



Cortical sparing adrenalectomy in sporadic and bilateral tumors

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Abstract: Complete removal of the adrenal gland has been the standard approach in the surgical treatment of tumors for decades. There, however, is bigger role emerging for organ sparing adrenalectomy especially in the era of minimal invasive surgery. Initially proposed for bilateral tumors in hereditary diseases and in tumors in a solitary gland, partial adrenalectomy gained also popularity in the treatment of spontaneous unilateral small masses. Various surgical techniques have been described so far with promising surgical and functional outcomes with increased quality of life compared to total adrenalectomy. Steroid replacement can be avoided in most cases even in bilateral disease and successful normalization of pathological preoperative endocrine levels were reported in various kinds of adenoma. Therefore, minimal invasive partial adrenalectomy, which seems to be still underused, is a valid treatment option for small hormonal active adrenal tumors whenever surgically possible.

Keywords: Partial adrenalectomy; laparoscopy; robotic surgery; steroid dependence; functional outcome

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Introduction

Minimal invasive total adrenalectomy is the recommended treatment of any benign adrenal mass requiring surgical resection by the International Consultation on Urological Diseases and European Association of Urology consultation without considering the size or location of the tumor (1). It has been first described by Gagner in 1997 (2). Since then it has gained wide acceptance and has been further developed making it the standard of care in benign adrenal tumors.

Although radical removal seems most feasible for disease control, there is on the other hand the chance of adrenal insufficiency, which requires a lifelong steroid substitution with a possible decreased health related quality of life (3). In addition the possibility of an emerging Addisonian crisis is up to 10–35% of patients after both sided adrenalectomy even with proper steroid replacement (4). Therefore, partial adrenalectomy has become the therapy of choice for patients being at highest risk of developing adrenal insufficiency

after surgery. Those are patients who have been diagnosed with hereditary syndromes like MEN 2 or patients that have already been treated with total adrenalectomy on the contralateral gland (5,6).

In addition organ sparing adrenalectomy has gained more popularity also in sporadic tumors such as Conn adenoma or Cushing's syndrome (7). One reason is that also patients who were treated by unilateral complete removal of the adrenal gland may demonstrate an inadequate response to stress situations. Furthermore, there are several side effects of chronic steroid substitution therapy. While too little steroid replacement puts the patient at risk for an Addisonian crises, a too high dosage might lead to osteoporosis or diabetes.

Mainly due to the advances in minimally invasive surgery and the developing expertise also in robotic surgery partial adrenalectomy has shown to have a comparable surgical outcome and perioperative complications. This makes cortical sparing adrenalectomy a valid alternative with

satisfactory functional outcomes and recurrence data (7).

In this narrative review we will give an update on the current indications for partial adrenalectomy, advances in minimal invasive techniques and the latest data on perioperative and functional outcome.

Indications

The main indication for partial adrenalectomy has been the treatment of patients at highest risk of adrenal insufficiency especially those with bilateral tumors or patients with hereditary diseases as Von Hippel-Lindau syndrome. But also in patients with sporadic hormone active tumors requiring resection organ sparing adrenalectomy has become a valid option. A threshold of four centimeters was suggested to distinguish adrenal carcinomas from malignant entities with a sensitivity for adrenocortical carcinoma of 93% and a specificity of only 42% (8,9). When adrenalectomy is indicated for suspected carcinoma, partial adrenalectomy is not an option. Small incidentalomas without hormone production are not considered malignant. Therefore surgery, even in a minimal invasive approach, is not necessary in the majority of cases. *Table 1* gives an overview over the most recent studies on adrenalectomy according to the various indications.

Pheochromocytomas

Partial adrenalectomy is recommended in selected cases of pheochromocytoma by an endocrine society practice guideline published in 2014 (26). Pheochromocytomas, producing catecholamines, occur bilaterally in 3–11% of all patients and in up to 60% of patients with hereditary syndromes, including Von Hippel-Lindau (VHL) disease and multiple endocrine neoplasia two (MEN2) (27,28). Both sporadic and hereditary forms of pheochromocytoma were treated with partial adrenalectomy successfully (18–20,29,30). The first laparoscopic partial adrenalectomy for this indication has been described in 1998 (31). In patients with hereditary syndromes and pheochromocytoma, additional extra-adrenal paraganglioma must not be overlooked. Also these paragangliomas can be removed by means of laparoscopy.

Conn's adenoma

Conn's adenomas producing aldosterone, are usually detected at a small size, due to the extensive hormone

production (32,33). Because of the small size at diagnosis and the benign character these tumors might be the ideal indication for adrenal sparing surgery. Since its first description by Janetschek and co-workers in 1997 (34), it became a widely accepted treatment possibility with further technical development in the last years. As an example a series of 10 patients with Conn's syndrome undergoing robot-assisted partial adrenalectomy has been published recently by Simone *et al.* with promising perioperative and functional outcomes (10).

Cushing's syndrome

Adrenalectomy is the first line treatment for Cushing's syndrome with an improvement of classical cardio-metabolic co-morbidities as high blood pressure, diabetes mellitus and obesity. In about a quarter of patients an autonomous cortisol producing tumor can be diagnosed whereas bilateral adrenal macronodular or micronodular hyperplasia are infrequent conditions (<1%). A rather large series on laparoscopic partial adrenalectomy has been published in patients with Cushing's adenoma <5 cm by He *et al.* performing 87 adrenal sparing procedures demonstrating feasibility and safety of the surgical method (22).

Partial adrenalectomy for relapse

Especially in hereditary bilateral pheochromocytoma, the risk of relapse is high, and this is not a problem of surgical technique but of the underlying disease. In fact, this risk is the main argument to perform partial adrenalectomy in VHL and MEN2 even if only one adrenal gland is involved. Therefore, one has to be prepared to manage such a relapse. A relapse on the initially uninvolved side is not a problem. However, it has been shown that even a second laparoscopic partial adrenalectomy can successfully be performed after open and laparoscopic partial adrenalectomy (35,36).

Surgical techniques

Open surgery of the adrenal gland has now been widely replaced by laparoscopy because of its reduced morbidity and faster convalescence. The open approach is recommended only in individual situations as for bigger lesions or carcinomas (1,26). Therefore partial adrenalectomy has also been performed almost exclusively through an minimal invasive approach. Advances in surgical techniques made laparoscopic and robotic partial

Table 1 Current publications on partial adrenalectomy

Author, year	Surgical approach	Indication	Study design, number of patients
Simone, 2018 (10)	Robot assisted	Conn's syndrome	Prospective n=10
Vidal, 2018 (11)	Retroperitoneoscopic	MEN 2, VHL	Prospective Partial: n=6
Walz, 2018 (12)	Laparoscopic and retroperitoneoscopic	Pheochromocytoma and paraganglioma in children and adolescents	Prospective Partial n=39
Lowery, 2017 (13)	Posterior retroperitoneoscopic	Clinical and subclinical Cushing with bilateral disease	Retrospective Partial n=35
Morimoto, 2016 (14)	Laparoscopic	Bilateral aldosterone producing adenomas	Case report
Biteman, 2016 (15)	Laparoscopic/Bilateral	Bilateral pheochromocytoma	Case report
Goffredo, 2015 (16)	Open and Laparoscopic	Malignant pheochromocytoma	Retrospective Partial n=192
Chen, 2014 (17)	Laparoscopic	Unilateral aldosterone producing adenoma	Prospective; Partial n=16
Gupta, 2014 (18)	Laparoscopic	Pheochromocytoma in children	Retrospective Partial n=4
Fallon, 2013 (19)	Laparoscopic	Pheochromocytoma in genetic syndromes	Case reports (n=2)
Grubbs, 2013 (20)	Open and Laparoscopic	Hereditary pheochromocytoma	Retrospective Partial n=55
Gupta, 2014 (21)	Laparoscopic and robot assisted	Multiple ipsilateral pheochromocytoma	Retrospective Partial n=121 (10 for study)
He, 2012 (22)	Open and retroperitoneoscopic	Cushing adenoma	Retrospective Partial n=87
Cavallaro, 2011 (23)	Laparoscopic	Unilateral aldosterone producing adenoma	Retrospective Partial n=4
Wang, 2010 (24)	Retroperitoneoscopic	Conn's adenomas, Cushing syndrome Pheochromocytomas, nonfunctional adenomas	Retrospective Partial n=88
Walz, 2008 (25)	Posterior retroperitoneoscopic	Conn's syndrome	Prospective Partial n=47

adrenalectomy a safe and valuable option especially in those small and benign tumors.

As soon as the tumor is identified, mostly without dissecting the adrenal vessels, the mass can be directly

resected within a pseudo capsule. Maintaining of the adrenal vein enables that the remaining adrenal tissue can drain to the circulation and also provides better hemostasis (37). Furthermore operation time is shorter and a potentially

risky step of the operation is omitted (7). Hemostasis can be either achieved through electro-cauterization, harmonic scalpel, or locking clips (17,21).

Conventional laparoscopic partial adrenalectomy

The first conventional laparoscopic cortical sparing adrenalectomy was described more than two decades ago (34) and since then multiple studies have been published on LPA. Both, the transperitoneal and the retroperitoneal technique were described to be safe and feasible by Walz *et al.* in the treatment of pheochromocytomas (38,39). There are some studies suggesting superiority of retroperitoneoscopy in regards to postoperative pain and feasibility in adrenalectomy (40-42), but this could not be proved by prospective randomized trials using the lateral retroperitoneoscopic approach (43,44).

Chen *et al.* recently published their data on the surgical treatment of large adrenal masses and compared different laparoscopic and resection techniques (45). They treated 78 patients with adrenal masses over 5 cm either with retroperitoneoscopic or transperitoneal total adrenalectomy or partial adrenalectomy. Both approaches provided similar results in regard of estimated blood loss, conversion rates and postoperative complications. Fourteen patients were treated with retroperitoneoscopic partial adrenalectomy compared to 27 with total adrenalectomy. Partial resection showed a longer operation time (102.68 ± 30.92 min) compared to total (79.64 ± 28.39 min, $P=0.02$). On the one hand there was a higher estimated blood loss, but on the other hand there were no hormone substitutions in the cortical sparing cohort (0 *vs.* 48.15%, $P=0.02$).

Robot assisted partial adrenalectomy (RAPA)

The increasing use of robotic surgery has led to more surgical experience and to the subsequent implementation of new procedures over the last years. A recent systematic review and meta-analysis by Brandao *et al.* including 600 patients compared robotic and laparoscopic adrenalectomy RAPA to standard laparoscopy (277 in the robotic group and 323 in the laparoscopic group) (46). The authors did not find any difference in conversion rates, operating time or postoperative complications; however, length of hospital stay was shorter and there was less estimated blood loss in the robot assisted arm.

In 2006 the first case of RAPA was reported by St Julien *et al.* in a patient with VHL disease and bilateral

pheochromocytoma (47) and the largest series so far was published by Asher *et al.* in 15 patients with pheochromocytoma (48). No recurrences were observed after a median follow-up of 17.3 months (range: 6-45) and only one of the patients with a single gland needed steroid substitution postoperatively. RAPA has also been described for Conn's syndrome. Simone *et al.* published their data on 10 consecutive patients with Conn's adenoma, who have been treated with RAPA (10). With a rather small median nodule size of 18 mm (interquartile range 16-20 mm) all cases were completed robotically with a negligible intraoperative blood loss. After 3-month and 1-year clinical evaluation, all patients showed biochemical success (aldosterone level, plasmatic renin activity, and aldosterone-renin ratio within normal range) and at a median follow-up of 30.5 months no symptoms or imaging recurrence was observed.

Although partial adrenalectomy might be an ideal indication for robotic surgery, there is not enough evidence to support its use unconditionally. There is still a lack of comparative prospective studies between RAPA and standard laparoscopy and financial issues may limit the use of RAPA.

Laparoendoscopic single-site partial adrenalectomy (LESS)

LESS is a laparoscopic technique using a single skin incision with increased popularity during the last decade. It has the advantage of a better cosmetic outcome and early convalescence but it happens to be more surgically demanding due to the loss of instrument triangulation (49).

To date multiple case-control studies have shown equal outcomes for LESS and conventional laparoscopy if done by experienced surgeons (50). A systematic review and meta-analysis of LESS *vs.* conventional adrenalectomy could not show a difference in estimated blood loss or length of hospital stay, but surprisingly also in cosmesis, recovery time or port-related complications (51).

A transumbilical, a transperitoneal subcostal and a retroperitoneal subcostal approach were investigated by Wang and co-workers in patients undergoing LESS total or partial adrenalectomy (52) in regards of perioperative outcomes. They concluded that LESS adrenalectomy is an effective option using all the described approaches and that the selection is up to the surgeon's knowledge and patient characteristics. LESS cortical sparing adrenalectomy has been published to be performed safely and effectively too

through a retroperitoneoscopic approach using a custom-made single-access platform and standard laparoscopic instruments (53).

According to published data LESS partial adrenalectomy may be safe and technically feasible alternative, but there is still a lack of prospective trials to investigate long-term disease and steroid free rates.

Functional and long-term outcome

Besides intraoperative and postoperative surgical outcomes functional and long-term oncological outcomes have to be considered. On the one hand the adrenal remnant has to be sufficient enough to avoid steroid replacement on the other hand surgery must be radical enough to normalize pathological preoperative hormone levels. Furthermore, the risk of recurrence has to be taken into account.

Prior studies propose that a residual tissue of about one third is enough to avoid steroid substitution dependency (54-56). While others claim a remnant of at least 3 to 5 mm is required to obtain satisfactory results (5,37). Nevertheless, there is no clear consent about the amount of residual tissue that is sufficient to sustain physiological adrenal function and to avoid substitution therapy. Otherwise there would be the need for lifelong hormone therapy, which includes the chance of osteoporosis, diabetes and hypoandrogenism, and Addisonian crisis after bilateral adrenalectomy is reported in 25–33% of patients despite hormone replacement (57).

Conversely, the risk recurrence from the remaining tissue should be kept as low as possible and thoroughly weighed out against the downsides of adrenal insufficiency. One recent systematic review and meta-analysis identified 60 relevant articles on recurrence and functional outcome of partial adrenalectomy (7). They reported an overall recurrence rate of 8% (95% CI: 0.05–0.12) and 85% (95% CI: 0.78–0.9) were free from steroid replacement therapy. The retroperitoneoscopic group 1% and Conn's syndrome group 2% showed the best recurrence rate of 1% (95% CI: 0–0.04) and 2% (95% CI: 0.01–0.05) respectively. Steroid independence was best achieved in the Conn's syndrome population (97%; 95% CI: 0.85–0.99) and laparoscopic arm (88%; 95% CI: 0.75–0.95).

In 2010 another review was published on the results of cortical sparing adrenalectomy in 417 patients. Partial adrenalectomy was proven to have a minimal morbidity with a 3% recurrence rate. Furthermore and steroid replacement could be avoided in 90% of patients (58). They claim partial adrenalectomy a valid, safe and feasible option in small

hormonal active masses and conclude that it is nevertheless still underused.

One reason might be, that until recently there has not been clear consensus on outcome criteria and follow-up in adrenal surgery for primary aldosteronism making the results of existing studies and cohorts difficult to compare. In 2017 Williams *et al.* published a consensus paper on outcome measures and follow-up in unilateral primary aldosteronism on behalf of the Primary Aldosteronism Surgery Outcome investigators (59). Therefore they included clinical data from 705 patients recruited between 1994 and 2015, who underwent total adrenalectomy in 12 different centers. Consensus was reached for criteria for six outcome criteria based on blood pressure, use of antihypertensive drugs, plasma potassium and aldosterone concentrations, and plasma renin concentrations or activities. They were classified as complete, partial and absent success of clinical and biochemical outcomes. There was also an agreement on timing of follow-up assessment. These standardized criteria for example should be taken into consideration when conducting studies on the functional outcome of partial versus total adrenalectomy in Conn's adenoma.

Summary

Laparoscopic total adrenalectomy is the recommended gold standard in the treatment of small hormonal active masses. However, there is the risk of subsequent lifelong corticosteroid dependency even in patients with a healthy collateral adrenal gland. Therefore, the option of partial adrenalectomy gained more attention not only in patients at highest risk of developing postoperative adrenal failure and Addisonian crisis, which are patients with hereditary diseases and patients with a solitary gland, but also in patients with sporadic solitary tumors. Successful partial adrenalectomy has been reported in patients with pheochromocytomas, Conn's adenomas and Cushing's syndrome with satisfactory perioperative and functional outcomes.

One reason for the growing use of partial adrenalectomy might be the advances in minimal invasive surgery partial adrenalectomy. Standard laparoscopy has been the preferred approach for years but robot assisted surgery and LESS partial have been reported to be safe and feasible options. As well the transperitoneal as the retroperitoneal approach were performed successfully. The use of each methods strongly depends however on ability and surgeon's preference, because cortical sparing adrenalectomy has been

shown to result in decreased endocrinopathy independent of the surgical technique applied.

Nevertheless, there is still a demand for prospective studies comparing the outcome of partial versus total adrenalectomy with standardized outcome measures. Especially data on functional outcome, long-term efficacy and health related quality of life are necessary to recommend partial adrenalectomy as the new gold standard in small adrenal masses. Nevertheless, it has been shown to be a valid therapeutical alternative in selected patients.

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