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The role of stathmin expression in the differential diagnosis, prognosis, and potential treatment of ovarian sex cord-stromal tumors

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Abstract

Background Stathmin, a cytosolic microtubule-destabilizing phosphoprotein involved in the regulation of mitosis, is widely expressed in various malignancies and acts as an adverse prognostic factor. Our research analyzed its immunohistochemical expression on a large cohort of ovarian sex cord-stromal tumors, evaluating its potential utility in differential diagnosis, prognosis, and therapeutic application.

Methods We examined 390 cases of ovarian sex cord-stromal tumors including 281 adult granulosa cell tumors (AGCT), 5 juvenile granulosa cell tumors (JGCT), 33 Sertoli-Leydig cell tumors (SLCT), 50 fibromas/thecomas (F/T), 11 Leydig cell tumors/steroid cell tumors (LCT/SterCT), 5 sex-cord stromal tumors NOS (SCST-NOS), 3 Sertoli cell tumors (SCT), and 2 sclerosing stromal tumors (ScST). Immunohistochemical analysis was performed using TMAs.

Results Strong expression (> 50%) was observed in all cases of AGCT, JGCT, SLCT, SCST-NOS, SCT and 1 ScST. The other case of ScST exhibited mild expression (5–10%). The negative cases included exclusively F/T and LCT/SterCT, with F/T showing 24% of negative cases and LCT/SterCT comprising 64% of negative cases.

Conclusion The results of our study indicate that stathmin is neither a prognostic marker nor suitable for the differential diagnosis of challenging cases of ovarian sex cord-stromal tumors. However, its predictive value may be theoretically significant, as a decrease in stathmin expression potentialy influences response to chemotherapy treatment.

Keywords Stathmin, Immunohistochemistry, Ovarian tumors, Sex cord-stromal tumors, Ovary

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Background

Stathmin (also named stathmin 1, Oncoprotein18) is a major member of cytosolic phosphoprotein family and is significantly involved in microtubule dynamics regulation. It is regarded as a microtubule destabilizer as it contributes to rapid reorganization of the microtubule cytoskeleton by preventing tubulin polymerization and promoting microtubule destabilization. Its expression across the majority of proliferative cell populations underscores its significance in facilitating dynamic cellular processes essential for successful cell division [1–3]. In normal human tissues, the expression of stathmin is widespread, demonstrating highest levels in neural tissues, as well as in the female genital tract, colon, liver, testis, and bone marrow [4]. Overexpression of stathmin is common in malignancies of various locations such as CNS [5], lungs [6], gastrointestinal system [2, 7–13], breast (14–15), female genital system [16–20], urinary system [21], soft tissues [22], and skin [23–25], where it is associated with poor prognostic outcome and resistance to specific types of chemotherapy (26–27). The available data on stathmin expression in ovarian neoplasms is limited to epithelial tumors as no reports regarding sex cord-stromal tumors are available.

Ovarian sex cord-stromal tumors represent a heterogenous group of tumors with diverse biological behavior and are classified into three groups based on the origin of the tumor cells: (a) pure stromal tumors, (b) pure sex cord tumors, and (c) mixed sex cord-stromal tumors [28]. The predominant malignant tumor among ovarian sex cord-stromal tumors is the adult granulosa cell tumor, representing approximately 3–5% of all ovarian malignancies and being known for its risk of recurrence with high mortality rate [29–31]. The differential diagnosis of sex cord-stromal tumors primarily depends on their distinct morphological and immunohistochemical characteristics. However, some tumors exhibit overlapping features with other sex cord-stromal tumors and neoplasms of different histogenesis. Furthermore, recent advancements in identifying common mutations have enhanced the accuracy of differential diagnosis. For instance, missense mutations in *FOXL2* (c.402 C>G, p.(Cys134Trp)) are prevalent in the majority of adult granulosa cell tumors (AGCT), while *DICER1* RNase IIIb domain mutations are observed in a subset of Sertoli-Leydig cell tumors (SLCT) [32–35]. Since molecular testing is not yet widely accessible, the need for novel immunohistochemistry markers to improve the accuracy of differential diagnosis remains important.

In this study we focused on stathmin expression in a large cohort of 390 ovarian sex cord-stromal tumors including AGCT, juvenile granulosa cell tumor (JGCT), SLCT, fibroma/thecoma tumor (F/T), Leydig cell tumor/steroid cell tumor (LCT/SterCT), sex cord-stromal tumor NOS (SCST-NOS), Sertoli cell tumor (SCT), and sclerosing stromal tumor (ScST) with the aim to assess its potential use in differential diagnosis. Moreover, its prognostic significance was evaluated.

Methods

Samples

The archives of the pathology departments of the authors were searched for cases diagnosed as primary or recurrent ovarian sex cord-stromal tumors. All cases were evaluated by two experienced gynecologic pathologists (PD and KN) and fulfilled the diagnostic criteria. All disputable cases were excluded. In total, 390 cases were selected for immunohistochemical analysis, which included 281 AGCT, 5 JGCT, 33 SLCT, 50 F/T, 11 LCT/SterCT, 5 SCST-NOS, 3 SCT, and 2 ScST.

Patient clinical characteristics

Clinical data on the patient and tumor characteristics at the time of diagnosis and other survival data were obtained retrospectively from the medical records. However, it should be noted that the available data are limited as only AGCT had sufficient amount of cases matched with clinical data (Table 1).

Immunohistochemical analysis

Immunohistochemistry was performed on tissue microarrays (TMAs) using 4 μm thick sections of formalin-fixed and paraffin-embedded (FFPE) tissue. For the construction of the TMAs, eligible areas of each tumor were identified and two tissue cores (each 2.0 mm in diameter) were taken from the donor block using the tissue microarray instrument TMA Master (3DHISTECH Ltd., Budapest, Hungary). The immunohistochemical expression evaluation was performed using the antibody against stathmin (clone EP247, dilution 1:100, Bio SB USA). The staining was performed by Dako Omnis (Agilent Technologies, California, USA) and detection provided by EnVision FLEX kit. Adult liver tissue served as a negative external control, while testicular tissue was used as a positive external control. Only cytoplasmatic expression was regarded as positive. The immunohistochemical expression was double-blindly evaluated by two pathologists (AŠ, KN). Cases were classified based on the overall percentage of positive cells as negative (entirely negative or set as <5% of positive tumor cells) or positive (≥5% positive tumor cells) and also evaluated semiquantitatively using the H-score method, which has been widely used in previous studies evaluating immunohistochemistry [36].

Statistical analyses

All statistical analyses were performed using the R software v. 4.1.1 (2024-02-29, https://www.R-project.org/).

Table 1 Clinico-pathological, treatment, and survival characteristics of 390 cases of ovarian sex cord-stromal tumors

	AGCT (*n* = 281)	JGCT (*n* = 5)	SLCT (*n* = 33)	F/T (*n* = 50)	LCT/SterCT (*n* = 11)	SCST-NOS (*n* = 5)	SCT (*n* = 3)	ScST (*n* = 2)
Origin								
primary	232 (83%)	-	-	-	-	-	-	-
recurrences	49 (17%)	-	-	-	-	-	-	-
Age at diagnosis (years)								
Median (range)	57 (17–83)	26 (21–43)	48 (14–71)	-	61 (48–88)	52 (27–76)	47 (47–48)	17 (-)
Mean (SD)	55 (14.2)	30 (11.5)	43 (20.8)	-	64 (13.6)	52 (34.6)	47 (0.6)	17 (-)
FIGO								
I	143 (89%)	2 (-)	8 (89%)	-	-	1 (-)	-	-
II	10 (6%)	-	1 (11%)	-	-	-	-	-
III	7 (4%)	-	0 (0%)	-	-	-	-	-
IV	1 (1%)	-	0 (0%)	-	-	-	-	-
NA	*120*	*3*	*24*	*50*	*11*	*5*	*3*	*2*
Grade								
G1	-	-	8 (24%)	-	-	-	-	-
G2	-	-	23 (70%)	-	-	-	-	-
G3	-	-	2 (6%)	-	-	-	-	-
Survival status at last control								
living	141 (88%)	-	8 (100%)	-	5 (100%)	-	-	1 (-)
died	19 (12%)	-	0 (0%)	-	0 (0%)	-	-	-
NA	*121*	*5*	*24*	*50*	*6*	*5*	*3*	*1*
Disease status at last control								
NED	120 (75%)	-	7	-	5 (100%)	-	-	1 (-)
AWD	21 (13%)	-	1	-	0 (0%)	-	-	-
DOD	9 (6%)	-	0	-	0 (0%)	-	-	-
DUC	10 (6%)	-	0	-	0 (0%)	-	-	-
NA	*121*	*5*	*25*	*50*	*6*	*5*	*3*	*1*
Recurrences								
No	89 (58%)	-	5 (83%)	-	5 (100%)	-	-	1 (-)
Yes	64 (42%)	-	1 (17%)	-	0 (0%)	-	-	-
NA	*128*	*5*	*27*	*50*	*6*	*5*	*3*	*1*

AGCT – Adult granulosa cell tumor, JGCT – Juvenile granulosa cell tumor, SLCT – Sertoli-Leydig cell tumor, F/T – Fibroma/thecoma, LCT/SterCT – Leydig cell tumor/Steroid cell tumor, SCST-NOS – Sex-cord stromal tumor NOS, SCT – Sertoli cell tumor, ScST – Sclerosing stromal tumor, NED – no evidence of disease, AWD – alive with disease, DOD – death of disease, DUC – death of unknown cause, NA – data not available

Percentages are calculated based only on available data and are rounded up/down accordingly

Standard descriptive statistics were employed to summarize the dataset: categorical variables were reported as frequencies and percentages, while continuous variables as means with standard deviation (SD) or medians with interquartile range.

Given the predominant complete positivity observed across most diagnostic groups, stathmin expression was evaluated on a continuous scale as H-score rather than categorically (positive vs. negative). The Kruskal-Wallis H-test was utilized to compare stathmin expression among the diagnostic groups, followed by subsequent multiple-pairwise comparisons. The same approach was used to correlate expression with grade in a subset of SLCT. Binomial categorical variables were compared using Mann-Whitney U-test. Continuous variables were tested using linear model.

Only AGCTs were included into further statistical analysis, as only those had clinico-pathological data recorded.

Survival analyses were not conducted due to the limited number of cases with the event of interest in particular groups. Instead, survival status was tested solely as a categorical variable in terms of overall survival (living vs. deceased) in relation to stathmin expression levels in the AGCTs group.

The potential of stathmin expression to discriminate between selected diagnostic groups was evaluated using receiver-operating characteristic (ROC) analyses. These analyses were conducted using the "pROC" and "cutpointr" packages implemented in R. The optimal cut-off value of stathmin H-score and overall positivity was determined based on the area under the curve (AUC), sensitivity, and specificity.

All tests were two-sided an p-value < 0.05 was considered statistically significant.

Results

Immunohistochemical findings

The detailed overview of stathmin expression among the diagnostic groups is provided in Table 2. Strong expression (>50%) was observed in all AGCT, JGCT, SLCT, SCST-NOS, SCT, and 1 ScST. The other case of ScST exhibited mild expression (5–10%). Negative cases were observed only in F/T and LCT/SterCT, with F/T exhibiting 24% of negative cases and LCT/SterCT showing 64% of negative cases (Fig. 1). In a subset of LCT/SterCT cases, all cases diagnosed as LCT ($n=5$) and SterCT ($n=6$) were either negative or showed weak intensity of expression. Overall, the expression intensity was predominantly strong and homogenous.

The lowest H-score was detected in the LCT/SterCT group (median=3, mean=8±17), while the other groups reached H-score median between 100 and 280 (Fig. 2).

Overall, significant differences among groups were detected (Kruskal-Wallis H-test: H=128.4, df=7, $p<0.001$), mainly driven by the differences between F/T and both AGCT, JGCT, and SLCT, as well as between LCT/SterCT and AGCT, JGCT, and SLCT.

The potential of stahmin to distinguish between diagnoses of sex cord-stromal tumors

Given the diagnostic challenges posed by overlapping immunohistochemical (IHC) characteristics among AGCT and SLCT vs. F/T, we employed Receiver Operating Characteristic (ROC) analysis to evaluate the discriminative ability of stathmin between groups with sufficient sample size, specifically between AGCT vs. F/T, and between SLCT vs. F/T.

Stathmin emerged as a promising candidate for distinguishing between F/T and AGCT, exhibiting a high potential with an ideal H-score cut-off of 180 for (AUC=0.915, sensitivity=0.889, specificity=0.803, Fig. 3).

Similarly, stathmin exhibited good discriminatory potential in differentiating between SLCT and F/T. An ideal H-score cut-off of 185 yielded an AUC of 0.881 (sensitivity=0.757, specificity=0.860).

Prognostic significance of stathmin expression

The probability of later recurrences, regardless of tissue origin, showed no correlation with H-score (Mann Whitney U-test: U=2771, Z= -0.283, $p=0.777$).

No significant differences were found in FIGO stage when categorized as stage I vs. stage II-IV (Mann Whitney U-test: U=1058, Z=1.223, $p=0.221$), nor in FIGO stage I when categorized as FIGO IA vs. IB-IC (Mann Whitney U-test: U=1819, Z=1.211, $p=0.224$).

In AGCT, the association between stathmin expression and patient age was examined, indicating no significant correlation (ANOVA: F=3.35, $R=0.01$, R2=0.001, $p=0.068$).

In SLCT, grade was not associated with stathmin expression (Kruskal-Wallis H-test: H=0.39, df=2, $p=0.821$).

Discussion

Stathmin, a microtubule-destabilizing phosphoprotein, has a pivotal role in the orchestration of mitotic events within cells. Stathmin expression has been widely observed in a majority of malignant tumors, with research indicating its association with advanced stage, frequent lymph node and distant metastases, and accelerated tumor progression [2, 6–17, 19, 21–23]. This finding was further supported by a recent meta-analysis, which provided a comprehensive summary of data from 3571 patients [26]. Although the expression of stathmin

Table 2 Overview of stathmin immunohistochemical expression in 390 cases of ovarian sex cord-stromal tumors

Type of diagnosis	Adult granulosa cell tumor	Juvenile granulosa cell tumor	Sertoli-Leydig cell tumor	Fibroma/thecoma	Leydig cell tumour/Steroid cell tumor	Sex cord-stromal tumor NOS	Sertoli cell tumor	Sclerosing stromal tumor
abbrv. (no of cases)	AGCT ($n=281$)	JGCT ($n=5$)	SLCT ($n=33$)	F/T ($n=50$)	LCT/SterCT ($n=11$)	SCST-NOS ($n=5$)	SCT ($n=3$)	ScST ($n=2$)
Negative cases (< 5%)	0 (0%)	0 (0%)	0 (0%)	12 (24%)	7 (64%)	0 (0%)	0 (0%)	0 (0%)
Positive cases (≥ 5%)	281 (100%)	5 (100%)	33 (100%)	38 (76%)	4 (36%)	5 (100%)	3 (100%)	2 (100%)
Positivity 1+ (5–10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (27%)	0 (0%)	0 (0%)	1 (50%)
Positivity 2+(11–50%)	0 (0%)	0 (0%)	0 (0%)	5 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Positivity 3+ (> 50%)	281 (100%)	5 (100%)	33 (100%)	33 (66%)	1 (9%)	5 (100%)	3 (100%)	1 (50%)
Stathmin overall range (%)	55–100	90–100	60–100	0-100	0–60	70–100	90–100	8–85
Stathmin overall mean ± SD	98 ± 6	98 ± 4	96 ± 8	61 ± 40	8 ± 17	87 ± 13	93.3 ± 6	46.5 ± 54
Stathmin overall median	100	100	100	80	3	85	90	46.5
H-score mean ± SD	241.5 ± 55	257.8 ± 42	216.5 ± 63	99.6 ± 76	8 ± 17	189 ± 79	228.3 ± 6	101.5 ± 132
H-score median	260	280	215	100	3	160	205	101.5

abbrv. = abbreviation of type of diagnosis, SD = standard deviation

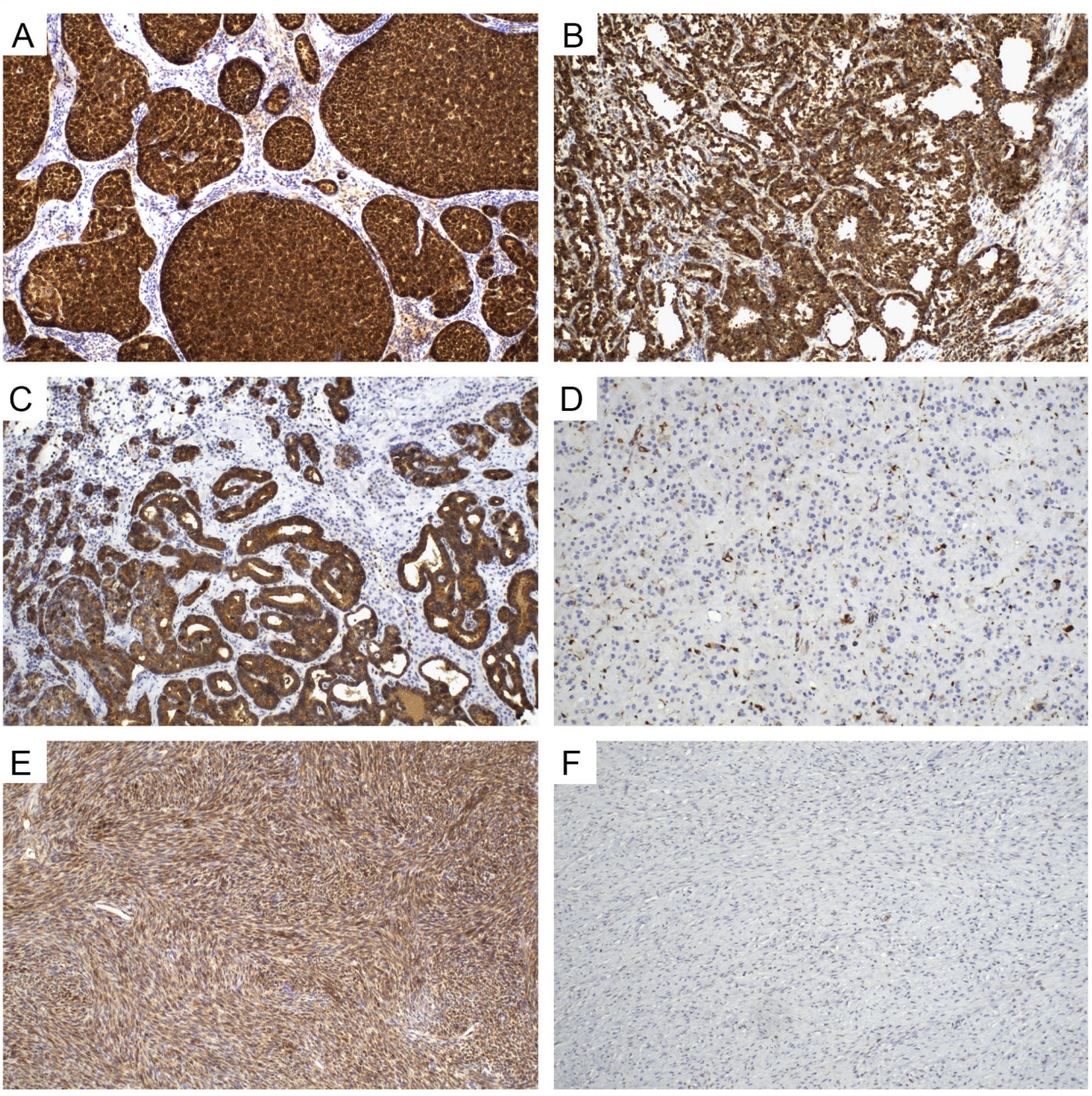

Fig. 1 Stathmin expression in different types of ovarian sex-cord stromal tumors: **A** – Adult granulosa cell tumor (100x), **B** – Juvenile granulosa cell tumor (100x), **C** – Sertoli-Leydig cell tumor (100x), **D** – Leydig cell tumor (100x), **E** – Cellular fibroma (100x), **F** – Fibroma (100x)

has been documented across a broad spectrum of malignancies, our understanding of its expression in ovarian tumors remains limited, with a notable absence of data regarding its expression in ovarian sex cord-stromal tumors. Initially, Price et al. conducted an immunohistochemical and mRNA analysis on 12 "malignant ovarian tumors," revealing elevated expression levels in malignant ovarian tissue. However, tumor typing was not provided in this study [18]. Němejcová et al. performed a comprehensive immunohistochemical study of the expression of stathmin in 250 serous ovarian tumors [19]. The results showed a robust expression of stathmin in HGSC (96%), with lower expression levels in LGSC (70%) and mSBT (66%). Only LGSC exhibited statistically significant prognostic value, with stathmin expression correlating with unfavorable patient outcomes [19]. In contrast to other malignant tumors of the female genital system, our results did not show any significant correlation between stathmin expression and the clinicopathological variables or prognostic significance in AGCT.

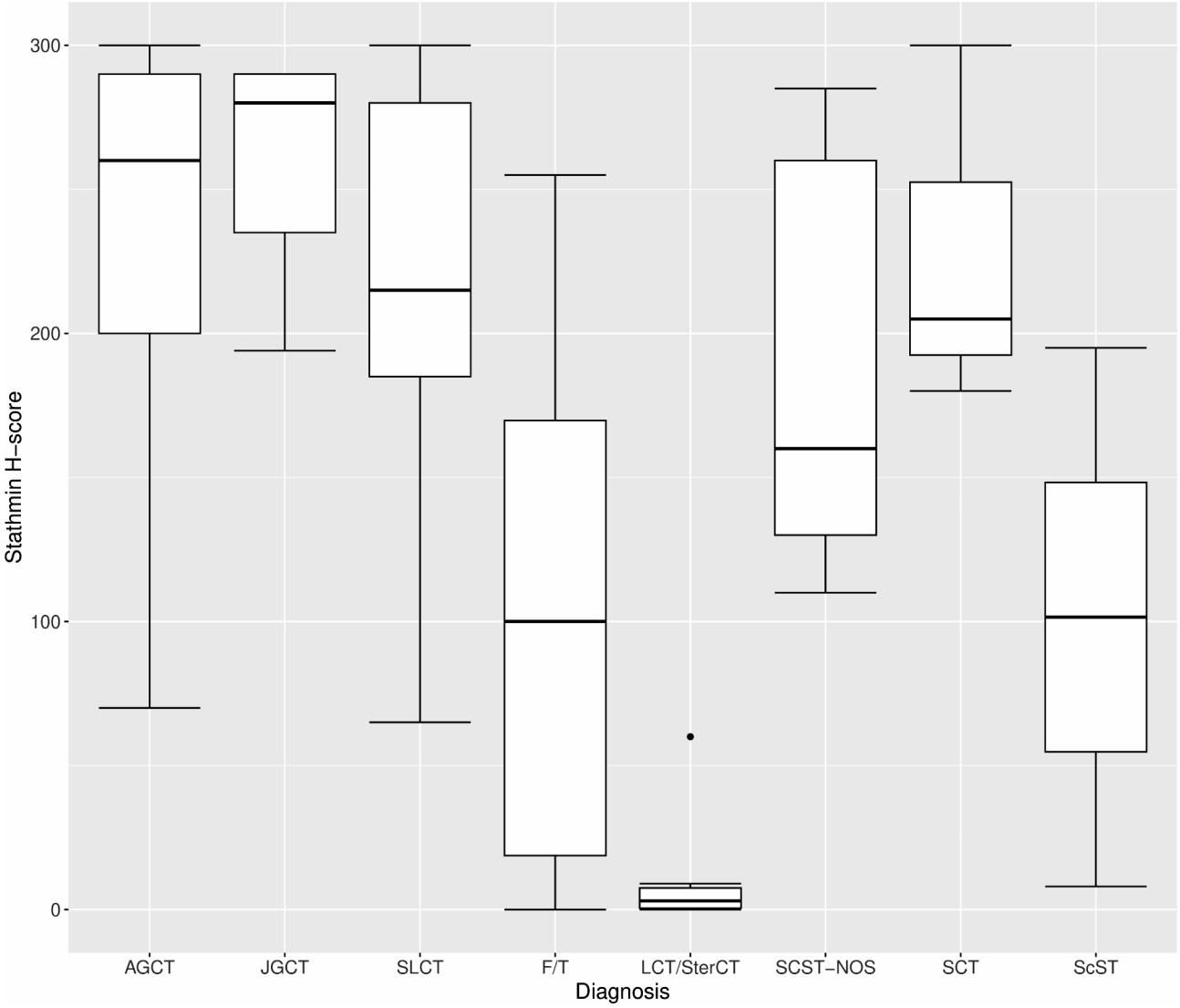

Fig. 2 Box plots illustrating the distribution of stathmin expression (H-score) among 390 ovarian sex cord-stromal tumors

In our study, we evaluated especially the differential diagnostic significance of stathmin expression. Diffuse (100%) expression was observed in AGCT, JGCT, SLCT, SCST-NOS, SCT, and ScST. Negative cases were only seen in F/T (24%) and LCT/SterCT (64%). Despite certain steroid cell tumors exhibiting malignant characteristics, our findings cannot indicate the biologic behavior or be useful in the differential diagnosis due to limited number of samples and both LCT and SterCT demonstrating positive expression in our sample set [37]. Although notable statistical differences were found between SLCT and F/T, the histopathological characteristics of SLCT markedly differ from those of F/T, making immunohistochemistry unnecessary for distinguishing between these tumor types. On the contrary, morphological characteristics of AGCT may exhibit similarities to F/T tumors, particularly in the case of diffuse growth pattern of AGCT which may resemble thecoma and potentially lead to misdiagnosis [38]. We found significant difference in the expression between AGCT and F/T tumors with positive expression in 100% cases of AGCT and 76% of F/T. Additionally, ROC analysis suggested stathmin as a good discriminating marker between these two diagnoses. However, the expression in F/T generally increased with cellularity as all cases diagnosed as cellular fibroma and thecoma were diffusely positive. This suggests that the practical value of this finding is limited, as stathmin may not serve as a suitable diagnostic marker for distinguishing between AGCT and F/T, given that typical fibroma does not pose a challenge in this regard.

Furthermore, recent research offers valuable insights into the potential predictive significance of stathmin expression as mRNA downregulation of stathmin inhibits tumor growth and increases sensitivity to

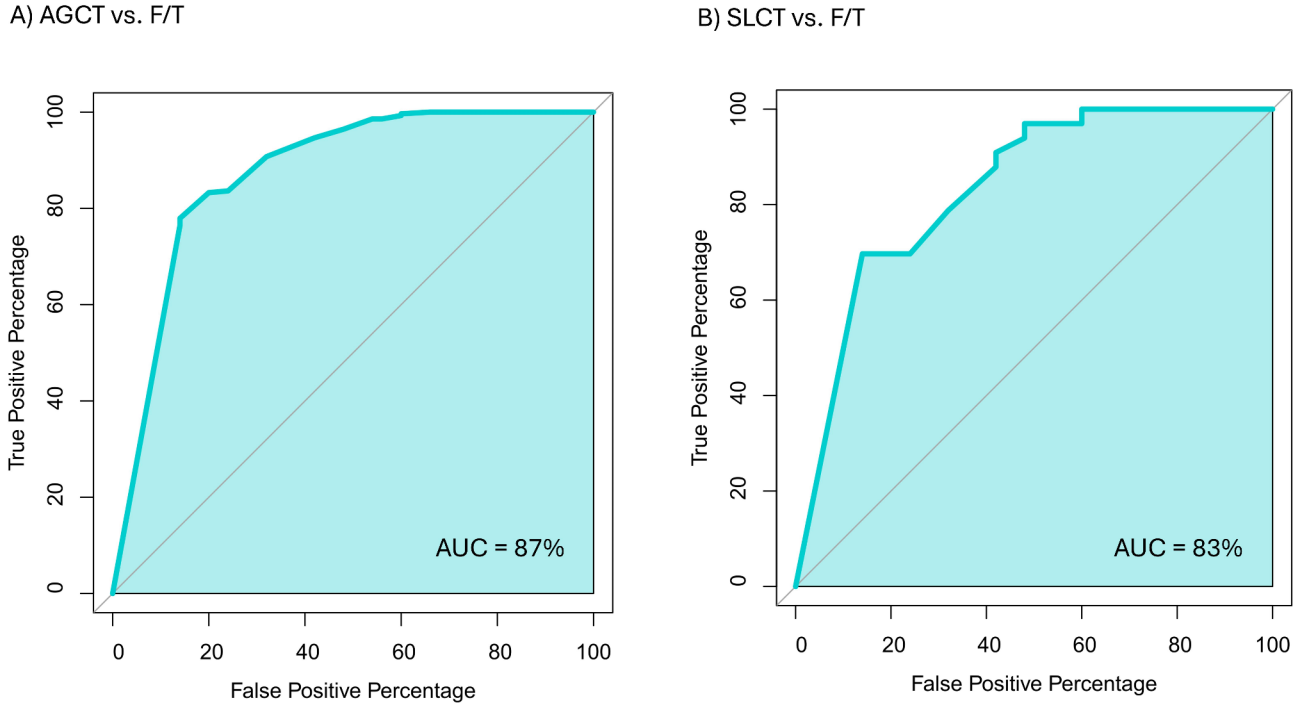

Fig. 3 The Receiver Operating Characteristic (ROC) curve for stathmin overall positivity (%) and the applicability of this marker in the differential diagnosis between AGCT and F/T (**A**) and between F/T and SLCT (**B**). AUC – area under curve

chemotherapeutic drugs that target tubulin, such as taxanes, potentially resulting in enhanced response to cancer treatment [27, 39–41]. While surgery remains the primary treatment method for the most prevalent malignant sex cord-stromal tumor AGCT, hormonal therapy and chemotherapy are also considered especially in cases of progressive disease and in managment of possible recurrencies. However, comprehensive data on these treatment modalities is limited. Our study may contribute to potential treatment strategies, particularly considering the possible use of taxane-based chemotherapy in AGCT treatment as mRNA dowregulation of stathmin expression reported to improve the sensitivity to this regime in numerous malignancies, including endometrial cancer [27, 41–43]. It is important to note that this theory needs to be further validated through clinical trials.

We acknowledge the limitations of our study, the main one being related to the use of tissue microarrays (TMAs). Although widely utilized, particularly in studies involving larger cohorts, this approach theoretically raises the risk of either underestimating or overestimating the immunohistochemical scoring. Another limitation of our study involves the lack of certain statistical analyses due to limited data availability, as only AGCT had sufficient number of cases.

Conclusions

We characterized stathmin expression on most extensive cohort of ovarian sex cord-stromal tumors to date, filling a gap in the existing literature. The results of our study showed stathmin is higly expressed in both benign and malignant ovarian sex-cord stromal tumors, as AGCT, JGCT, SLCT, SCST-NOS, SCT, and ScST showed diffuse expression with variable intensity. The lowest expression was seen in LCT/SterCT and F/T. Our results reveal that the expression of stathmin lacks significant diagnostic value in resolving problematic cases, as both morphological assessment and molecular biology provide more practical utility in this regard. The findings also indicate a lack of prognostic significance regarding stathmin expression in AGCT, in contrast to observations in numerous studies focusing on other malignant tumors. However, the knowledge about stathmin expression has a potential predictive significance as decreasing its expression theoretically enhances the response to specific cancer treatment.

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Author contributions
K.N. and P.D. conceptualized and designed the study. All authors contributed to material preparation, data collection, and/or analysis. Statistical analysis was conducted by RM. AŠ wrote the first draft of the manuscript. All authors provided feedback on previous drafts and approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
The study was approved by the Ethics Committee of the General University Hospital in Prague in compliance with the Helsinki Declaration (No. 2140/19 S-IV). The Ethics Committee waived the requirement for informed consent as according to the Czech Law (Act. no. 373/11, and its amendment Act no. 202/17), it is not necessary to obtain informed consent in fully anonymized studies.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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