

# Adrenal Surgery in the Era of Multidisciplinary Endocrine Tumor Boards

## Authors

Costanza Chiapponi<sup>1</sup>, Daniel Pinto Dos Santos<sup>2,3</sup>, Milan Janis Michael Hartmann<sup>1</sup> , Matthias Schmidt<sup>4</sup>, Michael Faust<sup>5</sup>, Roger Wahba<sup>1</sup>, Christiane Josephine Bruns<sup>1</sup>, Anne Maria Schultheis<sup>6</sup>, Hakan Alakus<sup>1</sup>

## Affiliations

- 1 Department of General, Visceral, Cancer and Transplant Surgery, University Hospital Cologne, Cologne, Germany
- 2 Department of Radiology, University Hospital Cologne, Cologne, Germany
- 3 Department of Radiology, Hospital of the Goethe University Frankfurt, Frankfurt am Main, Germany
- 4 Department of Nuclear Medicine, University Hospital Cologne, Cologne, Germany
- 5 Polyclinic for Endocrinology, Diabetes and Preventive Medicine, University Hospital Cologne, Cologne, Germany
- 6 Department of Pathology, University Hospital Cologne, Cologne, Germany

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70469 Stuttgart, Germany

## Correspondence

PD Dr. Costanza Chiapponi  
University Hospital Cologne  
Department of General  
Visceral, Cancer and Transplant Surgery  
Kerpener Str. 62  
50937 Cologne  
Germany  
Tel.: +49 221 4784803  
Costanza.Chiapponi@uk-koeln.de



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## ABSTRACT

Work up of adrenal masses includes assessment of endocrine activity and malignancy risk. There is no indication for surgical removal of nonfunctional adrenal adenomas, according to the guidelines. In the present study, we aimed at evaluating the impact of a university endocrine tumor board on the quality of the indications for adrenal surgery at our institution. One hundred consecutive patients receiving primary adrenal surgery at the University Hospital of Cologne, Germany were included. Their demographics, clinic-pathologic characteristics, treatment and outcome were analyzed. In 55 (55 %) cases, indication for surgery consisted in functional benign tumors, including Conn, Cushing adenomas and pheochromocytomas. Forty (40 %) tumors were referred to surgery for malignancy suspicion and 5 (5 %) myelolipomas were removed due to their size. Eighty-nine percent of surgeries were performed as minimally invasive procedures. Overall morbidity included two (2 %) self-limiting pancreatic fistulas after left laparoscopic adrenalectomy for pheochromocytoma. All functional tumors were confirmed benign by final histology. Only 33 (82.5 %) of 40 suspicious cases turned out to be malignant. Consequently, nonfunctional benign adenomas were “unnecessarily” removed in only 7 (7 %) patients, with 6 (85.7 %) of them having a history of extra-adrenal cancer and all of them fulfilling criteria for surgery, according to the international guidelines. In conclusion, the endocrine tumor board provided an excellent adherence to the guidelines with most surgeries being performed either for functional or malignant tumors. In nonfunctional tumors with history of extra adrenal cancer, CT guided biopsy might be considered for obviating surgery.

## Introduction

Incidentalomas are adrenal tumors that are discovered during diagnostic evaluation for other conditions [1]. Their prevalence has been reported to be 1–6 % in adults [1, 2] and to increase with the growing use of technological advances in imaging and with the ageing of the population [1]. Most of these tumors are nonfunctional and benign [3]: if they have an attenuation of 10 Hounsfield units or less in non-enhanced computed tomography (CT) and they are smaller than 4 cm in greatest diameter, they generally do not warrant intervention or long-term follow-up [1]. In a meta-analysis involving 4121 patients with such nonfunctioning adrenal lesions, adrenocortical carcinoma did not develop in any of the patients [4]. Subsequently, the risk is estimated to be < 2 % in these patients. In the presence of a history of or known current primary cancer, however, the risk of malignancy has been described to be up to 21 % [5]. Although adrenal surgery meanwhile is mostly minimally invasive and associated with low morbidity and almost no mortality, compromise of adrenal function is a serious possible consequence and indication should be posed judiciously. Therefore, the management of adrenal masses should be individualized and involve a multidisciplinary judgement.

In the last decades, most academic medical centers and some community hospitals have established multidisciplinary organ specific tumor boards in order to improve patients' care [6]. Multidisciplinary team care has been shown to be associated with improved survival, timeliness of treatment, and adherence to guidelines [7–13]. Besides providing best management through diagnostic and treatment recommendations generated according to a consensus-based method and supported by guidelines, tumor boards enable appropriate and timely patients' referral, identification of available clinical trials and educate clinicians by sharing expertise from each discipline in an open environment [13]. Endocrine tumor boards (ETBs), in contrast to classic oncologic boards include patients with both benign, beside malignant disease. The consensus opinions for diagnostic issues ranges from not pursuing any further testing to performing invasive procedures for more precise tumor characterization, including when to operate and how extensive a surgery should be performed [14]. A recent analysis showed that the suggested treatment was changed in 15 % of presentations, with additional imaging being the most frequent reason (43 %) [15]. Twenty-four percent of attendees reported intending to use a more evidence/guideline-based approach after attending [15].

At the University Clinic of Cologne, Germany an ETB has been established in 2014. The number of cases discussed by the board has increased from 120 in 2014 to 743 in 2020, including thyroid, parathyroid, adrenal pathologies, and neuroendocrine tumors. In the present study, we evaluated the indications and outcome of adrenal surgery recommended by the ETB, with focus on adherence to the guidelines for the management of adrenal incidentalomas published in 2016 by the European Society of Endocrinology in collaboration with the European Network for the Study of Adrenal Tumors [5].

## Patients and Methods

### Patients

The last consecutive 100 adrenalectomies taking place in our Department for Endocrine Surgery at the University Hospital of Cologne, Germany were included. The first surgery included was performed on 24.02.2016, the last one on 21.10.2021 (5 years and 8 months). Surgical procedures performed for extra adrenal pathologies with adrenal involvement (e. g., multivisceral resections of sarcomas) were excluded.

### The endocrine tumor board (ETB)

As mentioned above, at the University Clinic of Cologne, Germany an ETB has been established in 2014 and it is certified by the German Cancer Society (Deutsche Krebsgesellschaft, DKG). It takes place every Thursday from 1 PM to 2 PM. One nuclear medicine specialist (M.S.), one endocrinologist (M. F.), and one surgeon (C.C.) are in charge of the board. The presence of all three members or at least one deputy from every of their disciplines is required by the DKG. An experienced pathologist (A.M.S.) is also regularly present. Radiation therapy is only present when required, as well as ENT and radiology. Radiological material is generally presented by nuclear medicine specialists. Adherence to ETB recommendations and outcomes are checked on yearly basis. Once every three months a morbidity and mortality conference is performed.

### Standard diagnostic workup of adrenal masses

All endocrine masses included in this study received radiologic workup (using either enhanced or non-enhanced CT, MRI, or PET CT), at least minimal endocrinologic diagnostic including aldosterone/renin ratio, serum metanephrine and normetanephrine levels and a dexamethasone suppression test. In case of positive aldosterone/renin ratio, suggestive of Conn Adenoma, the next step consists of saline load test and selective adrenal vein sampling for patients > 35 years at our institution. Malignancy was suspected in tumors > 6 cm in diameter, with increasing size [*"if the lesion enlarges by more than 20 % (in addition to at least a 5 mm increase in maximum diameter) during 6–12 months"* [5]] or in the presence of elevated Hounsfield unit attenuation in non-contrast CT scan. Unclear tumors were followed up in 6–12 months with another radiologic modality including MRT and PET scan beside non-contrast CT scan. Our internal algorithm is based on the guidelines for the management of adrenal incidentalomas of the European Society of Endocrinology in collaboration with the European Network for the Study of Adrenal Tumors [5].

### Retrospective validation of the malignancy risk

For all included patients, radiological image data available in the institution's Picture and Archiving System (PACS) were identified and retrospectively reevaluated in a blinded fashion by an experienced radiologist (D.P.d.S.), who had not been involved in tumor board discussions. External examinations are regularly imported into the PACS preoperatively to be available in all operation rooms. However, they are removed after 6 months, in some cases, depending on the uploading procedure used, in which case they were not included in this study (n = 19).

## Surgery

Surgery was performed either as laparoscopic or retroperitoneoscopic adrenalectomy, according to the technique introduced 1995 in Germany by Professor Martin K. Walz [16]. Only in eleven cases (11 %), open adrenalectomy was performed for adrenal cell carcinoma and huge bilateral metastases with possible extracapsular infiltration. Laparoscopic access is chosen at our institution for masses suspicious of malignancy but without signs of extra-adrenal invasion, due to the lower risk of capsular disruption given by the larger space in transperitoneal access [17]. Retroperitoneoscopic access is preferred for functional benign tumors and in patients with previous abdominal surgery, where adhesions are expected. All patients were seen regularly one week postoperatively for wound control in the surgical department and in the endocrinological department for further follow up, especially in case of corticosteroid substitution.

## Histology

All histologic specimens were examined in the Department of Pathology of the University Hospital of Cologne and included Hematoxylin and Eosin (H & E) and respective IHC-staining depending on the case.

## Data Collection and Analysis

Electronic and paper data of the University Hospital of Cologne were retrospectively collected and analyzed. The study was performed according to the rules for retrospective analysis of the ethical committee of the University Hospital Cologne. Data were analyzed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA. Variables were expressed as median with range. If the data was normally distributed, groups were compared using the T-test. The Chi-square test of independence was used for testing hypotheses when the variables were nominal. A p-value < 0.05 was considered significant.

## Results

### Patients

One hundred consecutive patients undergoing adrenalectomy at our institution were included in this study. They consisted of 55 (55 %) men and 45 (45 %) women. Their median age was 54.8 years (range 21–87). Men were significantly older than women (57.5, range 21–87 vs. 51.4, range 22–73;  $p = 0.01$ ).

Indications for surgery included 22 (22 %) cases of primary hyperaldosteronism (PHA), 20 (20 %) pheochromocytomas, 13 (13 %) adrenal Cushing adenomas, 5 (5 %) myelolipomas (> 5 cm) and 40 (40 %) tumors, which were deemed suspicious of malignancy, including 3 (7.5 %) cases with additional functional activity.

Cushing adenomas were diagnosed significantly more frequent in female patients (92.3 vs. 7.7 %), whereas myelolipomas (80 vs. 20 %) and suspicious tumors (70.7 vs. 29.3 %) were seen more frequently in male patients ( $p = 0.001$ , ▶ **Table 1**).

Median age of patients was 45 (range 21–62) for primary hyperaldosteronism, 54 (range 41–72) years for Cushing, 58.5 (22–73) years for pheochromocytoma and 61 (range 25–87) years for malignant histology.

▶ **Table 1** Indications for surgery in 100 consecutive adrenalectomies.

|                          | Male n = 55 | Female n = 45 | Σ = 100 |
|--------------------------|-------------|---------------|---------|
| PHA                      | 11 (50 %)   | 11 (50 %)     | 22      |
| Pheochromocytoma         | 10 (50 %)   | 10 (50 %)     | 20      |
| Cushing                  | 1 (7.7 %)   | 12 (92.3 %)   | 13      |
| Myelolipoma              | 4 (80 %)    | 1 (20 %)      | 5       |
| Suspicious of malignancy | 29 (72.5 %) | 11 (27.5 %)   | 40      |

There was a significant gender specific difference with Cushing being diagnosed more frequently in females, myelolipomas and suspicious tumors being diagnosed more frequently in men ( $p = 0.01$ ).

## Imaging studies

In 81 cases, imaging studies were available at the University's PACS and could be retrospectively evaluated. Imaging modalities included native CT, contrast enhanced CT, MRI, contrast enhanced sonography and/or PET CT. Twenty-two (26.8 %) of patients received only one imaging study, 26 (31.7 %) two, and the rest 33 (40.7 %) received ≥ 3.

Median tumor size before surgery was 20 mm (range 10–53) for PHA, 23 mm (range 10–126) for metastases, 37.5 mm (range 16–66) for Cushing and 41 mm (range 16–62) for pheochromocytomas. Median non-enhanced CT attenuation before surgery was 9.5 (–4 to –30) in PHA, 10 (–14 to –33) in Cushing, 33.5 (14 to –53) in pheochromocytomas and 32.5 (20 to –41) in metastases. The three adrenal cell carcinomas included in this study measured 61, 116, and 160 mm before surgery and displayed non-enhanced CT attenuation values > 30 HU.

A significant increase (> 20 %) in tumor size 6–12 months after primary radiologic study was diagnosed in 24 (29.2 %) adrenal masses, including one hemangioma, one hematoma and two PHA adenomas in addition to 20 malignant tumors.

## Blinded validation of the malignancy risk

The blinded retrospective assessment of the malignancy risk by an independent experienced radiology consultant diagnosed a suspicion of malignancy in 48 (59.2 %) of 81 cases. However, final histology confirmed malignancy in only 31 (64.5 %) of these cases and classified as non-malignant 17 (35.5 %) cases (▶ **Table 2**).

These 17 cases wrongly assessed as suspicious based on sole radiologic criteria included 3 (30 %) of 10 Cushing adenomas, 1 (20 %) of 5 myelolipoma, 1 hemangioma, one 6 cm large benign adenoma with androgene and cortisol secretion, and one adenoma in a patient with a neuroendocrine tumor (patient 7, ▶ **Table 3**), beside 10 (83.3 %) of the 12 pheochromocytomas.

Only 1 (4.3 %) melanoma metastasis was wrongly classified as non-suspicious in blinded radiologic reassessment based on a non-enhanced attenuation of 0. 1 (4.1 %) NCC metastasis was classified as unclear (non-enhanced CT was not available).

Sensitivity of the radiologic reassessment for malignancy was 96.9 % (95 % CI 83.8–99.9 %), specificity 65.3 % (95 % CI 50.4–78.33 %).

The positive predictive value 64.6% (95% CI 55.3–72.9%); the negative predictive value 97% (95% CI 82.1–99.6%).

## Surgery

Most surgeries (89%) were performed in minimally invasive technique. 43 (43%) were performed transperitoneally as laparoscopic and 46 (46%) extraperitoneally as retroperitoneoscopic adrenalectomy. Eleven (11%) of surgical procedures were performed as open adrenalectomy for strong suspicion of malignancy and possible infiltration of nearby organs. There was no mortality. Morbidity included two self-limiting pancreatic fistulas in pheochromocytomas of the left adrenal gland after laparoscopic resection of two pheochromocytomas. One of them was hemorrhagic.

## Final histopathologic assessment of tumors removed for malignancy risk

Among the 40 tumors deemed suspicious of malignancy by the ETB, final histopathologic assessment diagnosed metastases in 30 (75%) and adrenal cell carcinomas in 3 (7.3%) cases. Metastases included 9 melanomas, 4 Non-Small Cell Lung Cancer (NSCLC), 8 upper GI tumors, 3 renal cell carcinomas, 2 lymphomas, 2 hepatocellular carcinomas, one lung carcinoid, and one thyroid carcinoma.

Seven (17%) tumors were non-functional and were surgically removed exclusively due to a wrongly assumed suspicion of malignancy based on guideline recommendations (non-enhanced attenuation > 20 HU, increasing size, history of extra-adrenal cancer): the final histopathology diagnosed adrenal adenomas. ▶ **Table 1** depicts the characteristics of these tumors.

In 6 (85.7%) of 7 cases patients had a history of extra adrenal neoplastic disease. In only 4 (57.2%) cases non-enhanced CT was available and attenuation was > 20 IU (▶ **Fig. 1**). In 3 cases (42.8%) an increase of tumor size > 20% in 6–12 months had been observed. Two cases had been deleted in the radiologic archive of the university and original radiologic material was not available, only the initial radiology report. In 3 (60%) of 5 cases with complete radiologic material, malignancy was also wrongly assumed in blinded reassessment, based on the current guideline recommendations.

▶ **Table 2** Results of the independent blinded radiologic reevaluation.

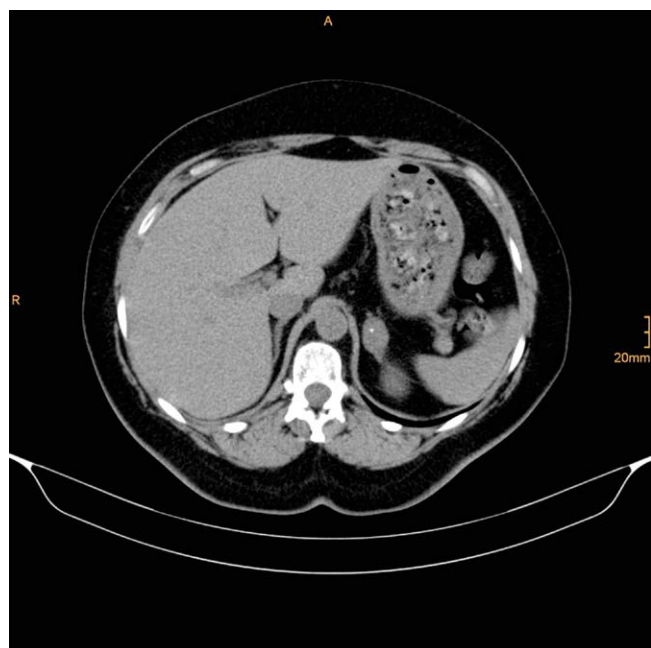
|                         | Histologic malignant | Histologic benign | Σ  |
|-------------------------|----------------------|-------------------|----|
| Radiologic suspicion    | 31                   | 17                | 48 |
| No radiologic suspicion | 2                    | 31                | 33 |
| Σ                       | 33                   | 48                | 81 |

Sensitivity of the radiologic reassessment for malignancy was 96.9% (95% CI 83.8–99.9%), specificity 65.3% (95% CI 50.4–78.33%). The positive predictive value 64.6% (95% CI 55.3–72.9%); the negative predictive value 97% (95% CI 82.1–99.6%).

▶ **Table 3** Nonfunctional adenomas removed by surgery.

| Patient | Gender | Age | Side  | Size     | Native HU density | Signal dropout on opposed-phase images (MR) | PET | History of cancer  | Histology  |
|---------|--------|-----|-------|----------|-------------------|---|-----|--|------------|
| Pt1     | f      | 59  | left  | 2 cm ↑   | contrast CT       |   |     | G2 NSCLC pT2 (3.1 cm) pN0 (0/35) L0 V0 pN0 R0, FD 1 year before  | adenoma    |
| Pt2     | f      | 35  | right | 2.5 cm   | 26                |   |     | B-symptomatic, unclear diarrhea  | adenoma    |
| Pt3     | m      | 57  | right | 3.6 cm ↑ | 20                | –   |     | Renal cell carcinoma of the right kidney, FD 1 year before   | adenoma    |
| Pt4     | f      | 56  | right | 3.5 cm ↑ | contrast CT       | +   |     | Appendix mucinous adenocarcinoma pT3, pN0 (0/16), L0, V0, R0 ; FD 3 years before                           | hematoma   |
| Pt5     | m      | 62  | left  | 1.5 cm ↑ | contrast CT       | –   |     | Poorly differentiated adenocarcinoma of the stomach ypT3, ypN0 (0/42), L1, V0, Pn1, R0 ; FD 3 years before | hemangioma |
| Pt6     | f      | 52  | left  | 2.5 cm   | 26                |   | +   | Hodgkin lymphoma in complete remission after chemotherapy, FD same year                                    | adenoma    |
| Pt7     | m      | 54  | left  | 4.8 cm   | 28                |   |     | Ileum G1 NET pT3, pN1 (4/29 ece+), L0, V0, Pn1, R0, FD same year   | adenoma    |

In these patients, malignancy risk was “wrongly” assessed. ▶ **Table 3** contains the last information available to the ETB for recommending surgery. The arrow represents a tumor increase > 20% (in addition to at least a 5 mm increase in maximum diameter) during 6–12 months, as recommended by the ENSAT; NSCLC: Non-small cell lung cancer; RCC: Renal cell carcinoma; NET: Neuroendocrine tumor; FD: Time of first diagnosis.



► **Fig. 1** Large tumor of 2.5 cm at the left adrenal gland in a 52-year-old patient with history of lymphoma. Beside a non-enhanced attenuation > 20 HU, this tumor was PET positive. It turned out to be a benign adenoma in final histopathologic assessment.

## Discussion

In the present study, we examined the quality of the indications for adrenal surgery recommended by the ETB at our institution. Demographics, clinic-pathologic characteristics, treatment and outcome of 100 consecutive adrenalectomies performed at our institution according to a recommendation of the endocrine tumor board, based guidelines for the management of adrenal incidentalomas of the European Society of Endocrinology in collaboration with the European Network for the Study of Adrenal Tumors [5] were analyzed.

First finding was a gender specific difference: male patients were older and had more frequently myelolipomas and suspicious masses, whereas female patients were younger and had more often cortisol secreting tumors, confirming the previous observations of Alesina et al. [18]. Secondly endocrine activity was present in 55 % of tumors, again in accordance with other surgical and non-surgical series [3, 19].

In 40 % of cases, the indication for surgery consisted in a suspicion of malignancy, confirmed in 33 (82.5 %) patients in final histopathology. A 33 % malignancy rate is higher than that recently reported for the Eurocrine data [19]. At the same time, our 7 % rate of nonfunctional benign tumors wrongly deemed suspicious and thus removed appears lower than in the Eurocrine data, considering that their reported rate of endocrine activity is 55 % and that of malignancy 15 %. One possible reason for that is that the Eurocrine data include cases from 21 different hospitals in Germany, Austria, and Switzerland with different volumes (658 surgeries, performed in 21 hospitals over 5 years) [19]; it is possible, that not all centers included have multidisciplinary preoperative boards. Because of

this 7 % rate of “unnecessary” adrenal surgery despite complete adherence to the international Guidelines [5, 20], we decided to focus on these cases.

The current Guidelines report a risk of 25 % malignancy for tumors > 6 cm and recommend surgery [5]. For tumors < 6 cm the risk of malignancy is recommended to be assessed in non-enhanced CT [5]. Wash-out CT with the established thresholds for absolute and relative percentage wash-out (APW/RPW) has been shown to be insufficient to reliably diagnose adrenal masses [21]. MRI is recommended in case non-enhanced CT is inconclusive [5]. In non-enhanced CT benign adenomas can be reliably diagnosed for masses with Hounsfield density of < 10 units. However, increasing the unenhanced CT tumor attenuation threshold to 20 HU increased specificity for ACC, while maintaining sensitivity in the EURINE-ACT study [22]. The first consideration is that most patients present with contrast enhanced CT scan in day-to-day clinical routine. Although non-enhanced CT is the adequate imaging modality for assessing malignancy, there is a comprehensible reluctance in requiring additional non-enhanced CT in younger patients, especially if radiology report already suggests a risk of malignancy and the patient is worried. The fact that for most patients (72.8 %) in the present study ≥ 2 radiologic studies, and MRI in 48 (59.2 %) cases were available, is explained by a certain selection due to the fact that patients were treated in a university oncologic center. In case the radiologic report of enhanced CT scan cannot clearly rule out malignancy, most patients are reluctant to undergo active surveillance, and follow up in 6–12 months.

Based on sole radiologic criteria, our independent retrospective blinded evaluation delivered a sensitivity of 96.9 % (95 % CI 83.8–99.9 %) and a specificity of 65.3 % (95 % CI 50.4–78.33 %), with 83.3 % of pheochromocytomas being classified as malignant. The mean unenhanced CT attenuation of pheochromocytoma was  $35 \pm 9$  HU in a Mayo Clinic cohort and 35.6 HU in 1217 tumors extrapolated from 23 studies [23]. This explains why pheochromocytoma can easily be wrongly classified as possibly malignant in the lack of information on their biochemical activity (► **Fig. 2**). It is unclear, why at least four benign adrenal adenomas had non-enhanced attenuation > 20 HU. One of them was even positive in PET scan.

Finally, this study confirms a high adherence to the current guidelines for the treatment of adrenal masses. A rate of 33 % for malignancy is high but due to the patients' selection seen in a university center. The 7 % rate of adrenal surgeries performed for non-functional benign tumors should be seen in the light of the medical history of the patients' undergoing adrenalectomy, who had had extra adrenal neoplastic pathologies in 6 (85.7 %) cases and criteria warranting surgery according to the guidelines in all cases. The ENSAT Guidelines suggest for patients with previous cancer history following steps: pheochromocytoma should be ruled out; no further specific adrenal imaging follow up, if the lesions can be characterized as benign by non-contrast CT; repeated imaging including PET scan, biopsy or surgery, if the lesions cannot clearly be characterized as benign by non-contrast CT. In day-to-day clinical routine, patients with a history of cancer are also willing to have tumors removed, even if malignancy is unlikely and rarely accept surveillance. A retrospective study reported even a 80 % rate of patients choosing surgery instead of surveillance due to anxiety





► **Fig. 2** Large pheochromocytoma of 4.5 cm of the left adrenal gland in a 46-year-old patient. This tumor was seen as possibly malignant in blinded radiologic assessment, due to its non-enhanced attenuation > 20 HU and its size.

related to potential malignant change [24]. Two thirds of them even had tumors < 4 cm [24]. Nonetheless, at least in some of them CT guided biopsy might have possibly obviated adrenal surgery and should be probably considered as option in ETB discussion, once ACC and pheochromocytoma have been ruled out.

## Conclusions

In summary, with a high adherence to the current European guidelines, non-functional adrenal adenomas were resected in only 7% of adrenal surgeries in the present study. A history of malignancy supported the indication to surgery in most cases and criteria warranting surgery according to the guidelines. Adrenal biopsy, however, might be an option for obviating surgery in these patients, once pheochromocytoma and ACC have been ruled out.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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