# Surgical Management of Metastases to the Adrenal Gland: Open, Laparoscopic, and Ablative Approaches

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**Current Urology Reports** 2009, **10:**67–72
Current Medicine Group LLC ISSN 1527-2737


The adrenal gland is a potential site of metastasis for various malignancies. Metastases to the adrenal gland are the second most common type of adrenal mass lesion after adenomas. Differentiation of a metastatic lesion from a primary adrenal lesion can be challenging and requires the selective use of radiologic imaging, serologic testing, and adrenal biopsy. In patients who present with an isolated adrenal metastasis, adrenalectomy is often considered to aid in cancer control. Numerous studies have reported improved survival with resection of solitary adrenal metastases for various types of primary tumors. Traditionally, open adrenalectomy was the preferred option for these patients. More recently, laparoscopic adrenalectomy has offered a minimally invasive approach, with its resultant advantages of improved perioperative parameters. Proper patient selection for the laparoscopic versus open approach remains paramount in deciding the best treatment for the individual patient.

## Introduction

Metastases to the adrenal gland have been reported for numerous malignancies. The most common metastatic lesions to the adrenal gland include breast, lung, colon, and kidney tumors, as well as melanoma [1••]. With the increasing use of abdominal imaging, adrenal masses in patients with a known primary malignancy are more commonly diagnosed [2]. Although many patients present with synchronous metastasis to the adrenal gland and other organs, some present with only an isolated adrenal metastasis. In these patients, surgical resection of the adrenal gland is often considered in an attempt to offer curative therapy.

Since its description in 1992, laparoscopic adrenalectomy (LA) has gained popularity for management of benign tumors of the adrenal gland and is now the preferred approach for resection of these lesions. Compared with open adrenalectomy (OA), LA is associated with decreased postoperative pain, shorter hospital stay, and improved cosmesis and convalescence [3–6]. Even though the first report of LA for malignancy was in 1999, the procedure has been slow to gain acceptance in this setting due to concerns regarding its oncologic efficacy.

The treating surgeon must be aware of the indications for resection of an adrenal metastasis, as well as the available surgical approaches. This article reviews the diagnosis and management of adrenal metastases, with a focus on recent reports that address minimally invasive adrenal surgery via a laparoscopic approach.

## Incidence and Diagnosis of Adrenal Metastasis

An autopsy review of 1000 patients showed a 27% rate of metastasis to the adrenal gland in patients with a known primary malignancy [7]. A recent retrospective 30-year review at a teaching hospital revealed an overall rate of metastatic tumors to the adrenal gland of 3.1% of autopsies performed [2]. Clinically, most patients with adrenal metastases are asymptomatic at the time of diagnosis. Many lesions are detected on routine surveillance imaging or on studies performed to evaluate nonrelated symptoms. Occasionally, symptomatic patients present with back pain, retroperitoneal hemorrhage, or Addisonian crisis [8]. Most adrenal metastases are discovered within 1 year of the detection of the primary tumor, with a mean latent period of 7 months in one study [2]. However, late recurrences have been described, particularly in cases of metastatic renal cell carcinoma (RCC) [9].

## Imaging

Radiologic imaging is essential in the evaluation of an adrenal mass. The cornerstone of adrenal evaluation is a properly performed CT scan with and without intravenous contrast. Thin 2- to 5-mm slices are vital in assessing adrenal lesions. Metastatic lesions can present with a wide array

of radiographic features. Unlike adenomas, which often have smooth margins and homogeneous density, malignant lesions can be heterogeneous and have an irregular contour. However, these findings do not allow accurate classification of all adrenal masses. Therefore, additional criteria, including determination of intracellular lipid content and vascular perfusion of the lesion, are used to aid in differentiation of malignant and benign lesions. In general, adenomas are high in intracytoplasmic fat content, which leads to lower attenuation on noncontrast CT scan (< 10 Hounsfield units [HUs]). Metastases are less likely to contain excessive fat and will usually have attenuation values greater than 10 HU on noncontrast imaging. Approximately 30% of adenomas are fat-poor and would be incorrectly classified as metastases using this criteria alone. Vascular perfusion differences can be used to further distinguish metastases from adenomas. After the administration of intravenous contrast, adenomas display faster washout of enhancement than metastases. As such, in delayed images a metastatic lesion would retain higher attenuation as compared to an adenoma [10]. Lymphadenopathy and local invasion are additional features noted on a CT scan that are more consistent with a malignant lesion.

Oftentimes indeterminate findings on a CT scan warrant further evaluation with MRI, as these scans can provide additional information. MRI can reveal small amounts of adipose tissue within lesions and can improve assessment of tissue planes and local invasion into surrounding structures. Additionally, T2-weighted images display heterogeneous enhancement and hyperintensity in cases of metastases or primary malignant tumors of the adrenal gland, as opposed to adenomas. Furthermore, the technique of chemical-shift MRI has proven to have the highest sensitivity as compared with T1, T2, or vascular enhancement in differentiating adenomas from metastases [10].

Positron emission tomography (PET) has shown promise in the diagnosis of adrenal malignancies. Advantages of PET scanning are the ability to image the area of the primary tumor, which is helpful in cases of an unknown primary, and its ability to detect other small metastases. For certain tumors, such as lung cancers, PET scan has repeatedly been shown to have both sensitivity and specificity greater than 90% for detecting adrenal metastases [11]. However, PET scanning has limited applicability to many metastatic genitourinary tumors in which the primary lesions do not exhibit uptake during PET scan.

## Serologic Evaluation

Once an adrenal mass is diagnosed, adjunctive testing is necessary to exclude a functional lesion. Metastasis to the adrenal gland cannot be definitively confirmed in a patient who has another malignancy, as more than 50% of adrenal masses in patients with a known malignancy are benign [12]. Although a complete discussion of the metabolic evaluation of adrenal lesions is beyond the scope of this review, a distinct effort to rule out the diagnosis of a pheochromocytoma is crucial, as dire consequences may result from a misdiagnosis. This can be accomplished by evaluating plasma-free metanephrines, along with confirmatory urinary catecholamine and metanephrine levels. A complete endocrinologic evaluation should also include measurement of serum electrolytes and urine levels of steroid hormones and their metabolites. In addition, stimulation studies such as the low- and high-dose dexamethasone suppression tests and measurement of plasma renin and aldosterone levels can be obtained. A review of the recommended work-up for the incidental adrenal lesion may be found in recent review articles [13,14].

## Adrenal Biopsy

Biopsy of an adrenal lesion is indicated when imaging is indeterminate or when the primary tumor is unknown. The accuracy of adrenal biopsy has increased with the use of fine-needle aspiration and CT guidance. Fine-needle aspiration is highly sensitive and specific for the diagnosis of adrenal metastasis, with a specificity that approaches 100% [15]. A critical part of maintaining a high yield for adrenal biopsy is the preparation of high-quality smears, which requires the presence of a cytopathologist or cytotechnologist who can immediately examine specimens for adequacy. The use of smaller needles for biopsy (22–25 gauge) is thought to have reduced the rate of adrenal hemorrhage from biopsy to less than 3% in a recent series of 300 patients [16]. In the case of large adrenal masses, biopsy may help distinguish between adrenal metastasis and primary adrenal cortical carcinoma. In general, the microscopic features that assist in the differentiation of malignancy versus adenoma include clusters of cells with increased nuclear-cytoplasmic ratio, hyperchromatic, pleomorphic nuclei, and variably prominent nucleoli. Immunohistochemistry can be used on biopsies in cases of difficulty with diagnosis or unknown primary tumor.

## Management of Adrenal Metastasis

Patients with adrenal metastases require multidisciplinary oncologic evaluation to determine their overall prognosis and the appropriateness of surgical intervention. Those with multiple metastatic sites or extensive tumor burden may be better served with systemic treatment or a palliative approach. Nevertheless, several series support surgical management of patients with adrenal metastasis for improving survival. These studies include patients with lung cancer [17,18], RCC [19,20], and other cancers [21,22]. Many authors have attempted to further stratify the patients who would be best served with adrenalectomy. In general, patients with solitary metastasis, lengthy disease-free interval after initial diagnosis, and

smaller tumor size respond better than patients without these features [8].

## Open Versus Laparoscopic Adrenalectomy

Earlier reports on the benefit of adrenalectomy for metastatic disease featured OA. The routine use of laparoscopic surgery in this setting has been extensively debated. Critics of LA note concerns regarding the ability to achieve adequate surgical margins, the potential for trocar site recurrences, as well as the risk of carcinomatosis via spread of tumor cells by the $CO_2$ gas used to create the pneumoperitoneum. Many of these reservations emanate from early case reports of local recurrence and peritoneal metastases in patients operated on for unsuspected adrenal cortical carcinoma [23]. A recent review of the literature regarding adrenal cortical carcinoma by McCauley and Nguyen [24] showed that local recurrence rates and incidence of peritoneal metastasis were similar for open and laparoscopic approaches. The authors suggest that avoidance of tumor entry or spillage coupled with the standard use of laparoscopic specimen bags should avoid the higher rates of port site and peritoneal metastasis that led to the adverse results in the initial reports [24].

The role for open surgery in cases of adrenal metastases is strongest in patients in whom preoperative imaging suggests local invasion into surrounding structures. Other indications for open surgery include large adrenal masses (> 9 cm), caval thrombus, or significant lymphadenopathy. Relative contraindications for LA include significant adhesions from prior surgery, morbid obesity, uncorrected coagulopathy, and cardiopulmonary disease that precludes hypercapnea that is associated with pneumoperitoneum. These cases must be evaluated on an individual basis, and the surgeon's experience and comfort level must be taken into consideration.

## Ablative Therapies: Cryoablation and Radiofrequency Ablation

Cryoablation has been used as a surgical alternative for the treatment of tumors in many tissues, including the prostate, lung, breast, pharynx, liver, and kidney [25–30]. Advances in cryosurgery delivery systems and ultrasound imaging modalities have allowed the application of this technology to adrenal gland lesions. Although the use of modern cryosurgery for adrenal tissue ablation in humans has not been extensively reported in the literature, the safety and efficacy of cryoablation in destroying adrenal tissue in a canine model has been demonstrated [31]. Experimental and clinical reports have demonstrated that temperatures between -40° C and -50° C are necessary for achieving certainty regarding cell death, which is of great importance in the case of adrenal tumors [32].

Although the exact mechanism of cellular destruction in the adrenal gland remains to be fully elucidated, cryoablation can effectively be performed in a controlled and reproducible manner. Adrenal cryosurgery may provide a new modality for adrenal tissue destruction and may be advantageous in cases of unresectable tumors. Further investigation is required in understanding the long-term effect of adrenal cryoablation.

Recent technological advances have permitted radiofrequency therapy to emerge as a treatment modality to ablate neoplasms in a variety of tissues, including liver, spleen, lung, bone, breast, prostate, and kidney [33–37]. Through the conversion of radiofrequency waves into thermal energy, radiofrequency energy exerts its cytotoxic effect, resulting in denaturation of intracellular and extracellular proteins, cell desiccation, and ultimately coagulative necrosis [38]. The conduction of this energy depends on several factors, such as surface area and geometry of the active needle electrodes, radiofrequency current, ablation time, distance from the electrode, and tissue impedance [39]. Preliminary work has shown that radiofrequency energy is effective, safe, and technically feasible for ablating both benign and malignant tissue. The few reports of radiofrequency application to adrenal tissue have been for cases of metastatic adrenocortical carcinoma, as treatment options for metastatic disease are limited. Patients with adrenal metastases may have a better quality of life if a less invasive alternative can provide similar results. Repeated local disease control with ablation would be advantageous to patients who would have otherwise benefited from aggressive surgical management.

As an alternative to surgical excision, Mayo-Smith and Dupuy [40] recently reported results from CT-guided radiofrequency ablation in 11 patients with metastatic lesions. The mean tumor size treated with this therapy was 3.9 cm. All procedures were conducted with intravenous sedation, and most were performed on an outpatient basis. Two patients (19%) had enhancement of residual tissue on follow-up imaging, which suggested residual tumor. Due to the short length of follow-up (mean follow-up 11.2 months), the utility of this procedure for adrenal metastases requires further investigation in order to assess its long-term durability.

## Operative Technique for Laparoscopic Adrenalectomy

Standard preparation for laparoscopic surgery is required, including appropriate positioning, padding, antibiotics, and intravenous access. The two most widely used laparoscopic approaches to the adrenal gland are via a transperitoneal or retroperitoneal approach. The transperitoneal approach is more familiar to surgeons because it is commonly used for most laparoscopic renal surgery. It offers ease in identifying, dissecting, and mobilizing intra-

abdominal structures, whereas potential disadvantages include ileus, adhesion formation, and injury to adjacent viscera. The retroperitoneal approach in actuality provides the most direct route to the adrenal gland, and by not entering the abdominal cavity, may be beneficial in those with extensive intra-abdominal adhesions. However, the working space is more confined, and the loss of easily identifiable landmarks may hinder the surgeon with limited experience using this approach. In terms of patient preparation, positioning, and trocar placement, adrenalectomy for metastasis is similar to standard LA for functioning or nonfunctioning adrenal adenoma and has been described previously [41].

## Results of Laparoscopic Adrenalectomy for Adrenal Metastasis

Several authors have recently reported on their experience with LA in the setting of metastasis, with a focus on determining which patients may benefit from laparoscopic versus open surgery. The first group to report their experience with a significant number of LAs for malignancy was Moinzadeh and Gill [23] in 2005, in which they described 33 LAs for malignancy, of which 26 patients had extra-adrenal primary tumors. At median follow-up of 26 months, 52% of patients were alive and 42% were disease free, with a cancer-specific survival of 53% at 42 months median follow-up. Tumors ranged in size from 1.8 to 10 cm. Seven patients (23%) had local recurrences in the series. Two of these recurrences were in the adrenal cortical cancer group, and five were in the metastatic group. Of note, only four patients (13%) had minor complications. The authors noted that their survival estimates compared favorably with other published series of OA.

The largest recent series describing a cohort of LAs was performed by Castillo et al. [1••]. The authors performed 34 LAs in 32 patients for suspected adrenal metastasis. Patients with tumors larger than 10 cm, with evidence of periadrenal infiltration, caval thrombus, or locoregional lymphadenopathy, were excluded from a laparoscopic approach. Of the 34 glands resected, 22 (64.7%) contained malignancy upon pathological analysis, with a mean tumor size of 5.1 cm. The mean survival time for patients with malignancy was 26 months. There were two (9.1%) positive margins, and no open conversions or port site problems were reported.

## Recent Results Comparing Laparoscopic and Open Adrenalectomy

A recent series by Strong et al. [42••] described findings from 31 attempted transperitoneal LAs for metastatic lesions, and compared these with 63 open adrenalectomies over an 11-year period. Eighteen (58%) patients had lung cancer as the primary tumor. Four patients (13%) required conversion to an open approach due to extensive adhesions or failure to identify anatomy in three patients, and the need to conduct concomitant ovarian surgery in the fourth case. Three of the open conversions involved adrenal tumors larger than 7.5 cm. Median survival was approximately 30 months and was not different for the open and laparoscopic groups. Several operative factors were significantly lower in the LA group, including operative time, length of hospital stay, estimated blood loss, and number of total complications, including major complications. Microscopic positive margin rate between the open and laparoscopic groups (29% for open and 22% for LA) was not significantly different. Subgroup analysis for all adrenal tumors less than 4.5 cm (24 LA and 25 OA) revealed similar benefits in terms of operative time, length of hospital stay, blood loss, and complications. Regarding follow-up data, the only independent predictor of survival was adrenal tumor size less than 4.5 cm. For the entire cohort, the median survival was 30 months and was not different for the LA group compared with the OA group.

Another group described their experience with LA for patients with metachronous lesions from RCC [43•]. These authors reported on 11 patients who had metastases ranging from 2 to 13 cm in diameter discovered at least 6 months (range 6–42 months) after primary renal tumor resection. Eight patients underwent LA, five of whom were contralateral to the original RCC, two ipsilateral, and one bilateral. The cases approached laparoscopically included adrenal tumors ranging from 1 to 3.5 cm, and pathology confirmed metastatic RCC in all cases. The three patients who underwent OA had masses between 12 and 13 cm. All patients in the laparoscopic group had negative surgical margins. Contralateral adrenal metastasis was associated with a shorter operative time as expected given lack of adhesions. Of the 11 patients who had resection of their adrenal metastases, nine were alive with no evidence of disease at a median follow-up of 34 months. The remaining two patients subsequently developed metastatic disease at other sites.

Eto et al. [44] reported on eight LAs that were performed for metastatic lesions. The authors used preoperative imaging and biopsies to diagnose adrenal metastasis and attempted LA for adrenal masses 10 cm or smaller. Median tumor size was 3.0 cm. Two patients had widely metastatic RCC that underwent adrenalectomy in order to acquire tissue for dendritic cell therapy. The authors noted that operative time, blood loss, and length of hospital stay were similar to their larger cohort of LA performed for benign diseases. There were no open conversions in the metastatic group. Regarding outcomes, they reported that seven patients (88%) were alive at a median follow-up of 20 months.

Adler et al. [45] recently compared eight patients who underwent OA for metastatic lesions with nine patients who underwent LA for similar tumors. The average adre-

nal mass size in patients who had LA was 4.0 cm and 8.8 cm in patients who had OA. LA was associated with decreased blood loss, fewer complications, and shorter length of hospital stay. At a total combined follow-up time of 97 months for all patients, there were no trocar site metastases in the LA group. There were no statistically significant differences in survival between the open and laparoscopic groups, although median follow-up in the two groups was slightly longer than 1 year.

## Conclusions

Metastasis to the adrenal gland can be a challenging clinical scenario. The treating clinician must assess whether surgery might offer a clinical benefit and which surgical approach may be optimal. Recent series have demonstrated that LA is a feasible and reasonable alternative for smaller adrenal metastases without evidence of local invasion or lymphadenopathy. For larger tumors or advanced local disease, an open approach may be a more suitable option. No recent studies have shown a worse survival for patients undergoing LA; however, many of the recent publications lack adequate follow-up. The ultimate decision to resect an adrenal metastasis and which approach to use remains an individualized decision that must take into account the patient's clinical status and the treating surgeon's experience.

## Disclosures

No potential conflicts of interest relevant to this article were reported.

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