Guidelines for the Minimally Invasive Treatment of Adrenal Pathology

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Preamble

The guidelines for the minimally invasive surgical treatment of adrenal pathology are a series of systematically developed statements to educate and guide the surgeon (and patient) in the appropriate use of minimally invasive techniques for the treatment of adrenal disease. It addresses the indications, risks, benefits, outcomes, alternatives, and controversies of the procedures used in specific clinical circumstances. The statements included in this guideline are the product of a systematic review of published work on the topic, and the recommendations are explicitly linked to the supporting evidence. The strengths and weaknesses of the available evidence are highlighted, and expert opinion is sought where published evidence lacks depth.

Disclaimer

Clinical practice guidelines are intended to indicate the best available approach to medical conditions as established by a systematic review of available data and expert opinion. The approach suggested might not be the only acceptable approach given the complexity of the healthcare environment. These guidelines are intended to be flexible, as the surgeon must choose the approach best suited to the individual patient and variables in existence at the moment of decision. These guidelines are applicable to all physicians who are appropriately credentialed and address the clinical situation in question, regardless of specialty.

Guidelines are developed under the auspices of SAGES, the guidelines committee, and are approved by the Board of Governors. The recommendations of each guideline undergo multidisciplinary review and are considered valid at the time of production based on the data available. New developments in medical research and practice pertinent to each guideline are reviewed, and guidelines will be periodically updated.

Literature Review Method

A systematic literature search was performed on MEDLINE in April 2011. The search strategy was limited to adult English language articles and is shown in Figure 1.

The literature search identified 79 relevant articles. The abstracts were reviewed by four committee members (DS, WWH, MG, and KWK) and divided into the following categories:

a. Randomized studies, meta-analyses, and systematic reviews
b. Prospective studies
c. Retrospective studies
d. Case reports
e. Review articles

Randomized controlled trials, meta-analyses, and systematic reviews were selected for further review along with prospective and retrospective studies when a higher level of evidence was lacking. For inclusion, prospective and retrospective studies had to report outcomes on at least 50 adrenalectomies. Studies with smaller samples were considered when additional evidence was lacking. The most recent reviews were also included. All case reports, old reviews, and smaller studies were excluded. Duplicate publications or patient populations were considered only once. Whenever the available evidence from Level I studies was considered to be adequate, lower evidence level studies were not considered. Newer relevant articles that were published after the original literature search date during the drafting of this guideline were also included. According to these exclusion criteria, 70 articles were selected for review.

The reviewers graded the level of evidence and searched the bibliography of each article for additional articles that may have been missed during the original search. Additional relevant articles (n=94) were obtained and included in the review for grading. A total of 164 graded articles relevant to this guideline were included in this review. To facilitate the review by multiple reviewers, these articles were divided into the following topics and distributed to the reviewers:

- Minimally invasive adrenalectomy outcomes and comparison to open
- Description and comparison of various MIS adrenalectomy techniques
- Management of large adrenal tumors
- Management of adrenal cortical carcinoma and metastatic disease
- Management of pheochromocytoma
- Other circumstances (i.e. partial and bilateral adrenalectomy, etc.)

The recommendations included in this guideline were devised based on the reviewers' grading of all articles.

Levels of Evidence

The quality of the evidence and the strength of the recommendation for each of the guidelines were assessed according to the GRADE system. There is a 4-tiered system for quality of evidence (very low (+), low (++), moderate (+++), or high (++++)) and a 2-tiered system for strength of recommendation (weak or strong) [1-2].

Introduction

Adrenal tumors have been found in 8.7% of autopsy series with adrenal incidentalomas being reported in 4%-7% of patients undergoing abdominal imaging studies. Adrenal pathology that requires surgical resection spans a large spectrum of diseases. A description of the presenting symptoms of adrenal disease and their diagnostic workup is beyond the scope of this guideline. Readers are referred to the existing comprehensive joint guideline by the American Association of Clinical Endocrinologists and the American Association of Endocrine surgeons (http://endocrinesurgery.org/documents/pguidelines/AdrenalGuidelines.pdf). This guideline focuses on minimally invasive surgical outcomes for adrenal disease and the comparison of different surgical approaches. The focus of the current guideline begins after the decision to perform an adrenalectomy has been made.

Outcomes of minimally invasive adrenalectomy

Since the first description of a laparoscopic adrenalectomy by Michel Gagner in 1992, laparoscopic adrenalectomy has quickly become the standard of care for removing the majority of adrenal masses [1-2]. Multiple prospective and retrospective studies have demonstrated minimal morbidity, short convalescence, and excellent cosmesis with laparoscopic adrenalectomy [1, 3-30]. These results apply to functional and nonfunctional tumors. Recently, similar outcomes have been published for the pediatric and non-adrenal cancer patient populations [31-37]. Most patients spend 1-2 nights in the hospital, with a few centers performing outpatient adrenalectomies in appropriately selected patients [15, 38-39]. However, as with many technologically advanced procedures, high volume surgeons continue to have the best outcomes [40].

Comparison with open adrenalectomy

Studies comparing open and laparoscopic adrenalectomy have demonstrated in the laparoscopic group improved postoperative pain levels [41-56], decreased morbidity [26, 41, 46, 57-58], lower [11, 42, 44-45, 48-49, 52-53, 59-63] or equivalent [47, 50, 54-55, 57, 64-65], operative blood loss, shorter hospital stays [11, 26, 41-48, 50-51, 57, 59, 64, 66], and quicker return of bowel function and recovery. No significant differences in mortality have been demonstrated for a procedure that in general is associated with very low mortality. Whether the open or laparoscopic approach leads to shorter operating time is less clear. Some series report longer times with the laparoscopic approach [41-42, 45-46, 48-52, 59, 64-65], others report similar duration [11, 17, 43-44, 47, 53-55, 57, 60, 62-63, 66-67], and others shorter duration [26, 61] compared with the open approach (Table 1).

Specifically for pheochromocytomas, which are generally more technically demanding resections due to the inflammatory process and increased vascularity surrounding the adrenal gland, comparative studies have reported lower estimated blood loss and postoperative length of stay for the laparoscopic approach [53-54, 56, 60-63, 65, 67]. Operative duration, morbidity, and mortality were found to be similar in the majority of published studies [53-55, 60-63, 67]. Furthermore, most studies report similar effects of the two surgical approaches on intraoperative patient hemodynamics [53, 55-56, 60, 62, 65, 67], while some have reported fewer episodes of intraoperative hypertension [54, 61] or hypotension [63] when the laparoscopic approach was used (Table 2).

Two retrospective studies comparing laparoscopic and open adrenalectomy in patients with hyperaldosteronism reported significantly decreased morbidity [57-58] and shorter length of hospital stay [57] in the laparoscopic group.

Recommendation: Minimally invasive adrenalectomy is associated with less postoperative pain, shorter hospital stay, earlier recovery, and similar long-term outcomes compared with open surgery and has been established as the preferred approach to all non-primary adrenal cancer pathology (+++, strong).

Adrenalectomy techniques

Several different techniques have been proposed and are currently being used for the resection of adrenal tumors. A description of each approach as well as advantages and disadvantages are described below (Tables 3-6).

Lateral transabdominal adrenalectomy (LTA)

LTA is the most common adrenalectomy technique used by the general surgeon [68]. Compared with the retroperitoneal approach, LTA provides greater working space that can be beneficial for very large tumors and morbidly obese patients, where use of extra-long bariatric instruments facilitates the procedure [1-2, 6-8, 24, 69-72] (Table 3). In addition, the lateral decubitus position used during this approach affords excellent exposure, since gravity pulls the abdominal contents outside the operating field. During left adrenalectomy, mobilization of the spleen medially is facilitated.

Relevant technical details

Patients are positioned at a 60-90 degree angle with tumor side up, and the table is flexed to maximally open the space between the tip of the 12th rib and the iliac crest. While variable, port positioning aims to establish instrument triangulation; the procedure can usually be accomplished with 3 ports for left adrenalectomy and 4 ports for right adrenalectomy (the fourth port is used for liver retraction). During left adrenalectomy, procedural steps include taking down the splenic flexure of the colon, freeing the splenic ligaments to mobilize the spleen and rotate it medially, and dissecting in the avascular plane between the tail of the pancreas and kidney, and controlling/dividing the adrenal vein as it enters the left renal vein. During right adrenalectomy,

procedural steps include mobilization of the right triangular ligament of the liver, a hockey stick incision between the retroperitoneal attachments of the right lobe of the liver and the lateral border of the IVC, dissection of the lateral edge of the IVC, and taking the right adrenal vein at the takeoff from the IVC. Superior retraction of the liver must be maintained by the assistant throughout the case to aid exposure of the right adrenal. Mobilization of the gland follows a superior-lateral to medial-inferior progression unless surgeon preference is for taking the adrenal vein early, in which case an inferior to superior and medial to lateral mobilization of the gland is preferred.

Posterior retroperitoneoscopic adrenalectomy (PRA)

Brunt first described the concept of PRA in a porcine model in 1993 [73]. Over the next decade, Walz perfected the technique and demonstrated its safety and enhanced visualization with use of higher insufflation pressures in the retroperitoneal cavity [74]. Advocates of PRA cite advantages of direct access to the adrenal gland that avoids the intra-abdominal cavity, making it attractive in the setting of prior abdominal surgery [7, 75]. Additionally, because the prone position facilitates equal access to the right and left side, bilateral procedures performed by PRA do not require repositioning between sides [2, 9, 70]. Disadvantages include lack of access to the intra-abdominal cavity for evaluation, difficulty in removing large tumors, and increased difficulty with increasing BMI due to the large distance between the gland and the skin and decreased working space from the additional fatty tissue [9, 74]. Comparative studies with other laparoscopic approaches have demonstrated a small yet significant benefit in pain medication requirement, time to oral intake, length of hospital stay, and overall convalescence for PRA (Table 4) [7, 22, 71-72, 76-79].

Relevant technical details

Patients are positioned on a rectangular support with bent hip joints at a 90-degree angle, allowing the abdominal contents to fall forward with gravity, with the table flexed to maximally open the space between the 12th rib and iliac crest. Three trocars are used for both right and left procedures, which are placed just under the 12th rib with a combination of direct palpation and finger guidance after the dorsal lumbar fascia is digitally perforated. With a balloon trocar in place in the middle port, the retroperitoneal space is insufflated with 20-30 mmHg of CO2. This high pressure insufflation starts the dissection of the space that is completed with blunt dissection of the area underneath the diaphragm and the fatty tissue above the superior border of the kidney. Landmarks that should be identified are the superior pole of kidney caudally, the paraspinous muscles medially, and the posterior surface of liver (right) or spleen (left) laterally. Dissection of the adrenal gland is facilitated by maintaining downward retraction of the kidney, and starts inferiorly in a plane close to the kidney surface. The adrenal gland can then be elevated, allowing identification and ligation of the adrenal vein in a medial or inferomedial position with either clips or a hemostatic device. Mobilization of the gland is completed by dissecting laterally between the diaphragm and the psoas; the superior attachments are divided last. An important aspect of the procedure is having the first assistant maintain the horizon of the camera throughout the case.

Anterior transabdominal adrenalectomy (ATA)

ATA is a sub-mesocolic approach and is the least common of the techniques employed for adrenalectomy. The main appeal is the conventional abdominal laparoscopic view that is familiar to all general surgeons [19, 80]. However, operating times are generally longer, and a greater number of ports are needed for a successful operation.

Relevant technical details

With the patient in the supine position, a camera port is placed at the umbilicus and three additional ports are placed in various configurations. Key steps for left adrenalectomy include elevating the transverse mesocolon, identifying the ligament of Treitz and the IMV, and opening the posterior retroperitoneum lateral to the IMV. By dissecting inferior to and elevating the pancreas, the left renal vein can be identified and followed to the left adrenal vein. After the vein is taken, the gland can be mobilized from inferior and medial to superior and lateral.

Lateral retroperitoneoscopic adrenalectomy (LPA)

LPA is the most common technique used by the urologic surgeon for adrenalectomy likely due to the familiarity with the anatomy of laparoscopic nephrectomy. Similar to PRA, LPA is advocated in patients with prior abdominal surgery [13, 76]. While tumor size is also an important consideration, it does not seem to be as important as in PRA [24-25]. Typically, the procedure has slightly longer operating times and requires more ports than LA or PRA but maintains the advantages of avoiding the peritoneal cavity as in PRA (Table 5) [22, 81].

Relevant technical details

The patient is positioned in a 60-90 degree angle with tumor side up, and the table is flexed similar to the lateral transabdominal approach. However, 4-5 trocars are needed to complete the procedure on either side. Landmarks that should be identified during the procedure are the superior pole of the kidney, parietal peritoneum, diaphragm, retroperitoneal fold, posterior renal fascia, and psoas muscle. The retroperitoneal fat outside Gerota's fascia and outside the posterior renal fascia must be cleared from inferior to the diaphragm to the iliac fossa until the fat prolapses into the fossa. A longitudinal incision in Gerota's near the diaphragm will facilitate dissection in three key planes: between the peri-renal fat and anterior renal fascia under the diaphragm, between the perirenal fat and posterior fascia on the lateral upper pole kidney, and between the adrenal gland and upper pole of the kidney. As in PRA, mobilization begins inferiorly to the gland along the superior border of the kidney, and elevation of the gland facilitates further mobilization, dividing the superior attachments last.

Recommendations: Several approaches to laparoscopic adrenalectomy have been described in the literature. Surgeons should choose the approach they are most familiar with, have had training in, and have the best patient outcomes with (+++, strong).

Surgeons should also take into consideration that in specific clinical circumstances some

approaches may be more beneficial than others:

- In patients with previous abdominal surgery, a retroperitoneal approach may be associated with less operative time and fewer complications (++, weak).
- For bilateral adrenalectomies, the posterior retroperitoneal approach may be advantageous, as it eliminates patient repositioning during the case (++, weak).
- In morbidly obese patients (BMI >35 kg/m2) and for large tumors (>6 cm), the lateral transabdominal approach may increase the feasibility of the procedure compared with the other approaches (++, weak).

Robotic adrenalectomy (RA)

Since the first robotic adrenalectomy by Horgan et al in 2001 [82], several other groups have successfully adopted the robotic approach. Brunaud reported the largest series to date of lateral transabdominal RA and found that after a learning curve of 20 cases, tumor side, previous clinical experience, and the first assistant's skill are the main predictors of operative time in RA [83-84]. The authors also reported that RA might be especially useful for patients with a high BMI (>30-35 kg/m2) and large tumors (>5.5 cm). Similarly, Nordenstrom and colleagues reported advantages in obese patients and large tumors in their series with robotic RPA (Table 6) [85]. Proponents of the robotic technique cite advantages of three-dimensional depth perception, an added element of dexterity with the "wrist" action of robotic instruments, and superior ergonomic conditions for the surgeon [86]. The main disadvantages addressed by most authors were cost and the learning curve of the entire surgical team [84-85, 87-88].

From a technical aspect, all authors stress the importance of training an entire operative team. For lateral RA, robotic setup is an extreme flank position with the robotic camera axis above and lateral to the umbilicus. The robotic cart is positioned at a 45-degree angle to the table

over the head of the patient with the working axis of the robot directed toward the ipsilateral clavicle [83, 89]. For retroperitoneal RA, the table is rotated 30 degrees clockwise, and the robot is brought in from the head and positioned between the shoulders [85, 90].

Recommendation: Compared with standard laparoscopic techniques, robotic adrenalectomy may offer advantages for large tumors and in morbidly obese patients (+, weak). However, given the increased cost, longer operative times, and lack of clear patient outcome benefits using this technique, additional higher quality evidence is needed before a firm recommendation can be provided.

Single port adrenalectomy

Outcomes with single incision adrenalectomy have been recently reported by several authors [91-95]. Published non-randomized series comparing conventional laparoscopic approaches and single port adrenalectomy have demonstrated no significant differences in patient length of stay or morbidity and a small benefit in cosmesis and postoperative pain but longer operative times with single port laparoscopy [96-98].

From a technical standpoint, a transabdominal single port adrenalectomy requires a 2-3 cm incision for a multiport device. Placement of the device has been described at the umbilicus, which requires extra-long instruments to reach the adrenal gland, and underneath the 12th rib for a more direct though less cosmetic location. For right adrenalectomies, an additional 2 mm needlescopic port is needed for liver retraction. With a retroperitoneal approach, specific recommendations regarding the multiport include placing the camera in the lower aperture position and using ports of different lengths [96-97]. Additionally, Walz describes the need for a more extended mobilization of the upper pole of the kidney compared with his conventional retroperitoneal approach [97].

Recommendation: Based on the available evidence, single port adrenalectomy is feasible and safe when undertaken by an experienced surgeon but offers little if any advantage over other standard laparoscopic approaches to adrenalectomy. Additional, better quality evidence is needed before this approach can be recommended (+, weak).

Partial adrenalectomy

The first modern clinical use of cortical sparing adrenalectomy was described by van Heerden for the treatment of bilateral hereditary pheochromocytomas in 1985 [99]. In the hopes of sparing patients from lifelong steroid dependence and the complications of adrenal insufficiency, over the past 25 years, laparoscopic partial adrenalectomies have replaced bilateral adrenalectomies for hereditary pheochromocytomas. Recently, cortical sparing operations have been reported for unilateral functional tumors [3, 81, 100]. Perioperative outcomes using this technique do not differ from outcomes of complete adrenalectomy. Studies reporting long-term outcomes after partial adrenalectomy have showed steroid-free outcomes in up to 91% of patients [14, 70, 100-102].

There is general agreement in the literature that the location of the tumor within the gland is the main determinant of the ease and ability to perform a partial adrenalectomy. Tumors anterior to and on the margin of the gland are generally more amenable to partial removal than those on the posterior surface. In the laparoscopic and open adrenalectomy literature, the reported amount of adrenal cortical tissue needed to preserve adrenal function is 1/3 of one gland or 15% of total adrenal cortical tissue [70, 103-105]. When preparing the remnant, it is suggested that the portion of adrenal cortex that is to be preserved should not be mobilized out of the retroperitoneum to preserve the blood supply, and all tumors should be resected with a 0.5-1 cm margin of normal adrenal tissue [104, 106]. Preservation of the adrenal vein is not essential and depends on the situation [2-3, 81, 101]. Additionally, liberal use of laparoscopic ultrasound should be employed, as it is a useful adjunct to show clear differentiation of the tumor from normal tissue [2, 89, 101, 104, 107]. It should also be noted that with the exception of partial adrenalectomies, extracapsular dissection with preservation of the capsule of the adrenal gland and resection of the surrounding fatty tissue is generally recommended by experts during removal of the adrenal gland.

Recommendations: Partial adrenalectomy is safe and feasible in the hands of appropriately trained surgeons. For patients requiring bilateral adrenalectomy, such as for hereditary pheochromocytomas, laparoscopic cortical sparing surgery may be the procedure of choice (++,

weak).

Additional evidence is needed before a recommendation can be provided for partial adrenalectomy of single gland, non-hereditary tumors.

Method and timing for taking the adrenal vein

For many years, surgeons learning the technique of open adrenalectomy were taught to take the adrenal vein early, especially in pheochromocytomas, to prevent catecholamine release during surgery that could affect the patient's hemodynamic parameters and potentially their outcomes. However, with the introduction of laparoscopic surgery, a significantly lower catecholamine surge has been described to occur [108]. This is believed to be due to the more gentle dissection and decreased gland manipulation when performed by an experienced laparoscopic surgeon. In addition, recent studies have demonstrated no difference in outcomes when the adrenal vein is taken first versus last or not at all during partial adrenalectomies [101, 109-110]. For vein control, most surgeons use metal clips, although other hemostatic devices such as the ultrasonic shears, Ligasure device, or electrothermal bipolar systems have also been used successfully. Comparative studies on the preferred type of vein control device are lacking [87, 97, 111-112].

Recommendation: The classic teaching for early vein control during open adrenalectomy has not been confirmed for laparoscopic adrenalectomy, because patient outcomes do not appear to be affected by early versus late ligation. Thus, the type and timing of adrenal vein control depends on surgeon preference and the specific anatomic variables associated with each case (+, weak).

Laparoscopic adrenalectomy for suspected or proven adrenal cortical carcinoma and adrenal metastases

Published data comparing laparoscopic and open adrenalectomy for adrenal cortical carcinoma (ACC) are limited. Advocates for an open approach cite the higher rates of local and peritoneal recurrence in the laparoscopic group, shorter time to recurrence, and a higher incidence of positive margins [4, 113-114]. Advocates for LA argue that for stage I and II ACC tumors, LA has outcomes similar to OA when performed in a large volume referral center with surgeons strictly adhering to standard oncologic principles [18, 115-116]. Many surgeons argue that for medium and large incidental tumors without preoperative indication of malignancy, it is appropriate to start the procedure laparoscopically, but the surgeon needs to convert to open surgery when signs of tumor adhesion or invasion, enlarged lymph nodes or a difficult dissection are encountered [5-6, 117]. The third international adrenal cancer symposium highlighted the limitations of the available literature and concluded that the most important variables for good patient outcomes were an appropriate oncologic resection performed at a specialized center [115].

Recommendations: For ACC, the best determinant of patient outcomes is an appropriate oncologic resection that includes *en bloc* resection of any contiguous involved structures and

regional lymphadenectomy. Thus, an open approach to resection may be best. If a laparoscopic approach is chosen (due to unknown malignancy status preoperatively or suspected early stage ACC), conversion to open surgery is strongly recommended when difficult dissection is encountered due to tumor adhesion or invasion or enlarged lymph nodes are seen (++, strong).

Adrenal metastases

Laparoscopic resection of metastases to the adrenal gland is performed in increasing numbers due to two concurrent developments. First is the adoption of laparoscopic adrenalectomy as standard of care for benign adrenal tumors because of the shorter hospital stay, quicker recovery, less blood loss, and overall lower morbidity. Second, over the past few decades, there has been an overall improvement and evolution of cancer treatment in general; patients live longer with their disease and more recurrences are limited to a single site. Before laparoscopy, the risks and morbidity of performing an adrenalectomy for a solitary cancer metastases did not, in general, appear to outweigh the benefits; however, in the past 15 years, the scales have tipped in favor of laparoscopic resection.

Laparoscopic resection of a solitary adrenal metastasis in a patient with an otherwise controlled cancer is a safe procedure with a very low morbidity and seems to have similar long term outcomes in the few selected published series [32-34, 118-124]. The most common cancers that metastasize to the adrenal gland are lung, breast, kidney, melanoma, GI, and lymphoma. The largest study that directly compared laparoscopic with open resection of metastases reported on 94 patients with up to 31 months of follow-up [34]. In this series, patients that underwent laparoscopic resection had shorter operative times and lengths of stay and less blood loss and overall morbidity (including laparoscopic conversions). However, they had similar rates of positive resection margins, local and overall recurrence, and disease-free survival compared with open resection. Three other small studies that also compared laparoscopic with open resection reported similar results [118, 120, 123].

Recommendations: Solitary metastases to the adrenal gland without evidence of local invasion can be approached laparoscopically by a surgeon skilled in advanced laparoscopy and adrenal surgery (+, weak). If local invasion is found intraoperatively, conversion to an open approach is warranted (+, strong).

Laparoscopic adrenalectomy in large adrenal masses

The use of laparoscopy for excision of large adrenal tumors is debated, and the literature on the subject is scant and retrospective in nature. As discussed in the section on laparoscopic adrenalectomy for suspected or adrenal cortical carcinoma, an open approach is recommend in patients with known or probable primary adrenal cortical carcinoma. Conversion from a

laparoscopic to open approach is also recommended in cases with intraoperative signs of carcinoma such as tumor adhesions or local invasion, enlarged lymph nodes, or a difficult dissection. The question on how to approach large adrenal tumors (>5-6 cm) with no preoperative (or intraoperative) evidence of malignancy, however, is a dilemma to the surgeon.

The overall safety of laparoscopy for large tumors without evidence of carcinoma has been reported in several small series [8, 29, 125-130]. In general, the outcome of laparoscopic adrenalectomy for large tumors is similar to small tumors with regard to operating room time [29, 128-129], hospital stay }[29, 128-130], and the complication rate [29, 128, 130]; however, tumor size ?7.5 cm has been shown to be an independent risk factor for longer operating times, more blood loss [8, 127-128], longer hospital stay [8], and a higher conversion rate to open surgery [29]. A shorter length of operating room time has been reported in patients undergoing laparoscopic adrenalectomy in tumors 5 cm [130].

Recommendations: Large adrenal tumors without pre- or intraoperative evidence of primary adrenal cortical carcinoma can be approached laparoscopically by a surgeon skilled in advanced laparoscopy and adrenal surgery (+, weak). Laparoscopic adrenalectomy for larger tumors may be associated with increased operating room times, blood loss, and conversion rate to open surgery (+, weak). If there is any evidence for carcinoma found intraoperatively, conversion to an open approach is warranted (should be strongly considered) (+, strong).

Pheochromocytoma

Despite early concerns regarding perioperative cardiovascular complications related to pneumoperitoneum, organ manipulation, and dissection, a number of published series have demonstrated the laparoscopic approach to pheochromocytomas to be safe and effective [56, 108, 131]. Nevertheless, compared with other adrenal pathologies, minimally invasive adrenalectomy for pheochromocytoma, even for experienced surgeons, can still be associated with longer operative times, more blood loss, increased complications, and longer hospitalization [132]. The following sections highlight a number of important considerations for surgeons taking care of patients with pheochromocytoma.

Preoperative Care

In patients with preoperative signs, symptoms, and biochemical evidence of catecholamine excess, alpha-adrenergic blockade should be initiated at least 10 days before surgery. Phenoxybenzamine has historically been considered the gold standard for preoperative alpha blockade. An initial dose of 10 mg PO BID can be titrated upward with regimens of 10-20 mg TID providing adequate blockade in most patients, particularly when combined other anti-hypertensive agents that most patients are taking at baseline. Phenoxybenzamine is a long-acting alpha antagonist, and its use in higher doses has been associated with frequent side effects including nasal congestion, nausea, abdominal pain, and tachycardia. Because of this, many surgeons and endocrinologists have transitioned to the use of shorter acting alpha blockers such as doxazosin, which tend to have fewer side effects. In addition, more rapid metabolism tends to translate into less postoperative hypotension related to residual unopposed alpha blockade [133-134]. Some authors have also advocated the combined use of alpha blockers along with metyrosine, which inhibits tyrosine hydroxylase, the rate-limiting step in catecholamine synthesis. Early data suggest that this combination may limit intraoperative hemodynamic instability to a greater degree than alpha blockade alone [135-136].

The clinical endpoint for preoperative blockade is control of hypertension. Adequate

preoperative alpha blockade can be confirmed by increasing the dosage until the patient develops mild orthostatic hypotension. For patients who also suffer from tachycardia or arrhythmias, the addition of beta-adrenergic blockade should be initiated only after adequate alpha blockade has been achieved. Patients with alpha blockade-induced orthostatic hypotension should be treated with oral and/or intravenous volume loading during the 24-48 hours before surgery. All patients should also be given 1-2 liters of intravenous crystalloid solution for intravascular volume expansion before induction of general anesthesia on the day of surgery [137-142].

Recommendations: Before laparoscopic adrenalectomy for pheochromocytoma, alpha adrenergic receptor blockade should be considered in all patients. When used preoperatively, alpha blockade should be continued until signs of orthostatic hypotension are evident (+++, weak). Short acting alpha blockers may be preferable to long acting ones. Beta blockade should also be considered in appropriately selected patients and should only be instituted following adequate alpha blockade (++, weak).

Intraoperative Management

Careful perioperative monitoring of hemodynamic status is critical to the safe resection of catecholamine producing tumors. Before the induction of general anesthesia, an arterial line should be placed. A central venous line is also recommended for infusion of vasoactive drips and monitoring of volume status. Despite appropriate preoperative medical management, intraoperative hypertension is common and is a valid concern. Continuous invasive monitoring and pharmacologic intervention by an experienced anesthesia team are necessary to avoid substantial cardiovascular instability. Drips should be prepared and ready to infuse at any point during the procedure. Hypertension is generally treated with nitroprusside, nitroglycerine, or nicardipine. Tachyarrhythmias can be managed with intravenous beta blockers and/or lidocaine[142]. Following ligation of the adrenal vein and removal of the tumor, significant hypotension can develop precipitously. Hypotension is treated with volume resuscitation and alpha-adrenergic agonists such as vasopressin. Depending on the degree of residual alpha blockade, some patients will require pressor support for hours or occasionally days following surgery.

In addition to relying on pharmacologic manipulation to treat intraoperative hypertension, there are a number of strategies that the surgeon can employ to minimize dramatic fluctuations in blood pressure during resection of pheochromocytomas. By avoiding excessive tumor manipulation, the effects of catecholamine surges can potentially be mitigated. During both open and laparoscopic adrenalectomy, tumor manipulation has been shown to be the most significant intraoperative stimulus for catecholamine release. Clinically, sudden increases in plasma catecholamine levels can result in episodes of dramatic and dangerous intraoperative hypertension that can be difficult to control even with rapid infusion of vasodilators. Intraoperative catecholamine monitoring has demonstrated that mean plasma epinephrine and norepinephrine levels can increase up to 34-fold during tumor manipulation [143-146]. Careful adrenal dissection and tumor handling are important strategies to avoid catecholamine-induced cardiovascular instability. These techniques require that the surgeon minimize direct manipulation or compression of the gland itself. In many cases, adjacent structures such as the

kidney, pancreas, and liver can be dissected and retracted away from the tumor and peri-adrenal fat and/or Gerota's fascia used as a handle such that the gland can be manipulated without actually placing direct pressure on the tumor. As mentioned earlier in this guideline, early ligation of the adrenal vein is not necessary during pheochromocytoma resection, as it has not been shown to impact hormonal release by the tumor. On the other hand, intra-abdominal insufflation during laparoscopic pheochromocytoma excision may cause an increase in serum catecholamines [147-148]. While the mechanism is unclear, the stimulus is thought to relate either to direct tumor compression or to a change in tumor perfusion. In addition, pneumoperitoneum with CO2 may lead to hypercapnia and acidosis, which are known stimuli of catecholamine secretion and hypertension. As a result, helium has been suggested as an alternate insufflation agent to eliminate the deleterious effects of CO2 during laparoscopic adrenalectomies for pheochromocytoma. In a prospective evaluation of 11 patients undergoing helium insufflation during laparoscopic pheochromocytoma resection, the authors demonstrated that its use avoided significant intraoperative hypercarbia or acidosis and provided greater intraoperative hemodynamic stability [143]. These data have not been substantiated by a large prospective series, and given the overall safety of CO2, most surgeons continue to use standard CO2 insufflation.

In addition to the problems associated with catecholamine liberation, large size and prominent vascularity compound the challenges of removing pheochromocytomas. Compared with other indications for adrenalectomy, both laparoscopic and open resection of pheochromocytomas has been associated with longer operative times, higher complication rates, greater blood loss and longer hospitalization in some selected series [1, 149]. In general, these tumors tend to be larger than other functional and nonfunctional adrenal lesions and often have a large number of arterial and venous tributaries that bleed with minimal manipulation. Generous use of clips in addition to vessel sealing technology is advisable for reliable hemostasis. Large tumors often encroach on the renal vessels, particularly on the left side. The renal vessels must be carefully identified and protected to avoid inadvertent injury during dissection. The need to operate around the renal hilum or to perform an en bloc resection of the peri-adrenal fat along with the adrenal gland does not mandate a conversion to laparotomy. However, conversion to an open procedure is warranted when laparoscopic dissection cannot be performed safely or a complete resection cannot be performed without undue trauma to the gland. In the setting of pheochromocytoma, this determination must be based on intraoperative findings of tumor invasion into adjacent structures, since radiographic and histological information, including intraoperative frozen section examination, are unreliable predictors of malignancy [150-151].

Recommendations: Invasive hemodynamic monitoring should be considered during LA for pheochromocytomas (++, strong). To minimize hemodynamic instability due to catecholamine release during surgery, minimization of direct manipulation or compression of the adrenal gland is necessary (++, strong). Early ligation of the vein does not prevent hemodynamic instability (+, weak). Due to the added challenge of intraoperative hemodynamic variability, frequent communication between the surgical and anesthesia teams is important for optimal perioperative outcomes.

Postoperative Management

During the immediate postoperative period, hypotension and hypoglycemia are the most common occurrences. Monitoring in an ICU setting for 24 hours postoperatively is advisable. The need for pressors or anti-hypertensive therapy postoperatively is dictated by the patient's hemodynamic status. For patients without evidence of underlying postoperative essential hypertension, all anti-hypertensive medications should be discontinued postoperatively with the possible exception of beta blockers. In patients who have been treated with long-term preoperative beta blocker therapy, postoperative management may necessitate a slow taper to avoid reflex tachycardia.

Since there are no definitive diagnostic criteria for malignancy in pheochromocytoma and the true malignant potential of pheochromocytomas is very difficult to predict, patients require long-term follow-up to confirm no recurrence. Recurrence rates in the literature following resection of benign-appearing lesions are approximately 6%-8%, and long disease-free intervals are not atypical, with recurrences often presenting several years to decades after initial surgery [150-154]. Thus, follow-up recommendations include annual blood pressure monitoring as well as serum and/or urinary metanephrines, and, in patients who demonstrate clinical signs or symptoms of recurrence, abdominal imaging is indicated [155].

Common histological features, such as capsular invasion, vascular and lymphatic penetration, nuclear atypia and mitotic activity, which almost always indicate malignancy in other tumors, do not always indicate malignancy in pheochromocytomas, nor does the lack of these pathologic features dictate that a tumor is benign. In 2002, a pheochromocytoma of the adrenal gland scaled score (PASS) was developed based on various degrees of cytologic atypia including invasion, necrosis, cellularity, mitoses, pleomorphism, and growth; a PASS score ³4 indicated an aggressive pathology [156]. However, although the utility of PASS was replicated in one large cohort, other smaller studies did not find the PASS score useful for predicting further malignancy and advocated for further refinement [157-160]. Additionally, two recent papers indicate that tumor size, location, and urinary VMA levels are important features for anticipating tumor recurrence [161-162]. Thus, it appears that individual tumor biology rather than the surgical approach may determine the chances of cure. Nonetheless, extreme care must be taken to avoid intraoperative capsular disruptions and possible iatrogenic pheochromocytosis as small case reports have described early local recurrence of pheochromocytoma after initial laparoscopic resection and tumor spillage. In that same context, adrenal specimens removed with minimally invasive techniques should be placed in an impervious extraction bag before removal and/or morcellation.

Recommendations: Due to the potential for hemodynamic instability after pheochromocytoma resection, all patients should be closely monitored in the early postoperative phase (++, strong). Capsular disruptions of the adrenal gland during surgery should be avoided to minimize the risk of disease recurrence. (+, weak). Given the lack of clear predictors of malignancy to detect recurrences, patients with pheochromocytoma should be monitored long term with blood pressure measurements and serum and/or urinary metanephrine levels (++, strong).

Learning curve

Throughout the laparoscopic literature, it is evident that extensive experience of the surgeon

and surgical team optimizes patient outcomes and cost effectiveness in the operating room. For laparoscopic and robotic adrenalectomy, the learning curve appears to be between 20 to 40 cases [1, 5, 23, 83, 153, 163]. In general practice, this number may be difficult to achieve due to the paucity of these procedures. There is controversy over which approach, anterior or posterior, requires more cases for the surgeon's operative time and patient morbidity to plateau [76-78]. Nevertheless, learning curve comparisons between different surgical approaches are difficult, as other factors such as the surgeon's previous experience and the familiarity and pre-implementation training of the operative team also significantly influence the procedure learning curve [75, 109, 152].

Recommendations: Minimally invasive adrenalectomy is associated with a learning curve that may be difficult to overcome given the paucity of these cases in general practice. Dedicated, advanced training should be pursued by surgeons unfamiliar with this technique. Until proficiency with laparoscopic adrenalectomy is attained, consideration should be given to referral to a center with expertise in minimally-invasive adrenal surgery (++, strong).

Limitations of the available literature

The available literature on laparoscopic adrenalectomy has several limitations. Few small controlled trials are available, and most studies are retrospective in nature with significant heterogeneity among them and increased risk for publication bias and other confounding factors. In addition, reporting of outcomes varies significantly as does the follow-up period, which generally tends to be short making it difficult to combine and compare such data. Finally, the majority of the studies do not report details on the expertise of their surgeons, and most have been conducted in a single institution making the generalization of their findings difficult. Based on these limitations of the literature, firm recommendations are difficult.

Summary of Recommendations

1. Minimally invasive adrenalectomy is associated with less postoperative pain, shorter hospital stay, earlier recovery, and similar long-term outcomes compared with open surgery and has been established as the preferred approach to all non-primary adrenal cancer pathology (+++, strong).
2. Several approaches to laparoscopic adrenalectomy have been described in the literature. Surgeons should choose the approach they are most familiar with, have had training in, and have the best patient outcomes with (+++, strong). Surgeons should also take into consideration that in specific clinical circumstances some surgical approaches to adrenalectomy may be more beneficial than others:
    - In patients with previous abdominal surgery, a retroperitoneal approach may be associated with less operative time and fewer complications (++, weak).
    - For bilateral adrenalectomies, the posterior retroperitoneal approach may be advantageous, as it eliminates patient repositioning during the case (++, weak).
    - In morbidly obese patients (BMI >35 kg/m2) and for large tumors (>6 cm), the lateral transabdominal approach may increase the feasibility of the procedure compared with the other approaches (++, weak).

3. Compared with standard laparoscopic techniques, robotic adrenalectomy may offer advantages for large tumors and in morbidly obese patients (+, weak). However, given the increased cost, longer operative times, and lack of clear patient outcome benefits using this technique, additional higher quality evidence is needed before a firm recommendation can be provided.
4. Based on the available evidence, single port adrenalectomy is feasible and safe when undertaken by an experienced surgeon but offers little if any advantage over other standard laparoscopic approaches to adrenalectomy. Additional, better quality evidence is needed before this approach can be recommended (+, weak).
5. Partial adrenalectomy is safe and feasible in the hands of appropriately trained surgeons. For patients requiring bilateral adrenalectomy, such as for hereditary pheochromocytomas, laparoscopic cortical sparing surgery may be the procedure of choice (++, weak). Additional evidence is needed before a recommendation can be provided for partial adrenalectomy of single gland, non-hereditary tumors.
6. The classic teaching for early vein control during open adrenalectomy has not been confirmed for laparoscopic adrenalectomy, because patient outcomes do not appear to be affected by early versus late ligation. Thus, the type and timing of adrenal vein control depends on surgeon preference and the specific anatomic variables associated with each case (+, weak).
7. For adrenocortical carcinoma, the best determinant of patient outcomes is an appropriate oncologic resection that includes *en bloc* resection of any contiguous involved structures and regional lymphadenectomy. Thus, an open approach to resection may be best. If a laparoscopic approach is chosen (due to unknown malignancy status preoperatively or suspected early stage carcinoma), conversion to open surgery is strongly recommended when difficult dissection is encountered due to tumor adhesion or invasion or enlarged lymph nodes are seen (++, strong).
8. Solitary metastases to the adrenal gland without evidence of local invasion can be approached laparoscopically by a surgeon skilled in advanced laparoscopy and adrenal surgery (+, weak). If local invasion is found intraoperatively, conversion to an open approach is warranted (+, strong).
9. Large adrenal tumors without pre- or intraoperative evidence of primary adrenal cortical carcinoma can be approached laparoscopically by a surgeon skilled in advanced laparoscopy and adrenal surgery (+, weak). Laparoscopic adrenalectomy for larger tumors may be associated with increased operating room times, blood loss, and conversion rate to open surgery (+, weak). If there is any evidence for carcinoma found intraoperatively, conversion to an open approach is warranted (should be strongly considered) (+, strong).
10. Before laparoscopic adrenalectomy for pheochromocytoma, alpha adrenergic receptor blockade should be considered in all patients. When used preoperatively, alpha blockade should be continued until signs of orthostatic hypotension are evident (+++, weak). Short acting alpha blockers may be preferable to long acting ones. Beta blockade should also be considered in appropriately selected patients and should only be instituted following adequate alpha blockade (++, weak).
11. Invasive hemodynamic monitoring should be considered during LA for pheochromocytomas (++, strong). To minimize hemodynamic instability due to catecholamine release during surgery, minimization of direct manipulation or

compression of the adrenal gland is necessary (++, strong). Early ligation of the vein does not prevent hemodynamic instability (+, weak). Due to the added challenge of intraoperative hemodynamic variability, frequent communication between the surgical and anesthesia teams is important for optimal perioperative outcomes.

12. Due to the potential for hemodynamic instability after pheochromocytoma resection, all patients should be closely monitored in the early postoperative phase (++, strong). Capsular disruptions of the adrenal gland during surgery should be avoided to minimize the risk of disease recurrence. (+, weak). Given the lack of clear predictors of malignancy to detect recurrences, patients with pheochromocytoma should be monitored long term with blood pressure measurements and serum and/or urinary metanephrine levels (++, strong).
13. Minimally invasive adrenalectomy is associated with a learning curve that may be difficult to overcome given the paucity of these cases in general practice. Dedicated, advanced training should be pursued by surgeons unfamiliar with this technique. Until proficiency with laparoscopic adrenalectomy is attained, consideration should be given to referral to a center with expertise in minimally-invasive adrenal surgery (++, strong).

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Table 1. Comparative studies on laparoscopic versus open adrenalectomy

Author/ Year	# of patients	Laparoscopic technique	EBL (ml)	Length of stay (days)	OR time (minutes)	Tumor Size (cm)	Morbidity (%)	Mortality (%)
Lang B/2008 [61]	108	Retroperitoneal						