

DIAGNOSTIC CHARACTERISTICS OF ADRENAL TUMORS: A COMPARATIVE ANALYSIS OF ADENOMA, PHEOCHROMOCYTOMA, AND ADRENOCORTICAL CARCINOMA

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ABSTRACT

Adrenal tumours encompass morphologically and biologically diverse lesions that require careful pathological distinction. This study compared the clinicopathological, histomorphological, immunohistochemical, tissue-staining, and molecular characteristics of adrenocortical adenoma, pheochromocytoma, and adrenocortical carcinoma (ACC) using secondary pathological datasets and representative H&E images. Adrenocortical adenoma showed clear to finely vacuolated cortical cells with relatively organized architecture, while ACC demonstrated markedly larger tumour size and lower tissue staining indices. Median tumour size was 2.85 cm in adenoma and 9.50 cm in ACC, with a significant difference between groups. Pheochromocytoma exhibited characteristic nested or alveolar architecture with vascular stroma and showed considerable pathological heterogeneity. Median PASS and GAPP scores were both 6.0, vascular invasion occurred in 20.0% of lesions, distant metastasis in 14.3%, and SDHB loss in 11.4%. Cross-tumour analysis demonstrated significant differences in TMA CTCTF, qPCR expression, and ELISA-derived concentrations among normal/control, adenoma, pheochromocytoma, and ACC groups. These ancillary findings supported the distinct biological profiles of the three tumour categories but were interpreted as complementary to conventional microscopy. Representative microscopy further highlighted lineage-specific cellular architecture, reinforcing the diagnostic value of direct tissue assessment alongside quantitative pathological and molecular measurements in practice. Overall, the findings support a pathology-first diagnostic framework integrating histomorphology with clinicopathological and immunohistochemical evidence to improve differentiation of major adrenal tumour types and characterize features associated with malignant potential and biological behaviour.

KEYWORDS: Adrenocortical adenoma; Pheochromocytoma; Adrenocortical carcinoma; Histopathology; Immunohistochemistry.

1. INTRODUCTION

Adrenal tumours are a diverse collection of tumours of the cortex and medulla, where correct diagnosis depends on a combination of gross, microscopic architecture, cytological features, immunophenotype and clinical data. The diagnosis of adrenal tumors is still primarily based on histomorphological findings despite the accumulation of biochemical and imaging data and molecular information (Zhou & Yang, 2021). The pathological diagnosis and terminology of adrenal cortical tumours have also been unified, specifically by distinguishing between adrenocortical adenoma, a benign tumour, and adrenocortical carcinoma (ACC), a malignant one (Mete et al., 2022). However, in certain adrenocorticoma lesions, both the overlying architectural and cytological features can be confusing (Agarwal, 2022).

Adrenocortical adenoma is a benign cortical neoplasm mostly made of cells that are similar to the normal adrenal cortical elements, often with a lot of clear or finely vacuolated cytoplasm due to the presence of lipid within the cells (Santi & Nesi, 2022). ACC is the malignant counterpart and can show an increase in tumour size, architectural disturbance, cytological atypia, mitotic activity, the presence of necrosis and invasive growth (Nesi & Santi, 2022). Histopathological evaluation is especially important since the abnormalities at the microscopic level must be evaluated together and not individually (Gambella et al., 2023). However, through large clinicopathological studies, it has been shown that certain morphologic features could be of discriminatory value in distinguishing a benign from a malignant adrenocortical neoplasm (Walz et al., 2020). Therefore, diagnostic strategies are increasingly using ancillary pathological parameters and morphology together when using traditional features is ambiguous (Viřtor et al., 2021).

Pheochromocytoma is very different from a cortical tumour as it develops from adrenal medullary chromaffin cells. The histological features of these tumours are characterised by nested or alveolar organisation, with an abundant vascular network, and biological risk assessment involves evaluation of various pathological parameters (Vocino Trucco & Volante, 2025). Histopathological examination of adrenal tumours shows that there is significant variation in the morphology of the individual tumours, highlighting the need for determination of the

cell lineage in the differential diagnosis of the tumour (Krishnan & Venkatesh, 2021). Clinicopathological experience also suggests that adenoma, pheochromocytoma, ACC and rare adrenal diseases are a wide diagnostic spectrum (Maiti et al., 2020).

Over the last few years, ancillary techniques have been more and more used together with the traditional morphology. Molecular studies have revealed that there is significant biological heterogeneity among adrenocortical neoplasms and have shown potential associations between histopathology and tumour biology (Juhlin et al., 2021). Additionally, immunohistochemical markers can help distinguish adrenocortical adenoma from ACC from pheochromocytoma in conjunction with morphology (Elshwarby et al., 2025). The integration of the cytopathological, histopathological, and molecular findings is crucial when the morphology deviates from the conventional ones, as demonstrated in the case of oncocytic adrenal neoplasms (Condello et al., 2025). Pathological findings are still important as they must be interpreted with the other information available such as endocrine and clinical assessments (Chung et al., 2023).

The purpose of the present study was to compare the pathological features of adrenocortical adenoma, pheochromocytoma and ACC on the basis of the available clinicopathological, tissue-staining, molecular, immunohistochemical and representative H&E data. Only variables which were represented in the analysed material were taken into the scope. The aims of this study were to characterize microscopic differences between tumour groups, compare clinicopathological features between adenoma and ACC, assess the pathological risk features of pheochromocytoma, and assess ancillary tissue and molecular differences between the three groups of adrenal tumours.

2. METHODOLOGY

2.1 Study Design and Data Selection

A secondary data comparative pathology design was used to examine the pathological and histopathological features of adrenocortical adenoma, pheochromocytoma and adrenocortical carcinoma (ACC). Clinicopathological data, tissue microarray data, molecular data, immunohistochemical data, and microscopic image data were all integrated and analyzed in the same analysis using previously published open access data from Rucinski (2025), Gan et al. (2024), Günler & Çordan (2026). Variables that were not explicitly related to the analyses presented in Results were excluded. The cases were divided into those diagnosed pathologically and were divided into the main three groups for comparison without considering unrelated adrenal lesions.

2.2 Adrenocortical Adenoma and Adrenocortical Carcinoma Assessment

The comparison assessment of adrenocortical adenoma and ACC consisted of age and tumour size and overall survival (where available) (Gan et al., 2024). The differences in the burden of the tumour between benign and malignant cortical neoplasm was evaluated by size of tumour. A tissue-level quantitative assessment was also carried out based on observations categorized as adrenocortical adenoma (ACC) or Rucinski (2025). The corrected total cellular fluorescence (CTCF), mean staining intensity (MSI) and maximum staining intensity (MS) were extracted and compared between both cortical tumour groups.

2.3 Pheochromocytoma Pathological and Immunohistochemical Assessment

The available clinicopathological and immunohistochemical variables were evaluated for pheochromocytoma and their related PPGL lesions (Günler & Çordan, 2026). Pathological features were tumour diameter, pathological T stage, Pheochromocytoma of the Adrenal Gland Scaled Score (PASS), Grading System for Adrenal Pheochromocytoma and Paraganglioma (GAPP) score, GAPP differentiation category (bad), vascular invasion, distant metastasis, Ki-67 proliferation index, and SDHB expression status. Immuno-histochemical profile was characterized by the HIF-2 α H-score, VEGF immunoreactivity score, and CD105 microvessel-density. No modification of scores or classifications was made, all were analyzed as recorded.

2.4 Histopathological Image Assessment

Representative haematoxylin and eosin stained microscopic images were qualitatively examined and the description of the morphological features of adrenocortical adenoma and pheochromocytoma was compiled. Adrenocortical adenoma images consisted of low, medium and high powers and a comparison between normal zona fasciculata and adenomatous tissue. The emphasis of assessment was on overall architecture, clear/cavitated cytoplasm, cellular organization and nuclear appearance. Slices of pheochromocytomas were studied at low, medium, and high magnification, with particular attention to: cellular architecture, nested or alveolar organization, vascular stromal organization, cytoplasmic characteristics, and nuclear morphology. Micro images were not classified or quantised in terms of morphometry and were simply described histopathologically.

2.5 Cross-Tumour Tissue and Molecular Analysis

By using tissue microarray, qPCR and ELISA measurements, ancillary comparisons were made between normal/control tissue, adrenocortical adenoma, pheochromocytoma and ACC (Rucinski, 2025). The main quantitative tissue staining parameter used was CTCF. The $2^{-\Delta\Delta C_t}$ values as reported and the calculated concentration values, respectively, were applied to the relative qPCR expression and ELISA analysis, respectively. Analytical components were treated as three separate sample sets, and were not paired

measurements. The measurements were regarded as additional pathological and molecular markers, and were not used as a substitute to the traditional histomorphological diagnosis.

2.6 Statistical Analysis

All data were presented as a median and interquartile range (IQR) for continuous variables and frequencies and percentages for categorical variables. The Mann-Whitney U test was used for comparing adrenocortical adenoma with ACC for continuous variables. Kruskal-Wallis test was used for comparisons among more than two diagnostic groups. The characteristics of pheochromocytoma were summarized descriptively, such as pT stage, GAPP differentiation, vascular invasion, distant metastasis and SDHB status. Medians and IQRs were used to summarize PASS, GAPP, Ki-67, tumour diameter and immunohistochemical measurements where appropriate. All the statistical tests were two-tailed, and a p value of < 0.05 was considered statistically significant.

2.8 Ethical Consideration

This study used only identified, publicly available secondary data and histopathological images. No new participants, clinical interventions, or specimen collection were involved. Therefore, additional ethical approval and informed consent were not required.

3. RESULTS

3.1 Comparative Pathological Profile of Adrenal Tumours

The clinicopathological and microscopic patterns of the three groups of adrenal tumours were different. The images in H&E that were available showed a predominantly clear-cell adrenocortical phenotype with abundant lipid-rich or finely vacuolated cytoplasm which supported the diagnosis of adrenocortical adenoma. The pheochromocytoma exhibited a neuroendocrine growth pattern and characteristic granular eosinophilic cytoplasm in polygonal cells, as well as prominent vascular stroma. The ACC dataset was largely composed of clinicopathological and quantitative tissue data, in contrast to the available data from this study, which was largely comprised of representative H&E sections. The big difference between adenoma and ACC was the size of the tumours and staining intensity of the tissues.

Median tumour size was 2.85 cm in the group with adrenocortical adenomas and 9.50 cm in the group with ACC, resulting in a considerable difference between the two groups. The median diameter of pheochromocytomas was 57 mm and the median TMA-derived CTCF values were lowest in ACC, with intermediate values in adenoma and pheochromocytoma. The major differences in pathology are outlined in Table 1.

Table 1. Comparative pathological characteristics of adrenocortical adenoma, pheochromocytoma, and adrenocortical carcinoma

Pathological characteristic	Adrenocortical adenoma	Pheochromocytoma	Adrenocortical carcinoma
Cellular origin	Adrenal cortex	Adrenal medulla/chromaffin lineage	Adrenal cortex
Predominant morphology in available images	Clear/lipid-rich polygonal cortical cells	Nested/alveolar tumour-cell arrangement with vascular stroma	H&E morphology not directly represented in uploaded images
Cytoplasmic appearance	Clear to finely vacuolated	Eosinophilic to granular	Not directly assessed microscopically in current images
Nuclear appearance	Generally relatively uniform with focal variability	Round-to-oval nuclei with variable size	Quantitative tissue data available; direct nuclear assessment unavailable
Median tumour size	2.85 cm	57 mm	9.50 cm
Main pathological risk assessment available	Benign cortical morphology	PASS and GAPP	Clinical malignant diagnosis; direct Weiss-variable dataset limited
Vascular invasion data	Not available	7/35 lesions, 20.0%	Not consistently available
Median Ki-67	Not available	2.0%	Not available in current analytical dataset
SDHB loss	Not applicable	4/35, 11.4%	Not applicable
Median TMA CTCF	8.06	8.19	4.27

Pathological characteristic	Adrenocortical adenoma	Pheochromocytoma	Adrenocortical carcinoma
Diagnostic interpretation from available evidence	Benign cortical neoplasm	Neuroendocrine adrenal tumour with variable biological risk	Malignant cortical neoplasm

In the representative adenoma pictures, the difference in histological characteristics of normal zona fasciculata and adenomatous cortical tissue was also illustrated. At higher magnification (Figure. 1), adenoma cells were also enlarged compared to the normal cortical cells and had a large amount of clear cytoplasm and greater variation in nuclear size.

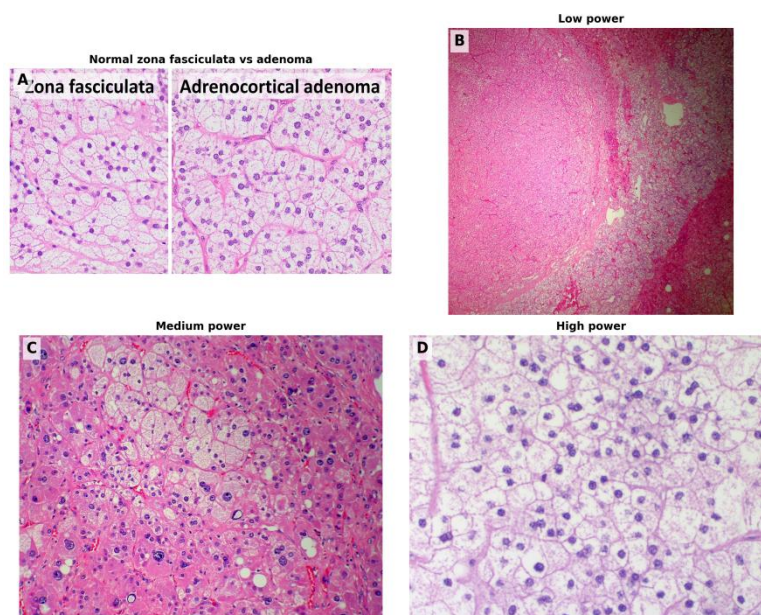


Figure 1. Representative histopathology of adrenocortical adenoma. (A) Comparison of normal zona fasciculata and adrenocortical, (B) low-power architectural appearance, (C) medium-power tumour-cell morphology and (D) high-power appearance of clear/lipid-rich cortical cells

3.2 Adrenocortical Adenoma versus Adrenocortical Carcinoma

The two groups of cortical tumours (benign and malignant) were clearly distinguished by a marked difference in tumour size. Finally, median age was not very discriminated against, with adenoma patients at 57.0 years and ACC at 58.0 years. ACC lesions were significantly larger however, with a median size of 9.50 cm [IQR 6.00-13.00] compared to 2.85 cm [2.00-3.00] for adenoma. The difference was statistically significant ($p < 0.001$) as demonstrated in Table 2.

Further separation was achieved by quantitative measurements at the tissue level. Adenoma demonstrated a median CTCF of 8.06 [6.32-13.74], whereas ACC demonstrated a lower median of 4.27 [2.40-8.92]. The mean staining intensity was also less in ACC compared to adenoma. The results show that malignant cortical tumours not only had different macroscopic tumour load, but they also had different tissue staining.

Table 2. Clinicopathological comparison of adrenocortical adenoma and adrenocortical carcinoma

Characteristic	Adrenocortical adenoma	ACC	p-value
Cases in clinical cohort	50	28	-
Age, years, median [IQR]	57.0 [49.0-62.0]	58.0 [48.0-62.25]	0.925
Tumour size, cm, median [IQR]	2.85 [2.00-3.00]	9.50 [6.00-13.00]	<0.001
Overall survival, months	Not available	27 [12-53]	-
TMA observations	68	20	-
CTCF, median [IQR]	8.06 [6.32-13.74]	4.27 [2.40-8.92]	0.004
Mean staining intensity, median [IQR]	12.48 [10.74-18.17]	8.70 [6.82-13.35]	0.004
Maximum staining intensity, median	66.0	69.0	0.070

The difference in tumour burden between the cortical groups provides a clinically relevant pathological distinction; however, tumour size should be interpreted together with microscopic characteristics rather than as an isolated diagnostic criterion.

3.3 Histopathological and Risk Characteristics of Pheochromocytoma

Characteristic morphology of pheochromocytoma was seen in the representative H&E sections across the magnifications. The low power view revealed a very cellular adrenal neoplasm, and the medium-power magnification showed a nested/alveolar pattern with thin vascular stromal elements. Neoplastic cells, at high power, were polygonal and had round to oval nuclei, and abundant eosinophilic-to-granular cytoplasm. The features are shown in Figure 2.

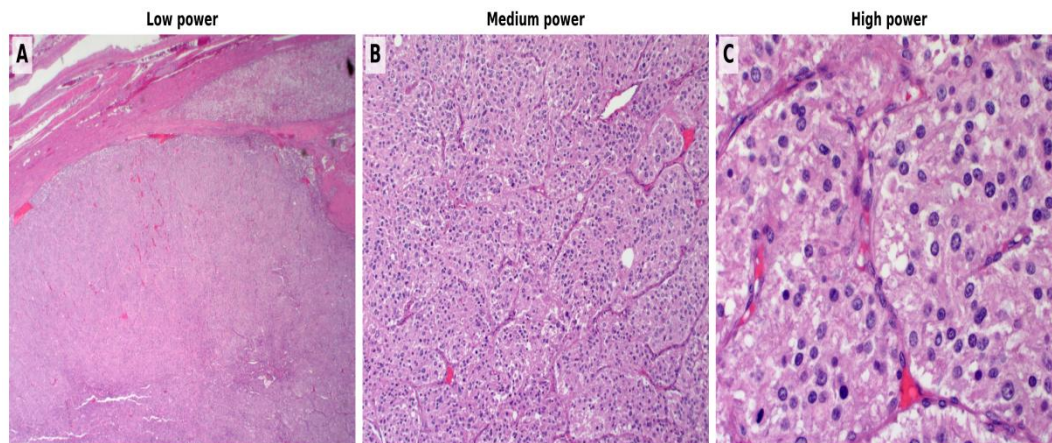


Figure 2. Representative H&E histopathology of adrenal pheochromocytoma. (A) Low-power architecture; (B) medium-power nested cellular arrangement with vascular stromal framework; and (C) high-power tumor-cell and nuclear morphology

The PPGL cohort was very heterogeneous, with a structured design. Median tumour diameter was 57 mm [36.5-73.5]. Of the 19 lesions, 16 were pT1 and 16 were pT2. The median PASS was 6.0, as was the median GAPP. Moderately differentiated 20 lesions, poorly differentiated 11 lesions and well differentiated 4 lesions were found on the basis of GAPP differentiation.

Vascular invasion was found in 7/35 lesions (20.0%) and distant metastasis in 5 lesions (14.3%). Median Ki-67 proliferation index was 2.0%, with some tumours having higher indices. In situ hybridization was performed for SDHB in 35 lesions, including 31 that had SDHB expression and four that did not. The results of these tests are shown in Table 3 and in Figure 3.

Table 3. Pathological risk and immunohistochemical characteristics of pheochromocytoma/PPGL

Characteristic	Result
Lesions	35
Patients	31
Tumour diameter, mm, median [IQR]	57.0 [36.5-73.5]
pT1	16 (45.7%)
pT2	19 (54.3%)
PASS score, median [IQR]	6.0 [3.25-8.0]
GAPP score, median [IQR]	6.0 [4.5-7.0]
Well differentiated	4 (11.4%)
Moderately differentiated	20 (57.1%)
Poorly differentiated	11 (31.4%)
Vascular invasion present	7 (20.0%)
Distant metastasis present	5 (14.3%)
Distant metastasis absent	26 (74.3%)
Metastatic status unknown	4 (11.4%)

Characteristic	Result
Ki-67, %, median [IQR]	2.0 [1.0-3.0]
SDHB retained	31 (88.6%)
SDHB loss	4 (11.4%)
HIF-2 α H-score, median	70
VEGF IRS, median	4
CD105 MVD, median	15

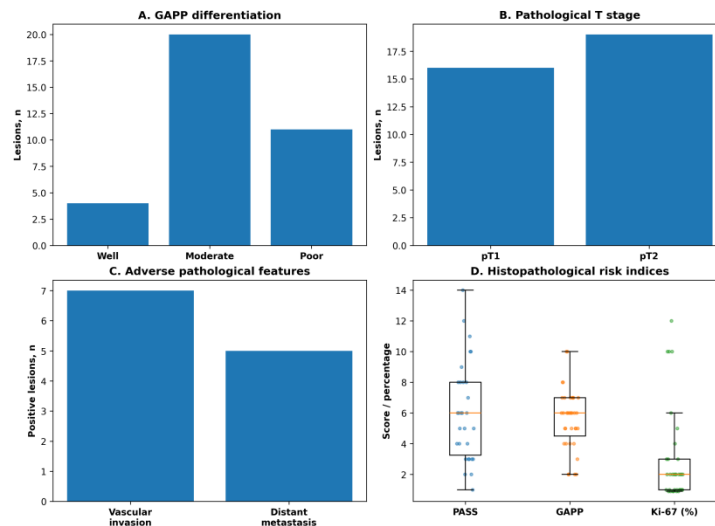


Figure 3. Pathological risk profile of pheochromocytoma/PPGL. The figure summarizes (A) GAPP differentiation, (B) pathological T stage, (C) vascular invasion and metastatic status together with PASS, (D) GAPP, and Ki-67 distributions

3.4 Cross-Tumour Tissue and Molecular Differences

The quantitative tissue analysis also showed that there was interclass heterogeneity for the three types of adrenal tumours. Median values of TMA CTCF were 8.06 in adenoma, 8.19 in pheochromocytoma, and 4.27 in ACC, as compared with 21.82 in normal adrenal tissue. The difference between the overall groups was statistically significant (Kruskal-Wallis $H=8.89$, $p=0.0117$).

The same was true of ancillary qPCR analysis ($H=18.15$, $p=0.00041$). The median relative expression value for adenoma, pheochromocytoma and ACC were 0.097, 0.079, and 0.324, respectively, as compared with 0.731 for controls. Table 4 shows that the measurement obtained by ELISA also varies between groups ($H=13.46$, $p=0.0037$).

Table 4. Cross-tumour tissue staining and ancillary molecular findings

Diagnostic group	TMA CTCF, median [IQR]	qPCR $2^{-\Delta\Delta Ct}$, median [IQR]	ELISA concentration, median [IQR]
Normal/control	21.82 [15.34-28.38]	0.731 [0.503-0.921]	515.38 [364.45-794.09]
Adenoma	8.06 [6.32-13.74]	0.097 [0.041-0.492]	1396.86 [917.16-1672.53]
Pheochromocytoma	8.19 [5.61-14.09]	0.079 [0.043-0.215]	1594.01 [991.17-1696.14]
ACC	4.27 [2.40-8.92]	0.324 [0.171-0.823]	950.77 [649.49-1419.89]
Overall p-value	0.0117	0.00041	0.0037

The cross-tumour distributions are presented in Figure 4. These findings should be interpreted as ancillary pathological evidence because the TMA, qPCR, and ELISA measurements were obtained from separate cohorts rather than paired samples from the same patients.

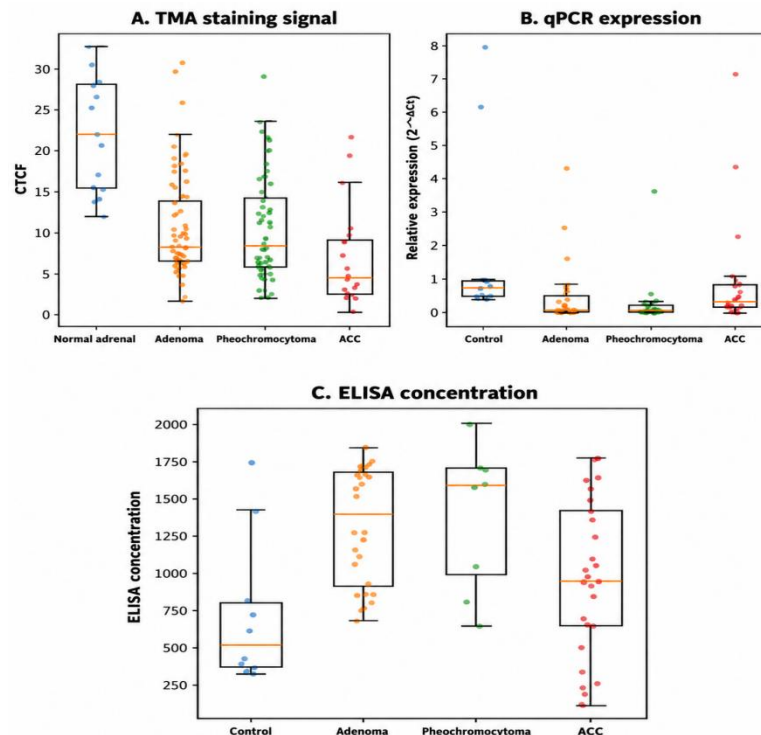


Figure 4. Comparative tissue and molecular profiles across adrenal tumour groups. (A) TMA CTCF; (B) relative qPCR expression; and (C) ELISA-derived concentration across normal/control, adenoma, pheochromocytoma, and ACC groups

4. DISCUSSION

The present findings illustrate some interesting differences between adrenocortical adenomas, pheochromocytomas, and ACC. The most obvious clinicopathological differences between the two cortical tumors concerned the size of the tumor; adenoma median diameter was 2.85 cm while ACC was 9.50 cm. This finding is consistent with clinical experience, which suggests that ACC is a more aggressive adrenal tumor often occurring as a significantly larger tumor than a benign cortical adenoma (Verlinde et al., 2025). However, the size of a tumor is not enough to define its malignant behavior as multiple pathological characteristics that need to be integrated to determine the difference between benign and malignant cortical tumors (Pennanen, 2020).

The H&E tissue from the adenoma available showed well-differentiated, and sometimes finely vacuolated, cortical cells with relatively well-organized architecture. Conversely, TMA staining intensity and mean staining intensity were significantly lower in ACC than in adenoma in the quantitative tissue analysis. Immunohistochemical analyses of ACC have revealed that the expression of tissue markers can give prognostic information when used in the right morphological context (Loncar et al., 2020). Metabolic immunophenotyping has also revealed significant biologic diversity among ACCs, and that tissue-based biomarkers are complementary (Duan et al., 2020). Because of this, the staining differences found in the analysis in the present study are secondary and not independent diagnostic criteria.

The available H&Es of the pheochromocytoma showed the characteristic nested/alveolar architecture with prominent vascular stroma. Median PASS and GAPP scores for the cohort were 6, and 20.0% and 14.3% of lesions, respectively, had vascular invasion and documented distant metastasis. Vascular and microenvironmental features have been shown to be useful in the biological heterogeneity of pheochromocytoma in previous histopathological studies (Gao et al., 2020). This is the reason why the observed differences in the levels of HIF-2 α , VEGF and CD105 are consistent with inter-tumoural variation in tumour-associated angiogenic activity.

The median Ki-67 index was 2.0% and 11.4% of PPGL lesions were identified as having SDHB loss. To further illustrate the different molecular phenotypes of adrenal tumour lineages, differential expression of proteins associated with autophagy was observed between cortical tumours and pheochromocytoma (Kim & Koo, 2021). Amine oxidase protein expression is also different between adrenal cortical neoplasms and pheochromocytoma, which is another evidence of lineage specific tumour biology (Kim & Koo, 2023). The molecular differences in the expression of epithelial membrane proteins also reflect molecular differences between cortical and medullary adrenal neoplasms (Cha & Koo, 2023).

There were also significant differences found between the normal/control group and all other groups in qPCR and ELISA measurements, as well as between the adenoma group and the pheochromocytoma and ACC groups. Immunohistochemical analysis of inflammatory elements of adrenal neoplasms indicates that microenvironmental features of the tumour may offer additional prognostic data to those obtained by routine morphological evaluation (Guadagno et al., 2020). However, it is not always true that these two types are mutually exclusive and mixed corticomedullary adrenal tumours have been reported (Kimura et al., 2022). The presence of both an

adrenocortical adenoma and a microscopic pheochromocytoma is another example of synchronous lesions of the cortex and medulla in a single adrenal gland (Sakai et al., 2023).

While imaging is still useful for lesion detection, localization and staging, histopathological confirmation is still the ultimate step for the characterization of diagnostically difficult adrenal malignancies (Ambrosini et al., 2024). Incidental adrenocortical adenomas may affect clinical presentation in a way that is related to functional status, but is not pathognomonic for the pathological classification (Hamidi et al., 2024). As an example of unusual oncocytic ACC, this further illustrates the situation in which immunohistology may be more important for resolving difficult morphology (Roy et al., 2025). Pediatric ACC has unique clinical and pathological implications and age-related context should also be taken into account. Taken together, the present results validate a patho-centred diagnosis based on microscopic morphology, with the immunohistochemical, tissue staining and molecular results used as supporting evidence.

5. CONCLUSION

The present study compares the pathological aspects of adrenocortical adenoma, pheochromocytoma and adrenocortical carcinoma (ACC) using histological, clinicopathological, immunohistochemical, tissue staining and molecular evidence in an adrenocortical pathology-centered approach. These differences in the morphology of both types of tumor and the differences in the staining index of the tissues suggest that there are clear pathological differences between benign and malignant cortical tumors, with adrenocortical adenoma having a benign cortex as indicated by the relatively organized architecture and a relatively high tissue staining index. Pheochromocytoma exhibited a typical nest-like or alveolar pattern, with abundant vascular stroma and was highly variable in terms of PASS, GAPP, Ki-67, vascular invasion, metastatic status, and SDHB expression. The TMA CTCF, qPCR expression and ELISA derived concentrations were also significantly different between the three tumor categories, showing that the three tumor categories have different biological profiles. These ancillary measurements must, however, be used in addition to conventional histomorphological assessment. The results underscore the need to consider the combination of morphology and clinicopathological and immunohistochemical features in evaluating adrenal tumors, especially those that have overlapping and atypical features. Generally, a pathology-first diagnostic strategy offers a broader context to differentiate adrenal cortical adenoma from pheochromocytoma and ACC, and also evaluate ACC features of biological behavior and malignant potential.

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