The Adrenal Incidentaloma

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Introduction

An adrenal incidentaloma is an asymptomatic adrenal mass discovered by chance during investigation for non-adrenal disease. Most authorities would consider a mass ≥1 cm to be an incidentaloma [1–5]. The basic aims of subsequent investigation are to quantify the risk of malignancy, to determine the functional status of the tumour, to assess the need for surgical intervention and to develop a suitable, individualised follow-up protocol [3]. There have been several attempts to standardise the management of this increasingly common clinical entity, taking into account the natural history of the condition, the cost-effectiveness of treatment and follow-up regimens, and patient-specific factors [6, 7].

Epidemiology

The incidence of adrenal incidentaloma in autopsy studies is between 2.3 and 8.7%, and increases with age [3–5, 8–10]. With modern imaging methods incidentalomas are noted in up to 5% of abdominal scans [4, 11–13]. As technology improves yet further, this percentage will approach the value observed in the postmortem studies. Kim et al. reported an increased incidence of incidentaloma with age, with the majority discovered in the sixth and seventh decades of life [14], whilst radiological evidence of an incidental adrenal tumour is apparent in 7% of those aged over 70 years [15]. The increasing prevalence with age has also been reported by other groups, with incidental adrenal tumours noted on 3% of radiological studies at 50 years old, increasing to 10% in the elderly [3]. In centres where the case mix contains higher proportions of patients undergoing scanning for a history of extra-adrenal malignancy, the rate of incidentaloma may be as high as 12% [16].

Differential Diagnosis

Myriad conditions constitute the differential diagnosis of adrenal incidentaloma (Table 25.1), although the vast majority are benign, non-secreting adrenal tumours.

The reporting of the frequency distribution of the variety of diagnoses is likely subject to considerable selection bias [3]. This may be either due to the reporting of a purely surgical cohort or due to the selective referral patterns to specialist centres. In both situations, smaller benign lesions may be filtered out of any reported cohort. As a consequence, the frequency at which individual diagnoses are reported varies considerably.

Adenoma, for example, is reported to account for a median 80% of adrenal incidentalomas in

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Table 25.1 Differential diagnosis of an adrenal incidentaloma

Adenoma	Nodular hyperplasia	Carcinoma
Ganglioneuroma	Phaeochromocytoma	Angiomyolipoma
Abscess	Amyloidosis	Cyst
Fibroma	Granulomatosis	Hamartoma
Haematoma	Lipoma	Liposarcoma
Myelolipoma	Teratoma	Pseudocyst
Metastasis	Schwannoma	Neuroblastoma

cohorts including all patients with an adrenal mass [3, 13]: this compares to a median 55% in purely surgical cohorts [3, 4]. There is a corresponding increase in the prevalence of adrenocortical cancer (ACC) (median 11% vs. 8% in general incidentaloma cohorts), phaeochromocytoma (10% vs. 7%) and metastasis (7% vs. 5%) in surgical cohorts [3, 4]. In some surgical cohorts, the proportion of patients with a diagnosis of phaeochromocytoma is as high as 25% [14]. Studies based on a radiological cohort identify functioning tumours in less than 1% of the total, although the vast majority of cases in this retrospective cohort were characterised radiologically and not clinically [13]. In almost all series, benign, non-functioning adenoma constitutes the majority of the diagnoses.

Thompson et al. performed a literature review of 2000 cases of adrenal incidentalomas and found that 82% of cases were benign, non-functioning tumours [17]. Benign secreting tumours accounted for a further 11%, with malignant adrenal tumours responsible for only 7% of the overall total [17]. Of those benign secreting tumours, phaeochromocytoma and cortisol-secreting (Cushing's) tumours made up 5% of the total each, respectively, with aldosterone-producing Conn's tumours responsible for only 1% [17]. In patients with incidental adrenal tumours and coexisting hypertension, the prevalence of Conn's tumours may be as high as 10% [18]. ACC constitutes 4.7% of incidentalomas, but with an incidence of 0.72 per million population per year remains a very rare malignancy. Adrenal metastasis constitutes the remaining 2.5% of adrenal incidentalomas, with metastases arising from a variety of solid organ tumours. The risk of primary malignancy in unselected incidentaloma is approximately 0.1% [17]. In a retrospective study of abdominal scanning in one US centre there were no cases of malignancy in 973 consecutive incidental adrenal tumours in patients without a history of malignancy [13].

Some diagnoses are found with such infrequency that their reporting is limited to case reports [19]. There are also cases reported in the literature of retroperitoneal pathology being misdiagnosed as an adrenal incidentaloma, and diagnoses such as leiomyosarcoma should be considered if imaging is not characteristic [20].

Investigation

Investigation of the adrenal incidentaloma aims to address several key questions:

- Is the tumour functioning or non-functioning?
- Is the tumour benign or malignant?
- Are there indications to resect the tumour?

The answer to the latter question will, to a large extent, be based upon the conclusions of the first two questions whilst also taking into consideration the size of the adrenal mass and the general medical condition of the patient. As a general rule, if bilateral adrenal incidentalomas are identified on imaging, both tumours should be assessed and managed independently, as outlined below. It is recommended that adrenal tumours be managed in the context of a multidisciplinary team (MDT) in the majority of cases. An MDT should generally consist of a minimum of a radiologist, an endocrinologist and a surgeon, each with an interest in adrenal disease, with additional members if local expertise allows. In addition, there is some evidence to suggest that management of patients in high-volume centres (≥10 adrenalectomies per annum) can lead to improved outcomes in surgical cases, particularly in cases

of malignancy, for example [21]. Current UK guidelines suggest that surgeons performing adrenalectomy should perform a minimum of six such procedures per annum to maintain competence [22].

Assessing Functional Status

As a minimum, the vast majority of patients should be evaluated with a low-dose [1 mg] overnight dexamethasone suppression test (ODST) and a 24-h urinary metanephrine analysis or plasma-free catecholamine assay, to screen for a cortisol-secreting tumour or a phaeochromocytoma, respectively [3, 5, 23, 24]. For patients with hypertension, either treated or not, plasma potassium (sodium) and aldosterone:renin activity should be measured to exclude a Conn's tumour. Virilisation, as well as alerting the clinician to the high possibility of malignancy, should prompt assessment of the sex hormone precursors DHEA and DHEAS. Similarly, the presence of gynaecomastia warrants oestradiol assay [3]. Imaging features consistent with ACC are another indication to assay sex hormones [3]. Genetic testing associated with a diagnosis of phaeochromocytoma is discussed in detail in Chap. 28.

When performing an ODST, a cut-off value to exclude excess cortisol secretion of ≤50 nmol/L is recommended [3]. For patients without clinical manifestations of excess cortisol but a post-ODST cortisol level of >138 nmol/L, the term 'autonomous cortisol secretion' should be applied, and such patients screened for hypertension and type 2 diabetes mellitus, respectively, with the prefix 'possible' added if the value falls between the aforementioned levels [3]. The association between autonomous cortisol secretion and type 2 diabetes, hypertension and cardiovascular events has been demonstrated in several cohort studies [25, 26], although not all studies concur [27]. Although an increased risk of mortality in patients with impaired cortisol suppression has been reported in some studies, further work is required to assess this potential association [28].

For patients with bilateral incidentalomas measurement of serum 17-hydroxyprogesterone should be considered to exclude congenital adrenal hyperplasia [3]. In addition, testing for adrenal insufficiency should be considered in patients with radiological evidence of bilateral infiltrative lesions or evidence of haemorrhage. The preferred method to screen for adrenal insufficiency is the short synACTHen test.

Assessment of Malignant Potential: Imaging

Cross-sectional imaging provides a crucial component of the investigation of adrenal incidentaloma. The first-line imaging modality requested depends very much on the nature of the initial investigation that highlighted the adrenal incidentaloma. For example, a high-quality non-contrast CT scan performed to investigate renal calculi may provide comprehensive imaging for an adrenal tumour negating the need for further radiological evaluation. Several suggested imaging algorithms for the investigation of the adrenal incidentaloma have been devised [2, 29].

The European Society of Endocrinology (ESE) and European Network for the Study of Adrenal Tumours (ENSAT) in their collaborative guidelines for the management of adrenal incidentaloma recommend the use of non-contrast computed tomography (CT) scanning to assess such lesions for benignity [3]. Furthermore, they suggest that no further imaging is required if the lesion itself is <4 cm, homogenous and lipid rich and has a density of <10 Hounsfield units [3]. Magnetic resonance imaging (MRI) scanning is preferable to CT imaging in children, adolescents, pregnancy and adults under the age of 40 [3].

Clinical Pearl

- In incidentalomas less than 4 cm, which are lipid rich on scanning (<10 HU), malignancy can effectively be ruled out.

The main purpose of cross-sectional imaging is to aid in the distinction between benign and

malignant tumours, although some functional tumours may also display characteristic radiological appearances. Whereas CT and MRI are generally utilised with the purpose of confirming benignity, positron emission tomography (PET)/CT is generally the imaging modality employed to detect malignancy. In any case of adrenal incidentaloma, where there is a lack of clear characteristics of benign disease, a referral to the regional MDT should be made [22].

Local invasion and distant metastases are diagnostic of malignancy, but are infrequent radiological findings. More subtle radiological features are typically called upon to stratify the risk of malignancy in adrenal tumours. Such features include a rapid increase in size on sequential scans, an irregular outline, necrosis, heterogeneous contrast uptake and relative contrast washout [2] (Fig. 25.1). Adenomas are classically lipid rich with a corresponding tissue density of <10 Hounsfield units (HU) on non-contrast CT [30]. A recently published systematic review and meta-analysis agrees that adrenal masses with ≤10 HU are unlikely to be malignant, although the authors stop short of making definitive statements regarding use of this parameter as a definitive diagnostic tool, largely due to insufficient evidence [12] (Fig. 25.2). If one considers patients with a history of extra-adrenal malignancy, the evidence is less convincing. In this setting 7% of adrenal metastases were reported as having a tumour density of <10 HU [12].

Clinical Pearl

- Keep in perspective the fact that the risk of malignancy in unselected incidentaloma cases is 0.1%.

However, 30–40% of adenomas are lipid poor, which may lead to elevated HU measurements on non-contrast CT imaging, and diagnostic uncertainty [20]. In addition to being low-attenuation lesions on non-enhanced scans, adenomas are also predicted by an absolute enhancement washout of ≥60% and/or relative contrast washout of ≥40% on contract-enhanced CT, or signal loss in opposed-phase MRI [2, 31, 32]. Malignant lesions will tend towards a slower contrast washout on [contrast] CT and, as with phaeochromocytomas, will remain unchanged in out-of-phase images [33]. A 15-min delayed image contrast 'adrenal protocol' CT is the preferred method for calculating adrenal washout [2, 3], and care should be taken in interpretation of contrast CT scans requested for an alternative

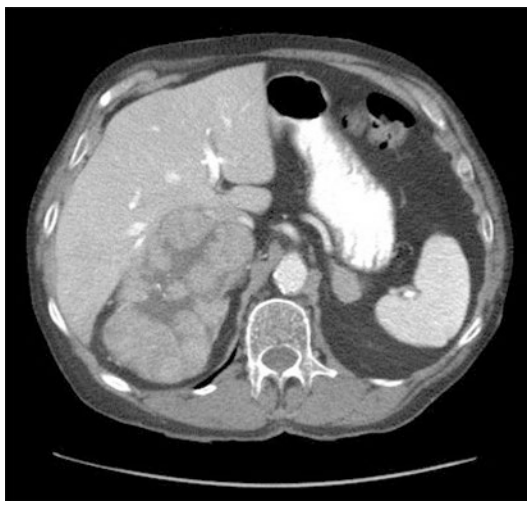

Fig. 25.1 A large right adrenal ACC with an irregular margin and heterogenous contrast enhancement

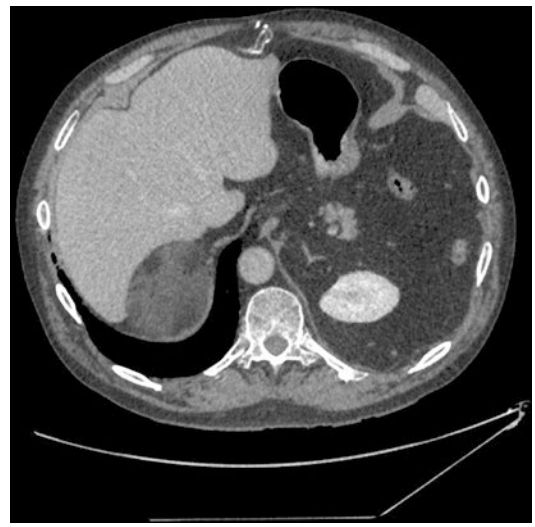

Fig. 25.2 A very-low-density fatty (negative HU) right-sided adrenal tumour which has a typical appearance of a myelolipoma

reason. In studies comparing MRI to CT in true adrenal incidentalomas, MRI was slightly inferior in terms of sensitivity and specificity, when predicting malignancy [12].

Novel risk stratification tools have been developed to aid with the diagnosis of malignancy and rationalise the use of surgical resection for potentially indeterminate lesions [34]. This tool, based on tumour size and HU on non-contrast CT, was developed with a retrospective analysis of historic patients. Despite initial promise, these results have not been replicated when applied to other retrospective cohorts [35].

Frilling et al. investigated the ability of a variety of imaging modalities to predict malignancy in adrenal tumours in oncology patients undergoing adrenalectomy [36]. In this small study comprising 31 adrenal metastases and 13 benign adenomas, both MRI and PET scanning had 100% sensitivity for predicting malignancy preoperatively [36]. Although MRI predicted benignity in each case, the specificity of PET scanning was inferior. CT scanning had 81% sensitivity and 39% specificity, whilst ultrasound scanning (USS) was generally inferior [36]. A large-scale meta-analysis of PET scanning in adrenal tumours demonstrated PET +/− CT to be both highly sensitive and specific in its ability to distinguish malignancy from benign pathology [37]. Combination scanning with non-contrast and delayed adrenal washout contrast-enhanced CT scanning has demonstrated sensitivity and specificity of 98% and 92%, respectively, for the identification of adenomas in 166 adrenal masses investigated [38].

^{18}F-2-deoxy-D-glucose (^{18}FDG)-PET scanning is growing in popularity as an imaging modality in some units. FDG-avid tumours include primary ACC, lymphoma, paraganglioma and adrenal metastasis [31] (Fig. 25.3). Recent UK guidelines recommend the use of preoperative ^{18}FDG-PET in addition to standard cross-sectional imaging in all patients with suspected ACC [22]. PET/CT is the most commonly used technique, combining the ability of PET to differentiate tissues with high metabolic requirements with the anatomical detail needed for localisation afforded by CT imaging. A tumour to liver standardised uptake value (T/L SUVmax ratio) of >1.53 is reported to be an independent prognostic factor for malignancy in FDG-PET/CT scans [39].

In certain cases of phaeochromocytoma, consideration to request ^{18}F-dihydroxyphenylalanine (DOPA) or ^{123}I-metaiodobenzylguanidine (MIBG) scanning can be given to provide more information and guide subsequent management [24, 31], especially when either paraganglioma or metastases are suspected. More recent advances, such as utilisation of ^{123}I-iodometomidate single-photon emission computed tomography (SPECT)/CT images to classify adrenal lesions, have not yet become mainstream imaging modalities but offer promise for the future [40].

Patient evaluation should include enquiries as to previous imaging, especially in patients referred from peripheral hospitals. Review of prior imaging may confirm not only the presence of an initially overlooked adrenal mass, but also a lack of interval change in the mass, conferring some degree of reassurance to patient and clinician alike. In certain circumstances stability for a period of ≥12 months may eliminate the need for follow-up [2].

Clinical Pearl

- A thorough review of a patient's previous imaging may reassure the clinician and negate the need for further radiological investigation and, in some cases, follow-up.

Assessment of Malignant Potential: Biopsy

The main indication to biopsy an adrenal incidentaloma is to diagnose a metastasis in patients with known or suspected extra-adrenal malignancy. A biopsy should only be undertaken when the information gained is predicted to alter or inform clinical management [3]. In practice the only other situation where an adrenal biopsy might be contemplated is when histological confirmation of malignancy in an otherwise irresectable tumour

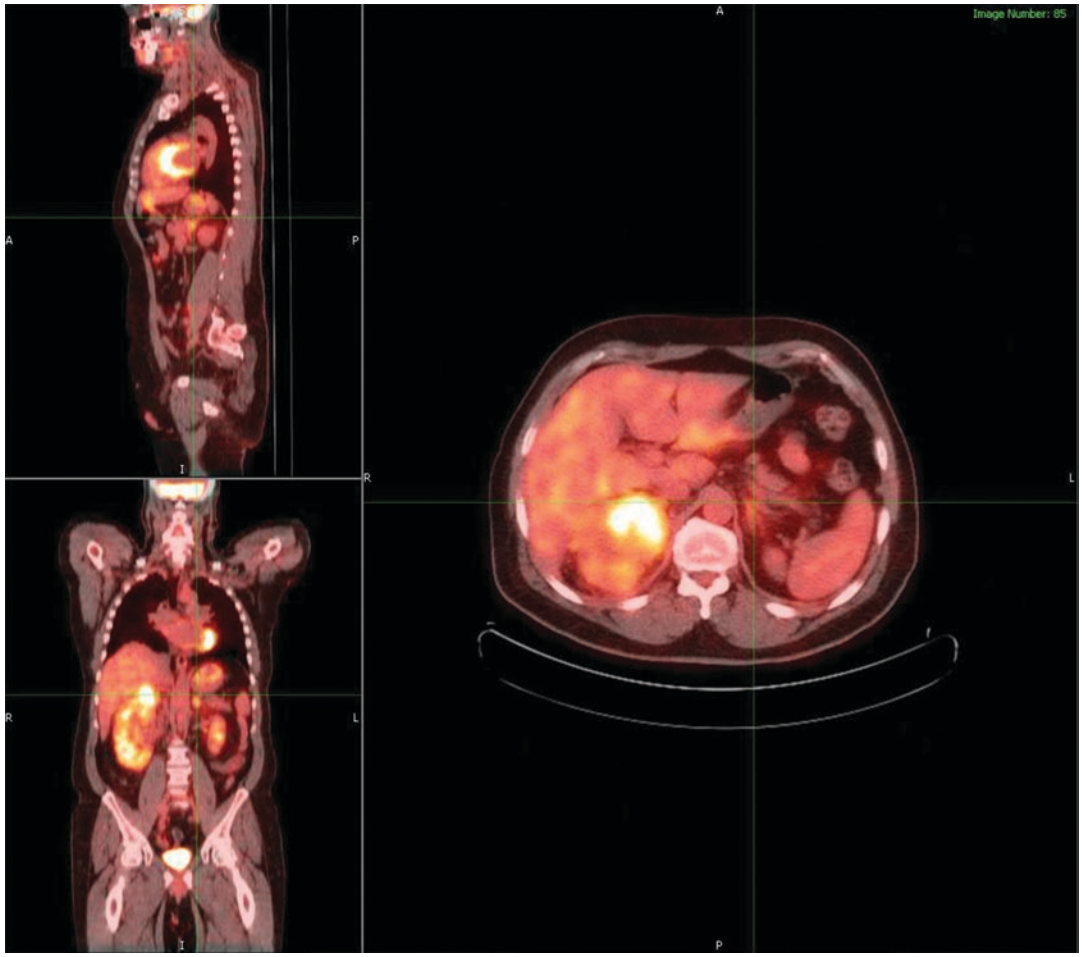

Fig. 25.3 A fused PET-CT image demonstrating avid FDG uptake in a right adrenal metastasis

might permit the use of adjuvant treatments, either as a palliative measure or as part of a clinical trial [3]. Fine-needle aspiration cytology cannot distinguish readily between adrenal adenoma and carcinoma, and is not suitable for the diagnosis of primary adrenal cancer [41]. Biopsy of phaeochromocytoma may precipitate a life-threatening hypertensive crisis, whilst histological evaluation of ACC is unreliable and the biopsy itself may lead to tumour seeding and compromise both the ability to achieve an R0 resection and disease prognosis [3]. Although one US study of patients with ACC found no negative impact on recurrence-free or overall survival in patients undergoing transcutaneous biopsy, when compared to those that had not undergone biopsy [42], the prevailing guidance is to avoid biopsy. Autopsy studies of patients with known malignancy report the prevalence of adrenal metastasis to be 8–38%. Conversely, in patients with no known primary malignancy the overall rate for discovering and adrenal metastasis is low [11]. Although the incidence of adrenal metastasis is rare in unselected incidentalomas, metastasis is the cause of the adrenal incidentaloma in approximately half of patients who have a history of malignant disease [43]. In some centres, rates of metastatic disease in apparent incidentaloma in oncology patients as high as 70–75% have been reported [36, 44]. As a general rule, patients with known extra-adrenal metastatic disease and an adrenal mass are more likely to have adrenal metastasis than benign

pathology, whereas oncology patients with an isolated adrenal incidentaloma without overt radiological features of malignancy are still more likely to have a benign adrenal tumour [2].

In a recent systematic review and meta-analysis evaluating the diagnostic value of adrenal incidentaloma biopsy, the non-diagnostic rate was estimated at 8.7%, and the complication rate at 2.5% [3, 44], although rates up to 11% have been reported [42]. Potential complications include bleeding, pneumothorax, viscus injury, pain and tumour spread through the needle track. These figures may underestimate the true values, due to a variety of methodological factors. The sensitivity of adrenal biopsy to detect malignancy overall was 87% (95% CI; 78–93%), falling to 70% (42–88%) when analysing ACC as an individual entity [3, 42].

Assessment of Malignant Potential: Other

ACC is most often a sporadic occurrence but can occasionally be associated with a genetic syndrome. A known family history of Li-Fraumeni syndrome, Carney complex, familial adenomatous polyposis coli, Beckwith-Wiedemann syndrome or, rarely, multiple endocrine neoplasia type 1, should alert the clinician to an elevated risk of ACC once an adrenal mass has been identified [33]. Whether an adrenal tumour in this context is truly an incidentaloma is debateable.

Indications for Resection

As a general guide, the decision to offer surgical resection of an adrenal incidentaloma should be based on both the likelihood of malignancy and the degree of hormone excess, in conjunction with the patient's age, general health and personal wishes.

NIH guidelines from 2002 suggested a simple algorithm for the resection of adrenal incidentalomas. The recommendation for functioning tumours was to either offer surgical resection or manage them medically. For non-functioning tumours greater than 6 cm, surgical resection is recommended, whilst for those under 4 cm a conservative approach is suggested, although no formal follow-up regimen is proposed [23]. In addition, it concluded that for suspected metastases, surgical resection conferred no benefit [23].

These guidelines contained several clinical 'grey areas' where a lack of available evidence limited the development of firm recommendation. These included the management of non-functioning tumours whose size ranges between 4 and 6 cm, the size at which excision of a functioning tumour should be considered best practice, and the follow-up regimens that should be utilised for non-functioning tumours of 1–4 cm and those 4–6 cm tumours managed conservatively.

The reason for this lack of clarity lies in the fact that malignant potential of an adrenal tumour is not related to its size in a linear fashion. The malignant potential of incidentalomas <4 cm is low, but may rise to 10% once this size threshold has been surpassed. A large retrospective Chinese study reporting on 634 patients found only 1 malignancy (3 cm) in a total of 249 adrenalectomy procedures performed when the incidentaloma was ≤4 cm [45]. The risk of malignancy in patients undergoing adrenalectomy in this study increased to 9.4% (8/85) and 33.3% (48/144) in patients with tumours of >4–≤6 cm and >6 cm, respectively [45]. Of interest in this cohort, two-thirds of patients (249/376) with a tumour ≤4 cm underwent surgical intervention, of which only 40 patients had biochemical evidence of excess hormone secretion [45]. When compared against current European guidelines, this may be considered over treatment in the low-risk patient cohort.

Once a size of >6 cm has been reached the risk of malignancy rises markedly to 25–90% [23, 46, 47]. In a large retrospective review of a US cancer registry, Kebebew et al. found that only 4.2% of ACC were ≤6 cm in diameter [48].

Establishing a definitive size threshold for surgical excision has proven difficult. In all cases some degree of compromise needs to be sought. If the bar is set too high, it risks missing early cases of malignancy that would be treatable and

potentially curable; too low, and many patients will undergo unnecessary surgery in order to identify the occasional small, malignant tumour. Whether such small tumours pose a realistic malignant potential is also controversial.

A more pragmatic approach might be to adopt a policy of observation and serial imaging. However such an approach may only heighten patient anxiety for those tumours that remain quiescent and harmless whilst allowing the rapid growth that may accompany malignant transformation to be missed for such a period so as to delay treatment, worsen prognosis or even render the tumour inoperable.

Population-based studies have suggested that the incidence of localised ACC diagnosed was essentially unchanged from 1973 until 2000. Although more operations for adrenal incidentaloma are being performed, patients with ACC are not being diagnosed earlier or treated at an earlier stage [48]. Any case that is suspicious for ACC should be managed in a specialist, high-volume unit, as better outcomes following surgery have been reported [21].

As a result of current best available evidence, many centres have adopted a policy to offer resection to patients with adrenal incidentalomas exceeding 4 cm in size, providing that the patient is a suitable surgical candidate [41, 49], and such parameters have been included in some guidelines [10]. More recent guidelines produced by ESE/ENSAT have recommended against performing surgery for asymptomatic tumours with no evidence of hormone excess and clear features of benignity on imaging [3]. The validity of this has been questioned, with some authors instead preferring to follow up patients for a minimum of 5 years irrespective of the evidence of benignity and lack of function at the initial assessment [50]. Another approach to patients with non-functioning tumours <40 mm and <10 HU may be to simply repeat a CT scan and screen for hypercortisolism at 5 years only [51]. In addition, some groups have adopted a policy where one indication for surgical resection is an adrenal tumour of >3 cm [52].

Surgical resection should be considered in patients with autonomous cortisol secretion, especially when associated with cortisol excess-related comorbidities [3]. There is weak evidence that comorbid conditions such as type 2 diabetes, hypertension and dyslipidaemia improve in some patients with autonomous cortisol secretion following resection; such improvements are not seen when patients are managed conservatively [53–55]. The increased hazard ratio for mortality in patients with autonomous cortisol secretion reported in a recent retrospective UK trial adds support to resection of responsible lesions [28]. In this context most deaths were attributable to cardiovascular disease or infective causes, whilst an association between abnormal cortisol secretion and cardiovascular disease and mortality has been replicated elsewhere [25]. Adrenalectomy is recommended for any unilateral tumour with clinically significant hormone excess, whereas bilateral adrenalectomy should be reserved only for those with evidence of overt Cushing's syndrome in the presence of bilaterally enlarged adrenals [3].

Choice of Procedure

Current guidelines have suggested that laparoscopic adrenalectomy is a feasible option, even for patients with radiological suspicion of malignancy, in unilateral tumours that are ≤6 cm and do not show frank local invasion [3]. One key benefit associated with laparoscopic surgery is a reduction in length of stay [56].

In contrast, evidence of local invasion mandates an open procedure [3]. Despite the recommendation for open surgery in suspected malignant disease, the evidence supporting this management is weak, with no conclusive evidence suggesting improvements in complete resection rates, or overall or disease-specific survival in open surgery compared to laparoscopic surgery [56–59].

It has been suggested that open resection improves the outcome for patients with ACC, both in terms of local recurrence and overall survival [60, 61]. One potential explanation for this is the locoregional lymph node dissection associated with an open procedure [60]. This is

a controversial issue, however, and consensus on what constitutes the lymphatic basin for adrenal tumours has not been widely agreed. Alternatively it may be that increases in positive resection margins or tumour spillage [56] increase the risk of peritoneal recurrence rates [61]. Open resection for >6 cm phaeochromocytomas is also recommended in recent Endocrine Society guidelines, in order to prevent incomplete excision, local recurrence or tumour rupture [24].

Partial adrenalectomy for small tumours in patients that have previously undergone contralateral adrenalectomy can be considered in certain circumstances, such as phaeochromocytoma, to prevent adrenal insufficiency [24, 62]. Such a scenario is exceptionally rare, except in the context of hereditary disease such as MEN2 or von Hippel-Lindau, in which case any contralateral tumour is unlikely to represent a true incidentaloma.

Any patients undergoing surgery that may result in post-operative adrenal insufficiency require adequate counselling and have perioperative care pathways in place [22]. All patients with a preoperative cortisol that does not suppress to ≤50 nmol/L following low-dose ODST should be given high-dose glucocorticoid cover perioperatively [3].

Natural History and Follow-Up

The natural history of apparently benign, non-functioning adrenal incidentaloma is poorly understood. This has made the development of robust follow-up protocols problematic. In addition, follow-up of adrenal lesions has two facets, namely the size of the lesion, and its functional status. Current UK guidance suggests that any adrenal incidentaloma lacking clear characteristics of benignity should be referred to a specialist multidisciplinary team for ongoing investigation and management [22].

There is a significant body of evidence that patients with cortisol excess without overt clinical features rarely develop Cushing's syndrome [3, 63]. Despite this, a thorough clinical evaluation should seek to identify the presence of any additional cortisol-related comorbidities, which may include obesity, dyslipidaemia and osteoporosis, respectively, although their association with autonomous cortisol secretion is debatable [64]. Several studies have reported a reduction in bone density and an increased fracture rate in patients with adrenal incidentaloma and 'subclinical hypercortisolism' [65, 66]. Once cortisol excess has been established, all potential surgical candidates should be investigated to ensure ACTH independence [3]. For patients with incidentaloma and a normal initial hormone status evaluation, further hormonal screening has been advised against, unless new signs of endocrine dysfunction develop, or existing comorbidities worsen [3]. For patients with autonomous cortisol secretion without clinical signs of Cushing's syndrome, an annual assessment of cortisol-related comorbidities should be undertaken [3].

Bülow et al. reported a large prospective Swedish study that involved 229 patients with adrenal incidentalomas followed up with serial CT scans and hormonal assessment. At a median follow-up of 25 months, they noted either no change or a reduction in size in 92.6% of patients. Seventeen (7.4%) patients had adrenal tumours that grew by 5 mm or more, 12 of which grew by ≥1 cm [67]. Of the 17 patients with enlarging tumours, 11 had the mass excised; 7 due to an increase in size (to between 3.0 and 6.5 cm) and 4 owing to the development of hormone hypersecretion [67]. A similar prospective cohort study involving both serial cross-sectional imaging and hormonal assessment for 24 months demonstrated no cases of malignancy or hormonal hypersecretion in 226 patients [52]. A prospective Finnish cohort study of 69 non-functioning, lipid-laden incidentalomas found no case of significant growth, malignancy or new autonomous hormone secretion at 5 years [51]. A large systematic review that included 1410 apparently benign incidentalomas estimated a 0.2% pooled risk for developing malignancy in such patients [68]. The very low rate of progression to malignancy has also been reported in other cohort studies [52]. At the

extreme end of this argument, some authors have concluded that the risk of developing a fatal malignancy from the ionisation radiation associated with certain follow-up protocols is equivalent to the risk of malignant transformation in an adrenal incidentaloma [68].

When considering the development of autonomous hormone secretion as the end point of follow-up it has been suggested that any tumour over 3 cm confers an increased risk of developing hyperfunction, although this may be confined to the first 2 years of follow-up [69]. The risk of an apparently benign incidental tumour developing 'autonomous cortisol secretion' is estimated at between 0 and 11.6% [3], with the highest figure corresponding to a study reporting greater than 5-year follow-up [26]; a systematic review, however, suggests a pooled risk of developing Cushing's syndrome at only 0.3% [68]. The risk of non-functioning tumours developing a Conn's adenoma or a phaeochromocytoma is lower still at 0–2%, respectively [3]. Taking both this and the associated risk of malignancy into account, Libè et al. suggest 6-monthly follow-up for the first 2 years followed by annual screening [69]. Other groups have reported that for small, benign lesions at baseline, follow-up regimens, both hormonal and radiological, do not increase the sensitivity for a diagnosis of hypersecretion or malignancy [52]. More recent consensus guidelines have recommended against follow-up imaging of clearly benign, non-functioning tumours of <4 cm [3]. These guidelines also suggest repeating a non-contrast CT or MRI scan at 6–12 months for indeterminate lesions, with surgical resection proposed in those exhibiting enlargement of >20% during this time interval [3]. Interval growth of ≤20% should undergo an additional scan within 6–12 months [3]. The exact interval between scans should be guided by the MDT and the perceived risk of malignancy. A period of 12 months would be adequate in indeterminate lesions with a low risk of malignancy, reducing to 6 or even 3 months in patients with an elevated risk, based on the initial radiological findings or clinical scenario. In such cases, a lack of interval growth is seen as an indicator of benignity.

Clinical Pearl

- Every MDT needs to write its own policy regarding follow-up. A policy of discharging patients in whom there is no interval growth for lesions <4 cm can be justified.

Follow-up protocols for adrenal incidentaloma have been well tolerated by patients. A patient-reported quality-of-life study bolted on to a prospective Swedish study that followed up non-progressive adrenal incidentalomas for 2 years, and reported reassuring patient satisfaction levels [70]. Although only 4% of 111 patients reported the follow-up programme as a negative experience, these patients were more likely to report anxiety [70]. However, a retrospective Chinese study stated that >80% of patients undergoing surveillance chose to undergo adrenalectomy due to anxiety relating to potential malignant change, including two-thirds of those with a tumour <4 cm [45].

Clinical Pearl

- Clinicians should be mindful that even when they have no concerns regarding malignancy/hyperfunction, this episode of clinical evaluation can lead to significant anxiety for the patient.

Despite the fact that both diagnostic and follow-up protocols for adrenal tumours are becoming more widely available as the evidence base expands, the vast majority of adrenal incidentalomas are ignored. In one Dutch study, based on a cancer centre, the rate of adrenal incidentalomas in 356 scans was 7% [16]. Only 16% of these patients were referred for specialist endocrine investigations, and, following a focused re-evaluation of the scans, the rate of reported incidentaloma rose to 12%. A UK study that evaluated 4028 CT scans performed in district general hospitals reported an adrenal incidentaloma rate of 1.8% (75 patients) [71]. In common with the Dutch study, only 17% of the UK patients were referred for specialist review by an endocrine team, whilst 80% underwent absolutely no hormonal testing [71], with similar findings reported in US community hospitals [72].

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