The incidence, diagnosis, and indication for resection of adrenal lesions in cancer patients are reviewed, and a pathway for evaluation and treatment is presented.

Management of Isolated Adrenal Lesions in Cancer Patients

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**Background:** Adrenal lesions are commonly identified in patients with extra-adrenal cancer. When lesions are present, it is important to identify if the lesion is a metastasis of the primary cancer or a primary adrenal neoplasm. If primary, the adrenal lesion must be evaluated for hypersecretion and its malignant potential determined for appropriate treatment planning.

**Methods:** Recent literature was reviewed that focused on the normal investigation of adrenal lesions including radiographic imaging and hormonal evaluations as well as specific focused therapeutic options available for isolated metastatic adrenal lesions.

**Results:** This review presents a pathway approach in investigating these lesions and also discusses various potential treatment options.

**Conclusions:** A proper investigative workup of an adrenal lesion in a cancer patient is critical for proper management. Isolated adrenal metastatic lesions in the cancer patient should be surgically removed when possible, but other options can be considered. In patients who do not have metastasis from extra-adrenal cancer, the decision for surgical resection is dependent on functionality of the tumor and its potential for malignancy. Observation plays a key role in those tumors that are nonfunctioning and have a low risk of malignancy.

**Introduction**

Within the cancer population, the discovery of an adrenal mass inevitably leads to a discussion of appropriate management. Since a high percentage of these masses are metastatic, tissue diagnosis may be essential to treatment planning. In many patients, the morbidity of an image-guided biopsy may be avoided and even contraindicated if the mass is a primary adrenal neoplasm. In this review, we explore the incidence, diagnosis, and indication for resection of adrenal lesions in cancer patients, and we suggest a pathway for evaluation and treatment.

Adrenal masses are among the most common of all human tumors, with the prevalence of adrenal incidentaloma at 3% in middle age and increasing to up to 10% in the elderly. Between 1% to 4% of all abdominal imaging studies reveal an adrenal incidentaloma, so with the prolific use of imaging, the number of incidentalomas is increasing. Most are benign, but 2.5% are metastatic disease to the adrenal from another cancer. In a meta-analysis of 32 studies ranging from 1982 to 2002, 19% of adrenal incidentalomas were metastases and 10% were primary adrenal cortical cancers. These studies included 20 or more patients and did not exclude patients with known cancers. Studies that excluded patients with...
known malignancies reported much lower incidences of incidental metastases.\textsuperscript{3} The median time from cancer diagnosis to identification of adrenal metastases was 2.5 years, although adrenal metastases have been discovered up to 22 years after initial treatment.\textsuperscript{4}

**Incidence**

Many metastases to the adrenal glands remain undetected. In a retrospective study over 30 years, Lam and Lo\textsuperscript{5} identified 464 patients with metastases to the adrenal gland. Of these, 435 (94\%) had metastases that were detected postmortem. A total of 49\% of the patients had bilateral adrenal metastases at the time of discovery. Adrenal metastases were the initial presentation in 6 patients, and in two-thirds of the patients, their metastases were detected at the same time as the primary. Of the remaining patients, the adrenal tumors were identified over a median duration of 7 months after the primary, with only 8 patients (< 2\%) having adrenal metastases detected over 5 years from the initial tumor diagnosis.

The most common malignant lesions that metastasize to the adrenal include malignant melanoma, renal, breast, colon, lung, and bronchial carcinomas. Lung and breast cancers account for 39\% and 35\% of adrenal metastases, respectively. Adrenal metastases can be seen in up to 40\% to 50\% of patients with late-stage melanomas and renal cell cancers.\textsuperscript{6-8}

However, with more cancers detected at earlier stages, fewer metastases are found. For example, in renal cell carcinoma, > 60\% of all new cases are now incidentally detected on imaging and present with early stage I or II disease. Adrenal metastasis should be suspected in any patient with a history of cancer who presents with an adrenal tumor, especially if the tumor is > 2 cm.\textsuperscript{9}

**Diagnosis**

Patients with adrenal metastases are typically asymptomatic. When they are symptomatic, they typically present with back pain representing local invasion, retroperitoneal hemorrhage from tumor necrosis, or adrenal insufficiency.\textsuperscript{6} Lam and Lo\textsuperscript{5} reported that 4\% of patients with adrenal metastases presented with symptoms. Also, 1\% of all patients were Addisonian due to lack of cortisol release. The low incidence of Addison’s disease in adrenal metastases may be attributed to the fact that > 90\% of the adrenal glands must be destroyed before there is functional adrenal cortical loss. Even in patients with a history of a known malignancy, 50\% of adrenal masses are benign and thus a definitive diagnosis must be made.\textsuperscript{10}

Imaging of the adrenal glands is largely performed by cross-sectional imaging modalities including computed tomography (CT) and magnetic resonance imaging (MRI). Ultrasonography (US) has a limited role in the evaluation of adrenal masses, though occasionally a suprarenal mass may be detected during abdominal or renal US performed for other clinical indications. Nuclear medicine studies such as I\textsuperscript{131} MIBG scans are often utilized once an adrenal lesion is detected and/or there is clinical suspicion for pheochromocytoma. Newer radiopharmaceuticals are also available in select cases for the evaluation of adrenal adenoma. Additionally, [18F]FDG positron emission tomography (PET) may help to differentiate between benign and malignancy lesions based on threshold standardized uptake value (SUV).

<table>
<thead>
<tr>
<th>Adrenal Lesion</th>
<th>Diagnostic Imaging Characteristics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>Unenhanced CT &lt; 10 HU</td>
<td>Most common mass</td>
</tr>
<tr>
<td></td>
<td>Signal suppression on chemical shift MRI &gt; 60% washout</td>
<td>Often detected incidentally</td>
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<tr>
<td></td>
<td></td>
<td>Can be hyperfunctional</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>Bilateral adreniform thickening</td>
<td>Usually stable over time</td>
</tr>
<tr>
<td></td>
<td>May suppress at chemical shift MRI</td>
<td>Can be hyperfunctional</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Hyperdense on CT</td>
<td>Often seen in trauma, anticoagulation, and sepsis</td>
</tr>
<tr>
<td></td>
<td>Hyperintense on T1-weighted MRI</td>
<td>Excludes underlying mass</td>
</tr>
<tr>
<td></td>
<td>Resolves over time</td>
<td></td>
</tr>
<tr>
<td>Cyst/pseudocyst</td>
<td>Fluid attenuation or signal intensity</td>
<td>Often sequela of hemorrhage or infection</td>
</tr>
<tr>
<td></td>
<td>Lack of enhancement</td>
<td></td>
</tr>
<tr>
<td>Myelolipoma</td>
<td>Macroscopic fat on CT or fat-saturated MRI</td>
<td>Larger lesions at risk for spontaneous hemorrhage</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Hyperintense signal on T2-weighted MRI Positive MIBG scan</td>
<td>Typical clinical presentation or elevated catecholamines Extra-adrenal pheochromangioma</td>
</tr>
<tr>
<td>Primary adrenocortical carcinoma</td>
<td>Large heterogeneous aggressive tumor with necrosis and hemorrhage</td>
<td>Often locally invasive May metastasize May be hyperfunctional</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>Large heterogeneous mass Often bilateral masses</td>
<td>Most commonly from lung, breast, gastrointestinal, renal, pancreas</td>
</tr>
</tbody>
</table>
When an adrenal mass is detected, characterization can be performed by several different imaging techniques (Table). The technique employed is usually determined by institutional preference and experience as well as other clinical factors such as patient history and presentation (ie, known malignancy or hypertension). However, adrenal masses are often detected incidentally at contrast-enhanced abdominal CT performed for other reasons such as abdominal pain or trauma. In this case, many masses are deemed indeterminate, and a dedicated examination is required for further characterization.

Unenhanced abdominal CT can reliably differentiate between lipid-rich adrenal adenomas and nonadenomas, with a specificity of 98% and a sensitivity of 71%. Lipid-rich adrenal adenomas demonstrate unenhanced attenuation values < 10 Hounsfield units (HU) due to the presence of intracellular lipids. The presence of intracellular lipids also allows for diagnosis of lipid-rich adenomas at chemical shift MRI, also known as in-phase and opposed-phase T1-weighted gradient echo (GRE) imaging (Figs 1A-C). Intracellular lipids and water protons process at different frequencies such that at a predetermined echo time based on magnetic field strength, the protons will be pointed in exactly opposite directions (“opposed” or “out of phase”). Therefore, any voxel containing both lipid and water will demonstrate signal suppression on chemical shift MRI. The signal intensity (SI) index can be used to quantify signal suppression, defined as:

\[
\frac{(\text{SI in phase} - \text{SI out of phase})}{(\text{SI in phase})} \times 100
\]

When the SI index is > 16.5%, chemical shift MRI can differentiate adenoma from metastatic disease with 100% accuracy and can identify lipid-rich adenomas with 100% sensitivity and 67% specificity. Unenhanced and contrast-enhanced CT with percentage washout calculation can also be used to evaluate adrenal masses. This technique requires the acquisition of unenhanced phase (U), early phase (E; 60 seconds), and delayed phase (D; 15 minutes) contrast-enhanced imaging for percentage washout calculation defined as:

\[
\frac{(E - D)}{(E - U)} \times 100
\]

Greater than 60% washout yields 96% sensitivity and 88% specificity for adrenal adenomas.

Several other common adrenal masses have specific imaging characteristics that allow for a confident diagnosis (Figs 2A-D). The presence of macroscopic or bulk fat with negative HU on CT or signal suppression on fat saturation MRI techniques indicates myelolipoma, an adrenal tumor containing myeloid and fatty elements. Pheochromocytomas classically demonstrate markedly increased signal intensity on T2-weighted MRI and accumulate MIBG on nuclear medicine scans. Adrenal hemorrhage demonstrate increased signal intensity on T1-weighted MRI and should resolve or decrease in size over time. Adrenal hemorrhage often occurs in the setting of trauma, anticoagulation, or sepsis, but an underlying lesion should be excluded. Adrenal cysts demonstrate similar imaging characteristics to simple cysts elsewhere in the body, such as fluid attenuated...
Adrenal hyperplasia usually presents with bilateral adreniform thickening of the adrenal glands that is often stable over time and can be hyperfunctional. Primary adrenocortical carcinoma and metastatic disease are typically large, heterogeneous masses that do not demonstrate signal suppression on chemical shift imaging and often show areas of hemorrhage and necrosis (Figs 3A-B and Fig 4). Metastatic disease is commonly bilateral.

Certain imaging characteristics of an adrenal mass may limit the differential diagnosis and require further evaluation, such as biopsy or PET. In general, adrenal adenomas measure > 3 to 4 cm, are rounded or ovoid in configuration, and demonstrate internal homogeneity. Conversely, malignant masses are often much larger, exceeding 5 cm with irregular margins and internal heterogeneity. Aside from adrenal cysts, most benign and malignant lesions enhance following the administration of iodinated or gadolinium-based contrast agents; therefore, enhancement alone is not a predictive feature of malignancy. Finally, lipid-poor adrenal adenomas, which may represent up to 30% of adrenal adenomas, do not demonstrate signal suppression at chemical shift imaging due to minimal intracellular fat, but they usually show other imaging characteristics suggestive of benignity such as small size and homogeneity. In this case, surveillance to ensure stability may be a reasonable management strategy. As the most common adrenal mass, adrenal adenoma should lead the differential diagnosis of an incidental adrenal mass, and imaging should be performed to confirm the diagnosis. In fact, one study noted that in 973 consecutive patients with an incidental adrenal mass and no history of primary neoplasm, no malignant lesions were identified. However, medical history plays an important role in other patients with primary tumor or signs of hypersecretion. In patients with known primary malignancy, metastatic disease should be excluded first since distant metastatic disease would upstage the patient and have a profound effect on management. Similarly, in patients with clinical signs of hypersecretion, imaging evaluation should be performed to diagnose hyperfunctional adrenal adenoma or pheochromocytoma.

Fig 2. — Common benign adrenal masses. (A) Contrast-enhanced abdominal CT demonstrates right adrenal myelolipoma with well-defined margins, measuring < 4 cm and containing a globular area of internal fat. (B) Fat-suppressed T2-weighted MRI demonstrates right adrenal pheochromocytoma with markedly increased signal intensity greater than that of the spleen. (C) T1-weighted MRI demonstrates adreniform thickening of the left adrenal and a right adrenal nodule in a patient with adrenal hyperplasia. (D) T2-weighted MRI demonstrates simple-appearing cyst of the left adrenal that did not enhance.
In the common clinical scenario of an adrenal mass detected in a patient with a known or recently diagnosed primary malignancy, unenhanced CT or chemical shift MRI could initially be performed in an effort to diagnose a lipid-rich adenoma. If the mass remains indeterminate, $^{[18F]}$FDG-PET has been shown to differentiate between benign and malignant disease with a sensitivity of 100% and specificity of 98% at a threshold SUV of 3.1.16

**Metabolic Studies**

All patients with adrenal masses should undergo biochemical evaluation for cortical or medullary hyperfunction, particularly prior to biopsy or therapy.17 Patients should be questioned for signs and symptoms of a metabolically active primary adrenal tumor such as hypertension, tachycardia, headache, palpitations, hirsutism, gynecomastia, sudden weight gain, change in body habitus (particularly truncal obesity), and progressive myopathy.6

A complete metabolic workup is necessary to identify a pheochromocytoma and any functional adrenal mass. Functional adrenal tumors effectively rule out a metastatic lesion. Anywhere from 26% to 94% of adrenocortical carcinomas are hyperfunctioning,3 and when multiple adrenal hormones are elevated, a primary adrenocortical carcinoma should be suspected.18 A metabolic evaluation should be performed to determine excess cortisol, aldosterone, and androgens as well as metanephrines. Supraphysiologic hormone production suggests primary adrenal neoplasia and not metastatic disease.

Plasma levels of testosterone and estradiol may be measured; however, hypersecretion of sex hormones is usually clinically evident by signs of virilization or feminization. Benign masses secreting androgens or estrogens are rare, and therefore all should be approached as if malignant.

Measuring the levels of fractionated plasma-free metanephrines is a more sensitive and convenient test for pheochromocytoma than measuring 24-hour urine levels of fractionated metanephrines, free catecholamines or vanillylmandelic acid (VMA). Levels of plasma catecholamines, however, are less specific than a urinary test.

Spontaneous hypokalemia ($\leq$ 3.5 mmol/L) combined with hypertension is highly suspicious for mineral corticoid excess. However, more than 50% of patients with primary aldosteronism are normokalemic. Although plasma potassium should be checked, a normal level does not exclude an aldosterone-secreting mass.19 The most effective test for screening for an aldosterone-secreting tumor is measurement of the plasma levels of aldosterone and renin activity checked with the patient sitting upright. An aldosterone-to-renin ratio $\geq$ 20 is suspicious for an aldosterone-secreting tumor if plasma aldosterone is also

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**Fig 3.** — Contrast-enhanced CT through the right adrenal. (A) A large, heterogeneous, irregular mass and (B) an ill-defined mass proven to be primary adrenocortical carcinoma presenting with rib metastasis are shown.

**Fig 4.** — Contrast-enhanced CT demonstrating large, bilateral, heterogeneous adrenal masses with areas of internal hemorrhage and necrosis in a patient with lung cancer and right pleural effusion.
A ratio of plasma aldosterone to plasma renin of > 30 combined with a plasma aldosterone level > 20 ng/dL has a sensitivity of 90% and a specificity of 91%. Kidney failure, beta blockers, antisympathetic agents, and calcium channel blockers all interfere with the aldosterone-renin pathway and may alter plasma aldosterone and renin levels. Additional testing with the 25-mg captopril test, salt-loading or saline infusion tests, or fludrocortisone suppression test should be used to confirm primary aldosteronism. If biochemical evidence of hyperaldosterism is obtained, selective venous sampling for aldosterone should be obtained prior to resection. A ratio of at least 3:1 confirms lateralization of production and subsequent correction after adrenalectomy. At least 60% of Conn’s syndrome is bilateral, even with imaging.

Adrenocortical carcinomas, adrenal adenomas, and bilateral hyperplasia may secrete cortisol. Screening for a cortisol-secreting tumor should include a 24-hour urinary free cortisol level or a fasting a.m. cortisol level, with an adrenocorticotropic hormone (ACTH) level and a dexamethasone suppression test to confirm autonomy.

A basal urinary free cortisol excretion > 3 times the upper limit of normal is diagnostic for hypercortisolism. Cortisol-secreting tumors may alter the circadian rhythm of cortisol secretion, leading to an elevated midnight cortisol level. Based on this premise, testing the midnight salivary cortisol level has gained popularity due to its higher sensitivity and ease of collection and should be performed on two consecutive days. The addition of the dexamethasone suppression test helps catch false-negative results in patients who were not identified by the urinary free cortisol test. Failure to suppress the cortisol level to < 1.8 mg/dL identifies autonomous production of cortisol. ACTH levels may be suppressed or normal on baseline but should suppress with dexamethasone. A dexamethasone level may be drawn concurrently to confirm compliance with taking the medication, particularly with equivocal results.

We recommend that all functioning adrenal lesions be removed, if practical (Fig 5).

**Indications for Resection**

In general, increased median and overall survival has been demonstrated for resection of clinically isolated adrenal metastases when compared to nonsurgical therapy. Since resecting isolated metastases in other organs has achieved long-term, disease-free survival, it is reasonable to expect that resecting isolated metastases to the adrenal gland should provide similar results. Numerous reports exist about patients who are cancer-free many years after resection of isolated adrenal metastases. Critics argue that these patients may have survived just as long without resection because their underlying disease is slow-growing.

Two studies reported improved survival in patients who had NSCLC with isolated adrenal metastases treated with surgical resection over those treated nonsurgically. Luketich and Burt reported a median survival of 31 months for patients who underwent adrenalectomy compared with a median survival of 8.5 months for those receiving chemotherapy alone. No patients in the chemotherapy group survived more than 22 months. In another study of patients with lung cancer whose solitary site of metastasis was to the adrenal gland, a review of 11 reports that included a total of 32 patients showed a median survival of 2 years, with one-third of the patients surviving > 5 years after adrenalectomy. In general, 1 in 4 patients achieve a 5-year disease-free survival; therefore, adrenalectomy should be offered to patients with isolated adrenal metastases, particularly when the primary cancer is well controlled.
Adrenal neoplasm in the extra-adrenal cancer patient

Positive

Hormonal evaluation for excess adrenal function

Negative

Isolated adrenal neoplasm

Yes

Metachronous presentation (>6 months from diagnosis)

Yes

Size > 4 cm

No

Imaging typical for lipid-rich adenoma

Yes

Positive for metastasis

FNA

Negative for metastasis

No

Change in malignant potential

Interval surveillance imaging every 3-6 months

No

Systemic therapy for primary cancer

Fig 5. — Algorithm for evaluation and treatment of an adrenal neoplasm in the extra-adrenal cancer patient.

1 Autonomous production of cortisol, aldosterone, metanephrines, and estradiol/testosterone.
2 In all cancer patients, consideration for surgery must include an overall assessment of prognosis and alternate treatments as influenced by the primary cancer.
3 Change in size (>4 cm or 1 cm/year); progression of features not consistent with lipid-rich adenoma.
Laparoscopic Vs Open Resection

Laparoscopy is the accepted approach of choice for benign adrenal lesions. Laparoscopy allows for inspection of the entire abdomen and facilitates dissection in the upper quadrants of the abdomen. Compared with open adrenalectomy, laparoscopic adrenalectomy is associated with less pain, lower blood loss, reduced morbidity, and shorter hospital stay. Laparoscopic resection of malignant tumors is more controversial. The question of whether laparoscopic adrenalectomy is oncologically comparable to open adrenalectomy with equivalent recurrence rates and disease-free survival is not completely answered, although oncologic principles of adequate margins should govern any surgical decision.  

Solitary adrenal metastases are usually confined within the capsule of the adrenal gland and thus are amenable to laparoscopic adrenalectomy. To reduce the risk of local recurrence, the periadrenal fat should be resected along with the adrenal gland. Laparoscopic resection has been shown to be safe if preoperative studies do not indicate local tumor invasion into adjacent organs, lymphadenopathy, extra-adrenal metastases, tumor size of > 9 cm, or inferior vena cava (IVC) thrombus.  

Strong et al compared 31 attempted laparoscopic adrenalectomies with 63 open adrenalectomies over an 11-year period. Four patients (13%) required conversion to open adrenalectomies. Local recurrence was 17%, and neither local recurrence nor disease-free survival differed between the open and the laparoscopic approaches. For the entire group, the median survival was approximately 30 months and did not differ between the two operative approaches. Similarly, for patients with tumors < 4.5 cm, the median survival was 40 months and did not differ between operative approaches. For patients with tumors > 4.5 cm, however, the difference in survival was significant, favoring the open adrenalectomy group. Microscopic margins were positive in 29% of the open adrenalectomy group and in 22% of the laparoscopic group without statistical significance. Laparoscopy was associated with fewer complications, less blood loss, reduced operative times, and shorter hospital stay.  

Outcomes

Castillo et al performed 34 laparoscopic adrenalectomies in 32 patients for suspected adrenal metastases. Patients with tumors > 10 cm with evidence of periadrenal infiltration, thrombus of the inferior vena cava, or locoregional lymphadenopathy were excluded. Of the 34 glands resected, 22 (64.7%) contained malignancy upon pathologic analysis, with a mean tumor size of 5.1 cm. The mean survival time of patients with malignancy was 26 months. Two positive margins and no open conversions or port site recurrences were reported. Similarly, in another series of 13 patients who underwent laparoscopic resection, none had positive margins and none had local recurrence.  

Port-site recurrences have been estimated at 0% to 6.25%, while open adrenalectomy has a wound recurrence rate of approximately 0.4%. Recent studies reported that local recurrence rates and incidence of peritoneal metastases were similar for open and laparoscopic approaches. Preventing tumor spillage, coupled with using standard laparoscopic specimen bags, reduces the higher rates of port site and peritoneal metastases. Currently, it is acceptable to begin all resections of isolated adrenal metastases laparoscopically except those that are > 9 cm or show local invasion or IVC thrombus. Conversion to an open approach is recommended if tumor adhesion, invasion into adjacent organs, or lymphadenopathy is evident or if the tumor is too large to be safely resected laparoscopically. We also recommend en bloc resection of peritumoral Gerota’s fat for margin.  

In a retrospective review of 37 patients who underwent open adrenalectomies for isolated metastases, Kim et al found a median length of stay of 8 days and a 19% incidence of complications with 1 perioperative death. A total of 43% of the metastases were synchronous with the primary carcinoma. The median disease-free interval for metachronous lesions was 15 months. The median disease-free survival was 11 months, with a 5-year disease-free survival rate of 21%. The median overall survival was 21 months, with a 5-year survival rate of 24%. A disease-free interval between resection of the primary tumor and adrenalectomy of the metastasis of more than 6 months and a complete resection were predictors of improved survival.  

In a retrospective review of 92 patients who underwent a combination of laparoscopic and open adrenalectomies for metastatic disease, the only predictors of decreased survival were adrenal size of > 4.5 cm and local recurrence. No one in the locally recurrent group survived 5 years. Overall, the 5-year survival rate was estimated to be 31%. The median survival for those with negative margins was 36 months compared with 18 months for those with positive margins. The majority of these patients had NSCLC as their primary tumor. Similarly, Lo et al demonstrated a median survival of
Alternatives to Surgical Resection

Not all patients are candidates for surgical resection due to medical comorbidities, local tumor invasion of surrounding viscera, the presence of multiple metastases, or personal preference. Although surgical resection extends survival, alternative therapies for patients who are not surgical candidates may also prolong survival and palliate symptoms.

Minimally invasive therapies can be divided into catheter-based therapies, ablative therapies, and thermal ablative therapies. Most of the experience with these therapies exists in treating primary liver malignancies or metastases to the liver. A few studies, which are discussed in the next section, have examined the use of these techniques in both benign and malignant adrenal disease. Tumor ablation is an attractive option for small adrenal tumors, for palliation of painful metastases not amenable to resection, and for treatment of patients who are not candidates for surgery. Most procedures can be performed on an outpatient basis under radiological guidance with sedation and minimal morbidity. In addition, the procedures may be repeated multiple times, can be used in conjunction with other treatment modalities, and may be less expensive than surgical resection.

Radiofrequency Ablation

RFA has been used to ablate tumors in multiple tissues. RFA produces coagulative necrosis via an alternating high-frequency electric current in the radiofrequency range (460 to 500 kHz). By converting radiofrequency waves to thermal energy, radiofrequency denatures the intracellular and extracellular proteins in a tumor. When compared to other ablative techniques, the use of RFA in the liver for hepatocellular carcinoma (HCC) has shown the best overall survival rate. Case reports in the literature have shown that RFA is a safe and well-tolerated procedure for unresectable adenocortical carcinoma as well as HCC metastases to the adrenal. RFA has been suggested to be superior to radiation for pain palliation because the onset of relief is faster and because there is less damage to surrounding tissues.

Lo et al reported on successful palliative ablation of bilateral adrenal metastases in a patient with metastatic lung cancer. The lesions were 4.7 cm and 4.3 cm. Six months after ablation, the patient was still pain free without signs of adrenal insufficiency. Mayo-Smith et al studied RFA in 13 adrenal masses in 12 patients. Eleven adrenal lesions were metastases, 1 lesion was a pheochromocytoma, and 1 was an aldosteronoma. The mean tumor size was 3.6 cm. At a mean follow-up of 11.2 months, 11 of the 13 tumors were successfully ablated after one session without any residual tumor or growth on imaging. Two of the 11 patients with metastases had enhancement of residual tissue on follow-up imaging, suggesting incompletely treated residual tumor. The mean size of these tumors was 6.0 cm vs a mean size of 3.4 cm in the successfully ablated masses, although the difference was not statistically significant. None of the patients who were completely treated had recurrent tumor or tumor progression, indicating adequate local control. Also, none of the patients developed hypertension. Complications included a self-resolving hematoma in a thrombocytopenic patient, shortness of breath that resolved with diuretics, and adrenal insufficiency in a
patient with bilateral metastases treated at separate sessions. As a result, the authors recommend ablation for masses < 5 cm. Although it is possible to treat bilateral adrenal metastases, caution is advised in this group of patients as posttreatment adrenal insufficiency may result.\(^5\)

Compared with other ablative therapies, RFA tends to have higher rates and severities of adverse events, including pain, fever, and cutaneous burns, with a reported mortality rate of 0.5% and complication rates of 8% to 35%.\(^4\)\(^3\)\(^,\)\(^5\)\(^1\)\(^,\)\(^5\)\(^2\). These outcomes are similar to surgical outcomes reported by Kim et al.\(^3\)\(^0\). The key limitation in RFA is creating adequate volumes of tissue destruction, particularly in areas close to blood vessels, which act as heat sinks.\(^4\)\(^2\). Complications from RFA can be broken into those related to electrode placement and those related to thermal ablation. Complications from electrode placement include bleeding, infection, and tumor seeding. The reported rate of needle track seeding is approximately 3%,\(^4\)\(^2\) which is similar to the laparoscopic port site seeding rate of 0% to 6%.\(^3\)\(^8\). Adrenal ablation offers little room for probe placement error due to the closely adjacent heat-sensitive structures. Right adrenal lesions are thought to be easier to ablate due to coverage by the liver. The left adrenal gland is surrounded by the

Fig 6. — Axial, sagittal, and coronal views of a patient treated with external beam radiation therapy in the prone position to the right adrenal bed following resection. Note that the patient has only one remaining right kidney and that the treatment field was able to avoid significant dose to preserve function.
spleen, pancreas, stomach, and colon. Complications from thermal ablation include damage to nontarget tissues, grounding pad burns, and metabolic complications such as acute malignant hypertension.\textsuperscript{53,54} Occurrence of malignant hypertension can be minimized by preoperative alpha blockade followed by beta blockade.\textsuperscript{55}

**Radiotherapy**

Technological advances in radiation planning and delivery have now expanded this noninvasive modality as another potential form of local therapy. Historically, external beam radiotherapy (EBRT) has been associated with the treatment of large target volumes with significant concern for normal tissue morbidity. Modern techniques, however, now permit the safe delivery of higher doses of radiation to the target region while sparing the adjacent normal tissues (Figs 6-7). This evolution has paralleled the integration of CT-based software into radiation planning systems so that the dose received by volumes of tissue can be measured. Radiation oncologists now use data from the dose volume histogram (DVH) to prospectively evaluate treatment plans for the individual patient.

Treatment of adrenal metastases with EBRT is challenging. First, with the location of the tumor in the upper abdomen, tumor motion associated with respiration is possible.\textsuperscript{56,58} In fact, these studies of upper abdominal structures have shown potential for significant respiration-associated motion in the superoinfero, mediolateral, and anteroposterore directions. Second, potential acute and late normal tissue toxicity is a concern, given the proximity of the adjacent kidney, liver, small intestine, stomach, and spinal cord. Third, the daily target treatment position is uncertain since organ motion (gastrointestinal tract filling, peristalsis) can vary from day to day.\textsuperscript{59}

Current techniques permit management of these issues so that treatment of adrenal metastases not only is technically possible but also may offer improved opportunities for local control with minimal toxicity. Data on how best to exploit the benefits of EBRT in this setting continue to emerge. One potential role for radiation would be in the adjuvant setting following surgical resection. Studies exploring this are limited; however, Oshiro et al\textsuperscript{60} recently reported their experience with 19 patients who were treated adjuvantly following resection of adrenal metastasis from lung cancer. With a metachronous metastasis, overall 1-, 2-, and 5-year survival rates were 83\%, 56\%, and 56\%, respectively.

Another consideration for EBRT is its role as definitive ablative therapy. With the translation of intracranial stereotactic radiosurgery techniques to extracranial ap-

![Fig 7. — Beam arrangement accompanying the images in Fig 1. This shows the patient in the prone position with multiple beams that were chosen to selectively target the right adrenal bed while sparing adjacent normal tissue as much as possible.](image-url)
Complications, stereotactic body radiation therapy (SBRT) is now available.64 This treatment differs from that of conventional 5- to 6-week therapy since it compresses the course to 5 days or less with a significantly more biologically potent dose strategy. Timmerman et al65 reported the confirmation of efficacy based on multiple prospective trials using SBRT in a variety of patient populations. In the abdomen, the largest SBRT trials to date have been conducted in those patients with liver metastases or with pancreatic primary lesions. Rusthoven et al66 reported the multi-institutional experience of treating 47 patients with 63 liver metastases with an SBRT dose of 60 Gy in 3 fractions, reporting a median survival of 20.5 months and a 2-year actuarial local control rate of 92%. Rule et al67 reported a 5-fraction, phase I dose escalation trial that did not reach the maximum tolerated dose on a series of 27 patients with liver metastases, showing an actuarial 2-year local control rate of 100%. Finally, Chang et al68 updated the Stanford single-fraction SBRT experience for their series of 77 pancreatic cancer patients, noting a rate of freedom from local progression at 12 months of 84%.

Reports are now emerging for outcomes with SBRT in the setting of adrenal metastasis. Torok et al69 reported data on 7 patients with 9 adrenal lesions treated. The primary malignancies in this series were mainly lung (4 non–small cell and 1 small cell), with 2 patients having primary HCC. Patients received 1- to 3-fraction SBRT, with a 1-year actuarial local control rate of 63% and a median overall survival of 8 months from SBRT. Japanese investigators reported a series of 10 patients treated with SBRT to 48 Gy with no patient developing significant toxicity and 5 patients achieving a complete response. The 1-year overall survival rate was 78% and the local control rate was 100%.67

As more studies evaluate the hypothesis that local control of oligometastatic disease might lead to improved systemic control, there may be an expanding role for high-dose, short-course stereotactic treatment.60,61 The ability to offer a noninvasive, well-tolerated form of therapy that can be given to patients who are medically inoperable or have surgically unresectable disease is readily advantageous. Now that advanced techniques have paved the way for the safe delivery of high-dose radiation to the adrenal gland while minimizing adjacent normal tissue toxicity, it is time for future trials to better characterize outcomes so that the role of radiotherapy as an alternative or adjunct to surgical resection can be better defined.

**Arterial Embolization**

Arterial embolization has been successful in ablating functional benign adrenal tumors in patients with one or two feeding vessels.70 A total of 88% were successfully treated as measured by loss of tumor stain on angiography and decreased CT enhancement and by normalization of adrenal hormone. The mean duration of success was 45 months, and most patients required multiple procedures.70 Complications included back or flank pain, mild fever, labile blood pressure, and pleural effusion. Hypertensive crisis has been reported with ethanol injection into the adrenal artery.71,72 Arterial embolization may be less effective for malignant masses than for benign adrenal masses since malignant adrenal tumors are usually fed by multiple blood vessels.73,74

A combination of RFA and chemoembolization has been used to treat primary HCC liver lesions with good response. Momoi et al73 retrospectively analyzed 20 patients with adrenal metastases from HCC. Seven patients treated with transarterial chemoembolization or percutaneous ethanol ablation had a median survival of 11.1 months. Because of a heat-sink effect, the size of the ablative zone resulting from RFA is influenced by blood flow. As both adrenals and HCC tumors are usually hypervascular, combining chemoembolization and RFA should augment both modalities.

Yamakado et al75 reported on 6 patients with 8 adrenal HCC metastases that were managed with combined-modality therapy. All patients either were not surgical candidates or refused surgery. In 7 of the 8 tumors, CT enhancement disappeared after a single RFA treatment. In the remaining tumor, CT enhancement disappeared after two treatments. During a mean follow-up of 37.7 ± 27.6 months, local progression occurred in 2 of the 8 tumors at 3.0 and 7.7 months. Both tumors were initially larger than 5.0 cm (5.9 cm and 7.4 cm) and in both tumors, progression was seen at the renal hilum. In all other tumors, enhancement continued to be absent and tumors regressed. Median survival was 24.9 months, with 2 patients surviving > 4 years. In patients with poorly controlled liver disease, mean survival time was 13.8 months.

Even combined with chemoembolization, tumors larger than 5 cm are difficult to control with RFA, which may be due to a combination of the heat-sink effect and an inability to embolize the entire tumor blood supply. Without treatment, the median survival time of patients with HCC adrenal metastases is as low as 5.64 months.74 Combined-modality treatment with RFA and arterial chemoembolization offers a safe, feasible treatment option for patients with HCC adrenal metastasis who are not surgical candidates.

**Chemical Ablation**

Xiao et al76 reported on the largest series of patients in the literature undergoing percutaneous chemical ablation for adrenal tumors. In their retrospective review of 37 patients with 46 tumors, 20 of which were metastatic lesions, acetic acid was injected into tumors > 3.0 cm and ethanol into those < 3.0 cm. Response was better in primary adrenal lesions than in metastatic lesions. Of the 20 metastatic lesions, 6 had a complete response and 14 had a partial response at 2-year follow-up. Transient pain was the only reported complication.
Percutaneous ethanol ablation was first reported in 1986 on a small series of patients with nonresectable HCC. Ethanol lyses cell membranes, denatures cell proteins, and induces vascular thrombosis. However, in order for ethanol to be effective, it must reach the entire tumor. Tumor heterogeneity caused by necrosis and fibrosis can impede effective distribution of ethanol within the target tumor.

Shibata et al78 reported on 7 patients with 9 metastatic HCC adrenal lesions treated with percutaneous ethanol ablation. The patients required two to four sessions, with adequacy of treatment judged by lack of tumor enhancement on CT imaging. The main side effects were pain and fever during injection. At a follow-up of 6 to 36 months, 4 patients were alive, and 3 had died (1 of liver failure at 8 months, 1 of brain metastases at 15 months, and 1 of multiple metastases at 36 months).

**Other Therapies**

Cryoablation has been used as a surgical alternative for the treatment of tumors in many tissues. Cryoablation of adrenal masses has been reported as safe and efficacious in canines. In humans, however, the majority of cases reported in the literature have been complicated by acute malignant hypertension during the procedure. Therefore, preoperative treatment with alpha blockade and possibly beta blockade is recommended at a minimum of 10 to 14 days before the procedure.

CT-guided or MR thermotherapy-controlled laser-induced interstitial thermotherapy has also been used to ablate metastatic adrenal tumors in 9 patients. At a mean follow-up of 10 months, 7 of 9 tumors were completely ablated, while the remaining 2 tumors had progressed at 5 and 6 months. Mean tumor size was 4.3 cm.80 Further studies are indicated since this is a single case study.

**Conclusions**

Although the adrenal gland is a common site of metastasis for many malignancies, primary adrenal lesions are also commonly found in cancer patients. The extensive use of cross-sectional imaging for staging and follow-up has substantially increased the identification of isolated adrenal lesions. Stratifying these tumors based on risk of malignancy and hypersecretion allows for appropriate treatment planning. Complete biochemical and radiologic workup should be completed prior to initiating treatment for metastatic disease to assess for hypersecretion of cortical hormones and metanephrines and to determine the risk of malignancy. Hypersecreting tumors should be surgically resected. Benign adenomas by imaging criteria can be followed by serial, cross-sectional imaging. Tumors with higher malignant potential should be resected. Resection of solitary metastases, specifically metachronous lesions, can improve long-term survival and should be considered as primary treatment. Synchronous adrenal metastasis or metastasis associated with additional metastatic disease should be treated with systemic therapy and may be considered for palliative ablative therapies. When surgical resection is not an option, several minimally invasive treatment options and newer radiotherapy techniques exist to palliate symptoms with some success.

**References**
