Partial Adrenalectomy in Patients with Multiple Adrenal Tumors

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Most adrenal tumors are found incidentally and appear as small solitary nodules on abdominal imaging. Occasionally, work-up demonstrates multifocal or bilateral adrenal tumors. Certain patients are predisposed to multiple lesions, such as those with hereditary forms of pheochromocytoma as seen in von Hippel-Lindau disease, multiple endocrine neoplasia type II, and von Recklinghausen's disease. Partial rather than total adrenalectomy should be considered for these patients in an attempt to preserve endogenous adrenocortical function. Partial adrenalectomy has also been used to resect other types of adrenal tumors, especially in patients with a solitary adrenal gland. A discussion of the indications for partial adrenalectomy and of the surgical technique follows.

Introduction

Adrenalectomy has long been the gold standard for the treatment of functioning adrenal tumors. Total adrenalectomy assures complete resection of most lesions, removes associated or undetected satellite nodules, and provides satisfying hemostasis of the adrenal vasculature. In most cases, the surgery is curative. While the removal of one adrenal gland is well tolerated, the removal of both glands results in the need for lifelong corticosteroid replacement, a proposition not without risk for the patient.

In patients with bilateral adrenal disease, a single remaining adrenal gland, or hereditary tumor syndromes predisposed to multifocal adrenal tumors, the ability to spare adrenocortical tissue is appealing. A viable option is adrenal-sparing surgery, which is indicated for such patients as long as sparing some functional adrenal cortex does not compromise adequate tumor resection. Partial adrenalectomy (PA) has thus found a niche in the treatment of patients with bilateral adrenal tumors, patients with a single adrenal gland, and patients predisposed to multiple (hereditary) adrenal tumors such as those associated with von Hippel-Lindau disease (VHL), multiple endocrine neoplasia type II (MEN-2), and von Recklinghausen's disease.

Indications for Partial Adrenalectomy

Partial adrenalectomy should be considered when the sparing of adrenal cortex might prevent lifelong steroid replacement and when principles of cancer surgery are not compromised. Adrenal replacement therapy can have long-term complications related to fixed daily steroid overdosing (obesity, osteoporosis, and other manifestations of Cushing's syndrome) or to steroid underdosing in times of stress [1,2]. Of all patients undergoing bilateral adrenalectomy, acute adrenal insufficiency develops in 25% to 33%, 30% encounter significant fatigue, and 48% consider themselves handicapped [3,4]. For patients with a solitary adrenal gland and for patients with bilateral tumors, PA is thus preferable to total adrenalectomy. Whether the tumor or tumors are manageable by partial resection and whether such an approach is likely to yield negative margins (and leave viable adrenal cortex) must be decided. Patients with hereditary adrenal tumors may choose either to be cured by bilateral adrenalectomy and live with that associated morbidity, or to live with the risk of recurrence after PA. Our bias has been to attempt PA in patients with hereditary pheochromocytoma who are at risk for recurrent adrenal tumors such as those with MEN-2 or VHL.

Partial adrenalectomy has been used to treat a variety of adrenal tumor types. In the 1980s, adrenal-sparing surgery was reported for the treatment of pheochromocytomas, aldosteronomas, Cushing's adenomas, and carcinomas or solitary metastases. By the late 1990s, laparoscopic PA had been reported, starting with the enucleation of an aldosterone-producing adenoma by Janetschek *et al.* [5] in 1997. Laparoscopic techniques have since been successfully applied to aldosteronomas, Cushing's adenomas, pheochromocytomas, and nonfunctioning tumors suspicious for malignancy. In patients with hereditary tumor syndromes, the issue of recurrent or new lesions after PA arises. Adrenal

pheochromocytomas have recurred in a minority of patients with hereditary tumor syndromes after PA, but these have been successfully managed with repeat surgery and without the development of metastatic disease [6,7,8•].

Aldosteronoma

Adrenalectomy is the traditional treatment of choice for aldosterone-producing adenomas. An isolated report has shown a putative benefit of PA over unilateral adrenalectomy for aldosteronoma in terms of preserving patients' cortisol and aldosterone responses to provocative biochemical testing postoperatively [9]. Although it is tempting to enucleate an isolated aldosteronoma, between 7% and 38% of these tumors are associated with micro- or macronodular disease in neighboring areas of the gland (as reviewed by Ito *et al.* [*10*]). It is not currently possible to distinguish functioning from nonfunctioning nodules pre- or intraoperatively; therefore, adrenalectomy provides the best chance at cure when anything but a discrete, solitary tumor is present.

Partial adrenalectomy was first performed laparoscopically to treat Conn's syndrome in 1997, and several reports support its feasibility [5,11,12,13•,14••]. Some have pointed out that solitary aldosteronomas may present the best indication for laparoscopic PA because these tumors are usually small, discrete, and sometimes located in the corners of the adrenal gland [14••]. The average tumor diameter was only 1.48 cm in a 35-patient aldosteronoma series [15]. If there is any question of nodularity, however, or if other lesions are noted in the affected adrenal gland, we continue to recommend unilateral total adrenalectomy for these patients.

Cushing's adenoma

Few resections of glucocorticoid-producing adrenal adenomas have been performed as PAs. The adrenals become atrophic with an active Cushing's adenoma, and the adenoma is often several centimeters in size, making it a technical challenge to leave viable adrenal tissue in place. Rarely are these tumors multifocal. Walz *et al.* [13•] performed PA on four patients with 2- to 3-cm Cushing's adenomas, all of whom were cured but required steroid replacement at short published follow-up (2.25 months), a problem in that remaining atrophic adrenal tissue may require more time to recover. The treatment of Cushing's syndrome with PA is reasonable in the hopes that by preserving adrenal cortical parenchyma, the patient will have a greater chance of regaining enough functionality to allow a more rapid taper of steroid replacement. However, because many of these lesions present when they are large and leave little viable adrenal around them, PA may continue to prove difficult and unrewarding.

Clinically, patients with Cushing's syndrome secondary to a small adrenal adenoma cannot be differentiated from those with a cortisol-producing adrenocortical cancer. The latter tumor, although rare, is best treated surgically with wide excision. A PA in the setting of an adrenocortical carcinoma may provide less satisfactory oncologic results.

Pheochromocytoma

Pheochromocytoma is optimally managed with preoperative catecholamine blockade followed by surgical resection. This medical treatment has all but obviated early control of the adrenal vein by open surgical approaches. Indeed, laparoscopic adrenalectomies, open PAs, and laparoscopic PAs for pheochromocytoma have been performed safely over the last few decades [16–19].

Sporadic bilateral pheochromocytomas have been treated with PA [20], but PA is especially relevant to the treatment of pheochromocytomas in patients with hereditary tumor syndromes such as MEN-2, VHL, and VHL type II (pheochromocytoma-predominant VHL disease) [7,18,21,22••,23]. In these patients, the recurrence or metastatic spread of disease is of particular concern [24], and the preservation of adrenal cortex is an important long-term issue. PA has been shown to preserve adrenocortical function in MEN-2 patients with a 0% to 33% risk of locally recurrent pheochromocytoma and 0% metastasis over 54 to 88 months of follow-up [3,7,25,26], which is similar to our experience with VHL patients [8•]. Fortunately, recurrent pheochromocytomas in VHL and MEN-2 patients can be detected very early in their development with the advent of modern imaging (CT, MRI, and MIBG scanning) and highly sensitive biochemical testing [27–30]. Thus, even small subclinical pheochromocytomas can be identified in remnant adrenals and safely treated with repeat PA early in their development [8•,21]. Although the average tumor diameter in a recent series was 2.3 cm, occasional tumors larger than 4 cm in diameter were successfully treated by PA [8•]. For patients with hereditary, localized pheochromocytomas, PA may be offered in an attempt to maintain quality of life at the cost of possible tumor recurrence.

Nonfunctioning tumor

The indications for PA in this subset of patients, which include those with hormonally inactive or minimally active tumors, are variable. Sporadic nonfunctional lesions larger than 4 to 6 cm in diameter are at higher risk of malignancy and should be resected radically, usually by unilateral adrenalectomy with adequate margins. Smaller tumors can theoretically be excised by PA if viable cortex can be left in situ. Imai *et al.* [14••] reported on two cases of subclinical Cushing's syndrome caused by adrenal adenomas which were successfully treated with PA. Because the natural history of this syndrome is not well defined and its association with Cushing's syndrome unclear, the role of surgery in these asymptomatic patients remains to be defined [31]. Similarly, adrenal cysts and myelolipomas are benign lesions that need not be addressed unless size criteria or other suspicious findings on imaging studies suggest they should be resected. If the contralateral adrenal is normal and the patient has

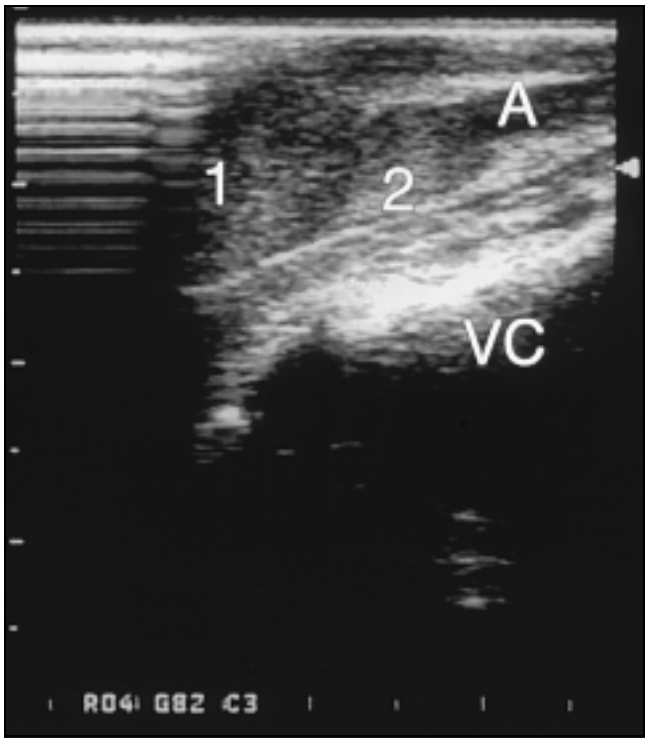

Figure 1. This intraoperative sonogram demonstrates two adrenal nodules (1 and 2), as well as normal surrounding adrenal parenchyma (A) and vena cava (VC) in a von Hippel-Lindau disease patient. One of these lesions (2) was detected only by the sonogram. Both nodules were confirmed to be pheochromocytomas after partial adrenalectomy. (*From* Renal and Adrenal Tumors – Biology and Management. Edited by Belldegrun A, Vaughan Jr ED. Oxford, UK: Oxford University Press, In press; with permission.)

no evidence of a hereditary tumor syndrome, unilateral adrenalectomy is a time-tested approach for suspicious nonfunctioning tumors. As patients with one adrenal do not evidence difficulties with adrenal function, the rationale for PA in solitary nonfunctioning tumors is in evolution at best. Nevertheless, PA has been performed in such cases, without reported recurrences or complications related to the adrenal-sparing procedure [11,13•].

Technical Considerations for Partial Adrenalectomy

Both laparoscopy and open surgery allow rapid access to the adrenals, more so on the right due to that gland's location just beneath the peritoneum and adjacent to the vena cava. The incision is made (or the laparoscopic ports are placed) with the same considerations as for adrenalectomy, taking into account the preferences and experience of the operating surgeon as well as the location of the tumor. For open surgery, a right or left flank incision, or a modified posterior approach (especially for the right side) is recommended. For laparoscopy, both the transperitoneal and retroperitoneal approaches are feasible. Regardless of approach, the partial adrenalectomy itself is performed in similar manner whether by laparoscopic or open means.

Once the adrenal gland is exposed, lesions 1 cm or larger are usually apparent. For smaller lesions, or when there is a question of multiple lesions, intraoperative sonography is helpful. Intraoperative ultrasound (IOUS) transducers of 7.5 MHz identify small adrenal tumors if the area is irrigated to produce an appropriate transducing medium. Ten-millimeter laparoscopic IOUS probes are available at this frequency and have been used to identify lesions in patients with a variety of adrenal pathologies [14••,32], including subcentimeter tumors in a VHL patient undergoing bilateral partial adrenalectomy (Fig. 1) [22••].

Knowledge of the vascular anatomy of the adrenal glands is important for PA, especially for avoiding bleeding or for tracking down unexpected bleeding during the resection. The three-vessel arterial supply to the adrenals (inferior phrenic, aorta, and renal artery) divides into smaller arteries that feed the glands circumferentially, but generally leave the anterior and posterior surfaces avascular. This tripartite arterial inflow to the adrenals is helpful in maintaining the viability of cortical tissue after PA, but can cause troublesome bleeding during the procedure. The venous system consists of drainage into a central vein, which enters the vena cava posteriorly on the right (the short right adrenal vein) and the renal vein superiorly on the left (the left adrenal vein). The artery of Belsey (an inferior phrenic branch close to the esophageal hiatus on the left) and its associated inferior phrenic vein also supply and drain the left adrenal gland and can be the source of troublesome bleeding if unanticipated.

Because the arterial supply to the adrenals is redundant, one can take vessels that feed the partial adrenalectomy bed as necessary without excessive worry about devascularizing adrenal cortex. As long as the remaining cortex remains attached to kidney or connective tissue via a wide strip of undisrupted tissue, typically containing both small arteries and veins, it will remain viable. In fact, as long as periadrenal attachments to the remnant cortex are preserved, the main adrenal vein may safely be divided (although peripheral tumors can also be excised with the vein left intact). Various authors advocate not taking the adrenal vein, the theoretic advantage being that the remaining adrenal cortex stands to suffer less congestion if outflow is not compromised [11,14••,33•]. Given the numerous smaller tributaries to and from the adrenal, it is doubtful that ligating the vein would cause complete disruption of remaining cortex, but many feel it is important to leave it intact. In a four-patient study of bilateral PA for pheochromocytomas in VHL patients, Neumann *et al.* [18] were careful to leave the adrenal vein intact in all cases. They report cure of pheochromocytoma as well as intact adrenal function at 2 to 24 months postoperatively. A pragmatic approach that we favor is to attempt to preserve the vein, unless taking the vein would make the procedure substantially safer or allow a definite tumor margin [13•,22••].

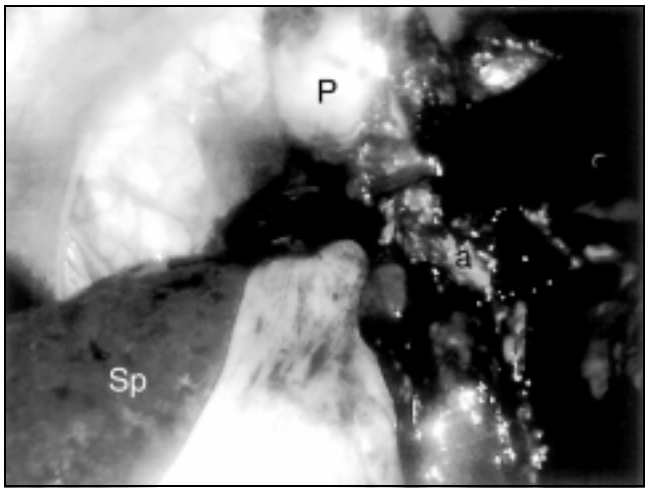

Figure 2. A harmonic scalpel is being used to separate a pheochromocytoma (P) from adrenal parenchyma (a). The spleen (Sp) is also seen at left. (*From* Renal and Adrenal Tumors – Biology and Management. Edited by Belldegrun A, Vaughan Jr ED. Oxford, UK: Oxford University Press, In press; with permission.)

To bisect the adrenal gland at the point of choice, several techniques have been used with success. We have found the harmonic scalpel most effective to divide adrenal parenchyma and cauterize simultaneously. Its use keeps bleeding to a minimum, and because it does not appreciably char tissue edges it allows for excellent pathologic examination of the margins of resection. The clamp and suture method or vascular stapler effectively achieves hemostasis, and these techniques can be used as adjuncts to dissection with the harmonic scalpel (Fig. 2) [13•,22••,33•]. Bipolar coagulation can also be used to good hemostatic effect, whereas a suture ligature (figure-of-eight or running) or a vascular stapler is appropriate for controlling bleeding from the subcapsular plexus. Surgical clips can also be a helpful adjunct during PA [11,14••,22••]. Frozen section analysis of the resection margin is routinely performed, and while one waits for this, we routinely decrease insufflation pressure to 8 mm Hg in laparoscopic cases to check for bleeding prior to closure. Regarding how much adrenal cortex need be preserved to maintain endocrine function, it has been suggested that at least 20% of adrenal cortex must remain [7]. However, Lee *et al.* [7] were unable to correlate the amount of remnant adrenal with subsequent endocrine functionality in their 30-year series of PA for hereditary pheochromocytomas.

Conclusions

Partial adrenalectomy is a satisfying parenchymal-sparing procedure. An experienced surgeon can perform PA with relative ease by open surgery or laparoscopy. Attempts to preserve endocrinologically viable adrenal cortex are generally successful if vascularized cortex can be left behind. Partial adrenalectomy is recommended for patients with a single adrenal gland, patients with bilateral adrenal tumors, and patients with hereditary adrenal tumors. Most importantly, partial adrenalectomy is the procedure of choice for hereditary pheochromocytomas.

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