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Adrenal “nonadenoma” — clinical characteristics and risk of malignancy

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Abstract

Introduction: There is an increasing number of adrenal tumours discovered incidentally during imaging examinations performed for many different indications. Based on imaging results, it is possible to differentiate benign from malignant adrenal masses, although there is still a number of equivocal imaging findings. Our study presents 77 cases of adrenal tumours in which imaging was inconclusive and the final diagnosis was stated only after surgery and histopathological examination.

Material and methods: Retrospective data analysis: 77 cases of indeterminate adrenal tumours with a presumptive diagnosis of “nonadenoma” in patients operated within a 16-year period (2004–2019). None of the patients had a history of malignancy, and all tumours were hormonally inactive. On contrast-enhanced CT, the native density of all tumours was higher than 10 Hounsfield Units (HU), and the absolute percentage washout (APW) and relative percentage washout (RPW) were lower than 60% and 40%, respectively.

Results: The most common findings were adrenal adenoma (25.9%), macronodular adrenal hyperplasia (16.9%), ganglioneuroma (15.6%), and haemorrhage with posthaemorrhagic changes (13%). In total, there were 12 various histopathological diagnoses in this group. There were only 2 (2.6%) malignant (adrenal cancer and leiomyosarcoma) and 3 (3.9%) potentially malignant (pheochromocytoma) lesions in this group.

Conclusions: It is often impossible to make a correct diagnosis in a clinical setting until it is histologically verified. “Nonadenoma” adrenal tumours constitute a heterogeneous group including very rare pathologies. The risk of malignancy in indeterminate adrenal tumours is relatively low.

Key words: adrenal nonadenoma; indeterminate adrenal mass; adrenal surgery; risk of adrenal malignancy

Introduction

Incidental adrenal masses are detected in approximately 4–5% of patients undergoing CT examinations. The incidence of adrenal incidentalomas increases with age, from less than 0.5% of adrenal nodules revealed in patients in their 20s compared with up to 7% in patients older than 70 years [1–4]. The majority of adrenal incidentalomas are non-functional, benign lesions that account for 82.5% of cases. These non-functional, benign lesions comprise adenomas (61%), myelolipomas (10%), adrenal cysts (6%), and ganglioneuromas (5.5%). The remaining adrenal pathologies include malignant adrenocortical carcinomas and metastatic lesions, as well as potentially malignant pheochromocytomas [5–7].

According to all guidelines, CT is currently the imaging of choice in the evaluation of the “benign” or “suspicious” (i.e. potentially malignant) character of the adrenal lesions. In this evaluation, the first step is to measure the tumour radiodensity in an unenhanced CT. The recommended threshold for CT density measurements to identify benign lipid-rich adenomas is ≤ 10 Hounsfield Units (HU). At this threshold, pooled sensitivity and specificity were 71% and 98%, respectively [8]. However, lipid-poor adenomas with an attenuation value of more than 10 HU represent 10–40% of all adenomas [9]. Malignant lesions and pheochromocytomas have density > 10 HU, although metastases of clear cell renal cell carcinoma or (in incidental cases) pheochromocytoma may have density lower than 10 HU before contrast medium [10]. Characterization of adrenal masses using contrast-enhanced CT

has the advantage of a specific perfusion pattern of adenomas. They enhance rapidly after contrast administration and demonstrate a rapid loss of contrast medium; this phenomenon is termed contrast enhancement washout. An absolute contrast washout of > 50% 10 minutes (or > 60% 15 minutes) after the contrast injection and a relative contrast washout of > 40% characterize an adenoma with sensitivity and specificity of 98 and 92%, respectively [11, 12]. Malignant lesions, including metastases, enhance rapidly but demonstrate a slower washout of contrast medium [13]. Pheochromocytomas demonstrate both patterns of contrast washout: sometimes named “radiological chameleon”, adrenal medulla tumours can imitate both adenoma and carcinoma or metastatic tumour.

Other features that indicate a risk of adrenal tumour malignancy are large tumour size, irregular margins, presence of necrosis, area of haemorrhage, and calcifications. Regardless of all these features, presumptive diagnosis is often delusive because of numerous pathologies, which may exist in the adrenal area.

The “indeterminate adrenal mass” term appears to have arisen from the inability of unenhanced CT to distinguish adrenal adenomas with high attenuation from benign or malignant adrenal lesions [14].

This study aimed to present our experience with 77 patients who underwent adrenalectomy with presumptive diagnosis of “nonadenoma”. All these tumours had native density higher than 10 HU, and contrast washout was lower than 60% and 40%, for absolute and relative, respectively.

Material and methods

This is a single-centre retrospective analysis of patients with a presumptive diagnosis of “nonadenoma” referred to our centre from departments of endocrinology throughout Poland. To identify patients with such a diagnosis, medical records were reviewed. Pre-operative clinical, radiological, and biochemical data and details of operations and histology reports were retrieved from patients’ medical records, either in paper form or from computerized files. Hence, radiology and pathology reports were intentionally not re-evaluated, implying the data were purely observational. All the patients were initially evaluated and followed outside our hospital. All the patients had had CT with adrenal protocol performed. Native,

enhanced, and delayed density was measured, and absolute contrast washout and a relative contrast washout were calculated.

Between 2004 and 2019, 564 patients with various adrenal tumours were referred for surgical treatment to our centre. Initial diagnostic procedures (hormonal status, imaging examinations) were performed mostly in referring centres. The indications for surgery were based on appearance in cross-sectional imaging and/or hormonal activity.

In this group 77 (13.6%) patients with tumours classified pre-operatively as “nonadenoma” were identified. In these cases, a presumptive diagnosis was not established, but their phenotype was estimated as not typical for adenoma. Patients with tumours with apparent suspicion of malignancy, i.e. with suspicious hormonal activity and /or with radiographic features such as irregular margins, presence of necrosis, or area of calcifications, were not included in this analysis. The reason for initial imaging was unrelated to endocrine or local tumour-related symptoms in all cases. Fifty-four patients were female, and 23 patients were male. The female/male ratio was 2.3, and the age range was 25–82 years. The mean age at the time of operation was 54.3 ± 14 years (mean ± SD), and it was similar for men 54.4 (SD 16) and for women 53.9 (SD 14).

All patients underwent laboratory tests to exclude hormonal activity. Subclinical hypercortisolaemia, pheochromocytoma, and primary hyperaldosteronism were excluded. None of the patients had a previous history of any malignancy.

All patients were operated under general anaesthesia with appropriate antibiotic prophylaxis using the second generation of cephalosporin (cefuroxime) according to hospital standards. All patients received perioperatively low-molecular-weight heparins as venous thromboembolism prophylaxis. Cross-matched blood was reserved for patients with large tumours or essential comorbidities.

The typical surgical approach was transabdominal lateral flank. Forty-three left adrenalectomies and 34 right adrenalectomies were performed. A total of 37 laparoscopic operations were done. The laparoscopic technique has been used in our facility since 2013; therefore, most adrenalectomies are performed by laparoscopic transabdominal access.

Results

Tumour appearance and CT characteristics are presented in Table 1. Mean tumour size on preoperative CT was 42.33 mm (SD 21.7), range 11–108 mm. All these tumours had native

density higher than 10 HU, and contrast washout was lower than 60 and 40% for absolute and relative, respectively.

In total, 12 various histopathological diagnoses were stated. Histopathological findings are presented in Table 2. Only 2 (2.6%) of the tumours were malignant (leiomyosarcoma and adrenocortical adenoma).

Of all tumours, 16 (20.8%) were 5 cm or more in diameter on preoperative CT. In this group, non-functioning adenomas prevailed — 6/16 followed by ganglioneuromas 5/16, haemorrhage with posthaemorrhagic changes — 3, haemangioma — 1, schwannoma — 1, and macronodular hyperplasia — 1. None of the tumours larger than 5 cm was malignant.

There were 3 patients with a history of tumour growth in the subsequent CT-examinations. Histopathological findings for these tumours were: 2 cases of macronodular hyperplasia and 1 adenoma with haemorrhage; tumour sizes before operation were 30, 42, and 52 mm, respectively.

In 15 patients (19,5%), progressive enhancement on delayed phase postcontrast imaging was observed. For this group, postoperative histopathological diagnosis was as follows: ganglioneuroma — 6, haemangioma — 3, schwannoma — 2, leiomyoma — 1, leiomyosarcoma — 1, adenoma — 1, haemorrhage with post-haemorrhage changes — 1.

A total of 2 malignant tumours (2.6% — adrenocortical cancer and leiomyosarcoma) and 3 potentially malignant tumours (3,9% — pheochromocytomas) were found. All of them were smaller than 5 cm on preoperative CT. Adrenocortical cancer had 45 mm on CT with density 29/114/47 (native, post-contrast, delayed) and value of APV and RPV 79 and 59, respectively. The corresponding parameters for leiomyosarcoma were 33 mm and 30/37/60 with progressive enhancement in all phases of CT.

None of the 2 malignant and 3 potentially malignant lesions had features that might indicate a risk of malignancy, such as irregular margins, presence of necrosis, areas of haemorrhage, and calcifications, because tumours with such features were not included in the study.

Malignant and potentially malignant lesions together — 5/77 (6.5%).

Discussion

Within this study, we have found that hormonally inactive adrenal masses that are indeterminate on CT represent a large variety of pathologies, ranging from benign non-functioning cortical adenoma to very rare leiomyoma or leiomyosarcoma.

The risk of malignancy of adrenal tumour is determined by several factors, including tumour size and radiographic features such as irregular margins, high density, slow washout of contrast medium, presence of necrosis, area of haemorrhage, and calcifications. Regardless of all these features, a presumptive diagnosis is often delusive because of numerous different pathologies that may exist in the adrenal area. A wide spectrum of histological profiles of the removed adrenal tumours was described previously [15].

The number of medical check-ups increases with abdominal imaging such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US), which are widely used. Consequently, the detection of adrenal incidentalomas is expected to increase. An incidental adrenal mass (or adrenal incidentaloma AI) is defined as an adrenal lesion > 1 cm identified in an imaging examination, performed as a result of a clinical question, not related to a suspicious-for-adrenal disease in patients who have no clinical suggestion of adrenal disease [16]. In patients who have non-functioning AI that is indeterminate by imaging, which means it is not clearly benign or possibly malignant, adrenalectomy is indicated. In fact, most AIs in this category turn out to be atypical adenomas or other benign lesions, such as ganglioneuromas or atypical myelolipomas [17].

We decided to analyse only preoperational CT imaging because, currently, despite several limitations, CT is considered the most useful imaging technique in the differential diagnosis of adrenal masses. Generally, CT represents the primary modality for both detection and characterization of adrenal tumours.

The absolute percentage washout (APW) and relative percentage washout (RPW) can be derived using a set formula [18, 19]. Both lipid-rich and lipid-poor benign adenomas show a faster wash-out of contrast medium than other adrenal masses. Wash-out is measured either as absolute or relative, and the diagnostic results of both methods seem to be equivalent [20]. Chemical shift imaging (CS-MRi) has decreased performance in lesions > 20 HU, and a lack of incremental diagnostic information has been shown when using both techniques for detection of benign lipid-rich lesions [21, 22]. High-density adenomas (20–30 HU on unenhanced CT) may remain indeterminate on CS-MRI, and adrenal CT with washout has been shown to outperform CS-MRI. Therefore, adrenal CT using a dedicated adrenal CT

protocol remains the primary tool in the workup of an adrenal mass. When choosing between adrenal CT and CS-MRI, there are also practical considerations, such as availability, patient convenience for a single examination, and cost, which usually favour CT [23]. Direct comparisons of CS-MRI with contrast-enhanced CT are in favour of the latter [24]. In the presented group of patients, all had non-typical appearance on CT. Although in nearly half of our patients a CS-MRI was performed, this examination revealed only “lack of lipids” or “small amount of lipids”, and this finding didn not resolve the problem if the lesion seemed to be malignant.

When an AI lesion is detected, the main task is to exclude malignant disease. However, accurate physical examination, checking for subtle signs and symptoms of adrenal dysfunction, and a laboratory work-up to exclude hormonal activity are mandatory.

All our patients underwent laboratory tests to exclude a hormonal overproduction: subclinical hypercortisolaemia, pheochromocytoma and primary hyperaldosteronism were ruled out according to up-to-date recommendations [25, 26].

Despite the fact that hormonal evaluation revealed no abnormalities, in the presented group three pheochromocytomas were finally recognized in the pathology report. It seems that in patients with no symptoms of unstable hypertension such misdiagnosis is unavoidable. Measurement of urinary fractionated metanephrines, as used in our centres, has a sensitivity varying from 85.7 to 97.1% and specificity from 68.6 to 95.1% [27].

We decided to classify pheochromocytomas as potentially malignant. According to current World Health Organization (WHO) guidelines, the terms “malignant pheochromocytoma” and “benign pheochromocytoma” are no longer in use in the WHO classification from 2004. This is because there is currently no histological system approved for the biological aggressiveness of this group of tumours. Thus, all pheochromocytomas could have metastatic potential, and the term “metastatic pheochromocytoma/paraganglioma” is used to replace “malignant pheochromocytoma/paraganglioma” [28].

In the presented material, the risk of adrenal malignancy in patients with indeterminate lesions is relatively low. It has been shown that most adrenal masses in patients with no known malignancy are benign [29]. In the absence of known primary malignancy, the risk of the adrenal lesion being malignant is approximately one in a thousand. [30]. In our material, comprising only tumours with “suspicious imaging phenotype”, the risk was still low — it was only 2.6% when pheochromocytomas were excluded and 6.5% including potentially malignant pheochromocytoma.

The size of the adrenal lesion, suspicious radiological findings, and history of malignancy are known factors associated with malignancy [31–33]. The most important oncological recommendation for surgical treatment of an incidentaloma is a suspicious radiological tumour image that does not correspond to adrenal adenoma. Additional criteria include tumour size (diameter > 5 cm) and fast tumour growth [25]. In the presented study, all malignant and potentially malignant lesions were smaller than 5 cm. In contrast, all lesions larger than 5 cm were benign.

The presented material also shows a great variety of pathologies preoperatively estimated as nonadenoma. Among 12 pathologic diagnoses, we found some uncommon and unexpected lesions, like Schwannoma, haemangioma, cysts, leiomyoma, and leiomyosarcoma.

Ganglioneuromas more frequently than the above-mentioned ones are benign; most of them are asymptomatic and detected by chance. Proper preoperative diagnosis is challenging, and most of these masses are described as poor lipid adenomas or pheochromocytomas. Low washout or progressive enhancement on delayed phase postcontrast imaging observed in presented material was previously observed [34, 35] and may be characteristic for these tumours. An adrenal cyst is an uncommon lesion detected by chance. On CT examination, it generally appears as a round, well-defined, non-enhancing adrenal mass. Sometimes the cysts may be complex, thus showing atypical imaging appearances. Haemangioma of the adrenal gland is a non-functional benign tumour, which is quite infrequent and generally asymptomatic. There are no characteristic signs on radiological studies, and most adrenal haemangiomas are diagnosed postoperatively because of the low frequency and the lack of specific symptoms [36].

Tumours like primary adrenal leiomyosarcoma are extremely rare, and to date, only approximately 30 cases with no typical appearance on cross-sectional imaging have been reported the English literature [37].

Since we introduced laparoscopy for adrenal surgery in our centre, all adrenalectomies in patients with tumours not larger than 8 cm and not suspected for ACC are performed this way. Based on increased laparoscopic expertise, the positional statement of the European Society of Endocrine Surgeons (ESES) on primary malignant tumours recommends laparoscopic resection of ACC/potentially malignant tumours with a diameter of less than 10 cm. This procedure should include removal of surrounding periadrenal fat, and it should result in an R0 resection without a rupture of the tumour capsule [38].

Even though in incidentally detected adrenal masses the available imaging and laboratory test can identify functional and malignant lesions with high diagnostic precision, many benign lesions still undergo surgery because of equivocal imaging findings. The principal challenge of managing incidental adrenal masses is to correctly identify rare, unexpected malignant lesions or hyperfunctioning adenomas. When we do not make every attempt to distinguish clinically significant from insignificant disease, we are at risk of overdiagnosis – a circumstance that arises when a disease is detected that will never affect patients over the course of their lifetime [39]. Most of the evidence on adrenal incidentalomas stems from retrospectives studies only. Consequently, indications given in currently available guidelines vary. There is very limited evidence about which recommendations can be made for the management of a small number of adult patients with an indeterminate adrenal mass with no hormonal function.

In the clinical setting, it is often not possible to make a correct diagnosis until it can be verified histologically, because adrenal malignancies constitute a heterogeneous group. Even up-to-date publications reveal discordant conclusions. Whereas cystic appearance in adrenal tumours on contrast-enhanced CT may have high specificity for distinguishing pheochromocytoma and malignant adrenal masses from adenomas [40], at the same time others investigators conclude that lipid-poor adenomas and pheochromocytomas may have similar imaging and washout characteristics [41]. Considering these disagreements, and the safety of adrenalectomy with the in-hospital mortality associated with the procedure for non-malignant tumours (including hormonally active) at 0.2% [42], it seems that in the case of doubts concerning an indeterminate adrenal mass, surgery is a reasonable option.

If adrenalectomy is not to be recommended or performed, based on the clinician’s opinion and patient choice, appropriate follow-up according to local protocols is essential. A subsequent increase in tumour size is an indication for surgical treatment [43].

It is difficult to pre-operatively definitively exclude or establish malignancy in patients with adrenal lesions referred for surgery, although based on our own experience it seems that the risk of malignancy in “nonadenoma” adrenal tumours is relatively low. The disadvantage of this study is the retrospective, single-centre nature of the data. Numbers in adrenal surgery are often too small for large-scale, randomised investigations; hence, research must make do with observational data.

Conclusions

In the clinical setting, it is often impossible to make a proper diagnosis until it can be verified histologically. “Nonadenoma” adrenal tumours constitute a heterogeneous group including very rare pathologies. The risk of malignancy in indeterminate adrenal tumours is relatively low.

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Table 1. Characteristics of CT tumours

	Non missing	**Density [HU]**	**Mean**	**SD**
Native	77	14–84	29.0	11.6
Enhanced	70	17–114	54.7	21.3
Delayed	68	16–78	50.4	15.3
Absolute percentage washout (APW)	68	PE*–50	38.1	21.8
Relative percentage washout (RPW)	68	PE*–41	18.8	13.2

*PE — progressive enhancement, applies to cases in which density in delayed phase was higher than 1 minute after contrast media; SD — standard deviation

Table 2. Histopathological diagnosis

Diagnosis	**Number**	**Percentage (%)**	**Sex F/ M**	**Age**	**Tumour size CT [mm]**	**Density [HU]**	**APV (%)**
Adenoma	20	26	15/5	32–81	13–91	14–59	*PE––61
Macronodular hyperplasia	13	16.99	11/2	43–75	13–43	15–84	21–56
Ganglioneuroma	12	15.6	6/6	29–61	11–92	19–40	*PE–

							61
Haemorrhage with posthaemorrhagic changes (incl. 4 in adenoma)	10	13	4/6	45–82	25–96	23–34	*PE–53
Haemangioma	7	9.1	5/2	34–77	20–49	19–37	*PE–NA
Schwannoma	4	5.2	3/1	25–78	26–108	33–44	*PE–NA
Cysts (incl. pseudocyst)	3	4.61	3/0	25–70	34–44	16–18	50
Pheochromocytoma	3	3.9	3/0	34–60	39–48	23–38	25
Leiomyoma	2	2.6	1/1	54.60	12.38	32.34	*PE
Collision tumour (adenoma + ganglioneuroma)	1	1.3	1/0	52–70	18–42	15.21	24–25
Leiomyosarcoma	1	1.54	1/0	80	33	30	*PE
Cortical carcinoma	1	1.54	1/0	40	45	29	79

*PE — progressive enhancement on delayed phase; NA — non available