MABP, and HR throughout surgery were studied. The MABP was calculated by dividing the sum of the SABP and two times the DABP by three. To measure HD fluctuations, the number of episodes that the SABP was above 200 mmHg, chosen as cutoff value for intraoperative hypertension, was scored. In addition, hypotensive complications were measured according to the number of episodes that the MABP was below 60 mmHg. Intraoperative tachycardia and bradycardia were defined as a HR above 100 and below 45 beats per minute, respectively.

Statistical Analysis

MEN2 patients were compared with the non-MEN patients regarding patients' demographics, disease- and treatment-related features, and regarding differences in outcome of HD instability. In addition, patients' demographics, urinary hormone levels, and tumor size, among other variables, were correlated with intraoperative BP fluctuations.

All data were analyzed with SPSS version 16.0 (SPSS, Inc., Chicago, IL). Independent samples *t* test was used for comparisons between groups. Pearson's correlation coefficient was used to correlate variables (*r* value). Multivariate linear

regression analysis was used to adjust for confounding factors. Statistical significance was established at $P < 0.05$.

Results

Between January 2000 and August 2010, total of 56 patients underwent 61 resections for pheochromocytoma. Almost all patients ($n = 52$) were operated by the same surgeon (IBR). Among those, five patients underwent bilateral adrenalectomy because of bilateral pheochromocytoma. Our study population consisted of 39% MEN2 patients.

Multiple Endocrine Neoplasia versus Non-Multiple Endocrine Neoplasia

Patient, tumor, and diagnostic characteristics for the MEN2 group versus the non-MEN group are given in Table 1. Significant differences between both groups included a younger age at diagnosis, less (cardiac) symptoms, lower preoperative urinary hormone levels, and a smaller tumor size on preoperative imaging for MEN2 patients.

Preoperative differences between MEN2 and non-MEN patients in terms of BP and HR (Table 2) were diminished after preoperative medication (Table 3). Anesthesia was similar between both groups (data not shown). Intraoperatively, MEN2 patients were similar to non-MEN patients in terms of hypertension, i.e. the number of hypertensive episodes, the maximum SABP, and the number of interventions needed to treat undesirable elevations in SABP. In contrast, MEN2 patients experienced less frequent and less severe hypotensive episodes after tumor resection (Table 2). The differences between MEN2 and non-MEN patients did not change after exclusion of patients with von Hippel-Lindau syndrome, mutation in succinate dehydrogenase B, C, and D, and neurofibromatosis (data not shown).

There were no significant differences between the two groups regarding postoperative course (Table 4).

Correlations with Tumor Size

The mean tumor size based on imaging studies for the total group was 4.2 cm (range 1 to 12). We found a correlation between tumor size and preoperative urinary hormone levels ($r = 0.64$, $P < 0.000$). There were weak correlations between tumor size and the number of (cardiac) symptoms and the presence of hypertension at diagnosis ($r = 0.29$, $P = 0.025$; and $r = 0.26$, $P = 0.050$, respectively).

Correlations of tumor size and systolic BP were significant regarding highest SABP at tumor manipulation ($r = 0.39$, $P = 0.002$) and lowest SABP at tumor resection ($r = 0.497$, $P < 0.000$), and hypertensive ($r = 0.50$, $P < 0.000$) and hypotensive episodes ($r = 0.60$, $P < 0.000$). Tumor size also correlated with the number of interventions of the anesthesiologist, i.e. the frequency of using antihypertensive medications during tumor manipulation ($r = 0.40$, $P = 0.002$) and need for vasopressors after tumor resection ($r = 0.66$, $P < 0.000$). These correlations were also significant in multivariate analysis after adjustment for familial syndrome status, preoperative BP and HR, preoperative urinary hormone levels, pretreatment

Table 1. Characteristics of MEN Versus Non-MEN Pheochromocytoma Patients

Characteristics	Patients		*P* Value (95% CI)
	MEN, *n* = 22	Non-MEN, *n* = 34	
Patient characteristics			
Percentage of total study population	39%	61%	
Classification, n	21 MEN2A, 1 MEN2B	26 sporadic, 3 VHL, 2 NF, 3 SDHB/C/D	
Age at surgery, y, mean ± SD	34 ± 12.1	46 ± 14.3	0.001 (4.74 to 19.74)
Female, n	8 (37%)	17 (50%)	0.344 (-0.40 to 0.16)
ASA physical status, mean ± SD	2.10 ± 0.3	2.26 ± 0.5	0.128 (-0.50 to 0.39)
Comorbidity, n			
History of cardiovascular disease	3 (14%)	13 (38%)	0.140 (-0.25 to 0.45)
Respiratory disease (pneumonia, COPD)	0	4 (12%)	0.444 (-0.43 to 0.56)
Endocrine disease (diabetes mellitus)	0	4 (12%)	0.444 (-0.43 to 0.56)
Tumor and diagnostic characteristics			
Bilateral localization, n	4 (18%)	3 (9%)	0.32 (-0.31 to 0.10)
Hypertension at diagnosis, n	6 (27%)	22 (65%)	0.009 (0.09 to 0.63)
Clinical manifestations, n	9 (41%)	23 (68%)	<0.000 (-1.23 to -0.40)
Manifestations per patient, n, mean ± SD	2.7 ± 2.5	3.9 ± 2.2	0.065 (-0.08 to 2.54)
Cardiac manifestations, n	2 (9%)	13 (38%)	0.010 (0.07 to 0.50)
Highest urinary hormone ratio,[a] mean ± SD	4.5	18.1	0.001 (5.91 to 21.32)
Metanephrine	3.4 ± 3.0	9.4 ± 20.1	0.102 (-1.25 to 13.22)
Normetanephrine	2.7 ± 2.9	9.7 ± 9.9	0.001 (3.08 to 10.98)[b]
Epinephrine	3.9 ± 4.2	6.8 ± 11.9	0.200 (-1.60 to 7.46)
Norepinephrine	1.2 ± 1.6	6.9 ± 7.1	<0.000 (3.08 to 8.24)[c]
Tumor size, cm, mean ± SD (range)	2.6 ± 1.7 (1.0 to 7.7)	5.2 ± 2.6 (1.3 to 12.0)	<0.000 (13.51 to 36.62)
Time symptoms to diagnosis, d, mean ± SD	56 ± 154	559 ± 952	0.007 (140.8 to 831.91)
Time symptoms to surgery, d, mean ± SD	226 ± 162	651 ± 939	0.021 (65.5 to 749.51)
Time diagnosis to surgery, d, mean ± SD	175 ± 117	92 ± 79	0.003 (-138.7 to -30.94)

Abbreviations: MEN, multiple endocrine neoplasia; SD, standard deviation; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; VHL, von Hippel-Lindau syndrome; NF, neurofibromatosis; SDHB/C/D, mutation in succinate dehydrogenase B, C, and D, respectively; CI, confidence interval.

[a] Multiplication of reference value

[b] After adjustment for tumor size this difference was not significant.[25]

[c] After adjustment for tumor size this difference remains significant.[25]

regimes, and laparoscopic or open surgery.

The correlation with variables associated with arterial BP was strongest for tumors larger than 3 cm. A tumor diameter larger than 3 cm was accompanied by significantly more hyper- and hypotensive episodes compared with a tumor diameter of 3 cm or less (2.02 versus 0.47, $P < 0.000$; and 2.51 versus 0.83, $P < 0.000$, respectively). A larger tumor led to more hypotensive episodes after tumor resection. Although the correlation between hypertensive episodes and tumors larger than 3 cm is high, small tumors can also lead to HD instability and especially to hypertension during surgery.

Table 2. Hemodynamic Characteristics of Pheochromocytoma in MEN versus Non-MEN

Characteristics	Patients		*P* Value (95% CI)
	MEN, *n* = 22	Non-MEN, *n* = 34	
SABP,[a] mmHg, mean ± SD			
At diagnosis	137 ± 22	157 ± 34	0.014 (4.1 to 35.2)
After preoperative medication	125 ± 16	126 ± 18	0.782 (-7.6 to 10.0)
Pre-start[b]	139 ± 20	146 ± 17	0.101 (-1.5 to 16.8)
After induction of anesthesia	93 ± 19	87 ± 20	0.287 (-15.5 to 4.7)
During tumor manipulation	191 ± 48	204 ± 62	0.382 (-17.7 to 42.8)
After tumor resection	94 ± 23	75 ± 23	0.001 (-31.5 to -8.1)
Intraoperative hypertension			
Hypertensive episodes, n, mean ± SD	1.3 ± 1.4	1.9 ± 2.0	0.162 (-6.7 to 35.4)
Maximum SABP, mmHg, mean ± SD	200 ± 57	220 ± 55	0.180 (-9.7 to 50.5)
Interventions needed to treat undesirable elevations in SABP, n, mean ± SD	11.4 ± 9.1	14.8 ± 18.8	0.439 (-5.31 to 12.1)
Intraoperative hypotension			
Hypotensive episodes, n, mean ± SD	1.04 ± 1.2	2.6 ± 2.6	0.003 (0.57 to 2.6)
Minimum MABP, mmHg, mean ± SD	52.5 ± 10	45.6 ± 12	0.015 (-12.6 to -1.16)
Interventions needed to treat undesirable decreases in MABP, n, mean ± SD	1.9 ± 3.8	5.1 ± 5.0	0.007 (0.9 to 5.6)

Abbreviations: MEN, multiple endocrine neoplasia; SABP, systolic arterial blood pressure; MABP, mean arterial blood pressure; SD, standard deviation; CI, confidence interval.

[a] Similar similarities and differences between MEN and non-MEN patients can be found for diastolic arterial blood pressure and heart rate, with similar *P* values.

[b] The first systolic blood pressure measurement in the operation room.

Table 3. (Pre)Operative Management for Pheochromocytoma in MEN versus Non-MEN

Characteristics	Patients		*P* Value (95% CI)
	MEN, *n* = 22	Non-MEN, *n* = 34	
Preoperative α-blockade, n	22 (100%)	33 (97%)	0.417
Daily doses, mg, mean ± SD	17 ± 12	24 ± 20	0.047 (-51.91 to -0.37)
Duration, d, mean ± SD	74 ± 50	48 ± 42	0.048 (0.11 to 20.43)
Preoperative β-blockade, n	10 (45%)	16 (47%)	0.906
Duration, d, mean ± SD	115 ± 150	56 ± 97	0.269 (-164.8 to 48.12)
Additional antihypertensive medications, n	1 (5%)	12 (35%)	0.005 (0.09 to 0.47)
Preoperative saline infusion, n	11 (50%)	20 (59%	0.647 (-0.22 to 0.35)
Preoperative admission, n	22 (100%)	34 (100%)	-
Duration, d, mean ± SD	3.5 ± 3.3	3.7 ± 3.4	0.833 (-1.68 to 2.10)
Laparoscopic surgery, n	20 (91%)	17 (50%)	0.004 (-0.59 to -0.12)

Abbreviations: MEN, multiple endocrine neoplasia; SD, standard deviation; CI, confidence interval.

Discussion

Due to considerable improvements in preoperative medical preparation and perioperative anesthetic control, mortality following pheochromocytoma resection is rare. However, (morbidity from) intraoperative HD instability remains a problem. The perioperative HD course of MEN2 patients with a pheochromocytoma has typically been reported only in case reports.[6,10,12,14] We report results of a large cohort study comparing patients with MEN2-related pheochromocytoma with non-MEN patients with pheochromocytoma. We mainly demonstrated that, MEN2 patients with pheochromocytoma do not distinguish themselves from sporadic cases of pheochromocytoma in terms of intraoperative hypertensive episodes. In addition, we also report results on hypotension during pheochromocytoma resection, where others have only focused on rises in BP and hypertensive crisis. Importantly, because the drop in BP associated with plasma catecholamine release following tumor resection is the major cause of death. Furthermore, we demonstrated that after multivariate analysis, tumor size is an independent risk factor for HD instability.

Table 4. Outcome of Surgery for Pheochromocytoma in MEN versus Non-MEN

Characteristics	Patients		*P* Value (95% CI)
	MEN, *n* = 22	Non-MEN, *n* = 34	
Duration of postoperative admission, d, mean ± SD	4.8 ± 2.2	6.6 ± 4.7	0.136 (-0.46 to 3.30)
Duration of total admission, d, mean ± SD	8.3 ± 3.8	10.3 ± 6.2	0.243 (-1.14 to 4.40)
Postoperative intensive care unit admission, n	7 (32%)	8 (24%)	0.708
Duration, d, mean ± SD	1.4 ± 1.4	1.5 ± 1.7	0.437 (-1.52 to 1.63)
Complications, n			
Blood pressure, heart rate or fluid related[a]	3 (14%)	6 (18%)	0.649 (-0.18 to 0.24)
Cerebrovascular event	0	0	-
Mortality	0	0	-
Other[b]	1 (5%)	4 (12%)	0.389 (-0.09 to 0.23)
Malignant pheochromocytoma, n	0	1 (3%)	0.437 (-0.05 to 0.11)

Abbreviations: MEN, multiple endocrine neoplasia; SD, standard deviation; CI, confidence interval.

[a] Including hypertension during the first postoperative days requiring additional antihypertensive medications, direct postoperative hypotension requiring vasopressors (mainly norepinephrine) and intravascular fluid therapy, atrial fibrillation, pulmonary edema, and cardiac stunning (caused by relative cardiomyopathy secondary to the pheochromocytoma in combination with intraoperative fluid therapy).

[b] Including wound infection, pneumonia, and intrauterine fetal death.

Clinically, pheochromocytoma in MEN2 patients differ from sporadic pheochromocytoma because they are often identified at an earlier stage because of annual screening of known mutation carriers. In most cases, earlier diagnosis leads to the identification of smaller tumors, often associated with fewer symptoms and less often and less severe hypertension. In our study indeed, 70% of the MEN2 patients were normotensive and only 43% had symptoms. Cardiovascular symptoms associated with pheochromocytoma occurred in two of our MEN2 patients. These results are in agreement with previous studies.[12,15]

However, despite preoperative differences between MEN2 and non-MEN patients, BP after preoperative medication and intraoperative HD instability in terms of rises in BP were similar in both groups. This might mean that the relatively small MEN2-related pheochromocytomas are easily provoked to secrete catecholamines during resection. In contrast with rises in BP, MEN2 patients experienced less frequent and less severe hypotensive episodes. These differences between groups were independent of doxazosin doses on the day of surgery.

Preoperative treatment in our study involved doxazosin in combination with metoprolol if indicated. In all of our patients, a mean SABP of 125 mmHg was obtained after blockade. Multivariate analysis in our study demonstrated that the titrated doses of doxazosin administrated preoperatively was not related to SABP after tumor resection (P = 0.927), indicating that in our patients a higher α-blocker doses did not lead to a more profound decrease in BP after tumor removal. Bruynzeel et al[10] and Prys-Roberts and Farndon[16] found similar results for doxazosin and phenoxybenzamine in terms of controlling arterial pressure and HR before and during surgery, but doxazosin caused fewer undesirable side effects both before and after surgery.[16] Theoretically, patients with pheochromocytoma have a reduced intravascular volume owing to catecholamine-mediated vasoconstriction.[17,18] Patients in our study, therefore received intravenous saline infusion therapy two days before surgery and a salty diet if they had tachycardia.

A recent report demonstrated a correlation between tumor size and HD instability (SABP above 160 mmHg) during pheochromocytoma resection,[10] although others failed to demonstrate tumor size to be a risk factor.[19,20] The results of our study confirm that tumor size may be correlated with HD instability. However, we found a cutoff size of 3 cm instead of 4 cm[11] for significant association (SABP > 200 mmHg), independent of preoperative hormone levels, preoperative medication, surgical approach, and the presence of a familial syndrome. This correlation, as stated, is independent of surgical approach. However, surgical skill in handling the tumor can be a risk factor in intraoperative HD instability.[19] In our study, almost all patients were operated on by the same surgeon, which makes surgical skill less likely to play a significant role in differences in intraoperative HD between patient groups.

Previous studies have demonstrated a direct relationship between tumor size and hormone levels in plasma and urine.[21-23] Preoperative urinary hormone levels in our study also correlated with tumor size and to an extent intraoperative hypertension, as an independent risk factor for HD instability. The latter is also shown in literature.[12,24] Our MEN2 patients had the highest urinary hormone ratio for epinephrine compared with (nor)metanephrine and norepinephrine. They also had significantly less norepinephrine secretion compared with our non-MEN patients. This is in agreement with previous studies.[25,26]

A limitation of our study is its retrospective design. Therefore, patients could not be randomized for different pretreatment regimes. However, our preoperative treatment protocol makes no distinction between familial cases of pheochromocytoma and sporadic cases. This is confirmed by the fact that doses of α-blockade is not a confounder in identifying risk factors for HD instability. Because

all HD data and use of medication during pheochromocytoma resection were recorded automatically, continuously, and digitally, only few data were missing. We used the hormone ratio to account for the differences in type of urinary hormone excreted in highest amount by the patient. Despite this, accurate correlation between tumor size and hormone level may still be affected. Computed tomography and magnetic resonance imaging were used for preoperative imaging, which can result in size measurement variations. In addition, multiple radiologists interpreted the preoperative imaging scans, producing operator variation in final size determination.

Conclusion

Despite earlier diagnosis and significantly smaller tumors, MEN2 patients with pheochromocytoma, do not distinguish themselves from sporadic cases of pheochromocytoma in terms of intraoperative hypertensive episodes. Therefore, pretreatment with α-blockade started at least two weeks before surgery in combination with β-blockade, if tachycardia is present, remains important; MEN2 patients or patients with small tumors are not excluded.

References

1. Desmonts JM, Marty J. Anaesthetic management of patients with phaeochromocytoma. *Br J Anaesth* 1984; 56(7):781-789.
2. Bravo EL, Gifford RW. Current concepts. Pheochromocytoma: diagnosis, localization and management. *N Engl J Med* 1984; 311(20):1298-1303.
3. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. *Lancet* 2005; 366(9586):665–675.
4. Lo CY, Lam KY, Wat MS, Lam KS. Adrenal pheochromocytoma remains a frequently overlooked diagnosis. *Am J Surg* 2000; 179(3):212-215.
5. Apgar V, Papper EM. Pheochromocytoma: anesthetic management during surgical treatment. *Arch Surg* 1951; 62(5):634-648.
6. Feldman JM, Blalock JA, Fagraeus L, Miller JN, Farrell RE, Wells SA Jr. Alterations in plasma norepinephrine concentration during surgical resection of pheochromocytoma. *Ann Surg* 1978; 188(6):758-768.
7. Kinney MA, Narr BJ, Warner MA. Perioperative management of pheochromocytoma. *J Cardiothorac Vasc Anesth* 2002; 16(3):359-369.
8. Miura Y, Yoshinaga K. Doxazosin: a newly developed, selective alpha 1-inhibitor in the management of patients with pheochromocytoma. *Am Heart J* 1988; 116(6 Pt 2):1785-1789.
9. Shupak RC. Difficult anesthetic management during pheochromocytoma surgery. *J Clin Anesth* 1999; 11(3):247–250.
10. Bruynzeel H, Feelders RA, Groenland TH, et al. Risk factors for hemodynamic instability during surgery for pheochromocytoma. *J Clin Endocrinol Metab* 2010; 95(2):678-685.
11. Goldstein RE, O'Neill JA Jr, Holcomb GW 3rd, et al. Clinical experience over 48 years with pheochromocytoma. *Ann Surg* 1999; 229(6):755-764, discussion 764-766.
12. Luo A, Guo X, Yi J, Ren H, Huang Y, Ye T. Clinical features of pheochromocytoma and perioperative anesthetic management. *Chin Med J* 2003; 116(10):1527-1231.
13. Van Heerden JA, Sheps SG, Hamberger B, Sheedy PF, Poston JG, ReMine WH. Pheochromocytoma: current status and changing trends. *Surgery* 1982; 91(4):367–373.
14. Hamilton BP, Landsberg B, Levine RJ. Measurement of urinary epinephrine in screening for pheochromocytoma in multiple endocrine neoplasia type II. *Am J Med* 1978; 65(6):1027-1032
15. Atallah F, Bastide-Heulin T, Soulié M, et al. Haemodynamic changes during retroperitoneoscopic adrenalectomy for phaeochromocytoma. *Br J Anaesth* 2001; 86(5):731-733.
16. Prys-Roberts C, Farndon JR. Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. *World J Surg* 2002; 26(8):1037-1042.
17. Iijima T, Takagi T, Iwao Y. An increased circulating blood volume does not prevent hypotension after phaeochromocytoma resection. *Can J Anaesth* 2004; 51(3):212-215.
18. Stenstrom G, Kutti J. The blood volume in phaeochromocytoma patients before and during treatment with phenoxybenzamine. *Acta Med Scan* 1985; 218(4):381-387.
19. Weismann D, Fassnacht M, Weinberger F, et al. Intraoperative haemodynamic stability in patients with phaeochromocytoma – minimally invasive versus conventional open surgery. *Clinical Endocrinology* 2006; 65(3):352–358.
20. Plouin PF, Duclos JM, Soppelsa F, Boublil G, Chatellier G. Factors associated with perioperative morbidity and mortality in patients with pheochromocytoma: Analysis of 165 operations at a single center. *J Clin Endocrinol Metab* 2001; 86(4):1480–1486.

21. Guerrero MA, Schreinemakers JM, Vriens MR, et al. Clinical spectrum of pheochromocytoma. *J Am Coll Surg* 2009; 209(6):727-732.
22. Huynh TT, Pacak K, Brouwers FM, et al. Different expression of catecholamine transporters in pheochromocytomas from patients with von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2. *Eur J Endocrinol* 2005; 153(4):551–563.
23. Eisenhofer G, Walther MM, Huynh TT, et al. Pheochromocytomas in von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2 display distinct biochemical and clinical phenotypes. *J Clin Endocrinol Metab* 2001; 86(5):1999–2008.
24. Kinney MA, Warner ME, van Heerden JA, et al. Perianesthetic risks and outcomes of pheochromocytoma and paraganglioma resection. *Anesth Analg* 2000; 91(5):1118–1123.
25. Eisenhofer G, Huynh T, Elkahloun A, et al. Differential expression of the regulated catecholamine secretory pathway in different hereditary forms of pheochromocytoma. *Am J Physiol Endocrinol Metab* 2008; 295(5):E1223-1233.
26. Eisenhofer G, Pacak K, Huynh TT, et al. Catecholamine metabolomic and secretory phenotypes in phaeochromocytoma. *Endocr Relat Cancer* 2010; 18(1):97-111.

Chapter 10

Unilateral Subtotal Adrenalectomy for Pheochromocytoma in Multiple Endocrine Neoplasia Type 2,
A Feasible Surgical Strategy

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Abstract

Objective To determine the best surgical strategy for pheochromocytoma in multiple endocrine neoplasia type 2 (MEN2) patients.

Background Pheochromocytomas occur in 50% to 60% of MEN2 patients, approximately half of them eventually develop bilateral disease. Unilateral subtotal adrenalectomy as primary surgery for pheochromocytoma in these patients may avoid or postpone the need for corticosteroid replacement therapy and the risk of Addisonian crisis, but is not yet widely accepted.

Methods We conducted a retrospective cohort study including 61 MEN2 patients with pheochromocytoma who were treated at the University Medical Center Utrecht, The Netherlands between 1959 and 2010. Surgery was classified into four adrenalectomy groups: bilateral total, unilateral total, bilateral subtotal, and unilateral subtotal.

Results Primary surgery involved 22 bilateral total, 30 unilateral total, 2 bilateral subtotal, and 7 unilateral subtotal adrenalectomies. Twenty-one patients developed ipsilateral or contralateral recurrence after a median follow-up of 13.4 ± 10.8 years (range 0.1 to 41.8). Unilateral total and unilateral subtotal adrenalectomy had similar rates of recurrence (P = 0.232) and an equal survival time (5.5 versus 8.8 years; P = 0.170). Steroid replacement after bilateral total adrenalectomy led to complications in eight patients. Reoperations for recurrence included unilateral total adrenalectomy in 12 patients, after which 10 needed steroid replacement (with complications in three) and unilateral subtotal adrenalectomy in five patients, after which none needed replacement therapy. Ipsilateral recurrence after reoperation was similar between these groups.

Conclusion Unilateral subtotal adrenalectomy is a feasible surgical strategy for pheochromocytoma in MEN2 patients. It has comparable recurrence rates and eventually less complications of steroid replacement compared with unilateral total adrenalectomy.

Introduction

Pheochromocytomas are rare neuroendocrine catecholamine-secreting tumors. Pheochromocytomas can occur as part of the familial syndrome multiple endocrine neoplasia type 2 (MEN2). MEN2 is subdivided in MEN2A and MEN2B. In MEN2A, patients develop medullary thyroid carcinoma, pheochromocytoma, and primary hyperparathyroidism.[1] MEN2B is associated with medullary thyroid carcinoma, mucosal neuromas, intestinal ganglioneuromas, and a marfanoid habitus.[2]

Pheochromocytomas, in MEN2 occur in 50% of the patients, are frequently bilateral and are less frequently malignant compared with sporadic cases. All known MEN2 patients should be screened once yearly for the presence of pheochromocytoma to prevent a potentially life-threatening hypertensive crisis associated with myocardial infarction, pulmonary edema, or epileptic seizures.[2-4]

Adrenalectomy is the treatment of choice for pheochromocytoma. Theoretically, the ideal operation for a pheochromocytoma in a patient with MEN2 would be to remove the pheochromocytoma and all of the medulla while saving the adrenal cortex to preserve ipsilateral adrenocortical steroid production.

From the mid-1980s through the mid-1990s and in some centers even until 1999, total bilateral adrenalectomy has been advocated,[3,5,6] even in case of unilateral disease[7] and especially in patients with a tumor size over 5 cm,[8] to prevent the risk of recurrence. Because it necessitates lifelong gluco- and mineralocorticoid replacement therapy, this method has been disputed. Complete steroid-dependency carries great social implications and the risk of a, potentially life-threatening, Addisonian crisis.[9,10] In addition, corticosteroid replacement therapy is a continuous challenge with possible chronic overreplacement leading to the risk of impaired glucose tolerance, obesity and osteoporosis and underreplacement with the risk of incipient crises and severe impairment of well being.[11,12]

Fortunately, improvements in imaging techniques – demonstrating a normal contralateral adrenal gland – and better pathophysiological insight allowed the introduction of more conservative surgical strategies, including the unilateral adrenalectomy.[13-17] Subsequently minimally invasive approaches were introduced, and cortical sparing approaches have been used both for initial operations and for reoperations. However, because of the rarity of the disease, only scarce data are available on unilateral subtotal adrenalectomy in MEN2 patients.

Most studies on subtotal adrenalectomy in MEN2 patients as primary surgery[18] or as secondary surgery for recurrent pheochromocytoma after unilateral total or bilateral subtotal adrenalectomy include only case reports or small retrospective case series.[9,19-24] Moreover, outcome of surgical treatment is often analyzed in conjunction with other familial syndromes.[25-29]

Two studies have presented original data on unilateral subtotal adrenalectomy in MEN2 patients as primary surgery.[19,28] Edström et al[19] reported one MEN2A patient who underwent unilateral subtotal adrenalectomy. Yip et al[28] conducted a study among 46 MEN2 patients. Recurrent pheochromocytoma developed in an adrenal remnant in three of 30 patients (10%) who underwent unilateral adrenalectomy or bilateral cortical-sparing procedures. Although these results are in

favor of cortical sparing adrenal surgery, the number of patients treated with unilateral subtotal adrenalectomy is not described, nor was data on follow-up available.[28]

We therefore sought to determine the feasibility of subtotal adrenalectomy as a primary surgical strategy for pheochromocytoma in MEN2 patients in a small study group with a large comparison cohort with a long-term follow-up.

Materials and Methods

The medical records of all MEN2 patients treated at the University Medical Center Utrecht, The Netherlands, a tertiary referral center for MEN2 patients since 1959, were reviewed for the presence of pheochromocytoma. MEN2 was defined as the presence of a germline mutation of the *RET* proto-oncogene.

Diagnosis of pheochromocytoma included biochemical testing of 24-hour urinary levels of catecholamines (epinephrine, norepinephrine and dopamine) and/or (nor)metanephrines in combination with at least one adrenal imaging study (computed tomography or magnetic resonance imaging, and in some cases additional iodine-131-meta-iodobenzylguanidine scintigraphy).

Data on patient characteristics, surgical strategy, and outcome were collected. Surgical intervention was classified into four adrenalectomy groups: bilateral total, unilateral total, bilateral subtotal (one side total and other side subtotal), and unilateral subtotal. The follow-up period was defined as the period between adrenal surgery and the last date of contact or date of death.

Data on outcome included the persistence, recurrence, and the time to recurrence of pheochromocytoma, complications of surgery and the need for and complications of steroid replacement therapy. Persistent disease was defined as disease not cured by initial surgery according to measurement of elevated 24-hour urinary levels of catecholamines and/or (nor)metanephrines within six months after initial surgery. Recurrent disease was defined as a new development of elevated urinary levels of catecholamines and/or (nor)metanephrines and documentation of a pheochromocytoma on imaging study after a period of normalization of biochemical examinations of at least six months after surgery. Recurrent disease included contralateral, ipsilateral and extra-adrenal recurrences.

Damage to neighboring organs, bleeding, hemodynamic instability during and after surgery, infection and 30-day mortality, were defined as perioperative complications. Addisonian crisis was defined as hospitalization because of adrenal insufficiency developing spontaneously or in response to infection or dehydration with symptoms of nausea, vomiting, hypotension, and severe electrolyte imbalances, improving after administration of corticosteroids.

The postoperative adrenocortical function was evaluated only in patients who underwent a secondary subtotal adrenalectomy by measurement of basal (morning) plasma cortisol (8.00 to 8.30) or a 250 µg adrenocorticotropic hormone challenge test to determine adrenal function.

Statistical Analysis

SPSS version 15.0 (SPSS, Inc., Chicago, IL) was used to describe the population. Kaplan-Meier survival analysis, with log-rank (Mantel-Cox) analysis, was applied for comparison. For comparison of means between groups, the Fisher's exact χ^2 test was used. An ANOVA analysis was applied to calculate the statistical difference in mean follow-up between intervention groups. Data are shown as mean ± standard deviation or median based on their distribution. $P < 0.05$ was considered statistically significant.

Results

Sixty-one patients (48%) of 126 MEN2 patients from the University Medical Center Utrecht MEN2 database were operated on for a pheochromocytoma between 1959 and 2010. Table 1 presents baseline demographics, clinical characteristics and diagnostic data. In the group of patients with pheochromocytoma, MEN2A was diagnosed in 58 patients (95% of 61 patients), three patients had MEN2B (5%). Fifty patients were identified from nine kindreds.

Table 1. Characteristics of Pheochromocytoma in MEN2 Patients

Characteristics	Data
Patient characteristics	
Classification, n	58 MEN2A (95%), 3 MEN2B (5%)
Female, n	24 (39%)
Age at surgery for pheochromocytoma, y, mean ± SD	33.0 ± 12.7
Mutation, n	
Cys634Arg	29 (485%)
Cys634Trp	15 (25%)
Cys634Tyr	2 (3%)
Cys618Arg	1 (2%)
Codon 611	1 (2%)
Unknown	13 (21%)
Diagnosis through screening, n	44
Symptoms and diagnostic characteristics, n	
Symptoms	31 (50%)
Classic triad	6 (10%)
Palpitations	19 (31%)
Headache	10 (16%)
Diaphoresis	8 (13%)
Other (nausea, tremor, anxiety)	13 (21%)
Preoperative hypertension, hypertensive crisis	2, 2 (8%)
Preoperative elevation of 24-hour urinary hormones[a]	41 (67%)
Other MEN2 associated features, n	
Medullary thyroid carcinoma	60 (98%)
Primary hyperparathyroidism	20 (33%)
Cutaneous lichen amyloid	2 (3%)

Abbreviations: MEN, multiple endocrine neoplasia; SD, standard deviation

[a] Metanephrines and/or (nor)epinephrine, data were missing from 18 patients.

The mean age at diagnosis of MEN2 was 25.1 ± 14.6 years (range 1 to 62). The mean age at first surgery for pheochromocytoma was 33.0 ± 12.7 years (range 13 to 71). In eight patients, pheochromocytoma was the presenting manifestation of the MEN2 syndrome in addition to medullary thyroid carcinoma. Forty-four were known MEN2 patients at diagnosis and were annually screened for symptoms, 24-hour urinary catecholamine and/or (nor)metanephrine levels and in some cases imaging studies to detect the presence of pheochromocytoma. Two of these patients had normal 24-hour urinary catecholamine and (nor)metanephrine levels.

Primary Surgery for Pheochromocytoma in Multiple Endocrine Neoplasia

Surgery was performed either laparoscopically or by laparotomy depending on the era of operation and tumor size. From 1993 until 1997, we have operated on these tumors laparoscopically via the lateral abdominal route and since 1997 via the posterior retroperitoneal route when tumor size was smaller than 7 cm.[30]

Primary surgery included 22 bilateral total, 30 unilateral total, 2 bilateral subtotal, and 7 unilateral subtotal adrenalectomies (Table 2).

Three patients developed surgery-related complications. These complications included intraoperative cardiac and respiratory insufficiency associated with catecholamine release necessitating admission to the intensive care unit (laparoscopic unilateral total adrenalectomy), hernia cicatricalis needing several repair surgeries (open bilateral total adrenalectomy), and rupture of the spleen (open bilateral total adrenalectomy).

Median follow-up after primary surgery was 13.4 ± 10.8 years (range 0.1 to 41.8). There were no significant differences in duration of follow-up between the four intervention groups (Table 2; P = 0.323, ANOVA analysis). Overall, the total study population was 9.5 ± 10.2 years (range 0.1 to 38.6) free of recurrent pheochromocytoma. None of the patients had persistent disease.

Ipsilateral or contralateral recurrent pheochromocytoma developed in 21 patients. All patients were diagnosed through annual screening during follow-up, with symptoms consistent of pheochromocytoma (n = 3), elevated 24-hour urinary catecholamine and (nor)metanephrine levels (n = 14) or both (n = 4). Symptoms were mild and included headache and nausea. None of the patients developed hypertensive crisis during follow-up.

Thirteen patients developed contralateral recurrence after unilateral total adrenalectomy. In the unilateral subtotal operated group, four patients developed a contralateral recurrence and one patient developed an ipsilateral recurrence. There were no significant differences for risk of recurrence between the unilateral total and unilateral subtotal adrenalectomy group (P = 0.232, Fisher's exact test). Comparison of means for disease and steroid replacement free survival time between unilateral total and unilateral subtotal adrenalectomy after primary operation was also not significant (P = 0.170, log-rank [Mantel-Cox] analysis).

Table 2. Outcome of Primary Surgery for Pheochromocytoma in MEN2

Type of Surgery	Number of Patients	Recurrence, n			Time to Recurrence, y, median (range)	Follow-up without Recurrence, y, median (range)	Follow-up,[a] y, median (range)	Corticosteroid Replacement, n	Complications of Replacement, n
		CL	IL	EA					
Bilateral total adrenalectomy	22	0	0	1	34.1 (0.0 to 34.1)	23.0 (0.1 to 34.1)	23.0 (0.1 to 35.2)	22	8
Unilateral total adrenalectomy	30	13	0	0	8.5 (0.5 to 9.9)	5.5 (0.1 to 38.6)	11.5 (0.1 to 41.8)	0	-
Bilateral subtotal adrenalectomy	2	0	2	0	7.1 (4.1 to 10.2)	7.2 (4.1 to 10.2)	14.5 (12.8 to 16.3)	0	-
Unilateral subtotal adrenalectomy	7	4	1	0	6.3 (1.8 to 9.7)	8.8 (1.2 to 16.2)	15.8 (1.2 to 31.9)	0	-

Abbreviations: MEN2, multiple endocrine neoplasia type 2; CL, contralateral; IL, ipsilateral; EA, extra-adrenal.
[a] The mean follow-up between the different surgical groups was not significantly different, $P = 0.323$.

Table 3. Outcome of Reoperation for Recurrent Pheochromocytoma in MEN2

Type of Surgery	Number of Patients	Ipsilateral Recurrence, n	Time to Recurrence, y	Corticosteroid Replacement, n	Complications, n		Follow-up without Recurrence, y, median (range)	Follow- up, y, median (range)
					Replacement	Surgery		
Extra-adrenal resection	1	0	-	1	0	0	1.1	1.1
Bilateral total adrenalectomy	1	0	-	1	0	0	13.7	13.7
Unilateral total adrenalectomy	12	1	10.0	10	3	2	9.6 (0.0 to 38.0)	9.8 (0.0 to 38.0)
Unilateral subtotal adrenalectomy	5	1	4.0	0	-	0	4.0 (0.0 to 9.0)	7.2 (0.0 to 16.2)

Abbreviations: MEN2, multiple endocrine neoplasia type 2.

Eight of the 22 patients who underwent bilateral total adrenalectomy developed complications of corticosteroid replacement. Three of those had an Addisonian crisis after a mean follow-up of 18.9 ± 7.3 years (range 13 to 20) and five had complaints of hypotension, fatigue and weakness, or loss of libido.

The diagnosis pheochromocytoma was confirmed by histology in all but three operated adrenal glands. In three patients who underwent a bilateral adrenalectomy (two bilateral total adrenalectomy, one bilateral subtotal adrenalectomy) pathology confirmed unilateral presence of pheochromocytoma. In none of the patients, malignant pheochromocytoma was diagnosed.

Reoperations for Recurrent Pheochromocytoma in Multiple Endocrine Neoplasia

Table 3 shows the results on reoperation for recurrent pheochromocytoma (n = 19). Two patients were operated for their recurrent disease elsewhere and therefore no further data on reoperative surgery of these patients were available. One patient underwent resection of an extra-adrenal recurrence after bilateral total adrenalectomy. One 34-year-old female patient had an ipsilateral recurrence 1.8 years after open unilateral subtotal adrenalectomy. The magnetic resonance imaging performed before the initial operation showed no evidence of a second primary lesion. Neither were there signs suggestive of a second lesion at the time of initial intervention, although an intraoperative ultrasound was not performed. This patient underwent a secondary bilateral total adrenalectomy, at her own request. The histopathologic report confirmed unilateral disease in this patient. Twelve patients had secondary unilateral total adrenalectomy, five had unilateral subtotal adrenalectomy. Ipsilateral recurrence occurred in two patients after reoperation. There were no significant differences for risk of recurrence after reoperation between the unilateral total and unilateral subtotal adrenalectomy group (P = 0.515, Fisher's exact test). Comparison of medians for survival time between unilateral total and unilateral subtotal adrenalectomy at reoperation was also not significant (9.0 versus 4.0 years; P = 0.102, log-rank [Mantel-Cox] analysis). But sample size was small with only one recurrence in both groups.

One patient underwent conversion from a laparoscopic approach to open surgery due to extensive adhesions. One patient developed a hernia cicatricalis necessitating several repair surgeries after open unilateral total adrenalectomy.

After a previous unilateral adrenalectomy, 11 patients who underwent a second unilateral total adrenalectomy became dependent of steroid replacement. Three of those patients had complications of replacement, with complaints of fatigue and weakness. Two patients who underwent unilateral total adrenalectomy for contralateral recurrence after previous unilateral subtotal adrenalectomy had sufficient adrenocortical function without replacement. One of them is now 27.8 years after surgery without replacement therapy or recurrence. None of the patients who underwent secondary subtotal adrenalectomy needed steroid replacement.

Twelve patients died during follow-up. Seven patients died of metastatic medullary thyroid cancer and five of unknown causes.

Table 4. Outcome of Subtotal Unilateral Adrenalectomy as Primary Surgery for Pheochromocytoma in MEN2 in Literature

Author, y	Study Period	Number of Patients	Type of Surgery	Recurrence, n	Time to Recurrence, y	Complications of Replacement, n	Follow-up,[a] y
Edstrom, 1999[19]	1984 to 1989	3 (MEN2A)	1 UniSub	1 CL	4	0 of 3	11
			2 BiSub	0			
Yip, 2004[28]	1962 to 2003	39 (MEN2A) 7 (MEN2B)	22 UniTot/Sub (≥ 9 UniSub)	4 CL (after UniTot) 3 IL (with 2 CL after UniSub)	19.3	ND	ND (< 4.6)
			24 BiTot/Sub	0	-	ND	4.6

Abbreviations: MEN2, multiple endocrine neoplasia type 2; BiTot, bilateral total adrenalectomy; UniTot, unilateral total adrenalectomy; BiSub, bilateral subtotal adrenalectomy; UniSub unilateral subtotal adrenalectomy; CL, contralateral; IL, ipsilateral; ND, not described.
[a] Duration of follow-up is reported in median.

Table 5. Outcome of Subtotal Unilateral Adrenalectomy as Reoperation for Pheochromocytoma in MEN2 in Literature

Author, y	Number of Patients[a]	Type of Recurrence	Primary Surgery	Reoperation, n	Recurrence, n	Complications of Replacement, n	Follow-up,[c] y
Brauckhoff, 2004[20]	1	IL	BiSub	1 UniSub	0	0	8
Edstrom, 1999[19]	1	CL	UniSub	1 UniSub	ND	ND	ND
Graaf, 1999[24]	3	IL	UniSub	1 UniTot	ND	ND	ND
		CL	UniTot	2 UniSub	0	ND	3.8
Jansson, 2006[27]	3	CL	UniTot	1 UniSub	0	0	1
		IL	BiSub	1 BiTot	0	ND	25
		IL[b]	BiSub	1 BiTot	0	ND	14
Lee, 1996[14]	3	CL	UniTot	3 UniSub	ND	ND	ND
Mugiya, 1999[21]	1	CL	UniTot	1 UniSub	ND	0 of 1	ND
Porpiglia, 2002[22]	1	CL	UniTot	1 UniSub	0	0	1
Yip, 2003[16]	4	IL	UniSub	4 UniSub	ND	ND	ND
Walz, 2002[23]	1	CL	UniTot	1 UniSub	ND	ND	ND

Abbreviations: MEN2, multiple endocrine neoplasia type 2; BiSub, bilateral subtotal adrenalectomy; BiTot, bilateral total adrenalectomy; UniTot, unilateral total adrenalectomy; UniSub, unilateral subtotal adrenalectomy; CL, contralateral; IL, ipsilateral; ND, not described.
[a] All patients included MEN2A patients, except one MEN2B patient[b].
[c] Duration of follow-up is reported in mean or median.

Discussion

This retrospective study presents data on subtotal unilateral adrenalectomy as primary surgery for pheochromocytoma in MEN2 in a small study group with a large comparison cohort. According to our present and previous data, unilateral subtotal adrenalectomy in MEN2 patients has evolved into a feasible surgical strategy for pheochromocytoma in MEN2 patients.

Pheochromocytomas may recur either on the contralateral side as a result of the nature of the disease or on the ipsilateral side even a long time after the initial operation.[14,31] Because of slow progression of the disease, in combination with an effective, protocolized screening program, yearly screening and timely surgery can minimize the risk of a hypertensive crisis from recurrent pheochromocytoma. None of our patients developed a hypertensive crisis during follow-up. Moreover, only half of the patients presenting with recurrent pheochromocytoma was symptomatic and had only mild symptoms. Other studies found similar or lower numbers of MEN2 patients with symptomatic pheochromocytoma.[32,33]

Furthermore, a "watchful waiting" strategy seems to be acceptable in hereditary pheochromocytoma, since malignant pheochromocytomas rarely occurs in patients with MEN2, in contrast to patients with sporadic pheochromocytoma.[13,33,34] None of the 61 patients in our study had malignant pheochromocytoma. There were also none among 58 MEN2 patients reported by Lairmore et al[13] nor among 18 MEN2 patients reported by Tibblin et al;[34] whereas, van Heerden et al[5] reported three MEN2 patients with malignant pheochromocytomas. Among 387 patients with MEN2 from previous reported series the overall malignancy rate was 3.9%.[14,34]

Unilateral subtotal adrenalectomy has the great advantage of preserving adrenocortical function, thereby preventing the need for and complications of chronic steroid replacement. Telenius-Berg described a significantly affected quality of life with 30% of patients experience significant fatigue and 48% considered themselves handicapped, due to social implications.[10] Patients have to be continually aware of the signs and symptoms of acute adrenal insufficiency and must be instructed how to handle such situations. The consequences of acute hypocortisolism – if not corrected with admission to the hospital and administration of intravenous saline and corticosteroids – begin with severe vomiting and diarrhea, electrolyte disturbances, hypoglycemia, confusion, lethargy, and eventually lead to death.[11,12] Many authors have reported on the morbidity, and even mortality related to adrenocortical replacement in patients after synchronous or metachronous bilateral adrenalectomy. Combined data from several studies indicate that 23% to 35% of patients developed Addisonian crisis with a total mortality rate up to 3%.[9,10,34] Howe et al[1] even reported that 23 of 33 MEN2 patients (70%) with bilateral adrenalectomy underwent at least one episode of Addisonian crisis in the follow-up of 12.9 years.

Eight of our patients who underwent bilateral total adrenalectomy developed complications of steroid replacement, including Addisonian crisis. After reoperation, only patients who underwent secondary unilateral or bilateral total adrenalectomy needed replacement therapy with complications occurring in three patients. On the contrary, none of the patients who underwent unilateral subtotal adrenalectomy,

either as primary or as secondary surgery, needed replacement of corticosteroids.

Results on unilateral subtotal adrenalectomy as primary and secondary surgery for pheochromocytoma in MEN2 patients presented in literature are scarce (Table 4 and Table 5). In the past, bilateral total adrenalectomy has been advised to prevent the risk of recurrence.[3,5] The results of our study support the idea that the risk of recurrent pheochromocytoma after bilateral total adrenalectomy is minimal, although not completely absent.[35] One patient from our study developed an extra-adrenal recurrence after bilateral total adrenalectomy after 34.1 years. We have, together with many others,[6,10,17,29] abandoned bilateral total adrenalectomy as first choice treatment because of earlier mentioned arguments related to adrenocortical insufficiency after total adrenalectomy.

The past years, there has been a trend towards cortical sparing procedures in MEN2 patients with pheochromocytoma. When performing a cortex-sparing adrenalectomy, the extent of resection is determined by tumor size and location, in relation to vascular supply. A large tumor in an unfavorable location may preclude sparing of a significant amount of the adrenal cortex.[17,22] When a pheochromocytoma is located laterally, a partial adrenalectomy is technically easier to perform. When a pheochromocytoma is located more medially, however, a partial adrenalectomy is more of a challenge, due to the medial located adrenal vein. Preoperative imaging by computed tomography or magnetic resonance image scanning suggests the possibility of a subtotal resection; however, the final decision concerning the possibility of subtotal adrenalectomy is made intraoperatively. Fortunately, most MEN2 patients will have small tumors because they are diagnosed early by routine screening in the setting of their syndrome. However, because preservation of the cortex may not be possible in every case of pheochromocytoma (and, therefore, may not be possible in a contralateral adrenal gland after primary unilateral total adrenalectomy), we want to emphasize the need to perform subtotal adrenalectomy as primary surgery.

Laparoscopic cortical-sparing procedures can be performed safely and successfully, even when a repeat surgical procedure is needed.[19,36,37] A few patients from our study experienced minor complications during repeat surgery. Overall, we believe that the risks associated with repeat adrenal surgery in case of recurrent pheochromocytoma does not outweigh the considerable risk of complications from steroid replacement therapy.

Although this is one of the largest studies on surgery in MEN2-related pheochromocytoma, inherent to being retrospective in nature, patients cannot be randomized. Moreover, the results of our single center study reflect the MEN2 population in the region of the University Medical Center Utrecht. Nonetheless, we advocate unilateral subtotal adrenalectomy as a feasible and desirable surgical procedure for MEN2 patients with pheochromocytoma.

Conclusion

Unilateral subtotal adrenalectomy is a feasible surgical strategy for pheochromocytoma in MEN2 patients. It has comparable recurrence rates and eventually less complications of steroid replacement compared with unilateral total adrenalectomy.

References

1. Howe JR, Norton JA, Wells SA Jr. Prevalence of pheochromocytoma and hyperparathyroidism in multiple endocrine neoplasia type 2A: results of long-term follow-up. *Surgery* 1993; 114(6):1070-1077.
2. Carney JA, Go VL, Sizemore GW, et al. Alimentary-tract ganglioneuromatosis. A major component of the syndrome of multiple endocrine neoplasia, type 2b. *N Engl J Med* 1976; 295(23):1287–1291.
3. Lips KJ, Van der Sluys Veer J, Struyvenberg A, et al. Bilateral occurrence of pheochromocytoma in patients with the multiple endocrine neoplasia syndrome type 2A (Sipple's syndrome). *Am J Med* 1981; 70(5):1051-1060.
4. Raue F, Frank-Raue K. Update multiple endocrine neoplasia type 2. *Fam Cancer* 2010; 9(3):449-457.
5. van Heerden JA. Sizemore GW, Carney JA, et al. Surgical management of the adrenal glands in the multiple endocrine neoplasia type 2 syndrome. *World J Surg* 1984; 8(4):612.
6. Modigliani E, Vasen HM, Raue K, et al. Pheochromocytoma in multiple endocrine neoplasia type 2: European Study. The Euromen Study Group. *J Intern Med* 1995; 238(4):236–237.
7. de Graaf JS, Nieweg OE, Oosterkamp AE, et al. Results of 25-year pheochromocytoma treatment in the Groningen Academic Hospital. *Ned Tijdschr Geneeskd* 1997; 141(3):148-151.
8. Tibblin S, Dymling JF, Ingemansson S, et al. Unilateral versus bilateral adrenalectomy in multiple endocrine neoplasia IIA. *World J Surg* 1983; 7(2):201-208.
9. de Graaf JS, Dullaart RP, Zwierstra RP. Complications after bilateral adrenalectomy for phaeochromocytoma in multiple endocrine neoplasia type 2 – a plea to conserve adrenal function. *Eur J Surg* 1999; 165(9):843-846.
10. Telenius-Berg M, Ponder MA, Berg B, et al. Quality of life after bilateral adrenalectomy in MEN 2. *Henry Ford Hosp Med J* 1989; 37(3-4):160-163.
11. Reisch N, Arlt W. Fine tuning for quality of life: 21st century approach to treatment of Addison's disease. *Endocrinol Metab Clin N Am* 2009; 38(2):407–418.
12. Hahner S, Allolio B. Therapeutic management of adrenal insufficiency. *Best Pract Res Clin Endocrinol Metab* 2009; 23(2):167–179.
13. Lairmore TC, Ball DW, Baylin SB, et al. Management of pheochromocytomas in patients with multiple endocrine neoplasia type 2 syndromes. *Ann Surg* 1993; 217(6):595–601, discussion 601-603.
14. Lee JE, Curley SA, Gagel RF, et al. Cortical-sparing adrenalectomy for patients with bilateral pheochromocytoma. *Surgery* 1996; 120(6):1064-1070, discussion 1070-1071.
15. Iihara M, Suzuki R, Kawamata A, et al. Adrenal-preserving laparoscopic surgery in selected patients with bilateral adrenal tumors. *Surgery* 2003; 134(6):1066-1072, discussion 1072-1073.
16. Yip L, Cote GJ, Shapiro SE, et al. Multiple endocrine neoplasia type 2: evaluation of the genotype-phenotype relationship. *Arch Surg* 2003; 138(4):409-416, discussion 416.
17. Asari R, Scheuba C, Kaczirek K, et al. Estimated risk of pheochromocytoma recurrence after adrenal-sparing surgery in patients with multiple endocrine neoplasia type 2A. *Arch Surg* 2006; 141(12):1199-1205.
18. Takami H, Ikeda Y, Takayama J, et al. Adrenal-sparing adrenalectomy in hereditary bilateral phaeochromocytoma. *ANZ J Surg* 2001; 71(10):623-624.

19. Edström E, Gröndal S, Norström F, et al. Long term experience after subtotal adrenalectomy for multiple endocrine neoplasia type IIa. *Eur J Surg* 1999; 165(5):431-435.
20. Brauckhoff M, Gimm O, Brauckhoff K, et al. Repeat adrenocortical-sparing adrenalectomy for recurrent hereditary pheochromocytoma. *Surg Today* 2004; 34(3):251-255.
21. Mugiya S, Suzuki K, Saisu K, et al. Unilateral laparoscopic adrenalectomy followed by contralateral retroperitoneoscopic partial adrenalectomy in a patient with multiple endocrine neoplasia type 2a syndrome. *J Endourol* 1999; 13(2):99-104, discussion 104-106.
22. Porpiglia F, Destefanis P, Bovio S, et al. Cortical-sparing laparoscopic adrenalectomy in a patient with multiple endocrine neoplasia type IIA. *Horm Res* 2002; 57(5-6):197-199.
23. Walz MK, Peitgen K, Neumann HP, et al. Endoscopic treatment of solitary, bilateral, multiple, and recurrent pheochromocytomas and paragangliomas. *World J Surg* 2002; 26(8):1005-1012.
24. de Graaf JS, Lips CJ, Rutter JE, et al. Subtotal adrenalectomy for phaeochromocytoma in multiple endocrine neoplasia type 2A. *Eur J Surg* 1999; 165(6):535-538.
25. Goldstein RE, O'Neill JA Jr, Holcomb GW 3rd, et al. Clinical experience over 48 years with pheochromocytoma. *Ann Surg* 1999; 229(6):755-764, discussion 764-766.
26. Neumann HPH, Reincke M, Bender BU, et al. Preserved adrenocortical function after laparoscopic bilateral adrenal sparing surgery for hereditary pheochromocytoma. *J Clin Endocrinol Metab* 1999; 84(8):2608–2610.
27. Jansson S, Khorram-Manesh A, Nilsson O, et al. Treatment of bilateral pheochromocytoma and adrenal medullary hyperplasia. *Ann N Y Acad Sci* 2006; 1073:429-435.
28. Yip L, Lee JE, Shapiro SE, et al. Surgical management of hereditary pheochromocytoma. *J Am Coll Surg* 2004; 198(4):525-534, discussion 534-535.
29. Inabnet WB, Caragliano P, Pertsemlidis D. Pheochromocytoma: inherited associations, bilaterality and cortex preservation. *Surgery* 2000; 128(6):1007–1011, discussion 1011-1012.
30. Schreinemakers JM, Kiela GJ, Valk GD, et al. Retroperitoneal endoscopic adrenalectomy is safe and effective. *Br J Surg* 2010; 97(11):1667-1672.
31. Evans DB, Lee JE, Merell RC, et al. Adrenal medullary disease in multiple endocrine neoplasia type 2. *Endocrinol Metab Clin North Am* 1994; 23(1):167–176.
32. Goretzki PE, Simon D, Dotzenrath C, et al. Surgery for pheochromocytoma in MEN II patients: a radical versus a limited approach. *Acta Chir Austriaca* 1996; 28:296-301.
33. Casanova S, Rosenberg-Bourgin M, Farkas D, et al. Pheochromocytoma in multiple endocrine neoplasia type 2A: a survey of 100 cases. *Clin Endocrinol (Oxf)* 1993; 38(5):531-537.
34. Tibblin S, Dymling JF, Ingemansson S, et al. Unilateral versus bilateral adrenalectomy in multiple endocrine neoplasia IIA. *World J Surg* 1983; 7(2):201-208.
35. Li LM, Fitzgerald PA, Price DC, et al. Iatrogenic pheochromocytomatosis: a previously unreported result of laparoscopic adrenalectomy. *Surgery* 2001; 130(6):1072–1077.
36. Baghai M, Thompson GB, Young WF Jr, et al. Pheochromocytomas and paragangliomas in Von Hippel-Lindau disease: A role for laparoscopic and cortical-sparing surgery. *Arch Surg* 2002; 137(6):682–689.
37. Nambirajan T, Janetschek G. Laparoscopic partial adrenalectomy. *Minim Invasive Ther Allied Technol* 2005; 14(2):71-77.

Chapter 11

General Discussion and Future Perspectives

In this thesis, we have addressed the management of patients with familial and sporadic endocrine tumors of the parathyroid glands and the adrenal glands.

Parathyroid Glands

Sporadic versus Multiple Endocrine Neoplasia-Related Primary Hyperparathyroidism

In *Chapters 2 through 4*, we show that sporadic, multiple endocrine neoplasia (MEN) 1-related pHPT and MEN2A-related primary hyperparathyroidism (pHPT) are very distinct and different entities, as is reflected preoperatively by differences in sex, age at diagnosis and preoperative calcium and parathyroid hormone (PTH) levels.[1,2,3] Clearly, these entities require a different approach to preoperative workup and operative strategy.

Great controversy still exists regarding the surgical management of pHPT in patients with MEN1 and MEN2A. From the meta-analysis on the surgical management of pHPT in MEN1 patients in *Chapter 2*, subtotal parathyroidectomy appears to be the optimal surgical treatment, despite the high recurrence rate after this procedure. Furthermore, the risk of permanent hypoparathyroidism (hypocalcaemia) is significantly lower than after total parathyroidectomy with autotransplantation.[4,5]

Because of multiglandular disease,[3] leaving behind parathyroid tissue has a high risk of recurrent pHPT in patients with MEN1. Limited resections of fewer than 3 glands (less than subtotal parathyroidectomy [<SPTX], including minimally invasive parathyroidectomy [MIP]), should not be performed in these patients, because it has the highest risk of persistent and recurrent disease, which necessitates reoperative surgery with its associated risks. Secondary surgery is more challenging because of postoperative fibrosis, leading to more difficulty in identifying the parathyroid glands and a higher risk of recurrent laryngeal nerve injury and hypoparathyroidism.[6,7]

However, after more extensive surgery with resection of all parathyroid glands (total parathyroidectomy [TPTX]), the risk of recurrence may be lower, but postoperative hypoparathyroidism frequently occurs.[5,8,9] Autotransplants do not always succeed and it may take days to months before they start producing PTH. The resulting hypocalcaemia can be very severe, leading to significant morbidity with a prolonged hospital stay for intravenous calcium infusion.

Subtotal parathyroidectomy (SPTX) is generally considered to be superior to TPTX because the risk of permanent hypoparathyroidism is much lower. However, there might be an increased risk of recurrence compared with TPTX since some parathyroid tissue remains in situ.[4,5,] Yet, the time to develop recurrent disease after SPTX is long and a reoperation is often required only after many years.

Recently, the DutchMEN1 Study Group, which has composed a large Dutch nationwide database containing all patients with MEN1 in The Netherlands, published the first information on the genotype-phenotype relationship regarding MEN1-related pHPT. They reported that, after <SPTX persistence and recurrence was significantly lower in patients with nonsense or frameshift mutations in exon 2, 9, and 10. This indicates that cure primarily depends on the amount of parathyroid tissue removed.[10] Therefore, the possibility of supernumerary and ectopic parathyroid glands should be

considered in the surgical treatment of pHPT in MEN1 patients.[11] After SPTX or TPTX recurrence is more common in patients without a bilateral transcervical thymectomy.[10] Therefore, a thymectomy should routinely be performed in these patients to search for supernumerary and ectopic glands.[5,12]

On the basis of the results from the DutchMEN1 Study Group, we have changed our surgical strategy over the last years. SPTX combined with bilateral transcervical thymectomy is now the preferred procedure in our institution.[10] Long-term follow-up by the DutchMEN1 Study Group will lead to more insight into whether this procedure provides the best balance between cure and postoperative hypoparathyroidism. Of course, a large randomized controlled, multicenter trial would offer a more reliable answer to which is the optimal type of surgical treatment of MEN1 related pHPT, but it is questionable if this is feasible.

Primary hyperparathyroidism in patients with MEN2A occurs much less frequently than in MEN1. Therefore, the studies that have addressed the surgical treatment contained small study populations.[8,12] PHPT in MEN2A is generally less aggressive and more often caused by uniglandular disease compared with MEN1-related pHPT. In *Chapter 3*, we show an evolving preference for minimal resection of parathyroid glands (MIP) over the aggressive, conventional exploration of all four glands to treat pHPT in patients with MEN2A. In these patients, MIP appears to be a feasible and safe approach. It has low rates of persistent and recurrent pHPT, and complications are minimal.

The MIP technique has become the standard of care for sporadic pHPT in institutions with substantial experience with the procedure. MIP can be performed if preoperative imaging studies are concordant. MIP has a minimal risk of damage to surrounding tissues. Furthermore, MIP provides better cosmetic results, patient comfort and a shorter duration of hospital stay.[13] Its role in the setting of familial pHPT is evolving. In the current time of genetic screening and prophylactic total thyroidectomy at a young age, almost all patients with MEN2A will undergo some form of neck surgery for medullary thyroid carcinoma (MTC) before the presentation of and surgery to treat pHPT. Taking the postoperative fibrosis and scarring after neck surgery into account, an image-guided minimally invasive procedure is preferred over more invasive approaches, like SPTX and TPTX.[12]

An international randomized controlled trial or a large multicenter study with a large number of patients with a long-term follow-up is necessary to answer some of the remaining questions. First, a longer postoperative follow-up of these patients after MIP may help to elucidate whether or not this is the best surgical therapy for this disease in terms of recurrent disease. Second, as in MEN1, some MEN2A families demonstrate a more aggressive presentation of pHPT. It is unknown if a genotype-phenotype relationship exists. Nonetheless, such a study design would be very problematic to accomplish in view of the rarity of this disease.

Despite different patient characteristics, patients with sporadic pHPT are very similar to MEN2A patients with respect to their operative approach and intraoperative

findings. As for MEN2A, for sporadic pHPT, we advocate to perform a MIP in case of two concordant imaging studies. If there is only one positive study we propose an unilateral exploration and if all imaging studies are negative or contradictory an upfront conventional neck exploration is advocated. Results of MIP for sporadic pHPT are good, with low persistence and recurrence rates. Also, the number of patients with postoperative hypoparathyroidism is minimal.[14]

In light of our findings in these three categories of patients; we advocate a more aggressive approach in MEN1 patients with pHPT compared with patients with sporadic and MEN2-related pHPT, who are quite similar in terms of operative findings and in whom a MIP can suffice. However, compared with sporadic patients, MEN2 patients require a more dynamic approach, also because of associated endocrinopathies. In our opinion, MEN patients should be concentrated and treated in a tertiary referral center.

Intraoperative Parathyroid Hormone Measurement

Current guidelines for patient selection for parathyroidectomy rely heavily on the presence of clinical manifestations of the disease. All patients with biochemically confirmed pHPT who have specific symptoms should undergo surgical treatment. There is growing consensus that surgery may eventually be appropriate in the majority of patients with asymptomatic disease, particularly in patients with high serum calcium levels, reduction in bone density, and age less than 50 years.[15]

The data in *Chapter 5,* confirm higher serum calcium and higher initial intraoperative PTH (IOPTH) levels in African American patients compared with white patients.[16,17] However, these findings do not appear to be associated with more severe clinical manifestations of pHPT.[16,18] African American and white patients had equivalent rates of “objective symptoms”, including osteoporosis and nephrolithiasis. The PTH level differences might be clinically insignificant and attributable to biochemical racial differences such as decreased skeletal sensitivity to PTH.[16]

African American patients with pHPT show significant differences in IOPTH curves compared with white patients. We found that African American patients undergoing surgery for pHPT had elevated levels of initial IOPTH and IOPTH at 5 minutes postexcision but an equivalent level of IOPTH at 10 minutes postexcision. However, a similar percentage of African American and white patients had an adequate drop in IOPTH level by the Miami criteria. We did observe a trend towards a higher rate of persistent disease among African American patients when Miami criteria alone were applied. This effect was abrogated when IOPTH level was required to drop to the normal range.

Vitamin D deficiency[17,19] and increased body mass index[20] could be other potential contributors to higher serum calcium and PTH levels at presentation, and different IOPTH kinetics in African American patients with pHPT. Also, disparities in access to health care can be considered a likely explanation for late presentation and more severe disease in terms of serum calcium and PTH levels.

It seems plausible that given the higher starting IOPTH level among African American patients, a drop of more than 50% should be expected. However, further studies with larger numbers of patients will be necessary to clarify whether African American race may be associated with lower sensitivity of the Miami Criteria in detection of multiglandular disease during parathyroidectomy, and if so, what percentage drop should be required. Additional investigation is also needed into the contribution of other variables such as vitamin D deficiency and body mass index to the racial differences we observed.

Adrenal Glands

Surgical Management of Adrenal Gland Tumors

Laparoscopic adrenalectomy is the procedure of choice for most adrenal tumors. There is still much debate in literature regarding the effect of tumor size and diagnosis on the short-term outcome of adrenal surgery. In *Chapter 6*, we show that tumor size is the most significant predictor of short-term outcome after laparoscopic adrenalectomy. Patients with tumors 3 cm and larger had a longer operation time, a higher conversion rate, more estimated blood loss, more intraoperative and postoperative complications, and a longer postoperative hospital stay compared with patients with tumors smaller than 3 cm. In addition, the clinicopathological diagnosis affects surgical outcome, however to a lesser degree than tumor size. Patients with adrenal metastasis, hypercortisolism, and pheochromocytoma had more blood loss than patients with aldosteronoma, while operation time for patients with pheochromocytoma was longer.

An increase in operation time and more blood loss for large adrenal masses can be explained by the larger surface to dissect and the associated richer vascularization that requires more care by the surgeon to avoid complications.[21,22,23]

This effect is amplified for resection of pheochromocytomas. To minimize complications, adrenalectomy for pheochromocytoma should be meticulous and deliberate. The procedure is sometimes paused to prevent or to treat blood pressure fluctuations. Pheochromocytomas are larger on average compared with aldosteronomas and vasculogenesis and angiogenesis make them prone to bleeding during dissection.[23,24,25]

Patients with hypercortisolism tend to have more comorbidities related to the underlying illness. They are frequently hypertensive, obese, weak, and immunosuppressed, and have parchment-like skin and poor overall tissue quality. These factors make surgery and postoperative recovery more difficult.[24,26] Those with chronic adrenocorticotropic hormone stimulations may have inflamed and hyperplastic adrenal glands, making their resection more difficult with more associated blood loss and a longer operation time.[24] However, in contrast with previous studies,[24,26] our multivariate analysis showed patients with hypercortisolism did not have more complications or a longer significant longer postoperative hospital stay than other patients.

The extra blood loss associated with adrenal metastasis can be explained by vasculogenesis accompanying cancerous growth. Adrenal glands containing small

metastases are readily operable laparoscopically. Larger ones tend to have significant large vessels on the surface of the gland, making the dissection more treacherous.

The results of our study indicate that the size of adrenal tumor correlates best with short-term surgical outcome of laparoscopic adrenalectomy. As a surgeon, it is important to be aware of the risk of possible complications of laparoscopic adrenalectomy, especially in patients with large tumors.

Identification and control of the adrenal vein are critical steps in laparoscopic adrenalectomy. In *Chapter 7*, we show that variants of adrenal venous anatomy occur in a significant percentage of patients, particularly in patients with pheochromocytomas[27] and large tumors. Variants include the number of veins draining the adrenal gland as well as the location of the adrenal vein in relation to the hepatic vein or inferior phrenic vein.

An increase in angiogenesis and vasculogenesis in pheochromocytoma may explain the high prevalence of variants in patients with these tumors.[28] Some patients had multiple small veins. These small periadrenal veins may be collateral venous drainage pathways. As the tumor grows, more collateral veins may become apparent. This is consistent with our finding of larger tumors in patients with variant adrenal venous anatomy.

Adrenal venous drainage including anatomic variants can be defined clearly during laparoscopic adrenalectomy. Because of magnification, laparoscopy provides better visualization of the adrenal anatomy. We show a similar rate of (bleeding) complications between patients with normal venous anatomy and those with variant venous adrenal anatomy. Laparoscopic adrenalectomy is a safe procedure, if the surgeon is aware of the possible anatomical venous variants.

Pheochromocytoma Crisis

The timing of surgery for pheochromocytoma patients presenting with crisis is controversial. In *Chapter 8*, we identify three surgical treatment strategies for resection of the pheochromocytoma: elective, after initial hospital discharge and adequate α-blockade; urgent, after stabilization and adequate α-blockade but during the same hospitalization for crisis; and emergency, immediately after crisis presentation or because of clinical deterioration without appropriate blockade or preoperative management.

We show that medical stabilization followed by appropriate α-blockade is safe and effective and pheochromocytoma crisis should be treated as a medical emergency rather than a surgical one. Management of patients with pheochromocytoma crisis should always include initial stabilization and subsequent α- and, if necessary, β-blockade in combination with elective or urgent surgery. Laparoscopic resection can be performed safely in crisis patients. Review of the literature shows that emergency resection of pheochromocytoma in crisis patients is associated with high morbidity and mortality.

Medical stabilization for pheochromocytoma crisis requires an individualized approach depending on clinical presentation. Extraordinary efforts may be needed to initially stabilize the patient. Crisis patients with significant cardiomyopathy or cardiogenic shock can be successfully treated with intra-aortic balloon pump or extracorporeal membrane oxygenation.[29,30]

In our series, the decision regarding elective or urgent surgery was usually based on clinical presentation and clinical judgment. Postoperatively, patients who underwent elective surgery had shorter hospital stays and fewer postoperative complications and were less often admitted to the intensive care unit compared with urgently operated patients.

This was the first study on the management of patients presenting with pheochromocytoma crisis in a large cohort. Further studies are necessary to provide more insight into the differences found between urgently and electively operated patients. Clinical judgment determined whether patients were operated urgently or electively. Larger, perhaps prospective cohorts are needed to find objective parameters to determine the exact timing for surgery and which stabilization protocol is best.

Pheochromocytoma in Multiple Endocrine Neoplasia

Due to considerable improvements in preoperative medical preparation and perioperative anesthetic control, mortality after pheochromocytoma resection is rare. However, (morbidity from) intraoperative HD instability remains a problem. The perioperative HD course of MEN2 patients with a pheochromocytoma has typically been reported only in case reports.[31,32]

Clinically, pheochromocytoma in MEN2 patients are often identified at an earlier stage compared with sporadic pheochromocytoma because of annual screening of known mutation carriers. In most cases, earlier diagnosis leads to the identification of smaller tumors, often associated with fewer symptoms and less frequent and less severe hypertension.[31,33]

In *Chapter 9*, we demonstrate that despite preoperative differences, MEN2 patients with pheochromocytoma do not distinguish themselves from sporadic cases of pheochromocytoma in terms of intraoperative hypertensive episodes. This might mean that the relatively small MEN2-related pheochromocytomas are easily provoked to secrete catecholamines during resection. Therefore, patients with MEN2 or small tumors, should not be excluded from preoperative treatment with α- and, if necessary, β-blockade before undergoing pheochromocytoma resection.

Furthermore, we demonstrate that after multivariate analysis, tumor size is an independent risk factor for hemodynamic instability during pheochromocytoma resection, independent of preoperative hormone levels, preoperative medication, surgical approach, and the presence of a familial syndrome.[32] Extra caution must be taken when pretreating or operating a patient with a large pheochromocytoma.

Pheochromocytomas in MEN2 occur in half of the patients, and are frequently bilateral. In *Chapter 10*, we show that unilateral subtotal adrenalectomy has evolved into a feasible surgical strategy for pheochromocytoma in MEN2 patients. Unilateral subtotal adrenalectomy has the great advantage of preserving adrenocortical function, thereby preventing the need for and complications of chronic steroid replacement.[34]

Pheochromocytomas may recur either on the contralateral side as a result of the nature of the disease or on the ipsilateral side even a long time after the initial operation. Unilateral subtotal adrenalectomy has comparable recurrence rates compared with unilateral total adrenalectomy. In addition, unilateral subtotal adrenalectomy eventually carries less complications of steroid replacement. Bilateral total adrenalectomy as first choice treatment is no longer considered because of the associated adrenocortical insufficiency after total adrenalectomy.[35]

A less aggressive, 'watchful waiting' strategy seems to be acceptable in hereditary pheochromocytoma for two reasons. First, because of the generally slow progression of the disease, in combination with an effective, protocolized screening program, yearly screening and timely surgery can minimize the risk of a hypertensive crisis from recurrent pheochromocytoma. Second, malignant pheochromocytomas rarely occur in patients with MEN2, in contrast to patients with sporadic pheochromocytoma.[35] Laparoscopic cortical-sparing procedures can be performed safely and successfully, even when a repeat surgical procedure is needed.[36]

Preservation of the cortex may not be possible in every case of pheochromocytoma and, therefore, may not be possible in a contralateral adrenal gland after primary unilateral total adrenalectomy. This emphasizes the need to perform subtotal adrenalectomy as primary surgery if possible.

Additional studies with longer postoperative follow-up are necessary to further investigate whether or not subtotal unilateral adrenalectomy as primary surgery is the best surgical therapy for pheochromocytoma in MEN2 patients.

General Comments and Future Perspectives

The management of patients with endocrine tumors has evolved immensely over the past decades, but remains individual and complex. For parathyroid and adrenal disorders, the treatment has changed from aggressive resections to minimally invasive approaches, with similar success rates but less surgical morbidity. Also, there is growing evidence to treat most adrenal disease diagnosis via laparoscopic surgery instead of open resection.

Patients with familial endocrine syndromes should be considered distinctly different from patients with sporadic endocrine disorders. These patients and their families require centralized multidisciplinary care. Advantages of centralizing patients include the provision of adequate experience and knowledge of the complexity of the problems, and the possibility of conducting research with relatively large study populations. The latter is useful to answer some of the remaining questions on the management of endocrine disorders in order to offer the patients the best surgical treatment.

Translational research has introduced a new concept in managing the individual patient with an endocrine tumor or syndrome.

Translational Research and Multiple Endocrine Neoplasia

As stated, recently information on the genotype-phenotype relationship regarding MEN1-related pHPT was published. For MEN2, the type of *RET* proto-oncogene codon mutation can provide insight into the MEN2 variant and the timing of preventive thyroidectomy because of MTC. Also, knowledge about the features within the family, can aid in recommendations about aggressiveness of surgical management and screening protocol.

For MTC, the *RET* proto-oncogen codon mutations can be stratified into three levels of risk. These three categories predict the MEN2 syndromic variant, the age of onset of MTC, and the aggressiveness of MTC. Surgery for MTC can, therefore if possible, be performed, before the age of possible malignant progression.

Pheochromocytoma has been found in kindreds with almost all *RET* proto-oncogene mutations. In some high risk mutations, it occurred as early as 5 and 10 years of age. The risk of developing pHPT varies considerably among the types of *RET* proto-oncogene mutations. MEN2B patients do not develop pHPT. For pheochromocytoma and pHPT, the type of mutation, as well as the familial pattern influences the appropriate age to start and the frequency of biochemical screening. Till now, unlike for MTC, it is unclear if a genotype-phenotype relationship exists which can influence surgical management of pheochromocytoma and pHPT in patients with MEN2.

Translational studies can provide information on the possibility of this relationship. For pHPT, it can demonstrate whether some families have more aggressive disease in terms of symptomatology, i.e. severity of bone disease or risk of recurrent pHPT after surgery. For pheochromocytoma, it can provide insight into why some patients present with more ‘dangerous’ tumors in terms of symptomatology (asymptomatic versus pheochromocytoma crisis) or are at higher risk for developing hemodynamic instability during resection.

References

1. Marx SJ, Simonds WF, Agarwal SK, et al. Hyperparathyroidism in hereditary syndromes: special expressions and special managements. *J Bone Miner Res* 2002; 17(Suppl 2):N37-N43.
2. Lourenco DM Jr, Coutinho FL, Toledo RA, Montenegro FL, Correia-Deur JE, Toledo SP. Early-onset, progressive, frequent, extensive, and severe bone mineral and renal complications in multiple endocrine neoplasia type 1-associated primary hyperparathyroidism. *J Bone Miner Res* 2010; 25(11):2382-2391.
3. Eller-Vainicher C, Chiodini I, Battista C, et al. Sporadic and MEN1-related primary hyperparathyroidism: differences in clinical expression and severity. *J Bone Miner Res* 2009; 24(8):1404-1410.
4. Malone JP, Srivastava A, Khardori R. Hyperparathyroidism and multiple endocrine neoplasia. *Otolaryngol Clin North Am* 2004; 37(4):715-736.
5. Tonelli F, Marcucci T, Fratini G, et al. Is total parathyroidectomy the treatment of choice for hyperparathyroidism in multiple endocrine neoplasia type 1? *Ann Surg* 2007; 246(6):1075-1082.
6. Carling T, Udelsman R. Parathyroid surgery in familial hyperparathyroid disorders. *J Intern Med* 2005; 257(1):27–37.
7. Hubbard JG, Sebag F, Maweja S, et al. Primary hyperparathyroidism in MEN 1 – how radical should surgery be? *Langenbecks Arch Surg*. 2002; 386(8):553–557.
8. Lee CH, Tseng LM, Chen JY, Hsiao HY, Yang AH. Primary hyperparathyroidism in multiple endocrine neoplasia type 1: individualized management with low recurrence rates. *Ann Surg Oncol* 2006; 13(1):103-109.
9. Hubbard JG, Sebag F, Maweja S, Henry JF. Subtotal parathyroidectomy as an adequate treatment for primary hyperparathyroidism in multiple endocrine neoplasia type 1. *Arch Surg* 2006; 141(8):235-239.
10. Pieterman CR, van Hulsteijn LT, den Heijer M, et al. Primary hyperparathyroidism in MEN1 patients: a cohort study with longterm follow-up on preferred surgical procedure and the relation with genotype. *Ann Surg* 2012; 255(6):1171-1178.
11. Langer P, Wild A, Schilling T et al. Multiple endocrine neoplasia type 1. Surgical therapy of primary hyperparathyroidism. *Chirurg* 2004; 75(9):900–906.
12. Dotzenrath C, Cupisti K, Goretzki PE, et al. Long-term biochemical results after operative treatment of primary hyperparathyroidism associated with multiple endocrine neoplasia types I and IIa: is a more or less extended operation essential? *Eur J Surg* 2001; 167(3):173–178.
13. Smit PC, Borel Rinkes IHM, van Dalen A, van Vroonhoven TJ. Direct, minimally invasive adenomectomy for primary hyperparathyroidism: An alternative to conventional neck exploration? *Ann Surg* 2000; 231(4):559-565.
14. Twigt BA, Vollebregt AM, van Dalen T, et al. Shifting incidence of solitary adenomas in the era of minimally invasive parathyroidectomy. A multi-institutional study. *Ann Surg Oncol* 2011; 18(4):1041-1046.
15. Bilezikian JP, Khan AA, Potts JT Jr; Third International Workshop on the Management of Asymptomatic Primary Hyperthyroidism. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. *J Clin Endocrinol Metab* 2009; 94(2):335-339.
16. Barker H, Caldwell L, Lovato J, Woods KF, Perrier ND. Is there a racial difference in presentation of primary hyperparathyroidism? *Am Surg* 2004; 70(6):504-506.

17. Kandil E, Tsai HL, Somervell H, et al. African Americans present with more severe primary hyperparathyroidism than non-African Americans. *Surgery* 2008; 144(6):1023-1026, discussion 1026-1027.
18. Jabiev AA, Lew JI, Garb JL, Sanchez YM, Solorzano CC. Primary hyperparathyroidism in the underinsured: a study of 493 patients. *Surgery* 2012; 151(3): 471-476.
19. Untch BR, Barfield ME, Dar M, Dixit D, Leight GS Jr, Olson JA Jr. Impact of 25-hydroxyvitamin D deficiency on perioperative parathyroid hormone kinetics and results in patients with primary hyperparathyroidism. *Surgery* 2007; 142(6):1022-1026
20. Adam MA, Untch BR, Danko ME, et al. Severe obesity is associated with symptomatic presentation, higher parathyroid hormone levels, and increased gland weight in primary hyperparathyroidism. *J Clin Endocrinol Metab* 2010; 95(11): 4917-4924.
21. Walz M, Petersenn S, Koch JA, et al. Endoscopic treatment of large primary adrenal tumors. *Br J Surg* 2005; 92(6):719–723.
22. Kazaryan AM, Mala T, Edwin B. Does tumor size influence the outcome of laparoscopic adrenalectomy? *J Laparoendosc Adv Surg Tech A* 2001; 11(1):1-4.
23. Morris L, Ituarte P, Zarnegar R, et al. Laparoscopic adrenalectomy after prior abdominal surgery. *World J Surg* 2008; 32(5):897-903.
24. Poulin E, Schlachta CM, Burpee SE. Laparoscopic adrenalectomy: pathologic features determine outcome. *Can J Surg* 2003; 46(5):340–344.
25. Kim A, Quiros RM, Maxhimer JB, et al. Outcome of laparoscopic adrenalectomy for pheochromocytomas vs. aldosteronomas. *Arch Surg* 2004; 139(5):526-529, discussion 529-531.
26. Chan J, Meneghetti AT, Meloche RM, et al. Prospective comparison of early and late experience with laparoscopic adrenalectomy. *Am J Surg* 2006; 191(5):682–686.
27. Parnaby CN, Galbraith N, O'Dwyer PJ. Experience in identifying the venous drainage of the adrenal gland during laparoscopic adrenalectomy. *Clin Anat* 2008; 21(7):660-665.
28. Zielke A, Middeke M, Hoffmann S, et al. VEGF-mediated angiogenesis of human pheochromocytomas is associated to malignancy and inhibited by anti-VEGF antibodies in experimental tumors. *Surgery* 2002; 132(6):1056-1063.
29. Huang JH, Huang SC, Chou NK. Extracorporeal membrane oxygenation rescue for cardiopulmonary collapse secondary to pheochromocytoma: report of three cases. *Intensive Care Med* 2008; 34(8):1551-1552.
30. Suh IW, Lee CW, Kim YH. Catastrophic catecholamine-induced cardiomyopathy mimicking acute myocardial infarction, rescued by extracorporeal membrane oxygenation (ECMO) in pheochromocytoma. *J Korean Med Sci* 2008; 23(2):350-354.
31. Luo A, Guo X, Yi J, Ren H, Huang Y, Ye T. Clinical features of pheochromocytoma and perioperative anesthetic management. *Chin Med J* 2003; 116(10) 1527–1531
32. Bruynzeel H, Feelders RA, Groenland TH, et al. Risk factors for hemodynamic instability during surgery for pheochromocytoma. *J Clin Endocrinol Metab* 2010; 95(2): 678–685.
33. Atallah F, Bastide-Heulin T, Soulie´ M, Crouzil F, Galiana A, Samii K, Virenque C. Haemodynamic changes during retroperitoneoscopic adrenalectomy for phaeochromocytoma. *Br J Anesth* 2001; 86(5):731–733.
34. Reisch N, Arlt W Fine tuning for quality of life: 21st century approach to treatment of Addison's disease. *Endocrinol Metab Clin N Am* 2009; 38(2):407–418.
35. Inabnet WB, Caragliano P, Pertsemlidis D. Pheochromocytoma: inherited associations, bilaterality and cortex preservation. *Surgery* 2000; 128(6):1007–1011, discussion 1011-1012.

36. Nambirajan T, Janetschek G Laparoscopic partial adrenalectomy. *Minim Invasive Ther Allied Technol* 2005; 14(2):71–77.

Chapter 12

Summary in Dutch

(Samenvatting in het Nederlands)

Dit proefschrift geeft inzicht in de moderne chirurgische behandeling van patiënten met familiale en sporadische endocriene tumoren. Endocriene tumoren ontwikkelen zich in hormonale klieren, zoals de bijschildklier en de bijnier. Endocriene tumoren kunnen sporadisch of als onderdeel van erfelijke endocriene syndromen voorkomen. De meest voorkomende syndromen zijn het multipele endocriene neoplasie (MEN) syndroom type 1 en 2. Deze syndromen worden autosomaal dominant overgedragen. Patiënten die lijden aan deze erfelijke tumorsyndromen hebben een verhoogd risico op het ontwikkelen van tumoren in verschillende endocriene organen. Zo is MEN1 geassocieerd met primaire hyperparathyreoïdie (pHPT), tumoren van het pancreas en adenomen van de hypofyse.

MEN2 is onderverdeeld in MEN2A en MEN2B. Vrijwel alle patiënten met MEN2 ontwikkelen een medullair schildkliercarcinoom. Daarom moeten alle MEN2 patiënten profylactisch een totale schildklierresectie (*thyreoïdectomie*) ondergaan op vroege leeftijd. Verder, ontwikkelt de helft van de MEN2A patiënten een feochromocytoom en ongeveer een kwart krijgt pHPT. In vergelijking met MEN2A, is MEN2B agressiever en minder vaak voorkomend. Naast het medullair schildkliercarcinoom, is MEN2B onder andere geassocieerd met het feochromocytoom.

De Bijschildklieren

Mensen hebben over het algemeen vier bijschildklieren, gelegen in de hals achter de schildklier en in sommige gevallen vlak bij de thymus. De bijschildklieren zijn verantwoordelijk voor de productie van bijschildklierhormoon (*parathyreoïdhormoon*, PTH), dat de calciumhuishouding van het lichaam en de botten reguleert.

Primaire hyperparathyreoïdie (*hyper,* “overmatig”; *parathyreoïd,* “bijschildklier”) is een veel voorkomende aandoening. PHPT komt over het algemeen voor zonder dat er sprake is van een erfelijke aanleg (*sporadisch*). Een deel van de patiënten, echter, ontwikkelt pHPT in het kader van een erfelijk syndroom (*familiaal*), zoals MEN1 en MEN2. Patiënten met pHPT hebben een hoge serum calciumwaarde en een verhoogde of niet onderdrukte PTH-concentratie. Dit kan leiden tot onder andere osteoporose, nierstenen, obstipatie en stemmingsstoornissen met depressieve kenmerken.

PHPT wordt in 90% van de gevallen veroorzaakt door een goedaardige (*benigne*) tumor (*adenoom*) in één bijschildklier. In 10% is vergroting van alle vier de klieren (*hyperplasie*) de oorzaak. Bijschildklierchirurgie is de enige genezende behandeling van pHPT. Vroeger was dubbelzijdige (*bilaterale*) of conventionele halsexploratie met visualisatie van alle vier de bijschildklieren en resectie van de vergrote klieren de standaard procedure voor patiënten met pHPT. Tegenwoordig verdienen, door verbetering in beeldvorming en *peri-operatieve zorg* (zorg rondom de operatie), conservatievere technieken de voorkeur in geval van solitaire bijschildklierziekte om de kans op complicaties te minimaliseren. Voorbeeld van zo’n conservatieve techniek is de minimaal invasieve bijschildklierresectie (*minimaal invasieve parathyreoïdectomie*, MIP). Complicaties van bijschildklierchirurgie zijn bijschildklierinsufficiëntie (*hypoparathyreoïdie*) leidend tot een te lage calciumwaarde

in het bloed (*hypocalciëmie*) en letsel van de stembandzenuw (*nervus laryngeus recurrens*). Acute bijschildklierinsufficiëntie kan leiden tot milde of zelfs ernstige neuromusculaire symptomen, variërend van neuromusculaire irritatie tot epileptische aanvallen. Ernstige hypocalciëmie moet worden behandeld met intraveneus calciumsuppletie. Minder ernstige bijschildklierinsufficiëntie wordt behandeld met (levenslange) suppletie van calcium en vitamine D. Eenzijdig letsel van de nervus laryngeus recurrens leidt tot heesheid, dubbelzijdig letsel leidt tot problemen met de ademhaling en onvermogen tot spreken.

Sporadische versus Multipele Endocriene Neoplasie-Gerelateerde Primaire Hyperparathyreoïdie

In *Hoofdstuk 2 tot en met 4*, hebben we laten zien dat sporadische, MEN1-gerelateerde en MEN2-gerelateerde pHPT verschillende entiteiten zijn, zoals weergegeven door verschillen in preoperatieve klinische kenmerken en de serum calciumwaarde. Deze drie verschillende ziektebeelden verdienen allen een verschillende benadering tot preoperatieve diagnostiek en operatieve strategie.

Alle MEN1 patiënten ontwikkelen op den duur pHPT. De etiologie van MEN1 gerelateerde pHPT is meestal multiglandulair (*meerdere klieren aangedaan*). Er bestaat veel controverse over het beste type chirurgische behandeling van pHPT in deze patiënten. Het is onduidelijk of alleen de aangedane bijschildklier, meerdere bijschildklieren of alle bijschildklieren verwijderd dienen te worden.

Resectie van minder dan 3 klieren kan leiden tot een hogere kans op herhaald voorkomen (*recidiveren*) en blijvend voorkomen (*persisteren*) van ziekte, wat kan leiden tot een reoperatie met de geassocieerde risico's. Secundaire chirurgie is lastiger uitvoerbaar, vanwege postoperatieve littekenvorming en fibrose, wat de identificatie van de bijschildklieren bemoeilijkt en leidt tot een hoger risico op bijschildklierinsufficiëntie en letsel van de nervus laryngeus recurrens. Echter, ook als 3 van de 4 klieren verwijderd worden, is de kans op recidief ziekte hoog. Echter, bij verwijderen van alle 4 de bijschildklieren (totale bijschildklierresectie, *totale parathyreoïdectomie*) bestaat weer een hoog risico op bijschildklierinsufficiëntie wat onbehandeld tot ernstige gevolgen kan leiden.

De resultaten van onze eigen studiepopulatie, beschreven in *Hoofdstuk 2,* laten zien dat resectie van 3-3½ bijschildklieren (subtotale bijschildklierresectie, *subtotale parathyreoïdectomie*) de meest optimale chirurgische behandeling van MEN1-gerelateerde pHPT is, ondanks het relatief hoge recidiefpercentage na deze behandeling. De meeste recidieven ontstaan gemiddeld pas na 10 jaar. Bovendien, is het risico op permanente bijschildklierinsufficiëntie significant lager dan na totale bijschildklierresectie met *autotransplantatie* (terugplaatsen van een deel van 1 van de bijschildklieren in de onderarm van de patiënt). Onze begeleidende literatuurstudie toont subtotale bijschildklierresectie tevens als beste chirurgische behandeling van pHPT in MEN1 patiënten.

In patiënten met MEN2A, komt pHPT minder vaak voor en is de ziekte vaak milder in vergelijking met pHPT in MEN1 patiënten. Bovendien is de aandoening vaker

geassocieerd met solitaire bijschildklierziekte. Ook over de chirurgische behandeling bij deze patiënten is onduidelijkheid. In *Hoofdstuk 3,* hebben we aan de hand van onze relatief grote patiëntenpopulatie laten zien dat het verwijderen van slechts 1 of 2 bijschildklieren via een minimaal invasieve ingreep (MIP) veilig is en een laag recidiefpercentage geeft. Echter, we zullen deze patiënten in de tijd moeten blijven volgen om het effect van deze behandeling op langere termijn te beoordelen.

Patiënten met sporadische pHPT lijken, ondanks verschillende patiëntkenmerken, veel op MEN2A patiënten met betrekking tot operatieve benadering en bevindingen. Sporadische pHPT wordt ook meestal veroorzaakt door een adenoom in één enkele bijschildklier. Daarom, net als voor MEN2A, adviseren wij minimaal invasieve resectie van 1 of 2 bijschildklieren, mits preoperatief beeldvormend onderzoek conclusief is. Voor de behandeling van sporadische pHPT, heeft minimaal invasieve chirurgie goede resultaten met minimale complicaties.

Peroperatieve Bijschildklierhormoon Meting

Echografie van de hals en technetium-99m-sestamibi scintigrafie worden tegenwoordig standaard toegepast voor de preoperatieve beeldvorming van de bijschildklieren. Peroperatieve PTH (*intra-operatieve PTH* [IOPTH], tijdens de operatie) meting is een snelle en relatief goedkope methode dat toegepast kan worden tijdens minimaal invasieve bijschildklierchirurgie in combinatie met preoperatief beeldvormend onderzoek om het succes van bijschildklierchirurgie te vergroten. De Miami-criteria bepalen dat de IOPTH-waarde 10 minuten na verwijdering (*excisie* of *resectie*) van het adenoom en de bijschildklier met 50% gedaald moet zijn ten opzichte van de hoogste waarde van PTH vóór excisie.

In eerdere studies wordt gesuggereerd dat Afro-Amerikaanse patiënten zich met meer vergevorderde ziekte presenteren met betrekking tot de calcium- en PTH-waarden in vergelijking met blanke patiënten met pHPT. Verschillen in toegang tot de gezondheidszorg en intrinsieke biochemische verschillen worden als oorzakelijke factoren gezien. In *Hoofdstuk 5,* hebben we gekeken naar de mogelijke invloed van etniciteit op de IOPTH-kinetiek en de optimale interpretatie van IOPTH-waarden. Zoals blijkt uit onze gegevens, hebben Afro-Amerikaanse patiënten een hogere calcium- en hogere initiële PTH-concentratie vergeleken met blanke patiënten, hoewel deze waarden niet geassocieerd blijken met klinische verschijnselen van een te hoge calciumwaarde.

Met betrekking tot IOPTH-metingen, hadden Afro-Amerikaanse patiënten een hogere initiële waarde en een hogere waarde 5 minuten na resectie, maar de waarde 10 minuten na resectie was vergelijkbaar met de waarde gevonden bij blanke patiënten. Beiden groepen hadden een vergelijkbaar percentage adequate daling van IOPTH. Er was wel een trend van meer persisterende ziekte in Afro-Amerikaanse patiënten wanneer alleen gekeken werd naar de Miami-criteria. Naast de in de Verenigde Staten bestaande verschillen in gezondheidszorgvoorzieningen, kunnen vitamine D deficiëntie en een hogere body mass index (gewicht in kilogram gedeeld door de lengte in meters in het kwadraat) bijdragen aan de gevonden

verschillen tussen Afro-Amerikaanse en blanke patiënten. Dit effect moet echter nog wel in grotere studies onderzocht worden. Bovendien is nog onduidelijk of het Afro-Amerikaans ras geassocieerd is met een lagere sensitiviteit voor de Miami-criteria met betrekking tot het aantonen van multiglandulaire ziekte tijdens bijschildklierchirurgie.

De Bijnieren

De bijnieren liggen in het retroperitoneum boven de nieren beiderzijds. De twee componenten van de bijnier zijn het centraal gelegen merg (*medulla*) en de buitenste schors (*cortex*). De schors is verantwoordelijk voor de productie van aldosteron (regulatie van de bloeddruk), cortisol (glucoseregulatie in reactie op stress, dag- en nachtritme en afweerreactie) en androgenen (voorloper van testosteron en oestrogeen, de geslachtshormonen). Het bijniermerg produceert de catecholaminen adrenaline en noradrenaline, welke functioneren als stresshormonen en zorgen voor een verhoging van de bloeddruk en hartslag via de alfa (*α*)-receptoren in de bloedvaten.

Vanwege het veelzijdig functieprofiel van de bijnier, is het niet verwonderlijk dat veel verschillende soorten goed- en kwaadaardige (*maligne*) tumoren hun oorsprong vinden in de bijnier. Voorbeelden zijn het aldosteronoom (overmatige aldosteron productie), het Cushing's adenoom (overmatige cortisol productie), het feochromocytoom (overmatige catecholamine productie), virilizerende tumoren (overmatige androgeen productie), niet-functionerende adenomen en minder vaak voorkomende aandoeningen als bijniercarcinomen, cysten en *myelolipomen* (gezwel uitgaande van vet- en bloedcellen). Tenslotte kunnen andere tumoren uitzaaien (*metastaseren*) naar de bijnieren.

Chirurgische Behandeling van Bijniertumoren

Laparoscopische bijnierresectie (*adrenalectomie*) is de behandeling van keuze voor de meeste bijniertumoren. In de literatuur is er veel discussie over de invloed van de grootte en aard van de bijniertumor op de korte termijn uitkomst van bijnierchirurgie. Over het algemeen is bijnierchirurgie geassocieerd met een lage complicatiekans en een sterfte van rond de 1.5%. In *Hoofdstuk 6*, hebben we aangetoond dat de grootte van de bijniertumor het meest voorspellend is voor de uitkomst van laparoscopische bijnierresectie. Patiënten met tumoren 3 cm en groter hebben een langere operatieduur, meer bloedverlies, een hogere kans op conversie naar een open procedure en meer peri- en postoperatieve complicaties in vergelijking met patiënten met tumoren kleiner dan 3 cm. Daarnaast, hebben patiënten met feochromocytomen, bijniermetastases en Cushing's adenomen meer bloedverlies vergeleken met patiënten met aldosteronomen.

Een langere operatieduur en meer bloedverlies bij grotere tumoren kan verklaard worden door een groter dissectie-oppervlak en een rijker vascularisatie-patroon dat meer zorg en aandacht vereist van de chirurg.

Identificatie en controle van de bijnierader (*bijniervene*) zijn belangrijke stappen tijdens laparoscopische bijnierresectie. De veneuze afvloed van elke bijnier is over het algemeen via een enkele bijniervene. Aan de rechter kant draineert deze direct in de onderste holle ader (*vena cava inferieur*) en aan de linker kant via de onderste middenrifader (*vena phrenica inferieur*) in de linker nierader (*vena renalis*). In *Hoofdstuk 7*, laten we zien dat varianten van de anatomie van de bijniervene vaak voorkomen, vooral bij patiënten met feochromocytomen en grote tumoren. Voorbeelden van varianten hebben betrekking op zowel het aantal venen dat de bijnier draineert, als de locatie van de bijniervene in relatie tot de leverader (*vena hepatica*) of vena phrenica inferieur.

Een toename van vaatnieuwvorming (*angiogenese en vasculogenese*) in feochromocytomen kan de hogere prevalentie van varianten in deze tumoren verklaren. Bovendien, als de bijniertumor groter wordt, kunnen normaal aanwezige kleine venen rondom de bijnier die een collateraal veneuze afvloed vormen, groeien en prominenter worden.

Het drainagepatroon van de bijnier, alsmede de variaties daarin, kunnen duidelijk gedefinieerd worden tijdens laparoscopische bijnierresectie. Door de vergroting op het beeldscherm, biedt laparoscopie beter overzicht van de anatomie van de bijnier. In onze studie, hadden patiënten met een variant van de anatomie van de bijniervene vergelijkbare peroperatieve complicaties als patiënten met een normale anatomie.

Feochromocytoom

Feochromocytomen zijn zeldzame neuro-endocriene catecholamine-producerende tumoren. Behalve in het merg van de bijnier, kunnen deze tumoren ook buiten de bijnier (*extra-adrenaal*) in het neuro-endocriene sympathisch zenuwstelsel voorkomen, langs de aorta en wervelkolom. Het extra-adrenale feochromocytoom wordt ook wel paraganglioom genoemd.

Feochromocytomen kunnen sporadisch of als onderdeel van een erfelijk syndroom, zoals MEN2 voorkomen. De klassieke presentatie van het feochromocytoom bestaat uit paroxysmale hypertensie, hoofdpijn, hartkloppingen (*palpitaties*) en overmatig zweten (*diaforesis*). Een gevreesde en mogelijk dodelijke complicatie van het feochromocytoom is een feochromocytoom crisis. Het feochromocytoom kan multipel en bilateraal voorkomen en tevens maligne ontaarden.

Chirurgie is de behandeling van keuze voor het feochromocytoom. De ingreep zelf, echter, kan levensbedreigend zijn door hypertensieve crisis en multiorgaan falen of ernstige hypotensie na tumorresectie. Preoperatieve behandeling met α-, beta (*β*)-, en/of calciumkanaalblokkers verlaagt het risico op peroperatieve ernstige bloeddruk-schommelingen (*hemodynamische instabiliteit*) en complicaties daarvan. Vooral een daling in de bloeddruk na resectie geeft een hoge kans op sterfte tijdens of vlak na de operatie.

Feochromocytoom Crisis

Het klinische beeld van een feochromocytoom crisis loopt uiteen van ernstige hypertensie tot circulatoire shock met betrokkenheid van meerdere orgaansystemen, inclusief het cardiovasculaire, pulmonale, neurologische, gastro-intestinale, renale, hepatogene en metabole systeem. Het feochromocytoom crisis is geassocieerd met een hoge mortaliteit. In *Hoofdstuk 8*, identificeren we drie behandelstrategieën met betrekking tot resectie van het feochromocytoom: electief, na adequate α-blokkade tijdens geplande heropname in het ziekenhuis; urgent, na stabilisatie en adequate α-blokkade tijdens dezelfde ziekenhuisopname als voor de crisis; en spoed, direct na crisispresentatie of vanwege klinische verslechtering van de patiënt zonder adequate α-blokkade of preoperatieve behandeling.

Behandeling van patiënten met een feochromocytoom crisis dient altijd te bestaan uit initiële stabilisatie en daarna α- en, indien nodig, β-blokkade, in combinatie met electieve of urgente chirurgie. Medische stabilisatie gevolgd door α-blokkade is veilig en effectief en vereist een individuele benadering afhankelijk van de klinische presentatie. In sommige gevallen zijn buitengewone maatregelen, zoals intra-aortale ballonpomp behandeling nodig. Laparoscopische resectie na stabilisatie is ook in crisis patiënten veilig uitvoerbaar. Spoedresectie van het feochromocytoom in crisis patiënten is geassocieerd met hoge chirurgische morbiditeit en mortaliteit.

Feochromocytoom in Multipele Endocriene Neoplasie

Feochromocytomen in MEN2 komen in de helft van de patiënten voor, zijn vaak bilateraal en zelden maligne in vergelijking met sporadische gevallen. Alle MEN2 patiënten dienen jaarlijks te worden gescreend op de aanwezigheid van het feochromocytoom door middel van urine- of bloedonderzoek en beeldvormend onderzoek om een potentieel levensbedreigende feochromocytoom crisis te voorkomen. Dit screeningsprotocol zorgt er voor dat feochromocytomen in MEN2 patiënten vaak in een vroeger stadium worden gevonden. In de meeste gevallen, leidt vroege diagnose tot de ontdekking van kleinere tumoren, welke vaak geassocieerd zijn met minder symptomen en minder vaak en minder ernstige hypertensie.

In *Hoofdstuk 9*, laten we zien dat, ondanks preoperatieve verschillen, MEN2 patiënten met een feochromocytoom vergelijkbare peroperatieve hypertensie hebben als sporadische gevallen met een feochromocytoom. Dit kan betekenen dat de relatief kleine MEN2-gerelateerde feochromocytomen makkelijk gestimuleerd worden tot het uitscheiden van catecholamines tijdens resectie. Daarom, moeten alle patiënten – MEN2 patiënten en patiënten met kleine tumoren niet uitgezonderd – preoperatief behandeld worden met α-blokkers en, in geval van een hoge hartslag, β-blokkers.

Tevens, tonen we aan dat de grootte van de tumor een risicofactor is voor hemodynamische instabiliteit tijdens feochromocytoomresectie, onafhankelijk van preoperatieve hormoonspiegels, preoperatieve medicatie, chirurgische benadering en de aanwezigheid van een erfelijk syndroom.

Feochromocytomen – zeker in geval van een erfelijk syndroom – kunnen recidiveren, aan de andere (*contralaterale*) zijde als gevolg van de biologie van de ziekte, of aan de zelfde (*ipsilaterale*) zijde zelfs jaren na de initiële operatie. Vroeger werd dubbelzijdige totale bijnierresectie (*bilaterale totale adrenalectomie*) voor patiënten met MEN2 aanbevolen om het risico op recidief te verkleinen. Vanwege de noodzaak tot levenslange hormoon- (*corticosteroïd-*) vervangingstherapie, met de nodige complicaties waaronder een acuut levensbedreigende crisis waarbij de cortisol niveau te laag is (*hypocortisolistische crisis*), wordt deze methode niet meer geadviseerd.

In *Hoofdstuk 10*, tonen we aan dat eenzijdige partiële bijnierresectie (*unilaterale subtotale adrenalectomie*) een geschikte behandeling is voor MEN2 patiënten met een feochromocytoom. Deze behandelmethode heeft het voordeel van behoud van de bijnierschors- (*adrenocorticale*) functie en vermijdt daarmee de noodzaak tot en complicaties van hormoonvervangingstherapie. Bovendien heeft deze behandeling vergelijkbare recidiefpercentages als eenzijdige totale bijnierresectie (*unilaterale totale adrenalectomie*).

Er zijn twee redenen waarom een minder agressieve benadering acceptabel is in patiënten met een erfelijk feochromocytoom. Ten eerste, omdat de over het algemeen langzame progressie van de ziekte, in combinatie met een effectief, geprotocoliseerd screeningsprogramma en tijdige chirurgie het risico op een hypertensieve crisis van een recidief feochromocytoom, minimaliseert. Ten tweede, omdat een kwaadaardig feochromocytoom zelden voorkomt in patiënten met MEN2 in tegenstelling tot sporadisch gevallen. Laparoscopische schors-sparende chirurgie is veilig en succesvol, zelfs in geval van een reoperatie.

Samenvattend, zien we dat de chirurgische behandeling van familiaire en sporadische endocriene tumoren over de afgelopen jaren is geëvolueerd tot gepast maatwerk, aangepast op de genetische achtergrond en het biologisch gedrag van de tumor en op de klinische kenmerken van de patiënt en zijn of haar familie. Bovendien, hebben verbeteringen in preoperatieve voorzieningen en peri-operatieve zorg geleid tot de opkomst van minimaal invasieve operatietechnieken en de mogelijkheid tot minimale resecties. Vooralsnog laten deze technieken goede resultaten zien met betrekking tot het risico op recidiveren of persisteren van de aandoening en tot de kans op complicaties.

Chapter 13

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Chapter 13

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Chapter 13

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Anouk Scholten was born on October 30th 1985, in Amersfoort, The Netherlands. She graduated from the athenaeum at 't Atrium, in Amersfoort, in 2003. She studied Medicine at the University of Utrecht from 2003 to 2009. During her last year she participated in several research projects at the Endocrine Surgery Department of the University Medical Center Utrecht under the supervision of Professor Dr IHM Borel Rinkes, Dr MR Vriens, and Dr GD Valk. Her research focused on the best surgical strategies in patients with familial parathyroid and adrenal disorders. In August of 2009, she graduated cum laude, after which she started working as a resident at the Department of Surgery, at the University Medical Center Utrecht. She also continued working on several research projects. Thereafter, she worked as a resident at the Department of Emergency Medicine at the same hospital. In September 2011, she received a Fulbright Scholarship to perform research at the University of California, San Francisco. Under the supervision of Professor Dr QY Duh and Professor Dr OH Clark, she continued researching the surgical management of endocrine disorders. In March 2012, she commenced working at the Department of Surgery of the Diakonessen Hospital, in Utrecht. In July 2012, she started residency in general surgery under Dr MS Ibelings' supervision at the Tweesteden Hospital, in Tilburg. During her residency, she will also work at the University Medical Center Utrecht under the supervision of Dr MR Vriens.

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Scholten A, Schreinemakers JMJ, Pieterman CR, Valk GD, Vriens MR, Borel Rinkes IHM. Evolution of surgical management of primary hyperparathyroidism in multiple endocrine neoplasia type 2A patients. *Endocr Pract 2011; Jan-Feb;17(1):7-15.*

Scholten A, Vriens MR, Cromheecke GJ, Borel Rinkes IHM, Valk GD. Hemodynamic instability during resection of pheochromocytoma in MEN versus non-MEN patients. *Eur J Endocrinol 2011; Jul;165(1):91-96.*

Schreinemakers JMJ, Pieterman CR, Scholten A, Vriens MR, Valk GD, Borel Rinkes IHM. The optimal surgical treatment for primary hyperparathyroidism in MEN1 patients; a systematic review. *World J Surg 2011; Sep;35(9):1993-2005.*

Scholten A, Valk GD, Ulfman D, Borel Rinkes IHM, Vriens MR. Unilateral subtotal adrenalectomy for pheochromocytoma in MEN2 patients, a feasible surgical strategy. *Ann Surg 2011; Dec;254(6):1022-1027.*

Cisco RM, Kuo JH, Ogawa L, Scholten A, Tsinberg M, Gosnell JE, Clark OH, Duh QY, Shen WT. The impact of race on intraoperative PTH kinetics: an analysis of 910 patients undergoing parathyroidectomy for primary hyperparathyroidism. *Arch Surg 2012; Nov;147(11):1036-1040.*

Tsinberg M, Duh QY, Cisco RM, Scholten A, Gosnell JE, Clark OH, Shen WT. Practice patterns and job satisfaction in fellowship-trained endocrine surgeons. *Surgery 2012; Dec;152(6):953-956.*

Scholten A, Cisco RM, Vriens MR, Cohen JK, Mitmaker EJ, Liu C, Shen WT, Duh QY. Pheochromocytoma crisis is not a surgical emergency. *J Clin Endocrinol Metab 2013; Jan;98(2):581-591.*

Cohen JK, Cisco RM, Scholten A, Mitmaker EJ, Duh QY. Pheochromocytoma crisis resulting in acute heart failure and cardioembolic stroke in a 37-year-old man. *Surgery 2013; Jan.*

Scholten A, Cisco RM, Vriens MR, Shen WT, Duh QY. Variant adrenal venous anatomy in 546 laparoscopic adrenalectomies. *JAMA Surgery 2013; Apr;148(4).*

Twigt BA, Scholten A, Valk GD, Borel Rinkes IHM, Vriens MR. Differences between sporadic and multiple endocrine neoplasia-related primary hyperparathyroidism; clinical expression, preoperative workup, operative strategy and follow-up. *Orphanet J Rare Dis 2013; Apr;8(1):50.*

Scholten A, Cisco RM, Hwang J, Tsinberg M, Gosnell JE, Vriens MR, Clark OH, Shen WT, Duh QY. Tumor Size is the Most Significant Predictor of Short-Term Surgical Outcome: Analysis of 523 Patients Undergoing Laparscopic Adrenalectomy. *Submitted to Ann Surg*