Adrenal Gland

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Adrenal lesions may present as an incidental finding, with locoregional symptoms or with symptoms related to hormonal secretion. They should be investigated for possible hormonal secretion, and the risk of malignancy, either primary or secondary, should be assessed. This chapter concentrates on adrenocortical carcinoma and pheochromocytoma since they represent the most common malignant adrenal lesions. The focus is made on surgical resection, which is the mainstay of treatment for locoregional and isolated metastatic disease. Other palliative options, such as radiation, chemotherapy, and other modalities may alleviate symptoms related to the mass effect and control hormonal secretion in inoperable cases. These options, as well as possible medical therapies, will also be reviewed.

22.1 The Adrenal Incidentaloma and Associated Risk of Malignancy

Adrenal incidentalomas may be found in 4–7 % of abdominal CT scans. Up to 5 % of these will be adrenocortical carcinomas (ACC), and 2.5 % will be metastatic cancers [1]. Figure 22.1 presents a suggested management algorithm for such incidentally discovered adrenal masses. Malignancy is suspected by combination of clinical, biochemical, and radiological characteristics. An endocrine syndrome can be found in 60 % of ACC, most commonly Cushing syndrome (50 %), virilization (<10 %), or a combination

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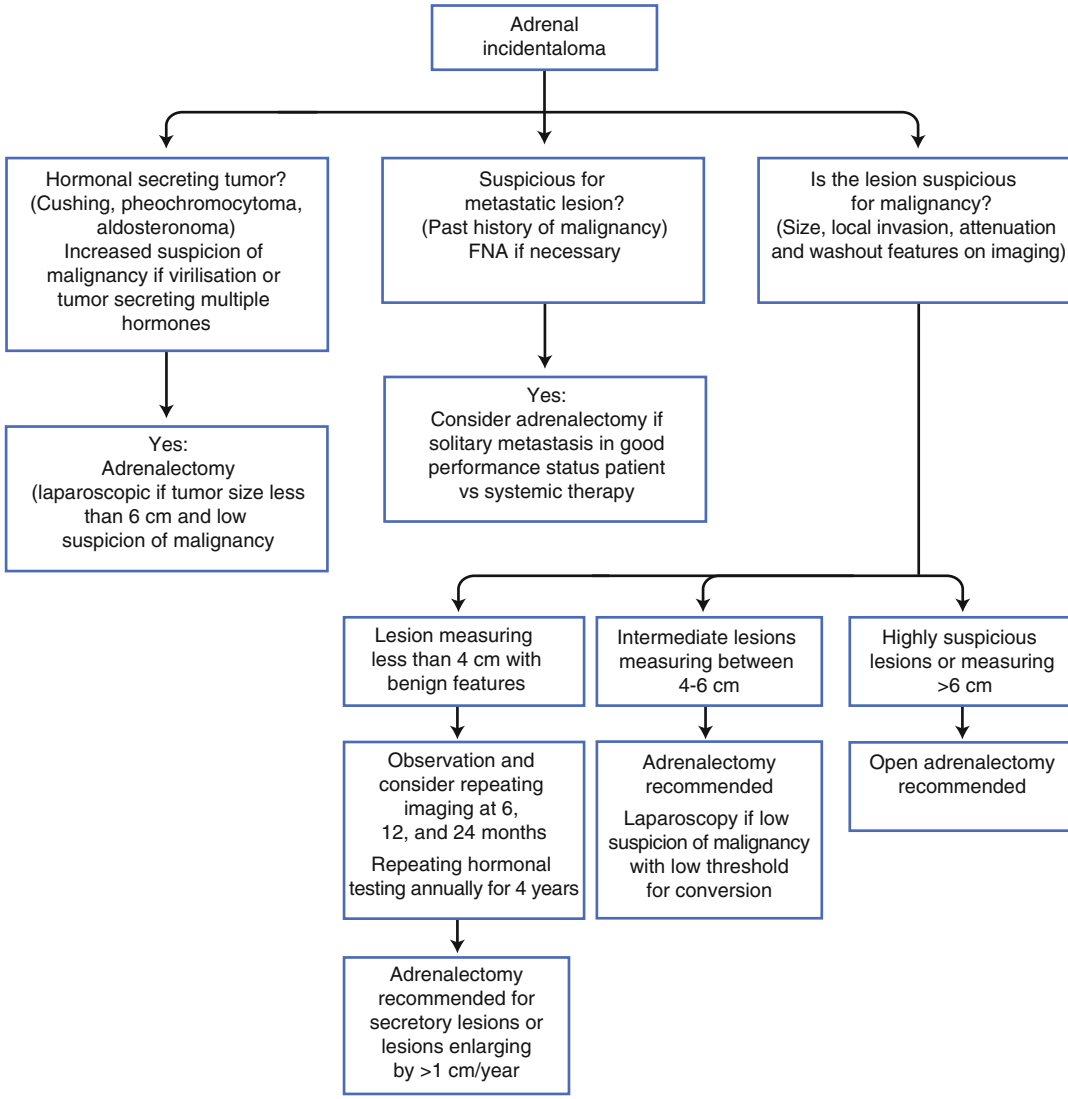

Fig. 22.1 Management algorithm for incidentally diagnosed adrenal masses

of both (25 %) [2]. On imaging, both size and appearance (attenuation and washout) are important. Ninety-five percent of ACC are greater than 5 cm at diagnosis [2]. Resection is recommended for incidentalomas >4 cm [1] since ACC is estimated to represent only 2 % of smaller lesions [3]. Tumor growth on serial radiologic imaging is also vital to consider. Other suspicious characteristics on imaging are an attenuation value of >10 Hounsfield units (HU) on unenhanced computerized tomography (CT) and >30 HU on enhanced scans as well as a delayed washout (less than 60 % at 15 min). CT scan and magnetic resonance imaging (MRI) are considered equivalent, but MRI may allow better assessment of extra-adrenal extension. Use of 18-Fluorodeoxyglucose (FDG)-PET may increase sensitivity and specificity, but due to limited experience and high costs, it is not routinely recommended [3]. Fine needle aspiration (FNA) biopsy can differentiate adrenal and non-adrenal tissue and is therefore indicated in suspicion of metastatic disease (once pheochromocytoma ruled out via biochemical testing) [1]. The idea that laparoscopy leads to

increased recurrence is now controversial, and some series suggest comparable outcomes, particularly for lesions <10 cm in diameter and when the surgery is performed by an experienced surgeon [4]. Current consensus with resection of *likely* ACC (local invasion, diameter of >6 cm or suspicious imaging features) is still via open surgery in order to avoid tumor rupture [3].

22.2 Adrenocortical Carcinoma (ACC)

ACC are very rare malignant tumors (1–2 per million per year) [2]. Randomized clinical trials are lacking, and thus, the majority of the data on its management comes from small published series. The malignancy of an adrenal lesion is determined on histology with Weiss score, graded from zero to nine with each of the following criteria administered one point if confirmed on pathology: high mitotic rate, atypical mitoses, high nuclear grade, low percentage of clear cells, necrosis, diffuse architecture of tumor, capsular invasion, sinusoidal invasion, and venous invasion. A score of three or greater is associated with malignancy. Ki67 immunohistochemical staining has been found to be helpful in confirming malignancy and correlating with prognosis [5].

22.2.1 Prognosis

The two major prognostic factors are disease stage and margin status on pathology from initial surgery. In presence of metastatic lesions, the 5-year survival drops from 58–66 % to 0–24 %, and survival is usually less than 13 months [5]. The most common sites for distant disease are the lungs, liver, and bones. Significant prognostic factors include a Weiss score of >3, a mitotic index of >6/10 HPF, and a large tumor burden (>12 cm) [3]. Survival is improved by complete tumor resection, but even in presence of radical resection, relapse is seen in 75–85 % of patients [6]. This supports the need for adequate surgery and adjuvant treatments.

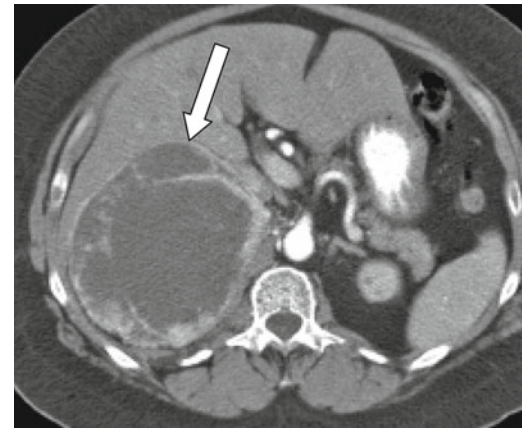

Fig. 22.2 A 38-year-old male presenting with an abdominal mass. Contrast-enhanced CT demonstrates a 10-cm right adrenal complex mass (*arrow*), proven to be adrenal carcinoma at histology (Used with permission from Boland [14])

22.2.2 Treatment

Treatment for ACC should consider patient factors and the oncology and potential endocrinology aspects of the tumor.

22.2.2.1 Surgery

Whenever feasible and safe, complete en bloc resection of the primary tumor and distant or recurrent disease should be performed [3, 7]. In particular, the threshold to perform nephrectomy should be low if invasion is suspected, providing preoperative confirmation of bilateral kidneys and good renal function is obtained. Direct invasion of the vena cava or intracaval tumor thrombus does not contraindicate surgery [3]. Surgical debulking may be considered in certain selected cases, but this approach has not demonstrated improvement in survival, and data are lacking to support it. Decision-making factors include the presence of symptomatic hormone hypersecretion, rate of progression, tumor grade, and patient performance status [3]. Debulking mainly serves to control tumor-related endocrine syndromes and possibly to increase the efficacy of other therapies although these patients, due to their reserved prognosis, may be better palliated medically. There is currently no role for neoadjuvant therapy in unresectable tumors. See Fig. 22.2.

22.2.2.2 Chemotherapy

The data on the use of adjuvant mitotane come from retrospective studies and the benefit on survival of these data is unclear. A published report [6] has shown that adjuvant mitotane, compared to surgery alone, led to prolonged disease-free survival (42 months vs. 10–25 months) and improved median overall survival (110 months vs. 52–67 months) in completely resected ACC. However, other series [7] have failed to demonstrate the same result. Mitotane should be considered for patients with the highest risk of recurrence, including high-grade disease, intraoperative tumor spillage, and presence of vascular or capsular invasion [6]. When used, a minimal duration of 2 years under the guidance of a medical oncologist is recommended [3]. While receiving mitotane, monitoring includes measurement of ACTH, urinary free cortisol, thyroid function, serum testosterone, lipids, and electrolytes [3]. Adrenal insufficiency must be supplemented, most commonly consisting of glucocorticoid and fludrocortisone. Other side effects include gastrointestinal (nausea, vomiting, diarrhea) and neurologic symptoms (lethargy, confusion, dizziness, ataxia). At this time, no other chemotherapy regimen, alone or in combination with mitotane, has been proven to be more effective than mitotane alone, but some centers do have combination protocols that are considered on a case-by-case basis. In the face of acknowledged palliative setting (locally advanced or metastatic disease), there is no survival benefit demonstrated with mitotane alone or in combination [8].

22.2.2.3 Radiation

ACC was previously thought to be radioresistant. Though not prospectively proven, some studies have shown a reduced local recurrence rate with adjuvant external beam radiation therapy (EBRT) [3]. Possible indications for EBRT include incomplete resection, uncertain resection status, intraoperative tumor violation, positive lymph nodes, diameter of >8 cm with evidence of vascular invasion, and a Ki67 of >10 %. Clear indications include palliation of metastatic disease to the brain and bone and with documented spinal cord compression or superior vena cava syndrome [3]. Radiation may also be considered in the presence of non-resectable persistent or recurrent local disease [3], but preferably administered in symptomatic cases only. It is generally well tolerated with mostly mild to moderate nausea, anorexia, and liver and kidney function impairment.

22.2.2.4 Additional Potential Palliative Treatment Options

Radiofrequency ablation (RFA) can be considered in inoperable patients or in the presence of metastatic disease, where the benefits of surgery are slim and do not outweigh the risks [3]. Its long-term efficacy and effect on survival remain unconfirmed. It is best considered in primary tumors that are <5 cm in diameter, located away from vital structures and large blood vessels [3], and in the treatment of liver metastasis. For arterial embolization, there is limited information, but it may provide adequate palliation of pain and a decrease in hormone production without major side effects [9]. Embolic agents include alcohol foam, stainless steel coils, ethanol, and gelfoam.

22.2.2.5 New Therapies/Under Investigation

Different immunotherapies are being studied in ACC, including the use of dendritic cells and DNA vaccination [3] and cytotoxic adenoviral gene therapy. Many growth factors have been found to be overexpressed in ACC (i.e., vascular endothelial growth factor, epidermal growth factor receptor, and insulin-like growth factor type 2) and may be promising targets as the field of oncogenomics develops.

22.3 Medical Management of Adrenal Hypersecretion

Palliative control of hypercortisolism is usually achieved with metyrapone and/or ketoconazole [2]. Their effect is apparent within a few days and is assessed by measuring the 24-h urine cortisol. If control is not achieved, mitotane and/or mifepristone (glucocorticoid receptor antagonist) can be added [2].

22.4 Pheochromocytoma (PCC) and Paraganglioma

Pheochromocytomas are part of the neuroendocrine tumor family. They commonly present with episodic hypertension, headache, diaphoresis, and tachycardia but can also be found incidentally. To diagnose a malignant PCC, the presence of local invasion and distant metastasis is needed, and such lesions are not curable. Up to 25 % are part of a hereditary syndrome, most commonly multiple endocrine neoplasia and von Hippel-Lindau. Initial management targets control of hypertension and prevention of hypertensive crisis. This starts with an alpha-adrenergic blocker and may then include beta-adrenergic and calcium channel blockade. Metyrosine, a catecholamine synthesis inhibitor, can also be used. Patients with malignant disease have an average 5-year survival of approximately 50 % [10]. Common sites for distant disease are the bones, liver, and lungs. Treatment options for malignant PCC include surgery (the mainstay of treatment), metaiodobenzylguanidine (MIBG) radiotherapy, and systemic antineoplastic therapy. There are no randomized control trials to determine which nonsurgical treatment is more effective. Therapies targeted at the adrenal bed, including EBRT, RFA, cryoablation, and arterial embolization, have been described in case series, and they should be used selectively [10]. As for other metastatic tumors, these modalities can also be considered for treatment of symptomatic metastatic lesions (e.g., EBRT to bone metastasis, RFA for liver lesions). See Fig. 22.3.

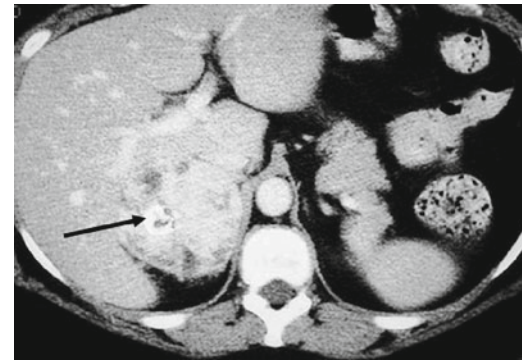

Fig. 22.3 A 56-year-old female with a pheochromocytoma. Contrast-enhanced CT image demonstrates a 5-cm hypervascular mass containing calcification (*arrow*) in the right adrenal gland. Although its imaging appearance is nonspecific, the patient had a history of "panic attacks" and laboratory evidence to support the diagnosis of pheochromocytoma. At surgical pathology, a pheochromocytoma was diagnosed (Used with permission from Hindman and Israel [15])

22.4.1 Surgery

Surgical resection after medical preparation for elevated catecholamine secretion should be considered in all cases of localized and isolated metastatic disease. Laparoscopy is the preferred approach for PCC with a low risk of malignancy [11]. However, in case of doubt, conversion to an open procedure should be performed. In a series of 176 operated patients, PCC had a 15 % rate of recurrence, and of those recurrences, 52 % were malignant. Risk factors for recurrent disease were familial cases of PCC, extra-adrenal tumors (paragangliomas), right-sided tumor, and operative capsule breach [12]. Although there are no firm data to support resection of metastasis, it appears to improve symptoms from abnormal hormone secretion and possibly increase survival [10]. Tumor debulking is considered a mainstay of treatment, palliating the hypersecretory state and possibly improving the efficacy of MIBG radiotherapy on residual lesions. However, its role is unclear in asymptomatic low-secreting tumors [10].

22.4.2 Chemotherapy

Systemic treatment, with a combination of cyclophosphamide, vincristine, and dacarbazine, is considered in patients with rapidly progressive and symptomatic disease and in cases negative for MIBG uptake or refractory to this treatment [10]. Tyrosine kinase inhibitors, such as sunitinib, appear promising but unproven.

22.4.3 MIBG Radiotherapy

MIBG is a selective treatment option when coupled with radioactive iodine. A retrospective

study of 116 patients [13] demonstrated partial tumor response in 24–45 % of patients. It is generally well tolerated with possible mild myelosuppression. This treatment option is considered in slow-growing disease with positive uptake on MIBG scintigraphy. The benefit of a high-dose regimen does not outweigh the risks of increased toxicity and is not recommended [10].

22.4.4 Combination Therapy

Overall, MIBG radiotherapy and systemic chemotherapy have approximately the same tumor response rate and toxicity profile. Superiority of one over the other has not been demonstrated regarding their effect on overall survival. A combination of both treatments has not been demonstrated beneficial in small series [10].

22.5 Summary

Adrenal lesions may present (1) as an incidental finding on imaging study performed for unrelated reason, (2) as clinical presentation with risk factors for or symptoms suspicious for adrenal mass, and (3) in evaluation for endocrinopathies. They are concerning for possible endocrine syndromes or malignancies (primary and secondary) and are best investigated and treated within multidisciplinary teams. Surgical resection is the mainstay of treatment for locoregional and isolated metastatic disease, but other palliative options may alleviate symptoms related to the mass effect and control hormonal secretion in inoperable cases.

References

1. Young Jr WF. The incidentally discovered adrenal mass. N Engl J Med. 2007;356:601–10.
2. Allolio B, Fassnacht M. Clinical review: adrenocortical carcinoma: clinical update. J Clin Endocrinol Metab. 2006;91:2027–37.
3. Schteingart DE, Doherty GM, Gauger PG, Giordano TJ, Hammer GD, Korobkin M, Worden FP. Management of patients with adrenal cancer: recommendations of an international consensus conference. Endocr Relat Cancer. 2005;12:667–80.
4. Brix D, Allolio B, Fenske W, Agha A, Dralle H, Jurowich C, Langer P, Mussack T, Nies C, Riedmiller H, Spahn M, Weismann D, Hahner S, Fassnacht M. German Adrenocortical Carcinoma Registry Group, Laparoscopic versus open adrenalectomy for adrenocortical carcinoma: surgical and oncologic outcome in 152 patients. Eur Urol. 2010;58(4):609.
5. Assié G, Antoni G, Tissier F, Caillou B, Abiven G, Gicquel C, Leboulleux S, Travagli JP, Dromain C, Bertagna X, Bertherat J, Schlumberger M, Baudin E. Prognostic parameters of metastatic adrenocortical carcinoma. J Clin Endocrinol Metab. 2007;92:148–54.
6. Terzolo M, Angeli A, Fassnacht M, Daffara F, Tauchmanova L, Conton PA, Rossetto R, Buci L, Sperone P, Grossrubatscher E, Reimondo G, Bollito E, Papotti M, Saeger W, Hahner S, Koschker AC, Arvat E, Ambrosi B, Loli P, Lombardi G, Mannelli M, Bruzzi P, Mantero F, Allolio B, Dogliotti L, Berruti A. Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med. 2007;356:2372–80.
7. Crucitti F, Bellantone R, Ferrante A, Boscherini M, Crucitti P. The Italian Registry for Adrenal Cortical Carcinoma: analysis of a multiinstitutional series of 129 patients. The ACC Italian Registry Study Group. Surgery. 1996;119(2):161.
8. Fassnacht M, Terzolo M, Allolio B, Baudin E, Haak H, Berruti A, Welin S, Schade-Brittinger C, Lacroix A, Jarzab B, Sorbye H, Torpy DJ, Stepan V, Schteingart DE, Arlt W, Kroiss M, Leboulleux S, Sperone P, Sundin A, Hermsen I, Hahner S, Willenberg HS, Tabarin A, Quinkler M, de la Fouchardière C, Schlumberger M, Mantero F, Weismann D, Beuschlein F, Gelderblom H, Wilmink H, Sender M, Edgerly M, Kenn W, Fojo T, Müller HH, Skogseid B, FIRM-ACT Study Group. Combination chemotherapy in advanced adrenocortical carcinoma. N Engl J Med. 2012; 366(23):2189.
9. O'Keeffe FN, Carrasco CH, Chamsangavej C, Richli WR, Wallace S. Arterial embolization of adrenal tumors: results in nine cases. AJR Am J Roentgenol. 1988;151:819–22.
10. Scholz T, Eisenhofer G, Pacak K, Dralle H, Lehnert H. Clinical review: current treatment of malignant pheochromocytoma. J Clin Endocrinol Metab. 2007; 92:1217–25.
11. Shen WT, Sturgeon C, Clark OH, Duh QY, Kebebew E. Should pheochromocytoma size influence surgical approach? A comparison of 90 malignant and 60 benign pheochromocytomas. Surgery. 2004;136(6):1129.
12. Amar L, Servais A, Gimenez-Roqueplo AP, Zinzindohoue F, Chatellier G, Plouin PF. Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. J Clin Endocrinol Metab. 2005;90(4): 2110.
13. Loh KC, Fitzgerald PA, Matthay KK, Yeo PP, Price DC. The treatment of malignant pheochromocytoma with iodine-131 metaiodobenzylguanidine (131I-MIBG): a comprehensive review of 116 reported patients. J Endocrinol Invest. 1997;20:648–58.
14. Boland GWL. Adrenal imaging. Abdom Imaging. 2011;36(4):472–82.
15. Hindman N, Israel GM. Adrenal gland and adrenal mass calcification. Eur Radiol. 2005;15(6):1163–7.