Supplemental Online Content

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eAppendix. The American Association of Endocrine Surgeons Adrenalectomy Guidelines

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. The American Association of Endocrine Surgeons Adrenalectomy Guidelines

ABSTRACT:

Importance: Adrenalectomy is the definitive treatment for multiple adrenal abnormalities. New advances in technology and care have advanced the management of adrenal disease and created a need for clinical best practice guidelines.

Objective: To develop evidence-based recommendations for appropriate, safe, and effective approaches to adrenalectomy.

Evidence Review: A multidisciplinary panel of experts developed 7 categories of relevant clinical concern to practicing surgeons. Questions were structured in a Population, Intervention/exposure, Comparison and Outcome (PICO) format and guided the review of medical literature from PubMed and/or Embase with publication dates from 1980-2021. Recommendations were developed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology, discussed until consensus was reached, and made with patient advocacy input.

Findings: Washout characteristics on an adrenal protocol computed tomography (CT) scan should be used to risk-stratify adrenal nodules when non-contrast Hounsfield units (HUs) are >10 and other clinical risk factors for malignancy are not present. Patients with an adrenal incidentaloma larger than 1 cm should undergo biochemical testing for autonomous cortisol secretion and those with hypertension or hypokalemia also require biochemical evaluation for primary aldosteronism. Patients with imaging findings that are indeterminate (non-contrast CT with HU>10) should undergo evaluation for pheochromocytoma. Patients with an adrenal lesion that has HU >20 on non-contrast CT are at a higher risk for malignancy as are those with tumors larger than 4 cm, or age younger than 18 years. Routine scheduled follow-up of a non-functional adrenal nodule with benign imaging characteristics and non-contrast CT with HU<10 is not

suggested. Resection of a myelolipoma or adrenal cyst to improve the quality of life is not recommended unless there are symptoms of mass effect. Adrenal vein sampling (AVS) may be deferred in patients ≤35 years of age with cross-sectional imaging that demonstrates a unilateral adenoma and a normal contralateral gland. Laparoscopic adrenalectomy is recommended for patients with primary aldosteronism or autonomous cortisol secretion associated with unilateral disease. Unilateral adrenalectomy should be considered in patients with Cushing's syndrome and bilateral macronodular adrenocortical hyperplasia to achieve biochemical remission. Bilateral laparoscopic adrenalectomy is indicated for patients with moderate to severe ACTH-dependent hypercortisolism refractory to source control. Empiric perioperative glucocorticoid replacement therapy is indicated for patients with overt Cushing's syndrome but in mild autonomous cortisol secretion (MACS), postoperative day 1 morning of cortisol or cosyntropin stimulation testing should be used to determine the need for supplementation. Patients with clinical and radiographic findings consistent with adrenocortical carcinoma (ACC) should be treated at high volume multi-disciplinary centers to improve outcomes. Regardless of operative approach, an *en bloc* radical resection with an intact capsule to microscopically negative (R0) margins should be performed because it improves survival. While open resection is preferred when ACC is suspected, the choice of operative approach should be determined based on the certainty of a complete R0 resection without tumor disruption. Complete *en bloc* radical resection with an intact capsule to negative margins without capsular disruption improves survival. Patients with systemic disease, in whom all sites of disease are reasonably amenable to resection, may be offered surgical intervention if performance status allows. Surgery may also be considered for palliation in patients with symptoms related to tumor burden or in patients with hormone excess medically refractory to steroidogenic inhibition. Neoadjuvant systemic therapy should be administered for

advanced ACC when R0 surgical resection is not initially feasible, but up-front resection is recommended when complete excision is possible. In patients with and without a history of extra-adrenal malignancy, a radiologically indeterminate adrenal mass should prompt directed hormonal evaluation. Image-guided biopsy should only rarely be performed; it should be reserved for patients in whom results would change overall disease management. Resection of metastatic disease to the adrenal gland may be offered to highly selected patients, after multidisciplinary review, because it improves survival more than systemic therapy alone. Selective or non-selective alpha blockade is recommended to safely prepare patients for surgical resection of paraganglioma/pheochromocytoma. Consideration of cortical-sparing adrenalectomy is suggested in patients with bilateral pheochromocytomas, if technically feasible. In selected cases of metastatic pheochromocytoma and paraganglioma, resection of the primary tumor may be performed to improve overall survival. When patient and tumor variables are appropriate, minimally invasive adrenalectomy is recommended over open adrenalectomy due to improved peri-operative morbidity. Retroperitoneal and transabdominal approaches have similar peri-operative outcomes and should be preferentially performed by a high-volume adrenal surgeon to optimize outcomes. There are inadequate data to recommend ablation, embolization, or stereotactic radiation as an alternative to adrenalectomy for patients with adrenal lesions.

Conclusions and Relevance: We provide 26 evidence-based recommendations with clinically relevant data to assist surgeons with perioperative adrenalectomy care. We highlight topics that have low quality data or little evidence available and propose these topics as opportunities for further research.

INTRODUCTION

Adrenalectomy is the definitive treatment for multiple adrenal abnormalities. To optimize clinical best practices for integration of current technology and care advances related to adrenalectomy, a multidisciplinary expert group was convened by the American Association of Endocrine Surgeons with the aim of creating guidelines addressing perioperative adrenal care. The panel was selected to be diverse and equitable based on age, gender, region of practice- all having been identified as experienced in adrenal management and known willingness to disagree without deflecting from the work. In a structured process, seven specific topics common and recurrent in everyday practice were thoughtfully categorized into incidentaloma, hyperaldosteronism, hypercortisolism, adrenocortical carcinoma, metastases and pheochromocytoma/paraganglioma. The specific subject problems were framed with subsequent questions considering technique, outcome, undesirable consequences, cost and safety; and contemporary literature review was utilized to provide evidence-based recommendations (Table 1). This guideline may be of use to surgeons who care for patients with adrenal tumors and also to endocrinologists, oncologists, radiologists, radiation oncologists, internists and pathologists. In addition, this guideline may be of utility to patients with adrenal tumors. Future directions for research opportunities are identified.

Disease, Incidence and Genetics

Incidentalomas

Adrenal lesions are common incidental findings. Defined as adrenal masses identified on imaging studies not performed for suspected adrenal disease,[1] adrenal incidentalomas are detected in approximately 4.5% of cross-sectional imaging studies.[2] Prevalence increases with

age; it is estimated at 5% of the adult population and up to 10% of adults >70 years of age.[3] A size cut-off of ≥1 cm has typically been used to recommend further diagnostic evaluation in the absence of concerning clinical features.[1,4,5] Adrenal incidentalomas may be benign or malignant and hormonally functional or non-functional (eTable 1). Evaluation for hormone excess and potential malignancy are of critical importance as functional and malignant tumors typically require surgical excision (eTable 2). However, >75% of adrenal incidentalomas are benign and non-functional.[6,7] Most benign and non-functional incidentalomas are adrenal adenomas although myelolipomas and adrenal cysts are also in the differential diagnosis and can often be identified by their characteristic imaging appearance. The heritability of adrenal adenomas is likely minimal although activating somatic variants in *CTNNB1* have been observed.[8,9] (eTable 3) Research in this area is limited as non-functional adenomas are not routinely excised and rarely biopsied.

Primary Aldosteronism

Primary aldosteronism (PA) is the most common cause of secondary hypertension.[10,11] Although PA was once thought to be rare, population-based studies have shown that it affects 3% to 13% of hypertensive patients, and 5.5% to 20% of patients with resistant hypertension.[11-14] PA remains significantly under screened and underdiagnosed, partially due to its non-unique clinical presentation.[15] Classic PA is characterized by hypertension and hypokalemia, but modern series demonstrate that hypokalemia is present in only a minority of patients.[11,16,17] PA may be caused by an aldosterone secreting adenoma (APA), unilateral adrenal hyperplasia, or bilateral adrenal hyperplasia (BAH). Unilateral causes are surgically curable while BAH is managed with mineralocorticoid antagonists.[18] Early subtype differentiation is critical for management as both disease severity and duration correlate with outcomes.[19-21] Studies demonstrate near-universal

benefit from surgical intervention in patients with unilateral disease, although complete clinical cure rates range widely, from 15% to 80%.[20,22-24] A small fraction of patients with primary aldosterone excess have a germline predisposition.[25] The rare condition familial hyperaldosteronism type I (also known as glucocorticoid-remediable aldosteronism) is due to *CYP11B1/CYP11B2* chimeric fusions, familial hyperaldosteronism type II is due to mutations in *CLCN2,* familial hyperaldosteronism type III to germline pathogenic variants in *KCNJ5*, and familial hyperaldosteronism type IV (also known as early onset primary aldosteronism with seizures and neurologic abnormalities, or PASNA) to variants in *CACNA1D*.[26-29] (eTable 3) Germline testing is indicated in PA patients diagnosed at less than 20 years of age, with a positive family history, or with a personal history of stroke at less than 40 years of age.[18] Although somatic tumor testing is not in widespread clinical use, more than 90% of primary adrenal adenomas associated with Conn's syndrome and confirmed to express CYP11B2 harbor somatic mutations in the major ion channel proteins.

Hypercortisolism

Hypercortisolism is classified by a combination of origin, site, and degree of cortisol oversecretion.[30] ACTH-independent cortisol-secreting adrenal tumors can be unilateral or bilateral; and patients can be categorized as either primary adrenal Cushing's syndrome or mild autonomous cortisol secretion (MACS), previously known as subclinical Cushing's syndrome, according to the degree of hypersecretion. Extra adrenal conditions causing adrenal hypercortisolism are known as ACTH-dependent hypercortisolism and include Cushing's Disease, when the ACTH excess if of pituitary origin, and ectopic Cushing's syndrome, when associated with extra-pituitary ACTH-secreting neuroendocrine neoplasms. The overall annual incidence of hypercortisolism is estimated at 0.2 to 5.0 cases per million, with a prevalence of 39

to 79 cases per million.[31-34] MACS has been reported in 0.2% to 2% of the general adult population.[30,35,36] Germline disease is associated with both micronodular and macronodular adrenal cortical proliferations that are usually bilateral. (eTable 3) Micronodular disease includes the characteristic primary pigmented micronodular adrenocortical disease (PPNAD) of Carney Complex as well as the non-pigmented variant micronodular adrenal cortical disease. These 2 diseases are usually associated with germline inactivating mutations of the protein kinase type-1-alpha regulatory subunit (*PRKAR1A*) gene or *PDE8B/PDE11A*.[37] Macronodular disease, known as primary bilateral macronodular adrenal cortical disease or hyperplasia (PBMAH) is associated with mutations in the *ARMC5*, *MEN1*, *FH*, *APC*, *PDE11A* and *PDE8B* genes and with mosaic mutations of *GNAS* in patients with McCune-Albright syndrome, but some cases are explained by the aberrant expression of GPCRs.[37] *PRKACA* gene variants have been reported in up to 40% of sporadic adrenal cortical adenomas associated with Cushing's syndrome, whereas *CTNNB1* and *ZNRF3* variants are usually associated with tumors that cause MACS.

Adrenocortical Carcinoma

Adrenocortical Carcinoma (ACC) is a rare cancer affecting 0.7 to 2.0 patients per million annually.[38] It is among the most lethal of human cancers, and surgical resection offers the only opportunity for cure.[39] Approximately 22% to 35% of patients with ACC have distant metastatic disease at initial presentation and advanced disease caries a poor prognosis.[40,41] In patients with stage IV cancer, 5-year survival ranges from 6% to13%, compared with 39% to 50% in subjects with stage I-III disease amenable to curative-intent surgery.[38,41-43] Approximately 50% to 60% of patients with ACC have evidence of hormone excess, most commonly hypercortisolism.[38] Susceptibility genes associated with ACC include *TP53* (Li Fraumeni syndrome),[44,45] mismatch repair genes (Lynch syndrome),[46,47] and *IGF1* (Beckwith-Wiedemann syndrome).[48,49] ACCs

have been reported in adults with pathogenic variants in *APC* (familial adenomatous polyposis (FAP) syndrome),[50] *MEN1* (multiple endocrine neoplasia type 1),[51,52] *NF1* (neurofibromatosis type 1),[53] *SDHx*,[54] and Carney complex.[55,56] (eTable 3) Somatic tumor testing has substantial implications for potential targeted therapies and is an area of heightened interest. Driver mutations most commonly include *TP53*, *CTNNB1*, *ZNFR3*, and *TERT*.[57-59]

Metastases to the Adrenal Gland

The adrenal glands are frequent sites of metastatic disease. In autopsy series, adrenal metastases are present in 3% of subjects; in patients with known malignancies, adrenal masses are metastatic cancer in approximately 75%.[4,60] The most common malignancies which metastasize to the adrenal gland include lung cancer, renal cell carcinoma, melanoma, sarcoma, and colorectal cancer.[61] Adrenal metastasectomy is an increasingly common procedure, although data on outcomes have historically been limited.[61,62] Secondary lymphoma to the adrenal gland occurs in approximately 5% of patients with non-Hodgkin lymphoma and is frequently bilateral.[63]Primary adrenal lymphoma is extremely rare. Biopsy may indicate this diagnosis and the treatment is non-surgical.

Pheochromocytoma and Paraganglioma (PPGL)

PPGLs are rare tumors of the autonomic nervous system. The term paraganglioma is applied for all tumors; those in the adrenal gland are called pheochromocytomas. PPGLs may secrete catecholamines, causing cardiovascular and metabolic effects. The historic presentation includes episodic hypertension, palpitations, tachycardia, anxiety, diaphoresis, and headache. However, the presentation may vary widely, and a growing number of PPGLs are identified incidentally on imaging.[64,65] PPGLs have the highest rates of heritable susceptibility gene

mutations of all human tumors, and therefore germline testing is recommended for all affected patients.[66] Rates of germline pathogenic variants range from 25% to 30% in pheochromocytoma, to approximately 40% in extra-adrenal paragangliomas, and may be higher in metastatic PPGL.[67-71]

There are now more than 12 susceptibility genes identified. The "cluster 1" or pseudohypoxia subgroup encompasses genes associated with metabolic or oxygen-sensing pathways, including *SDHx*, *VHL*, *FH*, *EPAS1*, and *EglN/PHD2*. Variants in these susceptibility genes cause constitutive activation of hypoxia-inducible factor (HIF) transcription factors, and are associated with noradrenergic, dopaminergic, or non-secretory biochemical profiles.[72] These tumors express somatostatin receptors and are well visualized with ^{68}Ga-DOTATATE positron emission tomography (PET)/ computed tomography (CT) or the less sensitive indium-labeled somatostatin. The "cluster 2" or kinase signaling subgroup includes *MEN2*, *NF1*, *MAX*, *TMEM127* and *KIF1B* and are associated with adrenergic secretion. These tumors can also be imaged with ^{18}F-DOPA PET/CT or iobenguane (metaiodobenzylguanidine;^{123} I-MIBG) scanning. "Cluster 3" tumors are less well-defined, but are typically associated with somatic variants causing altered *WNT* signaling and may be characterized by both adrenergic and noradrenergic secretion. [70] (eTable 3)

METHODS

Methodology

Writing Group and Conflict of Interest Disclosure

A group of experts was convened with consideration given for diversity. It included surgeons, endocrinologists, oncologists, pathologists, radiologists, and patient advocacy

representation from the National Adrenal Diseases Foundation. Conflicts of interest disclosure was mandatory and any member with a financial conflict of interest was not eligible for the discussion of recommendations relevant to the conflict.

Topics and Analysis of the Literature:

In October 2019, writing subcommittees were established for 7 topics and each was comprised of 2 to 5 coauthors. Questions were structured in a Population, Intervention/exposure, Comparison and Outcome (PICO) format (Table 1).[73] The format required the subcommittees to ask important answerable questions, and define inclusion and exclusion criteria, the type of data to be extracted, the type of synthesis and presentation of the results. The PICO questions were discussed and edited by the group. Subsequently, studies in English with publication dates from 1980-2021were were extracted from PubMed and/or Embase. A detailed review of the literature was performed and the quality of the studies was assessed using the Grading of Recommendations Assessment Development and Evaluation(GRADE) assessment approach.[73] The recommendations were discussed and modified through group consensus. Individual review of sections was performed prior to monthly 2-hour group meeting to discuss, edit and reach collective affirmation. The appropriateness of the PICO format and the application of GRADE assessments were also evaluated by a methodological expert (MAH). Three chairs (LY, QYD and NDP) collaboratively oversaw the process and led the writing.

Certainty of Evidence Assessment and Recommendations

- Using the previously described GRADE approach of evidence profiles and summary of findings tables described by Guyatt et al, certainty of evidence was assessed as high, moderate, low, or very low.[74] For therapy questions, evidence from randomized, controlled trials was initially eligible to be classified as high,

and that from observational studies was classified as low. For questions of prognosis, however, evidence from observational studies was initially eligible to be classified as high. We considered risk of bias, inconsistency, indirectness, imprecision, and publication bias as rating down domains. We rated up the certainty when we observed large magnitude of effect, dose-response relationship, and opposing confounders. In addition to certainty of evidence, recommendations were constructed considering resource utilization, practical approaches to contemporary adrenal management dilemmas, a parsimonious approach to investigation, and measures to reduce morbidity or mortality. Because these were framed as mostly therapeutic questions based around the discipline of Surgery, most required observational study analysis because of the paucity of randomized controlled trials in the field. As such, the quality of most recommendations was not eligible to be classified as high. Non-graded recommendations were presented as descriptions of the practice of the expert panelists in managing patients. The panelist were considered expert based on declared volume and prior authorship impact and academic interest.

AAES and Peer Society Input

Comments and suggestions were sought from AAES members by online survey. Constructive feedback was addressed, and consensus revisions were made as needed. The writing group had complete independence from the AAES in the production of guidelines. The process was based on current evidence at the time of writing. The guidelines do not represent the only approach to the management of the adrenal and are not meant to replace an individual physician's judgment. Adherence to the guidelines is not mandatory, do not apply to children,

may require adaptation in practice settings with barriers to implementation, and does not constitute a legal standard of care.

RECOMMENDATIONS

1. Incidentalomas, Myelolipomas and Cysts

1.1. In patients with an adrenal incidentaloma, does adrenal protocol CT improve diagnostic accuracy for malignancy or pheochromocytoma compared to other imaging modalities?

Recommendation 1.1. Yes, we suggest that washout characteristics on an adrenal protocol computed tomography (CT) be used to stratify the risk of malignancy for adrenal nodules when non-contrast Hounsfield Units (HU) are >10 and other clinical risk factors for malignancy are not present. Adrenal protocol CT does not improve diagnostic accuracy for nodules with non-contrast HU <10 nor does it improve evaluation for pheochromocytoma. (Weak recommendation, low quality evidence)

Most adrenal incidentalomas are benign and do not over-produce hormones (i.e. they are non-functional).[75] Their prevalence is age-dependent, and they occur in 5% of all adults and up to 10% of patients older than 70 years of age.[76] They are uncommon in patients younger than 30 years of age and nodules in young patients are more likely to signify functional or malignant lesions. A 1 cm cut-off has traditionally been used to define adrenal incidentalomas and to recommend further evaluation for hormonal secretion and the potential for malignancy.[1] This definition avoids excessive work-up for nodular or thickened adrenal glands.

Adrenal adenomas that are predominantly fat containing can be detected by both CT and magnetic resonance imaging (MRI). Tumor density of less than 10 HU (Hounsfield units) on non-contrast CT represents a lipid-rich adenoma.[77] An adrenal protocol CT refers to non-

contrasted images followed by administration of intravenous contrast and repeat imaging at 60 to 75 seconds (venous phase) at 15 minutes (delayed phase). Benign adenomas typically exhibit rapid contrast washout, defined as an absolute percentage washout (APW) greater than 60% or relative percentage washout (RPW) greater than 40% on the delayed phase, although washout alone is not specific because hypervascular primaries such as renal cell carcinoma and hepatocellular carcinoma and 1/3 pheochromocytomas can have washout >60% absolute. In a systematic review including 16 studies, of non-contrast CT with HU<10 had 100% sensitivity to rule out malignancy in patients without a known history of extra-adrenal cancer.[77] Contrast enhanced CT does not improve diagnostic accuracy for nodules with non-contrast HU <10.[78]

Additional benign entities including adrenal myelolipomas (predominantly fat containing) and cysts (lack of contrast enhancement if imaging with and without intravenous contrast was performed) do not need evaluation with adrenal protocol CT (eFigure 1).[78]

The pre-test probability of an adrenal metastasis is higher in patients with a history of extra-adrenal malignancy. The risk of an adrenal nodule being a metastasis in a patient with known cancer also depends on the primary and stage of the cancer. In a meta-analysis of 168 patients with adrenal nodules discovered during surveillance for extra-adrenal malignancy, 7% of adrenal nodules with non-contrast HU<10 were malignant.[77] The HU cutoff of 10 had a sensitivity of 93% with a wide confidence interval of 79 to 98%. A subsequent study in 353 patients at high risk for extra-adrenal malignancy reported no adrenal metastases in nodules with non-contrast HU <10.[79] Contrast enhanced CT lacks specificity to improve the diagnosis in these cases. At minimum, short-interval surveillance at 6 to12 months is recommended for patients with a history of malignancy even if an adrenal incidentaloma has benign imaging characteristics.

Non-contrast HU<10 has recently been suggested as an imaging criterion to rule out pheochromocytoma.[80-82] In a recent meta-analysis of 1,217 pheochromocytomas, HU>10 had 100% sensitivity to detect pheochromocytoma.[83] In another recent meta-analysis of 1,167 patients with pheochromocytoma, only 6 patients had non-contrast HU<10.[81] Evaluation for catecholamine excess is likely not needed for nodules with non-contrast HU<10. Although many pheochromocytomas have delayed contrast washout compared to benign cortical adenomas, one third of pheochromocytomas have rapid washout characteristics that overlap with adenomas.[82,84,85] Contrast enhanced CT does not improve diagnostic accuracy for detection of pheochromocytomas.

Approximately one third of benign adenomas have low lipid content and have imaging characteristics that overlap with malignant lesions or pheochromocytomas. Given the very high sensitivity of rapid washout on adrenal protocol CT to rule out malignancy, nodules with APW>60% and RPW>40% can be considered benign and do not require further evaluation.[85-87] However, delayed contrast washout lacks specificity to distinguish between benign and malignant adrenal nodules.[87,88] Therefore, lipid-poor nodules with non-contrast HU>10 that are between 1-4 cm in size and lack benign washout characteristics should undergo surveillance imaging in 3-12 months to evaluate tumor growth and determine the need for surgery or further testing (e.g. PET-CT).[77,78] Chemical shift MRI may occasionally be used to detect microscopic fat (lipid) in a lipid-rich adenoma with an attenuation between 10 and 30 HU on non-contrast CT. Nodules larger than 4 cm with non-contrast HU>10 should be discussed by a multidisciplinary team that includes an adrenal endocrinologist, radiologist, and an experienced adrenal surgeon due to the increased risk of malignancy. Lesions with HU> 20 on non-contrast CT are at higher risk for primary or metastatic malignancy.

1.2. In patients with an adrenal incidentaloma, should clinical and imaging characteristics influence the hormonal work-up?

Recommendation 1.2. Yes, we recommend that all patients with an adrenal incidentaloma larger than 1 cm undergo biochemical testing for autonomous cortisol secretion. Patients with hypertension or hypokalemia also require biochemical evaluation for primary aldosteronism. Patients with adrenal imaging findings that have non-contrast CT with HU >10 should undergo evaluation for pheochromocytoma. (Strong recommendation, low quality evidence)

Functional adrenal nodules are over-represented in surgical series, as they are more likely to lead to surgical resection. Their true prevalence can only be estimated from dedicated prospective studies. Retrospective series are limited by referral and selection bias and a lack of uniform hormonal assessment, particularly for cortisol secretion. However, several recent large international series allow for a modern estimation of the prevalence of functional adrenal incidentalomas.[80,88-90] Hyperaldosteronism and hypercortisolism have been reported in 1-4% and 5-12% of patients with adrenal incidentalomas, respectively.[1]

In a prospective, international multi-center study including 1,686 patients with incidentally discovered adrenal nodules enrolled in adrenal centers, the prevalence of hyperaldosteronism was 2.1%.[90] A cortisol-producing adenoma was diagnosed in 2.7% of patients, while an additional 33.9% of patients had mild autonomous hypercortisolism (defined as failure to suppress cortisol to <1.8 ug/dL after a 1mg dexamethasone suppression test in the absence of clinical signs or symptoms of Cushing's syndrome). Mild autonomous cortisol secretion (MACS) has been increasingly recognized as an important cardiovascular risk factor in

patients with adrenal incidentalomas, although the best management approach is still uncertain.[80,91]

The prevalence of pheochromocytoma has been widely reported between 0.8-8% of all adrenal tumors[6,7,89,92] and 64/million inhabitants in a nationwide study.[93] A recent retrospective single-institution study of 1,302 patients with adrenal incidentalomas who underwent complete biochemical workup identified 91 patients with pheochromocytoma (7.1%).[88] In a population setting of patients with adrenal tumors of whom only 15.2% of patients had complete biochemical workup, the prevalence of pheochromocytoma was much lower, at 0.8%.[80] (eTable 1)

1.3. In patients with an adrenal incidentaloma, what clinical and imaging characteristics increase the risk that malignancy is present?

Recommendation 1.3. We recommend that a primary adrenal malignancy be considered in patients with an adrenal nodule/tumor larger than 4 cm, and/or Hounsfield units >20 on non-contrast computed tomography and in any patient younger than 18 years old. We recommend that patients with a history of extra-adrenal malignancy be recognized to be at increased risk for adrenal metastases. (Strong recommendation, low quality evidence)

The risk of malignancy is size-dependent, with the majority (95%) of all ACCs larger than 4 cm at initial presentation.[7,88,90] The prevalence of ACC in incidentally discovered adrenal nodules is <0.5% for nodules smaller than 4 cm, 5% for nodules between 4-6 cm, and up to 35% for nodules larger than 6 cm at presentation.[6,90,92,94] Patients with a history of malignancy who undergo imaging for tumor staging or surveillance are not considered to have a true incidentaloma due to the increased risk of malignancy if an adrenal nodule is identified in this scenario. The prevalence of metastatic disease to the adrenal gland is 1-3% in patients without a

history of malignancy, and up to 8% in patients with a history of extra-adrenal malignancy.[90,95,96] (eTable 2) As discussed previously, other imaging features in addition to size such as smoothness, circumscribed margins and region-of-interest (ROI) for determination that is at least 2/3 of the size of the lesion should be considered when assessing risk of either a primary or secondary malignancy in an adrenal incidentaloma (Rec 1.1).

1.4. In patients with a non-functional adrenal incidentaloma, what are the outcomes during surveillance?

Recommendation 1.4 We do not recommend routine scheduled follow-up of a non-functional adrenal nodule (size <4 cm) with benign imaging characteristics and non-contrast HU<10 because the risk of developing malignancy is very low. Nodules between 1-4 cm in size with indeterminate imaging characteristics (such as non-contrast CT with HU >10) have a slightly increased risk of malignancy and should undergo at least one repeat image at 6-12 months to confirm stability (no growth). Autonomous cortisol secretion is the most common hormonal excess to develop during surveillance and thus may be reevaluated at a 2-5year interval. (Strong recommendation, low quality evidence)

Most non-functional adrenal nodules with benign imaging characteristics remain stable in size.[89,91,97] Up to 10% of adrenal incidentalomas will grow >1cm over 2-5 years of surveillance.[98-100] Studies are mostly limited to single-institution retrospective cohorts with bias due to loss to follow-up. In a recent systematic review of 2,023 patients with adrenal tumors characterized as benign at the time of diagnosis and followed for a mean of 41.5 months, only 2.5% had nodule growth >1cm.[97] A slight increase in nodule size is not a clear risk factor for malignancy, as ACCs grow rapidly and have early metastatic spread. The risk of developing

malignancy during surveillance is up to 0.5%, although several studies have reported no cases of malignant transformation in adrenal nodules initially characterized as benign.[6,98,101-103]

Prior guidelines have suggested that growth of >1cm or by >20% of maximal diameter on surveillance imaging at 6-12 months should warrant surgical resection.[1,104] Malignant nodules and pheochromocytomas are much more likely to enlarge compared to benign cortical adenomas.[89] However, there are insufficient data to recommend specific criteria for nodule growth during surveillance that should prompt adrenalectomy. Surgical resection may be considered for nodules that are >2cm at initial presentation and grow >1cm by 12 months, while smaller nodules or those with less growth may undergo repeat short-interval imaging at 6-12 months.

Non-functional nodules smaller than 4 cm with benign imaging characteristics (including non-contrast HU<10) do not require routine scheduled surveillance imaging unless there are clinical risk factors such as patient history of malignancy.[1] This contrasts older guidelines that recommended follow-up imaging even for small, benign appearing adrenal incidentalomas.[104] The minimal risk of developing malignancy does not justify the patient anxiety, healthcare costs, and potential radiation exposure associated with repeat imaging in this context. Nodules between 1-4 cm with indeterminate imaging characteristics that are observed should at least undergo repeat imaging in 6-12 months to evaluate stability. If not previously obtained, contrast enhanced adrenal protocol CT may be used as the repeat imaging modality to evaluate for benign washout characteristics.[105-110]

Autonomous cortisol production is the most common hormonal excess that develops during surveillance of initially non-functional adrenal incidentalomas. Up to 12% of patients will develop hypercortisolism by 2-5 years of follow-up, depending on the biochemical method of

screening.[6,91,97,99,103] Repeat evaluation for autonomous cortisol secretion with a dexamethasone suppression test may be considered at a time interval of 2-5 years after initial presentation. Pheochromocytomas may initially present as "silent" both clinically and biochemically, particularly when <2cm in size.[111] Pheochromocytomas will eventually be diagnosed in up to 2% of adrenal nodules characterized at first as non-functional.[6,99] Similarly, up to 2% of patients with adrenal nodules will develop evidence of aldosterone hypersecretion during follow-up, although data are lacking to differentiate between aldosteronoma and bilateral hyperplasia in these cases.[6] The low risk of developing hormonal excess does not justify annual biochemical screening in all patients with adrenal incidentalomas. Development of clinical symptoms or cardiovascular comorbidities should prompt repeat testing in any patient with a known adrenal nodule.

1.5. Does resection of a myelolipoma or an adrenal cyst improve quality of life compared to observation alone?

Recommendation 1.5. No, we do not suggest resecting a myelolipoma or adrenal cyst with pathognomonic imaging features in order to improve the patient's quality of life unless there are symptoms of mass effect. (Weak recommendation, low quality evidence)

Adrenal masses may be diagnosed as myelolipoma or adrenal cystic lesions based on imaging characteristics and are most commonly detected incidentally, but larger masses may present with symptoms of mass effect and/or hemorrhage. Imaging characteristics may be diagnostic in cases of myelolipoma and simple cystic lesions of the adrenal. Adrenal myelolipoma is a solid adrenal tumor composed of variable portions of mature fat and mixed myeloid and erythroid cells. The detection of macroscopic fat in an adrenal nodule/mass by CT or MRI is highly suggestive of a myelolipoma commonly appearing as a very low-density, with Hounsfield Units generally less than -30 and a marbled appearance.[112] Adrenal cysts include

endothelial cysts, which comprise both lymphangiomatous and hemangiomatous subtypes. These typically appear as thin walled, homogenous, low-attenuation lesions without internal enhancement. However, cystic adrenal lesions may be more variable in appearance and features may be less distinctive. Pseudocysts may follow adrenal hemorrhage and can contain macrocalcification. Furthermore, malignant pathologies including ACC and pheochromocytoma may be macro-cystic on imaging.[113]

Therefore, unless determined to be benign on imaging based on pathognomonic features, cystic adrenal lesions should be considered indeterminate and require hormonal evaluation followed by close observation or consideration of resection. It should be noted that imaging-occult adrenal cortical tumors may occur in approximately 6% of cases of myelolipoma, so even in the setting of pathognomonic benign imaging features, functional workup for autonomous glucocorticoid production may be considered.[114] In a study looking at 321 myelolipomas in 305 patients, those greater than 6 cm in largest diameter were more likely to cause symptoms of mass effect and were more likely to be associated with hemorrhagic change on imaging. Resection may be considered for indeterminate imaging, symptomatic tumors due to mass effect, substantive growth on surveillance, or those that have hemorrhaged. However, it remains unclear as to whether resection improves quality of life or alters survival in the setting of myelolipoma or benign adrenal cyst.

2. Primary Aldosteronism

2.1. In patients with primary aldosteronism (PA), does adrenalectomy compared to mineralocorticoid antagonist therapy alone improve related comorbidities and mortality?

Recommendation 2.1. Yes, we recommend that patients undergo adrenalectomy for unilateral disease because they are more likely to utilize fewer medications and lower defined daily doses

to achieve normalization of blood pressure and potassium levels, and have lower risks of new onset atrial fibrillation, chronic kidney disease, stroke, and all-cause mortality. (Strong recommendation, low quality evidence)

Primary aldosteronism (PA) has been reported in 3-10% of hypertensive patients.[115] A higher prevalence is observed in those with severe hypertension (SBP >180, DBP >110 mm Hg), in those with hypertension despite at least 3 antihypertensive medications, hypokalemia, and in some studies, hypertension and obstructive sleep apnea.[12,116,117] In meta-analysis, and compared to patients with essential hypertension, PA patients have a higher risk of cardiovascular morbidity including CHF (OR 2.05, 95% CI 1.11-3.78), atrial fibrillation (OR 3.52, 95% CI 2.06-5.99), stroke (OR 2.58, 95% CI 1.93-3.45), and MI (OR 1.77, 95% CI 1.10-2.83).[118] Thus the accurate identification and management of PA should improve health outcomes for this population.

Once PA is diagnosed, mineralocorticoid antagonists (MRAs) can be used to effectively manage PA-related hypertension and hypokalemia. When a unilateral source of hyperaldosteronism is demonstrated, adrenalectomy becomes a treatment option. In a systematic review by Muth et al, blood pressure normalization was equally likely in medically versus surgically treated patients.[119] However, after adrenalectomy, fewer antihypertensive medications are typically required to achieve normotension. In a retrospective multicenter registry study, blood pressure normalization was achieved more often after adrenalectomy (79% vs MRA 67%, $p=0.046$) utilizing fewer defined daily doses (DDD) (0.9 vs MRA 2.7, $p<0.001$)[120]. In a systematic review by Satoh et al, the mean number of required antihypertensive agents was lower after adrenalectomy (1.55 vs MRA 2.83, $p<0.001$).[121]

Hypokalemia (serum potassium ≤3.5 mmol/l) is present in 10% to 35% of PA patients overall but the incidence is higher in surgical series (80% to90%).[16] Achieving normokalaemia appears to be equally likely in patients treated medically versus surgically[119]. In a multi-institution study of 171 PA patients undergoing adrenalectomy, the mean preoperative potassium DDD was 2.0 compared to 0.0 postoperatively.[122] In a larger multi-institutional study, the rate of normokalaemia off all potassium supplements after surgery was 98%.[123]

Studies assessing whether adrenalectomy or MRA treatment alter the occurrence of cardiac or cerebrovascular events have mostly equivocal results. In a large retrospective national registry study from Japan including 740 adrenalectomy and 1247 MRA treated patients, the likelihood of a major cardiovascular related event was not associated with treatment type (p >0.3).[124] In a systematic review by Satoh et al, there was again no difference observed in risk of cardiovascular events between patients treated surgically versus medically.[121] However, in meta-analysis, MRA was associated with a higher risk of developing new onset atrial fibrillation compared to adrenalectomy (OR 2.83, 95% CI 1.76-4.57).[125]

Chronic kidney disease (CKD), defined as estimated glomerular filtration rate (eGFR) <60, is another relevant morbidity for PA patients. In a retrospective single institution study of 520 patients, MRA treatment was associated with an increased rate of CKD compared to adrenalectomy (55.6 events/1000 person years vs. 16.7, HR 2.3, 95% CI 1.22-4.35).[126] Furthermore, declines in eGFR over time were greater with MRA compared to patients with treated essential hypertension while eGFR changes stabilized after adrenalectomy.[126] In analysis of National Health Insurance data from Taiwan, rates of end stage renal disease for PA patients after adrenalectomy compared to those with essential hypertension were lower (adjusted HR

0.46, 95% CI 0.23-0.93, p=0.03) compared to no difference with MRA treatment alone (adjusted HR 0.93, 95% 0.72-1.2, p=0.6).[127]

Confounding the results of many studies is the inherent difference between patients who have a unilateral source (aldosterone-producing adenoma, APA) versus those who have adrenal hyperplasia and MRA treatment is the only therapeutic option. Biochemical differences exist between these two disease processes as APA are associated with a higher likelihood of hypokalemia and higher ARR.[128,129] In addition, the co-secretion of cortisol and aldosterone can occur in up to 15% to 20% of PA and the effects of chronic autonomous hypercortisolism may contribute to long-term morbidity in patients treated with MRA only.[130] Although there are no randomized studies, some have attempted to investigate these differences by comparing outcomes after adrenalectomy versus MRA treatment in the subset of PA patients who have or are likely to have an APA. In a retrospective multi-institutional study of 154 patients with a likely APA, the risk of cardiovascular events was equivalent in patients who received surgery versus MRA therapy.[131] Chang et al utilized the National Health Registry in Taiwan to identify 1047 patients with PA and APA. Compared to patients with essential hypertension, adrenalectomy was associated with a reduced risk of stroke (HR 0.75, p=0.049) while MRA was associated with an increased risk (HR 1.76, p<0.001).[132]

Reports of the impact of treatment type on mortality are variable. In a retrospective multicenter study comprised of a small cohort of 107 patients, there was no difference in mortality between patients treated with MRA versus adrenalectomy.[133] In a meta-analysis by Huang et al, an apparent unadjusted risk reduction in mortality from adrenalectomy compared to MRA failed to reach statistical significance (OR 0.6, 95% CI 0.36-1.01, p=0.05).[134] However, in a large retrospective National Health Registry study from Taiwan of 2516 MRA and 846

adrenalectomy patients, all-cause mortality was higher with medical treatment (16.7% vs. 3.8%, p<0.001).[132] When propensity matching for comorbidities, adrenalectomy was still associated with reduction in mortality (HR 0.23, p<0.001).[132] Thus, it is prudent to distinguish cases of PA due to unilateral aldosteronoma from those due to bilateral adrenal hyperplasia.

2.2. In patients with primary aldosteronism and cross-sectional imaging consistent with a unilateral adenoma, does preoperative adrenal venous sampling (AVS) increase the likelihood of a clinical or biochemical cure?

Recommendation 2.2. Maybe. We suggest that in patients ≤35 years of age with cross-sectional imaging demonstrating a unilateral adenoma and a normal contralateral gland, adrenal venous sampling may be deferred because adrenalectomy directed by CT imaging alone has a cure rate similar to adrenalectomy guided by AVS. However, AVS should still be considered for all patients >35 years of age. (Weak recommendation, low quality evidence)

Cross-sectional imaging with computed tomography (CT) is the most commonly utilized modality to distinguish PA due to bilateral hyperplasia from unilateral APA or, rarely, adrenal carcinoma. APAs are typically small and lipid-rich (<10 Hounsfield units (HU) on non-contrast CT scan). Although uncommon, a large adrenal lesion or indeterminate imaging features should raise a higher index of suspicion for an aldosterone-secreting adrenal carcinoma (see Incidentaloma).

Adrenal venous sampling (AVS) may be necessary for lateralization because a) bilateral hyperplasia is the most common etiology of PA (60-70%), b) APA are often small and may be below the size threshold for detection on cross-sectional imaging, and c) there is an age-related prevalence of non-functional adrenal adenoma which may be coincidentally present.[135] AVS is a highly specialized interventional radiology procedure which requires specific expertise to ensure

adequate cannulation of the right adrenal vein. There are different protocols for AVS but continuous ACTH infusion during AVS is often utilized and can stabilize some of the stress-induced alterations in aldosterone secretion. The cortisol level gradients between the adrenal veins and the inferior vena cava are used to confirm adequate sampling and the aldosterone levels are then cortisol-corrected as the inflow from the inferior phrenic vein causes dilution of the levels from the left adrenal vein. Different thresholds have been described but with ACTH infusion, the cortisol-corrected aldosterone levels should be >4x the contralateral side for lateralization.[136,137] AVS interpretation may possibly be altered in the presence of concurrent cortisol excess.[138,139]

Failure to successfully cannulate the right adrenal vein is probably the most common complication and occurs in 4-25%.[137] Adrenal hemorrhage occurs in 1-2% and adrenal vein rupture has been reported as a rare risk.[135] Other considerations include the added costs and necessary expertise which limits widespread availability. Additionally, patients often are required to stop their MRA for approximately 4 weeks which can add to procedural-related morbidity if their hypertension cannot be adequately controlled with other medications.

In meta-analysis, when cross-sectional imaging (either via CT or MRI) is used alone to identify a unilateral source in PA patients, the pooled sensitivity and specificity are 68% (95% CI 50-65%) and 57% (95% CI 50-65%).[140] Use of contrast-enhancement increases sensitivity. However, CT and AVS concordance rates range from 50-90% which varies by age.[141] The most common cause of discordance is the finding of a unilateral abnormal adrenal gland on CT but AVS identifies bilateral sources of aldosteronism (15-20%). Less often, AVS can lateralize contralateral to the abnormal gland seen on imaging (3-5%).[142] In either of these cases, the incorrect operation would have been performed if guided by imaging findings alone.

Despite the increased sensitivity and specificity with AVS, there is controversy regarding the routine use of AVS to improve biochemical and clinical cure rates for patients undergoing adrenalectomy. In a retrospective analysis of a multicenter observational registry of 1625 PA patients who had AVS, clinical cure was more likely when surgery was AVS-guided (40% vs. non-AVS guided 30%, p=0.027).[143] In another similar multicenter registry analysis i of 761 patients (235 CT only and 526 CT with AVS), use of CT only to guide surgical management was associated with a lower likelihood of complete biochemical success (OR 0.28, 95% CI 0.16-0.50, p<0.01) but no difference in complete clinical success was observed (38.6% vs CT with AVS 37.3%, p=0.72).[144] However, several smaller single institutions and retrospective studies did not identify any difference in either biochemical or clinical cure rates when AVS was utilized compared to when surgery was image-guided only. [145,146] In a randomized study using defined daily dosage (DDD) and number of medications needed to obtain target blood pressure at 1 year as the primary outcome measure, there were no differences observed between the AVS and non-AVS cohorts.[147] This study included both adrenalectomy and MRA-treated patients in the analyzed cohorts and ultimately may have been underpowered to truly assess if AVS-guided surgery altered outcomes.

Because of improved resolution with current cross-sectional imaging modalities and the low likelihood of nodular adrenal glands in younger patients (see Incidentaloma section), several studies have specifically investigated if there is added benefit to AVS in patients <35 years of age who have unequivocal unilateral imaging findings. While the number of patients included in these studies has been small and all are retrospective analyses, AVS and CT concordance ranges from 90-100% in this age group.[141,145,148]

A selective AVS approach reserving AVS for patients with a ≤1 cm adrenal nodule and/or contralateral adrenal enlargement has been described. Using this approach in a multicenter retrospective study, equivalent rates of biochemical and clinical cure rates were observed between the CT only compared to the CT with AVS groups.[149] In a subset analysis of a retrospective multicenter study, biochemical cure after adrenalectomy was observed in all patients who were age <35 years, had an adrenal mass >1 cm with a normal contralateral adrenal gland, and had characteristic biochemical parameters of PA (plasma aldosterone >30 ng/dL and spontaneous hypokalemia).[144] In summary, selective utilization of AVS accounting for imaging and patient features, can achieve equivalent clinical success rates, reduces the costs and risks associated with routine AVS especially since interventional radiology expertise is necessary to avoid non-informative results, and limits disparities when such expertise is often not readily available particularly since the health benefits of appropriate and successful adrenalectomy is potentially quite high.

2.3. In patients with primary aldosteronism due to unilateral disease, does laparoscopic adrenalectomy improve health-related quality of life and/or reduce healthcare related costs compared to medical management?

Recommendation 2.3. Yes, we recommend laparoscopic adrenalectomy for primary aldosteronism due to unilateral disease because it improves quality of life and reduces healthcare-related costs. (Strong recommendation, low quality evidence)

Preoperatively, hypertension and hypokalemia should be well-controlled. Postoperative hypoaldosteronism can occur but typically resolves spontaneously and the subsequent

hyperkalemia can be ameliorated by salt intake as well as by cessation of potassium supplements and MRA. Due to aldosterone-mediated glomerular hyperfiltration, decreases in eGFR may occur immediately postoperatively and are associated with preoperative hypokalemia and PRA level.[150]

Consensus criteria for assessing postoperative outcomes for PA includes evaluation for complete, partial, or absent clinical and biochemical cure.[123] Clinical cure is defined by number and amount of anti-hypertensive medications needed to maintain normal blood pressure while biochemical cure is defined as effect of adrenalectomy on potassium levels and ARR. Outcome assessment should be performed with the first 3 months postoperatively, at 6-12 months, and then annually.[123] In large retrospective multi-institutional studies, complete biochemical cure is observed in 93-94% but complete clinical cure (i.e. ability to stop all anti-hypertensive medications and maintain normal blood pressures) occurs in 30-40%.[123,151] The majority of adrenalectomy patients have either complete or partial clinical success with <20% requiring the same or higher doses of medication postoperatively. In meta-analysis, clinical improvement is more likely immediately postop (53.3%, 95% CI 36-70.5%) compared to ≥6 months after surgery (49.6%, 95% CI 40.9-58.3%, $p<0.001$) and higher in patients age <50 years (59.5% vs age >50 years 46.6%, $p<0.001$).[152]

Because of medication reductions and improvements in cardiovascular/renal parameters, several studies have investigated the relationship between adrenalectomy for PA and quality of life (QOL). The short form (SF) survey tool was used by Kunzel et al who assessed 132 PA patients treated with MRA versus surgery and used historical reference data from the general population for additional comparison.[153] Both MRA-treated and adrenalectomy patients had diminished QOL compared to the general population, but QOL was even lower in the medical

versus surgical cohorts. In another small single institution study using the 36-item short form survey tool (SF36), scores improved following adrenalectomy at a faster rate than after initiating MRA treatment.[154] In the only study to assess only surgical patients, Citton et al utilized the SF36 tool to evaluate 26 PA patients and compared scores to 15 patients who had adrenalectomy for a non-functional adenoma.[155] Interestingly, with long-term follow-up, physical, mental, and depression components all improved in the PA patients, but no change was seen in the physical component in the non-functional adenoma cohort.[155]

In post-hoc analysis of the SPARTACUS trial, Velema et al assessed both SF36 and European Quality of Life Five Dimension (EQ-5D) questionnaire in 184 PA patients treated with adrenalectomy or MRA.[156] Similar to prior studies, QOL was lower in all patients compared to the general population at diagnosis but initiation of either treatment improved QOL.[156] Furthermore, improvements at 1 year were greater after adrenalectomy compared to MRA irrespective of clinical and biochemical outcomes[156]. Specifically, adrenalectomy patients had higher physical and mental scores compared to MRA treated patients.[147] A meta-analysis has been attempted to address QOL considerations but due to the heterogeneity of tools used and variable correlations of treatment with clinical and biochemical success, the conclusions are largely descriptive.[157]

Costs associated with laparoscopic adrenalectomy compared to medical treatment have been investigated in 2 studies. Sywak et al compared single institution costs of surgery in 24 patients to extrapolated lifetime costs of medical therapy, and adrenalectomy was associated with a lower absolute cost.[158] Reimel et al performed a decision tree analysis using a 40-year-old otherwise healthy woman as the base case. Adrenalectomy was again demonstrated to be less costly than long-term MRA.[159] The analysis was sensitive to cost of surgery, cost of AVS, and

rate of absent clinical cure.[159] Studies to date have assessed cost outcomes after adrenalectomy via laparoscopy, and whether similar conclusions can be made utilizing other minimally invasive surgical approaches is not yet known.

3. Hypercortisolism

3.1. Do patients with mild autonomous cortisol secretion (MACS) who undergo laparoscopic adrenalectomy compared to conservative medical management have improvement in cardiometabolic comorbidities without major surgical (30-day) adverse events?

Recommendation 3.1. Yes, we recommend that patients with mild autonomous cortisol secretion secondary to a unilateral adenoma undergo laparoscopic adrenalectomy due to anticipated significant improvements in cardiometabolic comorbidities. (Strong recommendation, moderate quality evidence)

Overt autonomous hypercortisolism from adrenal enlargement requires resection and is not discussed here. Different from overt, mild autonomous cortisol secretion (MACS), previously known as subclinical Cushing's syndrome, has been reported in 0.2 to 2% of the general adult population[30,35,36] and in 5 to 30% of patients with an adrenal incidentaloma.[1,5,30] MACS' clinical spectrum is directly proportional to the amount and duration of glucocorticoid hypersecretion by the tumor.[160] While patients with MACS may lack the classical stigmata of hypercortisolism (e.g., frequent infections, weakness, thinned skin, or moon facies), they have a high prevalence of associated comorbidities such as obesity, arterial hypertension, type 2 diabetes (T2D), and vertebral fractures.[161-164] Compared to patients with non-functional adrenal adenomas, MACS patients have a higher prevalence of metabolic syndrome, T2D, and cardiovascular morbidity and mortality.[160,164-168] Initial biochemical screening for MACS in

patients with an adrenal incidentaloma should include measurement of cortisol after an overnight 1 mg dexamethasone suppression test (DST); cortisol levels ≥ 1.8 mg/dL with concomitant dexamethasone level >100-180 ng/dL (for 8 am draw following 1 mg dexamethasone taken between 11:00 pm and 12:00 am the previous evening) are diagnostic of MACS.[169,170] However, up to 30% of MACS patients may have DST cortisol levels greater than 5. ACTH is often low normal, but can be >20 pg/mL; exclusion of ACTH-dependent hypercortisolism from a pituitary source is critical.[171] While other tests for hypercortisolism can be considered including 24h urine cortisol and midnight salivary cortisol, these are both frequently normal in patients with MACS[1]. In patients with hypercortisolism who underwent resection of adrenal incidentaloma, improvement in metabolic parameters could be most accurately predicted by presence of at least 2 of the following preoperative parameters: urinary free cortisol (UFC)>70 mcg/24 h, ACTH<10 pg/ml, and morning cortisol after 1 mg-DST>3.0 mg/dl.[172] While laparoscopic adrenalectomy is indicated for the management of clinically overt Cushing's syndrome (CS) from an adrenal adenoma, its indication in MACS continues to be debated with variability in diagnostic criteria.[1,5,104,173] Some groups recommend adrenalectomy for all patients who meet biochemical diagnostic criteria and others feel it should be reserved for patients with at least one uncontrolled co-morbid condition resulting from the CS. Patients who are younger, planning pregnancy, or desire surgical treatment should be considered for such.

In the only prospective, randomized trial comparing long-term outcomes of laparoscopic adrenalectomy (n=23) to conservative management (n=22) for patients with adrenal adenoma and MACS, Toniato et al. found that all laparoscopic adrenalectomy patients experienced biochemical resolution of hypercortisolism with no major surgical complications.[174] Patients who underwent laparoscopic adrenalectomy experienced significant normalization or improvement of

their pre-operative hypertension with non-significant improvement or normalization of T2D, hyperlipidemia, and obesity at an average of 7.7 years of follow-up; no changes in bone mineral density (BMD) were observed in the patients with osteoporosis at baseline. In contrast, patients who underwent best available medical (conservative) management experienced worsening of T2D, hypertension, and hyperlipidemia.[174]

Two systematic reviews found consistent results.[36,175] Pooled data from 26 studies found that MACS patients who underwent adrenalectomy, compared to conservative management, experienced a statistically significant improvement in hypertension (RR 11, 95% CI: 4.3–27.8) and diabetes mellitus (RR 3.9, 95% CI: 1.5–9.9) and a non-statistically significant improvement in dyslipidemia (RR 2.6, 95% CI: 0.97–7.2) and obesity (RR 3.4, 95% CI: 0.95–12). In pooled data from 7 studies (n=230), patients undergoing laparoscopic adrenalectomy had low perioperative morbidity and cure or improvement in blood pressure, glucometabolic control, and obesity, without improvement in BMD, compared with conservative management.[36] Several observational studies identified similar metabolic improvements in patients with MACS and an adrenal adenoma who underwent laparoscopic adrenalectomy compared to conservative treatment.[168,176] Small studies have also observed improved glucose metabolism,[167,177-179] blood pressure,[167,177-179] lipid levels,[167] and decrease in the number of cardiovascular risk factors.[180]While there is variable improvement in BMD after adrenalectomy for MACS,[36,179] operative patients have a decreased fracture risk. At 3.3 years mean follow up, adrenalectomy patients had a 30% reduction in the risk of vertebral fractures compared to non-surgical patients (new vertebral fractures developed in 9.4% versus 52.2%, $p < 0.0001$).[181]

Laparoscopic adrenalectomy can be performed safely in these patients with low perioperative morbidity.[36,178,179] However, there is a high prevalence of postoperative adrenal

insufficiency after laparoscopic adrenalectomy for MACS (approximately 60%)[172,182-184] but a shorter time to achieve eucortisolism compared to patients with overt Cushing's syndrome (6.5 vs 11.2 months respectively; $p<0.001$).[182]

3.2. Do patients with Cushing's syndrome and bilateral macronodular adrenocortical hyperplasia who undergo unilateral laparoscopic adrenalectomy achieve biochemical remission of hypercortisolism when compared to patients treated with bilateral adrenalectomy?

Recommendation 3.2. Yes, in patients with bilateral macronodular adrenocortical hyperplasia and Cushing's syndrome (CS), we suggest consideration of unilateral laparoscopic adrenalectomy as an attempt to achieve biochemical remission of hypercortisolism without causing permanent adrenal insufficiency. (Weak recommendation, low quality evidence)

Bilateral ACTH-independent CS can be subdivided into macronodular (primary bilateral macronodular adrenal hyperplasia (PBMAH), previously called ACTH-independent macronodular adrenal hyperplasia (AIMAH)) and micronodular adrenal hyperplasia, subdivided into primary pigmented nodular adrenocortical disease (PPNAD) and isolated micronodular adrenocortical disease.[185,186] Patients with Carney complex make up 60% of PPNAD cases and PPNAD is more commonly familial than sporadic. The diagnosis usually occurs before age 30.

While bilateral adrenalectomy has been the standard treatment for those with symptomatic CS, the procedure produces lifelong steroid dependence and risk of adrenal crisis. Thus, there has been growing interest in whether unilateral adrenalectomy of the larger gland may produce biochemical normalization of hypercortisolism in select patients. Due to the rarity of the conditions, only relatively small, retrospective studies have evaluated biochemical normalization of autonomous cortisol secretion in both PBMAH and PPNAD, occurrence of adrenal

insufficiency, and impact of surgery on metabolic parameters. Surgical morbidity and mortality are minimal in these series.[36] Resolution of hypercortisolism occurred in 84-100% of patients with bilateral autonomous hypercortisolism who underwent unilateral resection of the largest gland.[187-191] Despite these immediately promising results, recurrence occurred in 13.3-68% of patients at 4 years.[187,189,190,192] In one study of 102 selected patients with adrenocortical hyperplasia who underwent unilateral adrenalectomy, authors felt that despite a 35% recurrence rate, this was a reasonable initial treatment.[193] The procedure can often be technically challenging because of body habitus.

Several studies have investigated the potential role of AVS to lateralize cortisol hypersecretion and predict success of unilateral adrenalectomy in the setting of bilateral structural disease. These small studies have heterogeneous adrenal imaging findings, degrees and causes of cortisol hypersecretion, and definitions of lateralization ratio but have found that some patients with bilateral imaging findings have unilateral cortisol hypersecretion (0-40%) and may be spared a bilateral adrenalectomy.[194-198] A selective strategy that involves imaging findings and/or AVS for lateralization may decrease need for total steroid supplementation while resolving biochemical hypercortisolism in a subgroup of patients.[194] However, until there are more rigorous and larger studies assessing mass size versus AVS lateralization ratios, evidence-based recommendations cannot be made.

After unilateral adrenalectomy, metabolic parameters all significantly improved at short-term (12 month) follow up including BMI,[187,191] blood pressure,[187,188,191,199] and DM2.[187,188,191] At 5 years of follow up, postoperative improvement in blood pressure persisted.[187] Postoperative adrenal insufficiency requiring steroid replacement occurred initially in 28.5-50% of patients[187,189,191] with some reports of persistent adrenal insufficiency at 5 years postoperatively. Adrenal-sparing

surgery is also being studied for treatment of PBMAH(total resection of one adrenal with subtotal resection of the contralateral gland) with promising results for control of CS with lower rates of adrenal insufficiency.[200] Deaths reported in these series during long-term follow up are a consequence of CS and related co-morbid conditions.[189,194] This finding is important as patients who do not have initial control of hypercortisolism after unilateral adrenalectomy may have increased risk of death during follow up.[187,189] In a small study (n=7), PBMAH (AIMAH) patients who underwent unilateral adrenalectomy of the larger gland experienced significantly improved physical and mental subjective perception of quality of life;[191] these postoperative QOL measurements were similar in another study that only measured postoperative values.[189]

3.3. In patients with ACTH-dependent hypercortisolism, does bilateral laparoscopic adrenalectomy improve disease-free survival or mortality compared to pharmacologic management?

Recommendation 3.3. Yes, we suggest that patients with moderate to severe ACTH-dependent hypercortisolism refractory to source control undergo bilateral laparoscopic adrenalectomy to ameliorate cortisol excess and improve disease-free survival and mortality. (Weak recommendation, low quality evidence)

ACTH-dependent CS results from pituitary Cushing's disease (CD) or an ectopic ACTH source. Although CS can be resolved in most patients with treatment of the primary source, a subset of patients experience persistent, symptomatic CS from incurable pituitary disease or metastatic or occult ectopic ACTH production. Medical therapies for pituitary CD include the dopamine-agonist cabergoline and the multi-receptor somatostatin analogue Pasireotide. Other therapies for CS include steroidogenesis inhibitors (metyrapone, ketoconazole, and LCI699), glucocorticoid receptor antagonist (mifepristone), and adrenolytic mitotane. Monotherapy is less

effective at cortisol normalization than multitherapy.[201] The success for medical therapy is 25-60% and up to 82% for mitotane compared to bilateral adrenalectomy (100%).[202] While 3% to 34% of patients undergoing bilateral adrenalectomy have residual cortisol secretion due to accessory adrenal tissue or adrenal remnants, fewer than 2% in a large systematic review had a relapse of CS.[203] Patients with CS who do not undergo treatment have a mortality rate of 4.6 (range, 2.4-16) times higher than the general population. [30]

All data comparing medical and surgical outcomes for patients with ACTH-dependent CS are retrospective and heterogeneous, including patients with both CD and ectopic CS. One retrospective study compared groups of patients with ACTH-dependent CS who underwent treatment with steroidogenesis inhibition with or without bilateral adrenalectomy. While both groups improved metabolically with treatment, fewer patients died in the highly selected surgical group (59% vs 29%) and deaths after bilateral adrenalectomy were attributable to sequelae of CS or progression of malignancy.[204] Patients with CD who undergo bilateral adrenalectomy are generally younger, have longer duration from time of diagnosis to adrenalectomy, and have longer survival than those with ectopic disease.[203-206] There is no difference in survival or outcomes between patients with an ectopic ACTH source that are known versus occult. [207] Modern surgical techniques permit most patients who require bilateral adrenalectomy to be managed with laparoscopic surgery. Operative morbidity in these patients is approximately 10% with surgical mortality approximately 3%.[205,207,208]

In a systematic review of bilateral adrenalectomy for ACTH-dependent CS (including 37 studies published 1981-2012), mortality was 17% (range, 0–88%) at a median follow-up of 41 months (range, 14–294 months). Ten-year mortality was higher in ectopic than pituitary-dependent CS (44% vs 3% respectively), and progression of ectopic CS was the cause of death in

most of these patients.[203,205] Notably, 46% of the patients who died did so in the first year after surgery; the etiology for this is unclear.[203]

In addition to the 2 primary outcomes – disease-free survival and mortality – it is also essential to consider operative morbidity, biochemical resolution of CS, symptom resolution, QOL, occurrence of adrenal crises, and development of Nelson's syndrome when selecting an appropriate treatment for patients with uncontrolled ACTH-dependent CS.[203] Patients report symptomatic improvement after bilateral adrenalectomy in muscular weakness, bodily stigmata of classical CS, arterial hypertension, DM2, obesity, and emotional stability.[203] With a mean follow up of 3.6 years, 89% of patients who underwent bilateral adrenalectomy for treatment of refractory pituitary CD reported an improvement in their Cushing-related symptoms and 91.7% would undergo the same treatment again.[208] In a QOL survey, over half of patients were in the top two-third of the national average for physical composite scores and 81% in the top for mental composite scores.[208] However, nearly one-third of patients continue to have fatigue and impaired work capability after bilateral adrenalectomy.[203]

Concerns regarding sequelae of bilateral adrenalectomy, namely risk of adrenal crisis or Nelson's syndrome (for pituitary disease), may prevent clinicians from recommending this treatment. In a large systematic review, adrenal crisis occurred at a rate of 0.93 per 10 patient-years with a median rate of 28% of patients having at least one adrenal crisis with median follow up 42 months.[203] Nelson's syndrome is characterized by: 1) growing residual pituitary tumor, 2) ACTH concentration >300 mg/dL, and 3) hyperpigmentation of the skin. While this occurred in 21% of patients (range, 0-47%) in a review of 24 studies with 768 bilateral adrenalectomy patients, [203] less than 9% of patients require additional pituitary surgery for Nelson's syndrome.[208]

3.4. Is the incidence of postoperative adrenal insufficiency after unilateral adrenalectomy different between patients with overt Cushing's syndrome compared to those with MACS?

Recommendation 3.4. Yes, the incidence of adrenal insufficiency after unilateral adrenalectomy is nearly 100% in patients with overt Cushing's syndrome and approximately 60% in patients with MACS. We recommend empiric postoperative glucocorticoid replacement therapy for all patients with overt Cushing's syndrome after undergoing only unilateral adrenalectomy. However, we recommend that in patients with MACS, postoperative day 1 morning cortisol or corticotropin stimulation testing could be used to determine the need for glucocorticoid replacement therapy. (Strong recommendation, low quality evidence)

Postoperative adrenal insufficiency is a life-threatening condition that should be prevented and promptly managed in patients undergoing adrenalectomy (eTable 4). HPA axis suppression occurs in all patients undergoing unilateral adrenalectomy for ACTH-independent CS and in over 60% of patients undergoing unilateral adrenalectomy for MACS.[172,182-184] The frequency of adrenal insufficiency postoperatively is associated with the severity of hypercortisolism preoperatively. [36,183,209-213] Patients with overt CS are initiated on steroids following adrenalectomy despite the small group of patients who may not be steroid-dependent.[214] For patients with MACS, baseline morning cortisol measurement and/or corticotropin stimulation should be performed the morning of postoperative day 1 in asymptomatic patients who do not have signs or symptoms of acute adrenal insufficiency, including fatigue, hypotension, anorexia, abdominal pain, weakness, syncope, back pain, nausea, vomiting, fever, or confusion.[36,182] To test for asymptomatic adrenal insufficiency in adults, 250 mcg IV corticotropin is injected after a baseline morning cortisol level is obtained. Either baseline cortisol <10 mcg/dL or peak cortisol levels that do not reach 16-20 mcg/dL at 30-60

minutes after injection are diagnostic of adrenal insufficiency.[182,184] Steroids may be weaned off slowly guided by lack of clinical symptoms, baseline morning cortisol level, or repeat corticotropin stimulation. Steroid replacement dose after unilateral adrenalectomy for CS has traditionally been twice daily dosing, hydrocortisone 25-50 mg/day, with a standard hydrocortisone dose 20 mg in the morning and 10 mg 6-8 hours after waking to imitate the normal cortisol circadian rhythm.[176]

Despite patients taking appropriate physiologic doses of steroid replacement, glucocorticoid withdrawal syndrome can occur after adrenalectomy for CS. This syndrome occurs due to dependence on supraphysiologic endogenous cortisol secretion prior to adrenalectomy and is manifested by symptoms including fatigue, arthralgia, myalgia, decreased quality of life, depression, and anxiety.[213,215] Preoperative patient counseling should explain that patients may feel poorly in the first several weeks to months after successful surgery, and that these symptoms may last for up to 12 months.[169]

Several studies have attempted to identify preoperative factors that will predict the need for or duration of postoperative glucocorticoid replacement. Higher preoperative cortisol levels (lack of suppression) after 1 mg overnight DST have been significantly associated with the need for steroid replacement postoperatively and longer duration of therapy.[183,210-213] In a prospective study of 60 patients undergoing unilateral adrenalectomy without overt CS, the presence of more than at least 3 parameters – including cortisol after 1 mg DST >5 mcg/dL, ACTH <10 pg/mL, elevated UFC, and elevated midnight salivary cortisol – had the highest odds ratio for predicting postoperative hypocortisolism (OR 10.45, 95% CI 2.54-42.95, p=0.001).[172] Similar findings have been reported in other studies.[210,213,216,217] Only a preoperative 1mg-DST of <1.2 mcg/dL rules out the probability of postoperative adrenal insufficiency.[182,218] In a systematic review, the time

to achieve eucortisolism was lower in MACS patients than in patients with overt Cushing's syndrome (6.5 vs. 11.2 months respectively: $p<0.001$). When diagnosed based on abnormal 1 mg overnight DST alone (cortisol 1.8-5 mcg/dL) with no other HPA abnormalities, incidence of adrenal insufficiency postoperative was 51.4%. With an abnormal 1 mg overnight DST and one additional abnormality (basal ACTH, UFC, dehydroepiandrosterone sulfate levels, serum midnight cortisol, or circadian rhythm of cortisol), incidence of adrenal insufficiency was 60.6% (eTable 4).[182]

Duration of steroid supplementation depends upon whether steroids are initiated routinely or selectively after adrenalectomy. Using a selective strategy, when all patients with preoperative cortisol hypersecretion, regardless of degree, underwent postoperative day 1 corticotropin stimulation, less than 60% of patients with MACS required supplemental cortisol.[184,214] In studies that use symptoms of adrenal insufficiency alone to initiate steroids postoperatively, 16.9% of patients required steroids and duration of steroid replacement was abbreviated (3 to 12 weeks).[210] In contrast, investigators who empirically initiate glucocorticoid replacement generally report longer duration of required supplementation.[209,212] Morelli et al., who initiated postoperative steroid replacement in all patients, found a much longer duration of postoperative hypocortisolism (>18 months in 50% of CS patients and 31% of adrenal incidentaloma patients) detected by corticotropin stimulation test every 6 months.[209]

4. Adrenocortical carcinoma

4.1. In patients with adrenocortical carcinoma (ACC), does treatment at a high volume multi-disciplinary center improve survival outcomes?

Recommendation 4.1. Yes, we recommend that patients with clinical and radiographic findings consistent with ACC should be treated at high volume multi-disciplinary centers to

improve recurrence outcomes; data on overall survival are inconclusive. (Strong recommendation, low quality evidence)

An extensive literature exists on surgical volume-outcome relationships, where higher hospital and surgeon volumes are both associated with better outcomes in diverse cancer types.[219-223] A similar volume-outcome relationship has been demonstrated in adrenal surgery, where higher surgeon volume is associated with lower complication rates, and higher hospital volume correlates with shorter length of stay.[165] Several definitions of a high-volume adrenal surgeon have been proposed, ranging from 4-7 annual adrenalectomies.[224-227] The American Association of Endocrine Surgeons requires a minimum of 10 adrenal operations for accreditation as a comprehensive Endocrine Surgeon.[228] These thresholds are low and should be considered as minimum volumes, with better outcomes anticipated with higher volumes. In ACC, complete surgical resection is essential for cure and therefore the volume-outcome relationship may be of particular significance.

In the United States, approximately half of patients with ACC are treated at community hospitals, and the majority of adrenal resections are performed by surgeons who do only one adrenalectomy annually.[41,165,229] Several retrospective studies have demonstrated no difference in overall survival based on hospital volume, however no prospective data exist. In one retrospective multi-institutional study of Italian hospitals, there was no significant survival difference between high volume centers (mean 0.8 ACC cases annually, 75th percentile) and low volume centers (mean 0.2 ACC cases annually).[230] A large retrospective study similarly demonstrated no survival benefit in patients undergoing surgery at a large tertiary cancer center.[231] In contrast, an older cohort from the same institution showed improved survival in patients who underwent index operation at the tertiary center.[232] Perhaps the strongest data come

from one large study of the NCDB database which showed no significant difference in survival at high volume centers (≥4 ACC annually, 90th percentile) in the US compared to low volume centers (HR: 0.89, 95% CI 0.70-1.12, p=0.53).[233]

In contrast to overall survival, surgery at a high-volume center may be associated with improved recurrence free survival. Lombardi et al found significantly longer time to recurrence (25.2 versus 10.1 months, p<0.001) in patients treated at high volume centers, although overall rates of recurrence were equivalent (6 vs 18.5%, p=non-significant).[230] Similarly, in the MD Anderson cohort, surgery at the cancer center was associated with reduced risk of local recurrence in both the recent cohort (HR: 0.603, 95% CI: 0.402, 0.902) and the historical cohort.[231,232] Of note, the majority of subjects in both cohorts (190/218 and 230/275) were referred to the cancer centerafter primary surgery at another institution, and therefore the study populations may have higher proportions of patients with recurrent disease.

In the absence of strong survival data, studies have shown a significant association between both surgeon and center volume and surgical performance metrics. High volume centers perform higher rates of radical resection,[230,233] lymph node dissection,[230,233] and open surgery,[233] consistent with more aggressive surgical treatment. Moreover, high volume adrenal surgeons exhibit lower intraoperative blood loss, shorter operative times, and lower complication rates, when compared to low volume surgeons operating on ACC patients.[165,234] Interestingly, the rate of positive margins following resection appears to be equivalent between high and low volume centers.[230,232,233]

While surgery is an essential therapeutic modality in ACC, multi-disciplinary care by definition encompasses all aspects of oncologic management. In stage 2 surgically treated ACC, prospective management at a specialized center is associated with improved survival despite

equivalent tumor pathology.[235] Of note, in 2 studies of the Dutch Adrenal Network there was a survival advantage for ACC patients who underwent surgery at a designated center despite the fact that no specific volume cut-off was required for specialized adrenal center status.[236,237] Although these 2 studies included overlapping patient populations and did not adjust for adjuvant therapy, this study supports the recommendation that specialized centers may provide advantages in multi-modality therapy even beyond higher surgical volume.

4.2. In ACC patients without evidence of distant metastatic disease at diagnosis, does operative technique affect survival?

Recommendation 4.2. Yes, regardless of operative approach, we recommend an *en bloc* radical resection with an intact capsule to microscopically negative (R0) margins because of improved survival. While open resection is preferred when ACC is suspected, the choice of operative approach should be determined based on the certainty of a complete R0 resection without tumor disruption. (Strong recommendation, low quality evidence)

ACC is a rare cancer, affecting 0.7-2.0 per million patients annually.[38] Survival outcomes are poor, and complete surgical resection is the only potential curative therapy.[238] Although randomized control data are lacking, in retrospective studies incomplete tumor resection (R1 or R2 margins) is associated with short overall survival.[41,239-244] Similarly, intraoperative tumor spillage and capsular rupture are risk factors for disease recurrence.[245,246] Given limited adjuvant therapies and the overall poor prognosis associated with recurrent ACC, complete resection to negative margins at the index operation is a key tenet of ACC management,[247,248] and surgical technique is highly scrutinized.[41,249] While radical surgery with *en bloc* resection and preservation of an intact tumor capsule is the standard of care for locoregionally invasive disease, the operative technique remains controversial and hinges on skill and experience.

Available data are entirely retrospective, consisting largely of single center studies with heterogeneous populations. In one single-institution study of 391 subjects (stage 1 to 4), an open surgical approach was independently correlated with improved overall survival (OS), but not progression free survival (PFS), when compared to laparoscopic resection.[238] Among studies specifically addressing stage 1 to 3 tumors, 9 reported no significant difference in OS or PFS based on surgical approach [250-258] while 2 showed benefit in OS and PFS with open surgery.[259,260] Of 2 studies which evaluated recurrent disease but not OS, one [261] demonstrated lower rates of recurrence with open surgery, and the second showed longer time to recurrence with open surgery despite similar rates of recurrence between laparoscopic and open approaches.[246] Stage-specific differences in OS and PFS between open and laparoscopic approaches were identified in 2 studies. A large analysis of the National Cancer Data Base (NCDB) data showed no OS difference in the total cohort, but in subgroup analysis of stage 2 patients, laparoscopic adrenalectomy was associated with worse 3-year OS (HR: 1.86, 95% CI: 1.02-3.38, p=0.04).[262] Moreover, one additional retrospective single institution study showed improved OS with open resection in stage 2 ACC, but not in stage 3 patients.[245]

Given the inherent limitations of retrospective data and the small size of most studies, several meta-analyses have been performed to quantify the effect of surgical approach on survival.[263-265] A sub-meta-analysis of European Network for the Study of Adrenal Tumors (ENSAT) stage 1 and 2 tumors found no differences in OS (pooled HR: 0.94, 95% CI: 0.42-2.10, p=0.87) or PFS (pooled HR: 0.85, 95% CI: 0.37-1.97, p=0.71) based on surgical technique.[263] The largest meta-analysis, including a total of 797 patients (from 9 separate cohorts) demonstrated no significant difference in disease-specific survival (OR: 0.68, 95% CI:0.44-1.05, p=0.08) or relative risk of recurrence (RR: 1.09, 95% CI:0.8-1.43, p=0.53) based on operative

approach.[265] However, a statistically significantly increased risk of developing peritoneal carcinomatosis after laparoscopic adrenalectomy was observed (RR 2.39, 95% CI 1.41-4.04, p=0.001).

Taken together, these data suggest that in subjects with stage 1-3 ACC, open surgery is not significantly associated with survival benefit but may be associated with a lower risk of recurrence. This risk may be related to tumor spillage or less complete resection.[245,246,253,265] Previous guidelines have recommended open adrenalectomy for tumors >6 cm in size.[248] Some authors have suggested laparoscopy may be safe in tumors up to 10 cm in experienced hands.[251] Review of the available literature does not support a distinct size cut-off. Therefore, our expert consensus is that excellent oncologic technique prioritizing complete resection of the tumor with an intact capsule should be the primary determinant of surgical approach. We recommend that open surgery be utilized for tumors with evidence of locoregional vascular or organ invasion, and for tumors where laparoscopy would jeopardize complete oncologic resection. For ACC confined to the adrenal gland and indeterminate lesions with a low suspicion for cancer based on imaging characteristics, laparoscopy may be considered based on surgeon skill and experience.

4.3. In ACC patients with systemic disease at diagnosis, does resection of the primary tumor improve survival?

Recommendation 4.3. Maybe. We suggest that patients with systemic disease be offered resection of the primary tumor if all sites of disease are reasonably amenable to resection or local treatment, and if performance status allows. Surgery may also be considered in patients with hormone excess medically refractory to steroidogenic inhibition. (Weak recommendation, low quality evidence).

Approximately 22% to 35% of patients with ACC have evidence of distant metastatic disease at initial presentation.[40,41] Advanced disease carries a poor prognosis. In patients with Stage 4 cancer, 5-year survival ranges from 6% to 13%, compared with 39% to50% in subjects with Stage 1-3 disease amenable to curative intent surgery.[38,41-43] Many patients who present with advanced disease may have no surgical option due to extent of disease. Cases with oligometastatic but potentially resectable ACC present a challenge to the clinician, as the benefits of primary resection and/or metastasectomy are incompletely understood.

Specific data on the benefit of surgery in metastatic ACC are limited, and no randomized control data exist. Most of the literature consists of retrospective cohort studies which are inherently limited by selection bias but may provide some clinical insight. One of the largest series is a multi-institutional study of 188 ACC patients, 95 of whom were Stage 3-4.[242] All patients underwent open surgical exploration, with 140 radical resections, 30 palliative resections, and 18 open biopsies alone. Both radical resection (median 5-year survival: 45%, $p<0.001$) and palliative resection (median 5-year survival: 4.5%, $p<0.005$) had a significant survival advantage compared to open biopsy (all patients deceased at 18 months). Similarly, in a recent multi-institutional retrospective propensity matched study of 339 patients with Stage 4 disease, patients who did not undergo cytoreductive surgery of the primary tumor had a significantly greater risk of death compared with those who underwent cytoreductive surgery (HR 3.18, 95% CI:2.34-4.32).[266] Although a significant selection bias must be assumed, these data are provocative.

As many published series are restricted to surgical patients, regional and national data sources have been utilized to capture non-operative cases. Population level studies suggest that surgery is increasingly utilized as an initial treatment strategy in Stage 3 and 4 disease.[267]

Analysis of the SEER database suggests that surgery is associated with a significant survival benefit in patients with Stage 3 and 4 ACC; however this study specifically excluded patients with distant metastatic disease.[268] Studies of insurance claims data suggest that the benefit of surgery may extend to patients with distant metastasis. Surgery alone (HR:0.52, 95% CI: 0.28-0.97, p=0.0394) and surgery combined with chemotherapy and/or radiotherapy (HR:0.31, 95% CI: 0.17-0.55, p<0.001) demonstrate a significant survival benefit compared to no therapy for metastatic ACC.[269] In contrast, chemotherapy/radiotherapy did not confer a survival benefit (HR: 0.65, 95% CI: 0.40-1.07, p=0.0928).

Resection may also contribute to improved pain control and relief of symptoms related to hormonally functional tumors.[270] However, medical management of functional tumors continues to improve. Inhibitors of steroidogenesis such as metyrapone, ketoconazole, and the recently approved oral cytochrome P450 11B1 inhibitor Osilodrostat as well as the glucocorticoid antagonist mifepristone, may be used in conjunction with mitotane or combination chemotherapy.[271-275] The expanding medical options have narrowed the indications for palliative surgery purely for hormonal control.

Although data are lacking, 2 additional important considerations in advanced disease are disease kinetics or trajectory, and overall burden of disease. While isolated recurrences after a long disease free interval, or low burden metastases may be amenable to surgical cure,[270,276,277] rapidly progressive, large volume, or multifocal disease should be considered a relative contraindication to surgery. Careful patient selection and clinical judgement should be integrated with the patient's goals of care. Based on these data, we suggest an aggressive surgical approach be utilized in subjects where all sites of disease may be amenable to complete resection and the patients' performance status allows. Debulking surgery may occasionally be considered for

palliation in hormonally active ACC in select patients who are refractory to steroidogenic inhibition. Aggressive surgery should not be pursued in unresectable, rapidly progressive, or multi-organ synchronous ACC.

4.4. In patients with advanced ACC, what is the role of neoadjuvant therapy followed by resection versus surgery with or without adjuvant therapy?

Recommendation 4.4. We recommend that neoadjuvant systemic therapy be administered for advanced ACC when R0 surgical resection is not initially feasible. We recommend up front surgical intervention when R0 resection is possible. (Strong recommendation, low quality evidence)

Neoadjuvant therapy plays an increasing role in multi-modality oncologic therapy. Neoadjuvant may be indicated to facilitate surgical resection by tumor down-sizing in Stage 3 disease, to select for treatment response in Stage 4, and to treat systemic micro-metastatic disease. Only the first of these indications is relevant in ACC, where treatment response is assumed to be poor, and the focus is on macroscopic disease. In ACC, the goal of systemic neoadjuvant therapy is therefore primarily to reduce the burden of disease to facilitate later potential complete resection. Few studies have directly examined the use of neoadjuvant chemotherapy [278,279] and none address neoadjuvant radiation in ACC. Therefore, the rationale for neoadjuvant treatment is extrapolated from the data on adjuvant therapy.

Mitotane is the most commonly utilized adjuvant chemotherapeutic agent in ACC. The data regarding survival benefit are conflicting. Several retrospective studies showed no difference in survival outcomes with mitotane.[280-284] Significantly better recurrence free survival (RFS) but not OS was observed in 4 studies,[232,238,243,285] while significantly worse RFS but not OS was shown in one investigation.[286] One study demonstrated both shorter RFS and OS with

mitotane administration.[284] Perhaps the most cited investigation is that of Terzolo et al, in which outcomes in Italian patients treated with radical resection and adjuvant mitotane were compared to two control groups of Italian and German subjects treated with radical resection alone.[287] In this large multi-institutional case-control study, adjuvant mitotane was associated with statistically significant improvement in both RFS (42 months versus 10 months and 25 months for controls) and OS (110 months vs 52 months and 67 months for control groups). Although this study has been criticized for the relatively high rates of recurrence in the two comparison cohorts, suggesting a potential bias, it represents one of the few multi-institutional studies and the only externally- controlled investigation. In the most recent international treatment guidelines for ACC, adjuvant mitotane is recommended after surgical resection of tumors with high risk of recurrence.[288]

Adjuvant radiotherapy may play a role in local tumor control or palliation of metastatic disease.[289] Data here are again retrospective and conflicting. In the modern era of stereotactic radiation, 2 studies have shown improved local recurrence with adjuvant radiation,[290,291] while one showed no statistically significant difference.[292] In patients with positive margins, adjuvant radiation decreases risk of death.[293] Interestingly, in a propensity-matched analysis of 78 patients, adjuvant radiation was associated with both improved local recurrence as well as longer RFS and OS.[294] One possible explanation for this observation is that radiation eradicates microscopic disease with metastatic potential. Alternatively, this may reflect selection bias in the treatment cohort. There is no role for neoadjuvant radiotherapy for potentially resectable ACC. Considered standard of care in unresectable ACC, combination chemotherapy with etoposide, doxorubicin and cisplatin combined with mitotane is associated with longer progression-free, albeit not overall survival.[295] Moreover, while combination radio- and chemotherapy is

increasingly considered in challenging cases of unresectable ACC, [296] the benefit of cytotoxic chemotherapy in the adjuvant setting is unknown and is currently being evaluated in the randomized A5 (American Australian, Asian Adrenal Alliance) sponsored trial.[297,298]

Emerging targeted therapies, most notably tyrosine kinase inhibitors (TKIs), have demonstrated limited promise in advanced ACC. However, a subset of patients with advanced ACC demonstrate durable response to therapy with inhibition of insulin-like growth factor receptor 1 (IGF1R).[299-301] Cabozantinib, a multi-TKI, also shows some limited promise and is under clinical investigation in locally advanced and metastatic ACC.[302,303] Phase 2 trials of pembrolizumab and nivolumab also indicate that a subset of ACC may respond to PD-1 blockade. While efficacy does not appear to correlate solely with microsatellite-high and mismatch repair deficient tumors, studies are ongoing in ACC to further explore single and combination therapy utilizing immune checkpoint inhibitors with and without glucocorticoid receptor inhibition.[304-308] While such targeted therapies have yet to be evaluated in the neoadjuvant setting, it is becoming increasingly apparent that subsets of ACC with different clinical behaviors are driven by unique genetic events. Understanding the vulnerabilities of these genetic variants is emerging as a critical next step in selecting the right systemic therapeutic strategy for each patient.[309-311]

While neoadjuvant therapy to facilitate surgical resection has not been systemically evaluated, for patients with no surgical option, neoadjuvant therapy may segue into definitive surgical treatment without delay. For advanced ACC, we therefore recommend assessment at a multi-disciplinary center for consideration of potential neoadjuvant therapy in unresectable or borderline resectable ACC.

5. Metastases to the Adrenal Gland

5.1. In patients with an adrenal mass, does history of an extra-adrenal malignancy influence the hormonal evaluation?

Recommendation 5.1. Yes, we recommend that a directed hormonal evaluation should be performed in patients with an adrenal mass regardless of history of extra-adrenal malignancy. (Strong recommendation, low quality evidence)

Adrenal metastasis may have imaging features that make them potentially indistinguishable from other pathologies, including adrenal cortical carcinoma, pheochromocytoma, and lipid-poor cortical adenoma. All of these pathologies may have high non-enhanced density and poor washout on CT, absent chemical shift with MRI, and increased standard uptake values on FDG-PET.[312] Functional evaluation is imperative prior to biopsy, ablation, or resection and should aim to exclude excess catecholamine production (pheochromocytoma) and autonomous glucocorticoid production (cortisol producing adrenal cortical carcinoma or lipid-poor adenoma). Resection or biopsy of an adrenal mass without the knowledge of functionality may result in unnecessary morbidity. If the patient has a history of hypertension, evaluation should also aim to exclude primary aldosteronism as approximately 4% of adrenal cortical carcinomas may secrete aldosterone.[313] The minimum evaluation should include either plasma metanephrine or 24-hour urine catecholamines/metanephrine and 1-mg dexamethasone suppression test. Further evaluation, including that for primary aldosteronism, may be guided by the presenting features and clinical scenario. In the circumstance of bilateral adrenal metastasis, adrenal insufficiency should be considered. In a single institution retrospective study analyzing 579 patients with adrenal metastasis, bilateral adrenal metastases were initially found in 24% of patients and ultimately progressed to 43% throughout the study course.[314] Adrenal insufficiency occurred in 12% of patients with bilateral adrenal metastases.

5.2. In a patient with a history of an extra-adrenal malignancy and an adrenal mass, when is image-guided needle biopsy recommended?

Recommendation 5.2. We suggest that in the setting of a radiographically indeterminate mass, image-guided biopsy be reserved for patients in whom results would change overall disease management and be performed only after confirming lack of hormone excess. (Strong recommendation, low quality evidence)

The literature examining image-guided adrenal biopsy includes retrospective studies focused on safety and efficacy with regard to diagnosis. No study evaluates whether image-guided biopsy alters outcomes when compared to resection without preceding needle biopsy. It is also unclear whether needle biopsy results in a change of management. However, image-guided adrenal biopsy may be performed in select patients with suspicion of adrenal metastasis with relatively low morbidity and high diagnostic sensitivity and specificity once hormonal workup has been completed to rule out catecholamine excess. A systematic review of the literature and meta-analysis regarding the diagnostic performance of adrenal biopsy, including 689 metastatic adrenal glands, found that biopsy for adrenal metastasis was 87% sensitive and 96% specific.[315] The non-diagnostic rate of adrenal biopsy among all pathologies is 8%. Morbidity rate, including pooled data of all pathologies not limited to metastasis, was 2.5%. Although infrequent, the most common complications described were adrenal hematoma, pancreatitis, and pneumothorax. Of 689 adrenal metastases biopsied, only one event of needle track seeding was reported in a patient with metastatic bronchogenic carcinoma after biopsy via a trans-hepatic

approach.[316] A more current study retrospectively analyzing image-guided adrenal biopsy in 418 patients demonstrated a morbidity rate of 4%.[317]

Image-guided needle biopsy of an indeterminate adrenal mass in the setting of non-adrenal primary malignancy should only be performed if the results are likely to impact the management plan, and only following exclusion of catecholamine excess to avoid morbidity. In a single center study examining image-guided biopsy in 418 patients with extra-adrenal malignancy, only 28% of these had pre-biopsy hormonal evaluation to exclude pheochromocytoma.[317] Two percent of all biopsies were unexpected pheochromocytoma. If the indeterminate adrenal mass is the only site of potential metastatic disease and appears resectable in an otherwise fit operative candidate, surgical resection rather than biopsy may be considered for both diagnostic purposes and potential therapeutic benefit. If the adrenal mass is not amenable to resection or if the patient is not a good surgical candidate, for any number of reasons, image-guided biopsy may be considered to help guide further non-surgical therapy. Diagnosis of secondary adrenal lymphoma or more rarely, primary adrenal lymphoma may be made with the use of image guided biopsy, although the diagnosis my be made based on imaging features and presenting symptoms. [318]

5.3. In patients with an adrenal metastasis, does resection improve survival compared to systemic therapy alone?

Recommendation 5.3. Maybe. We suggest that after multidisciplinary review, resection may be offered to highly selected patients to improve survival compared to systemic therapy alone. (Weak recommendation, low quality evidence)

Adrenal metastasis commonly occurs in patients with malignancy from the lung, kidney, breast, melanoma, and colon, but may occur from many other primary sites.[319] Adrenal metastasectomy may be performed in an open or minimally invasive fashion. Laparoscopic resection of an adrenal metastasis, when performed on a highly selected basis, results in similar oncologic outcomes to open resection.[320-322] Long-term survival following resection of an isolated adrenal metastasis in selected patients has been demonstrated in multiple series. In a retrospective study of patients with adrenal metastasectomy in the setting of metastatic renal cell carcinoma, long-term disease-free survival was demonstrated in 10 of 45 patients (mean 83 months) following resection of isolated adrenal disease.[323] In a recent multi-center study including 106 patients with adrenal metastasectomy, including multiple pathologies, prognostic factors negatively affecting survival were identified to be larger tumor size and synchronous occurrence.[324] In a separate cohort from a single center including 62 patients, shorter survival was associated with lung primary, short disease-free interval, and synchronous metastasis.[325] Notably, oligometastatic disease was not a predictor of shorter survival in this study. A more recent series, including 174 patients, specifically compared oligometastatic versus isolated adrenal disease for a variety of cancers with metastatic adrenal lesions and found that oligometastatic disease has a median survival of 3.3 years for patients with concomitant extra-adrenal metastases and 3.0 years for patients with isolated adrenal metastasis; $P = 0.816$.[326] Factors negatively associated with overall survival included adrenal tumor size ($P < 0.01$), renal primary versus other ($P < 0.01$), and adrenal resection margin status ($P < 0.01$). Showing that in selected patients undergoing adrenal metastasectomy, there were no significant differences in overall survival between patients with and without concomitant extra-adrenal metastasis.

While existing data demonstrate cohorts of highly selected patients with long-term survival following adrenal metastasectomy and highlight both negative and positive prognostic indicators, the literature regarding the comparative oncologic efficacy of resection of adrenal metastasis when compared to systemic therapy alone are extremely limited and are hindered by small sample size, retrospective study design, heterogenous patient groups, and selection bias. However, limited data regarding adrenalectomy for metastasis from specific primary malignant sites have shown improved survival favoring resection compared to best systemic therapy alone. In one study, isolated adrenal metastasis was found in 14 patients with non-small cell lung cancer, in which eight patients had resection after chemotherapy, and six received chemotherapy alone.[327] Median survival in the surgical group was significantly greater than that in the chemotherapy alone group (31 versus 8.5 months; $p = 0.03$). All patients in the chemotherapy alone group died by 22 months, while three-year survival in the surgical group was 38%. This has led to the extrapolation to other malignant pathologies allowing for the consideration of resection of isolated adrenal metastasis.

Currently there are no established criteria guiding patient selection for adrenal metastasectomy. Consideration should be given to disease pathology, synchronous vs metachronous, disease free interval, and tumor size to help select appropriate surgical candidates. Given the paucity of data and the complexity of the patient population, an individualized management plan after careful consideration by an expert multidisciplinary team is highly recommended where considerations may also be given to other non-surgical therapies. Resection may also be more difficult due to reaction from systemic treatment.

6. Pheochromocytoma and paraganglioma (PPGL)

6.1. In patients with pheochromocytoma/paraganglioma, how does selective alpha blockade affect perioperative hemodynamic stability when compared to non-selective blockade with phenoxybenzamine?

Recommendation 6.1. We recommend either selective or non-selective alpha blockade to safely prepare patients for surgical resection of pheochromocytoma and paraganglioma, depending on the drug availability/cost, experience, and preference of the care team. While there is no significant difference in morbidity or mortality between selective and non-selective alpha blockade, selective blockade (doxazosin, prazosin, terazosin) is associated with more intraoperative hemodynamic instability while non-selective blockade (phenoxybenzamine) results in more postoperative hypotension. (Strong recommendation, moderate quality evidence)

As recommended in the Endocrine Society Clinic Practice Guideline for PPGL, initial biochemical testing for PPGLs should include measurements of plasma free metanephrines or urinary fractionated metanephrines.[328,329] Given the sporadic release of catecholamines from PPGLs, measurement of catecholamines alone can miss the diagnosis. The metabolites of catecholamines (metanephrines) are more sensitive than catecholamines in the diagnosis of a functional PPGL.[328] Metanephrines and normetanephrines levels are typically greater than 2 to 3 times the upper limit of normal in functional PPGLs. It is important to realize that false positive results are relatively common (10-20% of tests) and most often due to interfering medications, which are discussed in detail in the Endocrine Society Guideline.[328] Measurement of methoxytyramine (metabolite of dopamine) should also be considered in patients with germline pathogenic variants in succinate dehydrogenase genes (SDHx) to diagnose dopamine-secreting tumors.

Following the diagnosis of a functional PCC or paraganglioma (PGL), preoperative blockade for at least 7 days is routinely recommended to prevent perioperative hemodynamic instability (HDI), although not causal to mortality, Endocrine Society Clinic Practice Guidelines suggest the use of alpha blockade.[328] Traditionally, phenoxybenzamine, a non-selective alpha blocking agent, has been used for perioperative blockade. However, given the significant difficulty in acquisition of phenoxybenzamine (cost, insurance coverage, availability) as well as undesirable side effects such as nasal stuffiness and postural hypotension, many providers have transitioned to use of more easily accessible and better tolerated selective alpha blockade (doxazosin, prazosin, terazosin). A recent publication highlighted the international practice in preoperative blockade using data from 2000 to 2017 at 21 international centers (total of 1860 patients).[330] Most centers used alpha blockade (1517 patients) versus 343 patients who did not receive preoperative blockade (more than two thirds of those not receiving blockade were from a single center). Of those using alpha blockade, 76% used phenoxybenzamine over other alpha blockers, however it should be noted that phenoxybenzamine is generally more widely available internationally.

Multiple small, retrospective studies have shown efficacy and safety (no increased morbidity or mortality) of perioperative blockade with selective alpha blockade when compared to phenoxybenzamine.[331,332,333,334] However, the majority of studies show a trend toward higher preoperative and peak intraoperative systolic blood pressures (i.e. more intraoperative HDI) with selective blockade (i.e. doxazosin) and more postoperative hypotension (i.e. more postoperative HDI) with non-selective blockade (phenoxybenzamine). One randomized controlled clinical trial involving 134 patients (66 phenoxybenzamine, 68 doxazosin) showed that blockade with phenoxybenzamine was more effective in preventing intraoperative HDI, required less

vasodilating drugs, and resulted in lower frequency and duration of SBP >160. However, the duration of time outside of the study's target SBP range (<60 or >160), morbidity and mortality were not different between the two groups.[335]

Based on the data available, both nonselective and selective alpha blockade can be used safely in the surgical preparation of PPGL. The risks and benefits of each option must be considered by the surgical team. Choice of blockade will be affected by multiple institution- and patient-specific factors including drug availability, experience of the anesthesia team, experience of the surgeon, and tolerance of intraoperative versus postoperative HDI. For example, a very experienced anesthesia team may be better prepared to deal with intraoperative HDI and hypertension, making selective blockade a better option due to easier availability, less postoperative hypotension and potentially shorter hospital stay. On the other hand, some teams may choose the benefit of less intraoperative instability with phenoxybenzamine accepting an increased difficulty and higher likelihood of transient postoperative hypotension that could potentially lengthen the post anesthesia care unit or hospital stay.

Some centers advocate for the use of calcium channel blockade (CCB) for preoperative preparation. Two small retrospective studies have attempted to compare the use of CCB to alpha blockade; however, the studies were small with unequal comparison groups.[336,337] In the study by Brunaud, et al. a total of 155 patients were retrospectively reviewed.[337] The majority (71%) were blocked with CCB (all patients in France), with only 26% undergoing alpha blockade (all patients in New York). No difference was noted in HDI between the groups. However, the alpha blockade group experienced less severe systolic elevations (>200), shorter duration of systolic pressure >160 and lower maximum systolic, diastolic and mean pressures. At this time, there are not overwhelming data to support the use of calcium channel blockers as routine first-line

treatment for PPGL. However, CCB may be considered in certain circumstances such as when alpha blockade is not tolerated, the patient is normotensive, or when additional medication is needed to achieve blood pressure control preoperatively, such as in large tumors or in the presence of metastatic disease. In these cases, use of CCB may help prevent toxicity from large doses of alpha blockade.

Some select high-volume adrenal centers advocate for surgical treatment of PPGL in the absence of pre-operative blockade, instead relying on the experience of the anesthesia team and short-acting vasoactive medications to maintain hemodynamic parameters. Groeben et al. report their experience with 276 patients: 110 undergoing alpha blockade (89% phenoxybenzamine) and 166 without blockade. They noted a significant increase in maximal systolic arterial pressure in the no-blockade group but no difference in SBP >250 between the groups.[338] While these data show no difference in morbidity and mortality, the treatment of these vasoactive tumors in the absence of preoperative blockade is not recommended outside of very high-volume, experienced centers.

6.2. In patients with bilateral pheochromocytomas (usually with genetic mutation), what is the impact of cortical sparing adrenalectomy compared to bilateral total adrenalectomy on steroid dependence and disease recurrence?

Recommendation 6.2. Because of the decreased rate of steroid dependence, we recommend consideration of cortical-sparing adrenalectomy in patients with bilateral pheochromocytomas if technically feasible. However, patient goals of care and a higher risk of recurrent pheochromocytoma should also be considered. (Strong recommendation, low quality evidence)

PCC and PGL have the highest heritability of all tumors, with approximately 40% due to germline mutations.[339,340] New causative mutations are being discovered almost yearly, so the percent of PPGLs due to germline mutations is sure to increase. Genetic testing is now recommended for all patients with PCC and PGL.[328,329] Almost 20% of sporadic PCCs (no family history) are found to have a germline mutation. Diagnosis of a germline mutation allows for evaluation of associated neoplasms and disease, stratification for risk of malignancy and recurrence, earlier diagnosis in related family members, and adjustment of treatment strategy, including surgical plan and follow-up strategy. For example, MEN2A patients should undergo evaluation for associated diseases like primary hyperparathyroidism and medullary thyroid cancer and be counselled on the indications for prophylactic or therapeutic thyroidectomy. SDHB mutations carry a 40% risk of metastases, which alters evaluation, surgical treatment, and follow-up. The risk of recurrence is higher in familial PPGL (33% vs. 13% non-familial), which can affect preoperative patient counseling and surgical decision making (i.e. consideration to not perform cortical preservation because of the risk of leaving cells of chromaffin origin -which have malignant potential). Given the autosomal dominant heritability of these mutations, first degree family members should be encouraged to undergo genetic counseling and testing.

Given the high incidence of germline mutations in patients with PPGLs, surgeons must consider the potential ramifications of a genetic diagnosis on surgical decision making. The 2013 North American Neuroendocrine Tumor Society (NANETS) consensus guidelines for management and treatment of neuroendocrine tumors recommend consideration for cortical-sparing adrenalectomy if familial or bilateral disease is present.[329] Therefore, many groups advocate for obtaining the results of genetic testing prior to surgical decision-making in any patient presenting with PCC. Cortical-sparing adrenalectomy has been successfully used to

preserve adrenal cortical tissue in patients requiring surgery for bilateral PCCs, preventing lifelong adrenal insufficiency and steroid dependency. Brauckhoff et al reported that approximately 30% of one gland or 15% of both glands must be preserved in order to maintain sufficient cortical function.[341] While it is not necessary to preserve the adrenal vein,[342] it is important to try to avoid disruption of tissues surrounding the remnant in order to preserve as much collateral blood supply and drainage as possible.

While studies are small and comparison groups are diverse, multiple studies report steroid dependency rates between 9% to 30% with recurrence rates between 9% to 30% in most series.[343,344,345,346] In a large retrospective review of 625 patients with bilateral PCCs from 45 centers across 19 countries, Neumann, et al, reported that 248 (76.5%) patients underwent cortical-sparing adrenalectomy with a reported steroid dependency rate of 30.6% and a recurrence rate of 13%.[344] Grubbs et al reported the largest single-center review over almost 5 decades including 96 patients, 39 of whom underwent cortical-sparing surgery. They reported that steroid dependency after cortical sparing surgery was 22% with a recurrence rate of 7% (compared to 3% after total bilateral adrenalectomy).[343] Median time to recurrence was 8.5 years (4.9-18.7 years) after cortical sparing adrenalectomy and 11 years (3.3-13.3 years) after total adrenalectomy.[343] Alesina et al reported their experience of cortical-sparing adrenalectomy in 66 patients with bilateral PCC over a 15-year period with a steroid dependency rate of 9% and no recurrences during a relatively short 48 month follow up period.[346]

While there are benefits to cortical-sparing adrenalectomy, one must consider the increased technical difficulty, feasibility of the technique based on tumor anatomy, surgeon experience and risk of recurrence in the adrenal remnant that could necessitate a re-operative adrenalectomy. Unilateral cortical preservation can be performed and viability assessed prior to

proceeding with contralateral total adrenalectomy. Ideally, cortical preservation should be unilateral. Both the size of the lesion and its location within the gland affect the technical feasibility of successful cortical-sparing adrenalectomy. A large and/or centrally-located tumor makes it difficult to successfully preserve sufficient cortex, whereas a smaller tumor located at one end of the gland is better suited for a cortical sparing technique. Surgeon experience is also a major factor in decision-making strategies. The cortical-sparing technique requires significant familiarity and experience with adrenal anatomy and adrenalectomy. It is important to remember that the primary goal is complete resection of the PCC. Therefore, if an attempt at cortical sparing adrenalectomy increases concern for tumor disruption or incomplete resection, a cortical-sparing adrenalectomy may not be appropriate. Like other areas in endocrine surgery, shared decision-making with the patient is important. After thorough discussion of the pros and cons of operative technique, many patients may prefer the chance of steroid independence with cortical-sparing adrenalectomy understanding the possible need for future surgery in the setting of recurrence, while others may accept the outcome of permanent adrenal insufficiency associated with bilateral total adrenalectomy in favor of lower recurrence rate and potentially fewer surgeries. Candidates for cortical-sparing adrenalectomy should be referred at the time of bilateral PCC diagnosis to a high-volume center where a multidisciplinary team can make appropriate recommendations based on each patient's unique set of circumstances.

While consideration of a cortical-sparing adrenalectomy is recommended in patients presenting with bilateral PCCs, there is debate amongst experts about the management of an initial unilateral PCC in patients with a known germline mutation. Future PCC may occur in either the ipsilateral remnant or contralateral gland. Recurrence in the remnant adrenal gland after cortical-sparing adrenalectomy would necessitate a re-operative completion adrenalectomy,

whereas contralateral recurrence could be managed by either total or cortical-sparing adrenalectomy. Patients with a germline mutation and unilateral PCC may benefit from referral to a high-volume adrenal center to discuss the pros and cons of an initial cortical-sparing versus unilateral complete adrenalectomy.

6.3. In patients with metastatic pheochromocytoma and paraganglioma, does surgical resection of primary disease improve survival compared to non-surgical treatment?

Recommendation 6.3. Yes, we suggest that in selected cases of metastatic pheochromocytoma and paraganglioma, resection of the primary tumor may be performed to improve overall survival. Patients should be carefully evaluated by a multidisciplinary care team to determine if the benefits of resection of the primary tumor outweigh the risks. (Weak recommendation, low quality evidence)

Approximately 2-25% of PCCs are metastatic as compared to 2% to 60% of PGLs, [347,348] and the management of metastatic PPGL is challenging. Not only is there concern for tumor burden and its effect on survival, but one must consider the effect of excess hormone production on symptom control and quality of life as well as consequences of local growth of an unresected primary tumor.

Several studies suggest a survival benefit associated with resection of the primary tumor in metastatic PPGL. One retrospective study over 5 decades reviewed 272 cases of metastatic PPGL and noted worse outcome with male sex, older age, metastases, larger size, dopamine production and lack of primary tumor resection.[349] A review of 113 patients (89 underwent surgery, 24 did not) by Roman-Gonzalez et al also showed a longer median overall survival in those who underwent surgery (148 vs 36 months).[350] Wu et al published a retrospective SEER

database review of 226 patient with metastatic PPGL (99 patients with PCC and 127 with PGL) just over half undergoing surgery. Survival was improved in the surgery group for PCC patients; however, there was no survival benefit for PGL patients (other than in cases of disease originating from aortic or carotid body tumors).[351]

In order to address the concern for bias, Roman-Gonzalez et al evaluated a cohort of 53 patients presenting with synchronous metastatic disease (33 underwent surgery, 20 did not) and matched patients for performance status, age, sex, primary tumor size and tumor burden. Even when controlling for each of these factors, a statistically significant survival benefit was still noted in those undergoing surgery for the primary tumor compared to those who did not[350] suggesting that resection of the primary tumor may be beneficial even in the setting of risk factors associated with worse outcome.

In addition to a potential survival benefit, other factors may favor resection of the primary tumor. While no significant data exist, decreasing overall tumor burden is anecdotally noted to decrease the symptoms of catecholamine excess and may also decrease the required doses of controlling medications, thereby decreasing medication side effects. Finally, there may be improved response to systemic radiotherapeutic treatment with lower tumor burden. The 2021 NANETS consensus guidelines for management of metastatic PPC and PGL recommend resection of the primary tumor in metastatic PPGL if the tumor is secreting, if resection may prevent local anatomic complications or if systemic therapy is an option (to help decrease tumor burden).[71]

More data are needed before these potential positive effects of surgery can be evaluated and validated. Given the rare nature of metastatic PPGL, all available studies are retrospective,

cover many decades and involve multiple variables with inherent bias. While there are potential benefits of surgery, one must also consider the extent of metastatic disease, the patient's functional status (i.e. ability to tolerate surgery), and the feasibility and associated morbidity of the surgery needed to resect the primary tumor. Therefore, patient care should be individualized, and treatment decisions should be managed by multidisciplinary teams at high-volume centers when possible.

7. Technical Aspects

7.1. In patients undergoing adrenalectomy what is the benefit of minimally invasive surgery compared to open surgery on perioperative outcomes?

Recommendation 7.1. When patient and tumor characteristics are appropriate, we recommend minimally invasive adrenalectomy over open adrenalectomy due to improved peri-operative morbidity. (Strong recommendation, low quality evidence)

Adrenal resections may be technically accomplished using either open or minimally invasive techniques via one of several approaches. Minimally invasive adrenalectomy via transabdominal and laparoscopic approach was introduced in the early 1990s [352,353] and has since become accepted as the gold-standard approach for most small benign adrenal pathology. This conversion was driven by observations such as decreased pain, shorter hospitalizations, and more rapid recovery with minimally invasive approaches. [354,355] Given the agreed upon benefits of minimally invasive adrenalectomy for appropriate adrenal resections, there have been no prospective randomized trials comparing laparoscopic to open adrenalectomy and it is unlikely that these will occur.

Lee et al utilized VA NSQIP records from 2001-2004 that included 358 laparoscopic and 311 open adrenalectomies for all indications.[356] Elfenbein et al examined NSQIP data in the subsequent period from 2005-10 during which NSQIP expanded to a broader set of hospitals beyond the VA system. This analysis included 2456 laparoscopic and 644 open adrenalectomies for all indications.[357] In the earlier study 54% of the cases were performed laparoscopically which increased to 79% in the later time period. This shift reflects the progressive adoption of laparoscopic adrenalectomy in the first decade of the 2000s.

Lee et al found that laparoscopic adrenalectomy compared to open adrenalectomy had shorter operative time (1.8 vs 3.9 hours), shorter hospital length of stay (4.1 vs 9.4 days), and lower morbidity rate (3.6% vs 17.4%) with all $p<.0001$. Elfenbein et al similarly found that laparoscopic adrenalectomy compared to open adrenalectomy had shorter length of stay (2 vs 5 days) and lower morbidity rate (6.4% vs 18.8%) with both $p<.01$. A weakness of both studies is the absence of disease specific variables such as detailed endocrine functional status.[356,357]

For patients undergoing unilateral adrenalectomy for pheochromocytoma a single institution retrospective study compared 49 open resections to 52 laparoscopic resections. They observed no appreciable difference in intraoperative hemodynamic parameters, but shorter ICU stay, hospital stay, less blood loss, and less post-operative pain (all $p<.01$).[358] In patients with non-malignant ACTH-dependent or -independent Cushing's syndrome, laparoscopic adrenalectomy has similarly been observed to be associated with shorter hospitalizations, less blood loss, and lower morbidity rates than open adrenalectomy.[359] Minimally invasive versus open adrenalectomy for adrenocortical carcinoma, and for metastasis to the adrenal from extra-

adrenal primary malignancy, are addressed in separate sections of these guidelines (see Section 4 and 5).

7.2. In patients who are appropriate candidates for minimally invasive adrenalectomy, does a retroperitoneal compared to a transperitoneal approach change perioperative outcomes?

Recommendation 7.2. No, we recommend either a retroperitoneal or transperitoneal approach because of similar peri-operative outcomes. The choice of approach should be determined by surgeon expertise and guided by tumor and patient characteristics. (Strong recommendation, moderate quality evidence).

The efficacy and morbidity of laparoscopic transperitoneal (LTA) versus posterior retroperitoneal adrenalectomy (PRA) have been investigated in 3 randomized and 12 retrospective studies. [360-378] Kozlowski et al randomized patients with tumors < 8 cm to LTA (n=33) and PRA (n=44) approach. Both were equally safe and effective, while the PRA group had a lower intensity of overall pain at 24 hours (3.4 ± 1 vs 4.2 ± 1, , $p<0.05$), lower prevalence of shoulder pain (2.3% vs 30.3%, $p<0.05$) and shorter hospital stay (1.14 ± 0.4 days vs 1.36 ± 0.5 days, $p<0.05$).[367] Barczynski et al randomized 65 patients, of whom 61 completed 5 years of follow up (PRA 30, LTA 31). Although both approaches had a similar safety profile, PRA was associated with shorter operative time (50.8 vs 77.3 minutes, $p<0.01$), less blood loss (52.7 vs 97.8 mL, $p<0.01$), less postoperative pain at 48 hours (6.63 vs 21.21 VAS, $p<0.01$), shorter hospital stay (2.94 vs 4.44 days, $p<0.001$), lower cost (1728 vs 2315 Euros, $p<0.001$) and lower incidence of incisional hernia (0% vs 16.1%,$p=0.022$). The study excluded tumors > 7 cm, history of major abdominal surgery and suspected malignancy. [361] Chai et al randomized 42 patients to LTA and 41 to PRA. Inclusion criteria included unilateral tumors < 7 cm (<5 cm in case of pheochromocytoma) and BMI < 35. They found both LTA and PRA approaches to be

safe and have similar operative time (59.7 vs 67.6 minutes, p=0.139), postoperative pain (3.6 vs 3.3 VAS on postoperative day 1, p=0.225) and length of hospital stay (2.2 vs 2.2 days, p=0.780).[363] The findings of the 12 retrospective studies comparing LTA and PRA were consistent with the 3 randomized studies.

In addition to tumor size, a number of retrospective studies have found anthropometric measurements which affect the success of PRA, [369,379] specifically perirenal fat thickness, distance from skin to Gerota's fascia, and posterior adiposity index (PAI, the sum of both). In a retrospective study of 56 patients, smaller tumors and PAI < 9 were associated with shorter operative times in PRA.

There is minimal published data regarding the frequency of capsular disruption for different technical approaches to adrenalectomy. A recent study based on Collaborative Endocrine Surgery Quality Improvement Program (CESQIP) data which represented surgeon self-reported data reported a higher rate of gross capsular disruption after PRA versus LTA.[371] In contrast, a single center study reported no cases of gross capsular disruption and <1% rate of microscopic capsular disruption in 112 PRA cases.[380] Another single center series comparing two techniques of PRA similarly reported no cases of gross capsular disruption in 130 cases.[381] While available data are limited, this suggests that surgeon technique may be more important to lesion integrity than choice of surgical approach.

Overall, both LTA and PRA are effective and safe approaches for removing adrenal tumors. Due to small working space in PRA, LTA should be considered in patients with large tumors. In patients with smaller tumors, either approach may be considered, although 2 of 3 randomized studies suggest less pain and faster recovery following PRA. In patients with extensive abdominal surgical history and/or bilateral tumors, PRA offers advantages in avoiding

scarring and extra time for repositioning. When choosing patients for PRA, anthropometric parameters should be reviewed. PRA may be more challenging in patients with increased perirenal fat and increased distance from skin to Gerota's fascia.

7.3. For surgeons performing adrenal surgery, does surgeon volume influence morbidity, and mortality?

Recommendation 7.3. Yes, we recommend that adrenalectomy be preferentially performed by a high-volume adrenal surgeon to optimize outcomes including lower rates of morbidity and mortality. (Strong recommendation, moderate quality evidence)

Surgeons performing adrenalectomy in the US and England have a median annual volume of 1 adrenalectomy per year, [225,382] and 83% of adrenalectomies performed in the US are performed by surgeons who average ≤5 adrenalectomies per year.[225] While mortality is infrequent following adrenalectomy (0.5 - 2%) postoperative complications are observed in 11-20% of cases. [165,224,225,383]

Due to the nature of the question available analyses that examine the relationship of surgeon or center volume of adrenal surgery to outcomes are limited to retrospective reviews. Several studies have used state or nation level datasets to explore the nature of the volume / outcome relationship in adrenal surgery.

Anderson et al utilized data from the National Inpatient Sample to evaluate the association of surgeon volume of adrenalectomy and patient outcomes for 6712 adrenalectomies. Of the 3496 surgeons included, annual adrenalectomy surgeon volume ranged from 1 to 70. After multivariate risk adjustment they demonstrated a decreasing likelihood of patients experiencing any postoperative complication with increasing surgeon volume ($p = 0.005$). Patients undergoing adrenalectomy by high-volume surgeons (defined as ≥ 6 adrenalectomies

per year) experienced lower rates of respiratory, urologic, or any complication (all p <0.008). They also had lower likelihood of in-hospital mortality (0.6% vs 2.4%), decreased cost of care, and shorter hospital stay (all p <0.005). [225]

Park et al evaluated 3144 patients undergoing adrenalectomy examining both hospital volume and surgeon volume. In this study, a low volume threshold of <4 adrenalectomies / year (the bottom quartile in this cohort) was associated with a greater overall risk of complication (OR 1.5, p = 0.002), but no association was seen between hospital adrenalectomy volume and patient complications suggesting that surgeon volume had a greater impact on patient outcome than facility volume.[165]

Lindeman et al evaluated 6054 adrenalectomies performed in New York State over 15 years. High volume adrenal surgeons (≥4 adrenal operations per year in this analysis) were found to have a lower median length of stay (2 vs 4 days), complication rate (9% vs 14%), and mortality rate (0.56% vs 1.25%) with all p<.004.[224] Confounding variables include low volume surgeons are more likely to operate at a non-teaching hospital (p<0.001), [224,225] and have patients who are older patients, identify as black race, and/or have higher Charlson comorbidity scores.[225]

Yet even for low-volume surgeons (≤6 per year), a relationship has been shown between volume and outcomes. Surgeons who perform 3 adrenalectomies per year have less than half the incidence of post-operative complication compared to a surgeon who performs 1 adrenalectomy per year (15% vs 36% respectively, p<0.05).[225]

Some analyses of adrenalectomy have not demonstrated a clear relationship between surgeon volume and patient outcomes. Stavrakis et al examined HCUP-NIS data from two states and found no difference between surgeon volume and outcomes however, this study analyzed a

more limited dataset, lacked robust risk adjustment, and reflected an earlier era of adrenal surgery.[384,385]

While some studies arbitrarily assign a volume threshold to stratify the cohort, the study by Anderson et al utilized more rigorous methods to arrive at the threshold of ≥6 adrenal resections per year to define a high-volume adrenal surgeon with associated improved patient outcomes.[225] Since not all patients will achieve access to high-volume adrenal surgeons, lower volume surgeons should exercise judgement and careful patient selection to provide safe care at their own center versus seeking referral or consultation with a more experienced adrenal surgeon when appropriate.

Hospital adrenalectomy volume has not been demonstrated to impact patient outcomes. Despite this, the surgeon must exercise judgement to assure that the appropriate facilities and personnel are available particularly for patients anticipated to have greater needs for advanced care such as adrenal malignancy, pheochromocytoma, and advanced Cushing's syndrome.

7.4. In patients with adrenal tumors, what is the efficacy of radiofrequency ablation and stereotactic radiation compared to adrenalectomy?

Recommendation 7.4. We conditionally suggest ablation and stereotactic radiation not be used as an alternative to adrenalectomy for patients with adrenal lesions because there are inadequate data to support these modalities. Surgeons should be involved in the decision making early in the treatment algorithm (Weak recommendation, low quality evidence)

The utility of percutaneous ablation, mainly with radiofrequency ablation, for the destruction of both hormonally active and inactive tumors has been investigated in small retrospective studies. Although most of the experience has been on ablation of aldosteronomas, the studies suffer from small sample sizes and heterogeneity. A review of 89 patients, who either

refused surgery or were not candidates for surgery, showed a resolution or improvement of hypertension in 75% of patients.[386] In the largest retrospective comparison study, Liu et al. compared 27 patients who underwent laparoscopic adrenalectomy and 36 patients who underwent percutaneous radiofrequency ablation. In this study, RFA was associated with shorter operative time, hospital stay and recovery. At a median follow up of 5.7 months, although resolution of primary hyperaldosteronism (92% vs 100%) and hypokalemia (100% vs 100%) was similar between the RFA and laparoscopic adrenalectomy groups, respectively, hypertension resolved less frequently after RFA (36%) versus laparoscopic adrenalectomy (70%). [387] The data on cortisol-secreting adenomas and pheochromocytomas are much too limited to make any recommendations.

Alternative therapies for the treatment of oligometastatic adrenal metastases include stereotactic body radiation therapy (SBRT) and percutaneous ablative therapies. Although there are no prospective comparison studies comparing the outcomes of these modalities to adrenalectomy, a cumulative analysis of 30 adrenalectomy, 9 SBRT and 6 percutaneous ablation studies of heterogenous mix of patients with adrenal metastasis (mostly lung, melanoma and renal cell cancer) showed a 2-year local control and overall survival of 84% and 46%, respectively, after adrenalectomy (n=818) versus 63% and 19%, respectively for SBRT (n=196).[388] Only one ablation study (n=5) reported clinical outcomes, with a local control rate of 80% at 2 years.[389] We conclude that there are insufficient data on how alternative treatment modalities of SBRT and ablation compare with adrenalectomy on the treatment of patients with isolated adrenal metastases. Based on retrospective data, and until more data are available regarding SBRT or ablation, adrenalectomy should be primary treatment modality in good-surgical risk patients with isolated resectable metastasis. In patients who are not good candidates

for surgery or without isolated adrenal involvement, SBRT may be considered if local expertise is available.

FUTURE DIRECTION AND RESEARCH OPPORTUNITIES

The recommendations and guidelines provided in this report on the evaluation and management of adrenal surgery represent a comprehensive evidence-based review utilizing both GRADE and PICO methodologies. The recommendations are provided both in the text and in the tables. Several suggested areas that are ripe for more research are listed below:

1. The natural history and duration of follow-up for non-functional adrenal incidentalomas is poorly understood. Whether standardized imaging characterization and routine use of sensitive initial biochemical testing can better identify those patients whose adrenal incidentalomas need long-term surveillance would improve healthcare resource utilization.
2. Our current clinical management of patients with MACS is largely limited to retrospective and comparative studies. Up to 30% of patients with adrenal incidentalomas have biochemical findings of MACS and whether routine or even pre-symptomatic surgical management can reduce the likelihood of cardiometabolic comorbid conditions remains unknown. A multi-institutional randomized study and collaborative database to assess long-term outcomes would be informative.
3. The role and type of neoadjuvant therapy for borderline resectable ACC is not well defined and for patients who present with locally aggressive disease, optimal treatment options are needed. Given the rarity of ACC, a multi-institutional trial would likely be needed to achieve disease-specific outcome measures.

4. Postoperative adrenal insufficiency can have significant consequences for patient quality of life and appropriate preoperative counseling, diagnosis and treatment are essential. Continued research in cortical transplantation and for better adaptive pharmacological options should be encouraged and financially supported.
5. While there were insufficient data to provide any current recommendation on the role of ablative and stereotactic radiotherapy options, such non-operative techniques likely have a role for patients with small benign functional tumors, ACTH dependent Cushing's refractory to medical therapy, or in select patients with oligometastatic disease involving the adrenal. Future directions to further define these techniques are needed.

CONCLUSION

We provide 26 evidence-based recommendations with clinically meaningful data to primarily assist surgeons with perioperative adrenal care. Multiple disciplines and patients may also find these recommendations useful. We highlight topics that have low quality data or little evidence available and propose these topics as opportunities for further research.

Supplemental Work: Technical Pearls and Emerging Technologies

It is not possible to provide a technical recommendation that would fit every patient and work for each surgeon. There are controversies about the limitations of laparoscopy, the choice of a lateral transabdominal or posterior retroperitoneal approach, conduct of the procedure (e.g. vein first versus last approach) and the use of advanced technologies such as robot-assistance and intraoperative imaging. Unfortunately, the lack of data restricts an evidence-based recommendation for these different choices. Nevertheless, the expert panel agreed on the importance of adherence to general principles for technical success (eTable 5).

The greater the concern for an invasive cancer, the lower the threshold should be for an open operation. Most open adrenalectomies can be done without the need for a thoracoabdominal incision by using a midline or modified subcostal incision. Whether the procedure should be started open or minimally invasive depends on the surgeon's skill level and familiarity with adrenalectomy. Similarly, the upper size limit of adrenal tumors that can be safely removed laparoscopically or with minimally invasive techniques also depend on the same parameters.

A "no touch technique" (no grasping the capsule) and including periadrenal tissue in the dissected specimen minimizes the risk of capsular disruption. Whether the surgeon can achieve this laparoscopically, robotically or in open surgery varies from surgeon to surgeon. The consequences for breaching the capsule of certain tumors (i.e. pheochromocytomas, ACC, and metastatic cancers to the adrenal gland) are more severe and the surgeon should adhere to more strict surgical technique. It is important to study the patient's vascular anatomy beforehand and understand the relationship of the tumor with the inferior vena cava, trajectory of the renal vessels, splenic vessels and celiac axis.

Although no evidence-based recommendations may be given for resecting the adrenal vein first or last, there may be advantages in taking the vein last to avoid venous congestion and optimizing exposure. On the other hand, taking the vein first may facilitate the rest of the dissection for some tumors. Depending on the individual case, it is beneficial to be facile with both of these techniques.

Both in open and laparoscopic approaches, obtaining adequate exposure by mobilization of the liver on the right side and the pancreas, spleen and colonic splenic flexure on the left side are critical. Posteriorly identifying and protecting the kidney and its hilar vessels, vena cava and aorta are important. The expert panel acknowledges the value of developing expertise in different surgical approaches and also establishing a surgical routine to standardize the technique. Finally, the surgeon should also be familiar with the hormonal pathophysiology to tailor the surgical technique and perioperative management.

Safe and effective adrenalectomy requires specific training and expertise in adrenal pathophysiology and adrenal specific surgical technique.[390] While core surgical competencies are essential in adrenal surgery, adrenalectomy requires different techniques of dissection, and clear understanding of the specific physiologic and neoplastic behaviors of adrenal pathologies. Approaching adrenal surgery as though it were equivalent to any other extirpative procedure may result in suboptimal outcomes in terms of patient selection, choice of technical approach, cure, morbidity, and mortality.

Various authors have reported on the utility of robotic adrenalectomy, via both lateral transabdominal and posterior retroperitoneal approaches.[366,391-395] There are no randomized or prospective studies comparing laparoscopic with robotic adrenalectomy. Retrospective studies have described benefits of the robot in terms of ergonomics and removing large tumors.

Retrospective studies have reported similar perioperative outcomes between laparoscopic and robotic posterior retroperitoneal adrenalectomy,[366] fewer conversions to open and shorter operative time with robotic compared to laparoscopic adrenalectomy for removing large (> 5 cm) tumors. [396] The outcomes of robotic versus laparoscopic adrenalectomy were similar for pheochromocytomas [397] and also tumors removed in obese patients.[398] Robotic approach was reported to be a more costly procedure than laparoscopic adrenalectomy.[391] Although robotic adrenalectomy has been shown to be feasible and safe in experienced hands with a low rate of capsular disruption,[380] prospective comparative studies are necessary to analyze benefits compared to laparoscopic adrenalectomy (eTable 6).

Laparoscopic ultrasound [362] and indocyanine green [399,400] have been used for intra-operative tumor localization, but comparative data on their impact on outcomes are not available. These adjuncts may provide benefit in delineating anatomy, especially with the posterior approach with laparoscopic ultrasound and indocyanine green imaging, to confirm remnant viability, but lack evidence for impact on outcomes.

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NDP and LY had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

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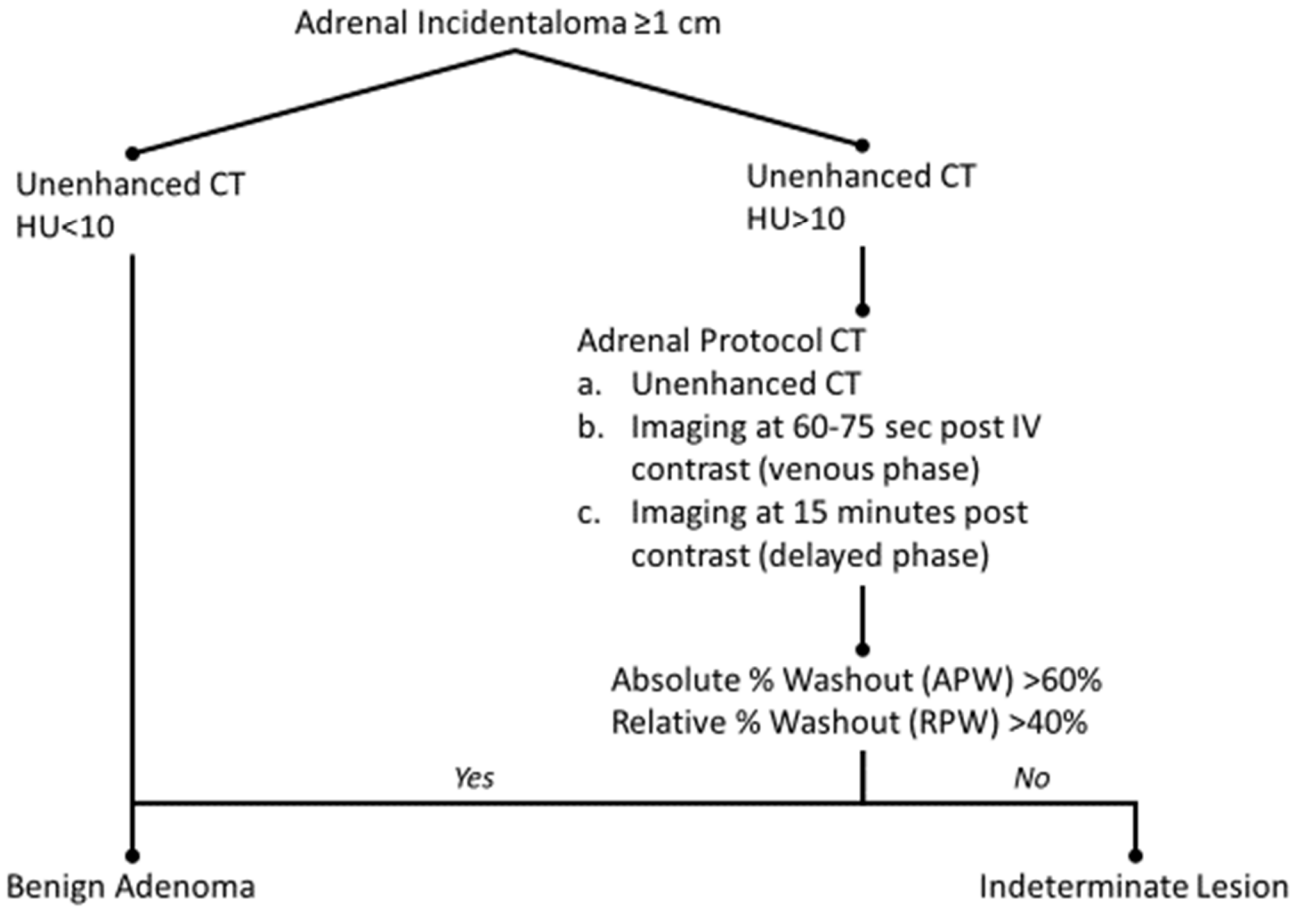
eFigure: Indications and Interpretation of Adrenal Protocol CT Results



eTable 1. Adaptation of simplistic overview of the hormonal work up in patients with adrenal tumors

Adrenal hormone excess	Indication for testing	First line testing	Second line or confirmatory testing	Final diagnostic considerations
Adrenal hypercortisolism (overt Cushing's syndrome or mild autonomous cortisol secretion)	All patients, regardless of symptoms	1 mg dexamethasone suppression test (abnormal: >1.8 µg /dl)	ACTH, DHEA-S Repeat 1 mg or perform 8 mg dexamethasone suppression test, consider testing dexamethasone concentrations. 24 h urine cortisol Late night salivary cortisol test	Patients with autonomous cortisol secretion will have abnormal dexamethasone suppression test, low ACTH and DHEAS. 24h urine cortisol is usually normal in mild autonomous cortisol secretion. DHEA-S may not be an accurate parameter in postmenopausal women
Adrenal hyperaldosteronism (primary aldosteronism)	Patients with hypertension with or without spontaneous hypokalemia	Morning aldosterone and renin or renin plasma activity (abnormal: aldosterone >10-15 ng/dL and suppressed renin). Note that aldosterone cutoff is only a suggestion (aldosterone concentrations vary based on assays, intra-individual variability, and severity of disease)	Unnecessary if positive first line test and hypokalemia. Otherwise, consider salt loading test, saline infusion test	Patients with confirmed primary aldosteronism will need subtype evaluation with cross-sectional imaging +/- adrenal vein sampling to differentiate between unilateral aldosteronoma and bilateral hyperplasia.
Catecholamine excess	Patients with indeterminate adrenal mass (non-contrast HU>10), regardless of symptoms	Plasma or urine metanephrines (abnormal: >2-fold above upper limit of normal; consider interfering medications and comorbidities that may lead to false positive results)		In confirmed pheochromocytoma, consider genetic testing and further evaluation in hereditary cases
Androgen excess, steroid precursor excess	Patients with a large indeterminate adrenal mass (non-contrast HU>10-20), regardless of symptoms; not needed in patients with confirmed pheochromocytoma	Serum: DHEA-S, androstenedione, testosterone, 17-OHprogesterone, 17-OH pregnenolone, pregnenolone, estradiol, progesterone, 11-deoxycortisol 24h urine: urine steroid profiling		Androgen excess is demonstrated in 50% of ACCs[90]. Steroid precursor excess is demonstrated in >90% ACCs. Steroid profiling can also be used as biomarker for recurrence[401].

eTable 2. Prevalence of any malignancy in population data[80]

Age	**<18 years: 62%** 18-39: 4% 40-64: 6% >65: 11%
Sex	No sex differences overall, however, higher risk of ACC in women and higher risk of adrenal metastases in men
Hounsfield units on non-contrast computed tomography	<20 HU: 1% 20-29 HU: 11% >30 HU: 20%
Tumor size	1-2 cm: 6% 2-4 cm: 9% **>4 cm: 34%**
Laterality	Unilateral: 7% **Bilateral: 16%**
Mode of discovery:	Incidental: 3% **Cancer staging: 43%** Hormone excess: 3% **Adrenal mass effect/B symptoms: 37%**

Footnote: Table includes prevalence of malignancy for all adrenal nodules, including nodules discovered for extra-adrenal cancer staging or surveillance. Risk of malignancy is dependent on the combination of all variables and should not be based on a single clinical factor.

eTable 3. Genetic Susceptibilities Associated with Adrenal Disorders and Tumors

	Gene Involved	Type of Genetic Change
Adrenal Adenomas	*CTNNB1*	Somatic mutations
Primary Aldosteronism		
Familial Hyperaldosteronism*		Germline
Type I	*CYP11B1/CYP11B2*	Chimeric fusion
Type II	*CLCN2*	-
Type III	*KCNJ5*	-
Type IV (associated with seizures and neurologic abnormalities)	*CACNA1D*	-
Hypercortisolism		
Carney Complex	*PRKAR1A or PDE8B/PDE11A*	Germline
Primary bilateral macronodular adrenal cortical disease/hyperplasia	*ARMC5, MEN1, FH, APC, PDE11A, PDE8B*	Germline
McCune-Albright Syndrome	*GNAS*	Mosaic
Cortisol-secreting Adenomas	*PRKACA*	Somatic
Adrenal Cortical Carcinomas		
Li-Fraumeni	*TP53*	Germline
Lynch Syndrome	*Mismatch repair genes*	Germline
Beckwith-Wiedemann Syndrome	*IGF1*	Germline
Familial Adenomatous Polyposis Syndrome	*APC*	Germline
MEN1	*MEN1*	Germline
Neurofibromatosis type 1	*NF1*	Germline
SDH-syndromes	*SDHx*	Germline
Carney Complex	*PRKAR1A or PDE8B/PDE11A*	Germline
Pheochromocytomas and Paraganglioma		
Cluster 1: Pseudohypoxia	*SDHx, VHL, FH, EPAS1, EgiN/PhD2*	Germline
Cluster 2: Kinase signaling	*MEN2, NF1, MAX, TMEM127, KIF1B*	Germline

eTable 4. Immediate Postoperative Management of Glucocorticoid Medication

Who	1. Patients undergoing unilateral adrenalectomy with preoperative hypercortisolism 2. After cortical-sparing adrenalectomy and contralateral total adrenalectomy 3. After bilateral total adrenalectomy
Why	Nearly all patients with overt Cushing's syndrome or who undergo bilateral total adrenalectomy will have postop adrenal insufficiency Adrenal insufficiency in 60% of patients with MACS and in 20-30% of patients who undergo cortical-sparing adrenalectomy
How	If overt Cushing's or bilateral total adrenalectomy, hydrocortisone 20 mg in the morning and 10 mg 6-8 hrs after waking If MACS or after cortical-sparing adrenalectomy, adrenal insufficiency if: a. Baseline AM serum cortisol <10 mcg/dL b. Corticotropin stimulation test: i. Corticotropin 250 mcg IV after baseline AM cortisol obtained ii. Serum cortisol at 30-60 min after injection is <16-20 mcg/dL c. Symptoms are present including fatigue, hypotension, anorexia, abdominal pain, weakness, syncope, back pain, nausea, vomiting, fever, or confusion
Duration of Therapy	Glucocorticoid Withdrawal Syndrome: due to dependence on supraphysiologic endogenous cortisol preop and may last for up to a year postop

eTable 5. Perioperative Considerations in Adrenalectomy

	Preoperative Testing	Operative Approach	Postoperative Management
Adrenal Incidentaloma	• Directed hormonal evaluation • Imaging characterization	Minimally invasive*	
Primary Aldosteronism	• CT localization • Adrenal venous sampling (especially if age >35 years, small adenoma, or contralateral gland abnormal)	Minimally invasive*	Monitor for postoperative hypoaldosteronism (hyperK) and for further decrease in eGFR
ACTH-Independent Hypercortisolism Mild autonomous cortisol secretion (MACS) Overt Cushing's	• CT localization	Minimally invasive*	 • 60% risk of adrenal insufficiency - Need for postop steroids can be assessed by POD1 AM cortisol or corticotropin stimulation testing • ~100% risk of adrenal insufficiency - Empiric postop steroids
PPGL	• CT localization • Preoperative alpha-blockade • Genetic testing especially if bilateral	Either minimally invasive* or open • Consider cortical-sparing if bilateral PCC	• Genetic testing if not performed preop
Adrenocortical Carcinoma	• Imaging to stage disease • Directed hormonal evaluation • Consider neoadjuvant therapy if R0 not initially feasible	*En bloc* resection with intact capsule, and microscopically negative margin (R0) • Usually open approach	• If preop testing consistent with primary aldosteronism or hypercortisolism, follow according management • Adjuvant therapy
Metastasis to Adrenal	• Imaging to stage disease • Directed hormonal evaluation • Rarely image-guided biopsy and only if changes management	Either minimally invasive* or open	• Depends on primary disease process

*Minimally invasive may be either laparoscopic or robotic-assisted and via a transabdominal or retroperitoneal approach. Approach depends on surgeon expertise as well as patient and tumor specific characteristics

eTable 6. Type of Operative Approaches for Adrenalectomy

	Indications	Pearls
Open	1. Adrenal cortical carcinoma 2. Malignant Pheo/PGL 3. PGL 4. Intraoperative necessity	Procedure of choice if *en bloc* tumor resection anticipated Usually via midline or subcostal incision
Minimally Invasive* Laparoscopic Robotic-Assisted Transabdominal Retroperitoneal	1. Benign-appearing adenomas 2. Encapsulated and reasonably sized indeterminate tumors*	Laparoscopy: Less costly than robotic-assisted Robotic-Assisted: Improved surgeon ergonomics Possibly preferred for larger (>5 cm) tumors Transabdominal: Familiar anatomy and patient positioning for operative team Retroperitoneal: Avoids intra-abdominal adhesions Lower incidence of incisional hernia No repositioning needed if bilateral Adrenalectomy Possibility of a long term consequence of subcostal nerve paresthesia or pain

* For more detail, see "Technical Pearls and Emerging Technologies"