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Sex cord-stromal tumors of the testis — a rare group of benign and malignant gonadal neoplasms. Literature review

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Abstract

This article discusses a less common group of testicular tumors, including sex cord-stromal tumors and gonadal stromal tumors. Among the sex cord-stromal tumors, we can distinguish androblastoma (Leydig cell tumor and Sertoli cell tumor), fibroma-thecoma group tumors, stromal tumors, and sex cord tumors. Based on a literature review, we present the epidemiology, diagnosis, and treatment of these testicular tumors. In our opinion, due to the rarity of this group of tumors and limited data in the EAU guidelines, this topic deserves attention, which is why we chose to explore it in our study.

Keywords: testicular tumor, sex cord-stromal tumors, leydig testicular tumor, sertoli tetsicular tumor, diagnosis, treatment, orchidectomy, testis sparing surgery

Introduction

Testicular cancer is the most common malignancy in men aged 15 to 34 [1], with an estimated prevalence of 1–1.5 % [2]. Germ cell tumors of the testis are the most frequent type, accounting for 95% of all testicular tumors [2]. Sex cord-stromal tumors belong to the category of primary non-germ cell testicular tumors, which constitute only 5% of all gonadal neoplasms, making them relatively rare [2, 3]. Table 1 [2, 4] presents the histological classification of the testicular tumors discussed in this article.

Sex cord-stromal tumors exhibit significant immunohistochemical and morphological diversity. These tumors also vary in malignancy, often displaying a tendency towards a benign nature [5]. Interestingly, in the case of sex cord-stromal tumors, there is no substantial correlation observed with undescended testes, unlike embryonal tumors of the testis. Genetic factors appear to play a more significant role although they are 17–29% less prominent than in germ cell testicular tumors [6]. It has been shown that boys with precocious puberty have an increased risk of developing sex cord-stromal tumors [6]. Some studies suggest that men with tall stature have a higher risk of testicular tumors although findings from other authors do not confirm this correlation [6].

The subsequent part of the article discusses each type of sex cord-stromal tumor based on global literature review and guidelines from scientific societies such as European Association of Urology (EAU) and the World Health Organization (WHO). However, due to the rarity of tumors in this group, there are very few recommendations in the EAU guidelines on management of patients with these tumors. Therefore, this topic was chosen for the study. This study aimed to provide insight into issues related to this rare group of testicular tumors. With the advancement of modern imaging techniques, such as improved ultrasound and MRI devices, the detection rate of these tumors may increase [5].

Leydig cell tumor

Leydig cell tumor of the testis constitutes about 1% of all testicular tumors [7]. It is the most commonly

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Table 1. Classification of sex cord-stromal and gonadal stromal tumors of the testis [based on the European Association of Urology (EAU) and the World Health Organization (WHO)] [2, 4]

Sex cord-stromal tumors of the testis				
Leydig cell tumor	**Sertoli cell tumor**	**Granulosa cell tumor**	**The fibroma thecoma family of tumors**	**Mixed and other sex cord-stromal tumors**
	Large cell calcifying Sertoli cell tumor	Adult granulosa cell tumor	Tumors in the fibroma thecoma group	Mixed sex cord-stromal tumor
		Juvenile granulosa cell tumor		Signet ring stromal tumor
				Myoid gonadal stromal tumor
				Sex cord-stromal tumor not otherwise specified

diagnosed sex cord-stromal tumor of the testis [6]. This tumor typically presents unilaterally, with bilateral occurrence reported in only 3% of cases [8]. Leydig cell tumors usually exhibit a benign nature (80–90% of cases) [9]. Malignancy is observed in 10–20% of affected men [10]. In the majority of cases (80%), Leydig cell tumors affect individuals aged 20 to 60, while only 20% occur in children [7]. In children, Leydig cell tumors are typically benign [6]. Interestingly, genetic studies have shown sporadic cases of positive correlation between renal cell carcinoma (RCC) and Leydig cell tumor of the testis (mutations in the *FH* gene) [6].

In adults, besides testicular tumors, Leydig cell tumors can manifest with gynecomastia, testicular atrophy, decreased libido, erectile dysfunction, or prostate atrophy. These symptoms are attributed to the production of female sex hormones (progesterone and estradiol) as well as testosterone by Leydig cell tumors [7, 8]. In children, symptoms of premature puberty and gynecomastia may also be present [7]. Azoospermia is an exceptionally rare manifestation of this testicular tumor [11].

Tumor markers typically remain within normal range. Immunohistochemical examination reveals characteristic Reinke crystals and the absence of intratubular growth in Leydig cell tumors [12]. On ultrasound (US), Leydig cell tumors typically appear hypoechoic with limited internal structure compared to adjacent tissues. According to the literature, magnetic resonance imaging (MRI) is particularly significant for Leydig cell tumors, as it enhances the preoperative diagnostic accuracy compared to other testicular tumors [6]. However, definitive characterization of the tumor can only be achieved through histopathological examination of the excised lesion. Therefore, inguinal orchidectomy is recommended for treatment. In cases where the tumor is peripheral, testis-sparing surgery (TSS) can be performed to preserve testicular parenchyma [12].

According to the current literature, testis-sparing surgery can be considered when the tumor is located peripherally in the testis, tumor dimensions do not exceed 1 cm, in patients with bilateral testicular tumors, or in those with a solitary testis. Observation of lesions with oncological concern below 1 cm is currently not recommended [13].

It is noteworthy that Leydig cell tumors exhibit low sensitivity to radiotherapy and chemotherapy [14, 15]. Studies conducted on a group of adult males by other authors confirm the safety and efficacy of performing testis-sparing surgery for Leydig cell tumor treatment [14–18]. Even in the case of malignant Leydig cell tumors, the 5-year survival rate is 91% [19, 20].

Sertoli cell tumor

Sertoli cell tumors constitute less than 1% of all testicular tumors, similar to Leydig cell tumors [21, 22] and typically display a benign nature. They mostly present unilaterally [6]. Tumor markers usually remain within normal range, with slight elevation of AFP observed in some cases [23, 24]. Over the years, the histological classification of Sertoli cell tumors has evolved. Presently, the WHO distinguishes only two variants: Sertoli cell tumor and large calcifying Sertoli cell tumor [4]. The standard approach for Sertoli cell tumor treatment remains inguinal orchidectomy if the clinical presentation suggests malignancy [6]. In cases of malignant Sertoli cell tumors, the 5-year survival rate in stage I is 77%. Thus retroperitoneal lymph node dissection (RPLND) is recommended even for stage I disease [19, 20].

Large calcifying sertoli cell tumor

Large calcifying sertoli cell tumor (formerly referred to as sclerosing) is typically benign. However, 17% of cases may exhibit malignancy or local invasion of adjacent tissues. These tumors are often unilateral and singular [6, 25–27]. Moreover, this tumor is associated with Carney syndrome and Peutz-Jeghers syndrome [28, 29]. Men with these syndromes are predisposed to malignant forms of this tumor [25, 26]. To date, 90 cases of calcifying Sertoli cell tumors have been described in the world literature, of which only 16 cases demonstrated malignancy [30]. According to the literature, to classify this tumor as malignant,

at least two of the following criteria must be met: tumor size above 4 cm, vascular invasion, cell atypia, necrosis features, and increased mitotic activity [28].

Symptoms of this tumor usually include a palpable hard mass in the testis, which may show skin involvement. The testis is not painful upon palpation. On US, there is the characteristic presence of calcifications within the tumor mass and typically central vascularity on color Doppler is [31]. On immunohistochemical examination, large calcifying Sertoli cell tumor usually shows positive reactivity for alpha-inhibin (90% of cases), pan-cytokeratin, epithelial membrane antigen (EMA), S-100 protein, desmin, vimentin, neuron-specific enolase, and chromogranin. It shows negative reactivity for OCT4, CD10, CD99, and Melan-A. It may also exhibit negative reactivity for alpha-inhibin; however, it is generally accepted that negative alpha-inhibin reactivity does not rule out the diagnosis [32]. Tumor markers for testicular tumors (Beta HCG, LDH, AFP) may be normal [31]. The authors of the cited study [33] demonstrated that PRKAR1A immunohistochemical testing can also aid in diagnosing large calcifying Sertoli cell tumors.

For patients suspected of having this tumor, radical inguinal orchidectomy is the recommended approach. In cases of malignancy, if retroperitoneal lymph nodes are involved by the tumor, retroperitoneal lymph node dissection is necessary [32]. However, due to the predominantly benign nature of large calcifying Sertoli cell tumors, and similar to Leydig cell tumors, in cases where the tumor mass is superficial, peripheral, small, and bilateral, we would also consider the possibility of performing tumor resection, with potential subsequent addition of inguinal orchidectomy if malignancy is confirmed by histopathological examination. Other authors cited in this study share a similar view [34].

Granulosa cell tumor

This tumor does not originate from testicular tissues [35] and typically displays a benign nature [6]. In the 2023 WHO classification, granulosa cell tumors are divided into two subtypes: adult-type granulosa cell tumors and juvenile-type granulosa cell tumors [4].

Adult-type granulosa cell tumor

The first case of this subtype of testicular tumor was described in 1952, and since then, only 73 cases of this neoplasm have been reported in the literature [36, 37]. These are usually large and benign tumors (in the vast majority of cases), measuring between 10 to 14 cm, which may have cystic components. They typically present unilaterally, with an average age of onset at 42 [6]. The oldest documented patient diagnosed with this tumor type was 87 years old [38]. Gynecomastia is a symptom in 50% of cases. This tumor is associated with a FOXL2 gene mutation [6]. Immunohistochemically, it usually shows positive reactivity for inhibin A. On microscopic evaluation, the tumor cells resemble "coffee bean nuclei" [39].

Inguinal orchidectomy is considered the gold standard treatment. However, for patients with testicular atrophy or a single testis, TSS is proposed [40]. In cases of TSS, intraoperative frozen section analysis should be used for differential diagnosis between malignant and benign lesions [13]. Subsequently, radiation therapy on the remaining testicular parenchyma is recommended to prevent the transformation of germ cell neoplasia *in situ* (GCNIS) into an adult-type granulosa cell tumor in the future [41].

Juvenile granulosa cell tumor

This tumor is usually firm and exhibits a cystic structure [6, 42]. It is an extremely rare testicular tumor, primarily occurring in infants up to 6 months of age, and is characterized by a benign histological nature [6, 35]. No malignant character of this tumor has been reported in the global literature so far [43]. Exceptionally, this tumor subtype can occur in adult males [43]. It is commonly presented as a painless testicular mass [42]. Children with cryptorchidism or karyotypic abnormalities are more predisposed to this tumor [42].

In differential diagnosis of this tumor, it is crucial to consider the possibility of yolk sac tumor (YST) [44]. Furthermore, it is important to note that the cells of juvenile granulosa cell tumors do not resemble "coffee bean nuclei," as observed in adult-type granulosa cell tumors [42]. Contrary to YST, juvenile granulosa cell tumor shows positive reactivity for inhibin alpha like all sex cord-stromal tumors [42]. AFP levels in this testicular tumor remain within normal range. Due to the benign nature of all described cases of juvenile granulosa cell tumors in the literature, TSS is considered sufficient treatment [42].

Fibroma-thecoma group tumors

Fibroma-thecoma tumors are exceptionally rare [6]. Only a few cases of these tumors in the testes have been reported in the literature so far [45, 46]. These tumors have a benign nature and are sporadically found in the testes. They are more frequently described in postmenopausal ovaries of women [45]. These tumors typically measure from 0.5 to 8 cm and are usually hard or elastic with a yellowish-gray color upon sectioning. They may be connected to the tunica albuginea of the testis but do not exhibit a connection with the testis itself.

Laboratory tests for tumor markers such as beta-HCG, AFP, and LDH remain within normal range in affected individuals. Immunohistochemically, positive reactivity is observed for vimentin and BCL2, with weak staining SMA. Immunohistochemistry,

however, is negative for inhibin-alpha, STAT6, KIT, Melan-A, S-100, desmin, CD34, calretinin, and CK AE1/AE3. The Ki-67 index for this tumor is very low [45]. Microscopically, the tumor is characterized by spindle-shaped fibroblasts [6].

Cases have been described in the literature where radical orchidectomy was chosen as treatment due to suspicion of malignancy (rapid tumor growth) [45]. This decision was influenced by preoperative diagnostic challenges. In some cases, when the tumor's nature is not obvious, MRI can help decide further treatment [47]. However, in our opinion, TSS seems to be a safe and sufficient approach, as suggested by tumor characteristics (the tumor often lacks connection to the testis, tumor markers remain within normal range, and the Ki-67 index is low). TSS can always be complemented with orchidectomy in cases where histopathological confirmation of malignancy is obtained.

Mixed and other sex cord-stromal tumors

Mixed sex cord-stromal tumor

These tumors have mixed characteristics and several features that resemble other tumors, making it challenging to classify them as a specific neoplasm. A mixed sex cord-stromal tumor can present as a gelatinous mass in the testis. Tumor markers usually remain within the normal range. Macroscopically, including on US, the tumor may display cystic structures in the central part with areas of hemorrhage. The tumor can also be adjacent to the testicular parenchyma and tunica.

Histologically, the tumor exhibits characteristics of spindle cells at its periphery. Additionally, it may have Sertoli cells and features resembling adult-type granulosa cell tumors [48]. Due to diagnostic difficulties, orchidectomy is often performed before surgery. However, in cases where the clinical presentation suggests a benign nature of the tumor, we propose TSS with the possibility of complementing treatment with orchidectomy.

Until recently, gonadoblastoma was classified within this group. However, in the latest WHO classification of testicular tumors, gonadoblastoma has been classified within the group of germ cell tumors as an *in situ* form [4], which is why this article omits discussing gonadoblastoma.

Signet ring stromal tumor

In the latest EAU guidelines (2023), this tumor was classified as a distinct testicular tumor [2]. The signet ring stromal tumor in the testis was first described in the literature in 2005 [49]. The same author notes that if these tumors affect the testis, they are asymptomatic [49]. These tumors are more frequently described in the ovaries.

Currently, among experts, it is believed that this tumor is always benign and unilateral, and the vast majority of them are solitary [49, 50]. Global literature data indicate that tumors occurring in the testis are smaller than those observed in the ovaries, usually not exceeding 0.5–2.8 cm (average 0.9 cm). Thus far, no cases of malignant signet ring stromal tumors of the testis have been reported in the literature. Recurrence tendencies have also not been noted [50, 51].

Immunohistochemically, this tumor resembles a sertoli cell tumor [51, 52]. It shows positive reactivity mainly for beta-keratin and vimentin [21, 49, 50, 52]. In the literature, only isolated cases of this type of tumor have been found in the testis [49–51]. The authors of one of the cited works were the first to note positive CD99 immunohistochemical reactivity in signet ring stromal tumors [45].

The tumor's name comes from the microscopic appearance of ring-like protrusions. In histopathological differential diagnosis, distinguishing the signet ring stromal tumor from Leydig cell tumors and Sertoli cell tumors is important. Notably, the presence of Reinke crystals is not observed in the histological image of the signet ring stromal tumor [50].

Due to the rarity of these tumors in the testis, there are no official recommendations for management. Considering the reported benign nature of the tumor, TSS appears to be an appropriate approach in these cases. Recurrence has not been reported in the literature in patients treated for signet ring stromal tumors of the testis.

Myoid gonadal stromal tumor

In the 2023 EAU guidelines, this tumor is also recognized as a separate entity [2]. Recent global literature data suggest that this tumor also appears to be benign [53–55]. Tumor markers are usually within the normal range. It is primarily observed in adult men (around 40 years of age), with sizes usually not exceeding 3 cm. The largest reported size for this tumor so far is 4.3 cm. In an analysis of a case series [53], these tumors were asymptomatic. Due to uncertainty in histological diagnosis, orchidectomy was performed in these patients despite frozen section analyses.

The myoid gonadal stromal tumor shows positive immunohistochemical staining for FOXL2, S100, SF1, and inhibin [53]. Other authors note that the distinguishing feature of this tumor from other testicular tumors is epithelial differentiation [55].

Due to the rarity of this type of tumor in the testis, there are no specific treatment recommendations. Considering the reported benign nature of these tumors in the literature and the absence of metastatic tendencies or recurrences [53, 55], TSS appears to be an appropriate treatment.

Sex cord-stromal tumor not otherwise specified (NOS)

These tumors exhibit numerous individual characteristics distinct from specific tumor types. They often resemble other testicular tumors in terms of characteristics. Literature reports suggest that these tumors can be malignant in adults [6]. The treatment approach for mixed and other sex cord-stromal tumors and NOS is the same as for other sex cord-stromal tumors, which involves TSS or orchidectomy based on intraoperative frozen section analysis or the urologist's decision.

Immunohistochemistry of sex cord-stromal tumors of the testis

These tumors are characterized by highly diverse immunohistochemistry. A brief immunohistochemical profile of sex cord-stromal tumors is presented in Table 2 [56–58].

Chemotherapy for malignant metastatic types of sex cord-stromal tumors of the testis

Sex cord-stromal tumors of the testis are considered insensitive to chemotherapy and radiotherapy. In cases of malignant tumors, secondary changes usually occur in the retroperitoneal lymph nodes and the lungs.

The preferred treatment method is surgical resection and/or chemotherapy. There have been reports in the literature of responses to chemotherapy in sex cord-stromal tumors, excluding Leydig cell tumors [59–61].

In cases of advanced-stage disease, first-line chemotherapy based on platinum derivatives has been used. Chemotherapy regimens such as BEP or EP have been described [37]. For second-line chemotherapy, regimens based on ifosfamide or paclitaxel have been employed [62].

In the case of Leydig cell tumors, which secrete steroid hormones, therapies involving ortho-para-DDD (mitotan), a steroidogenesis inhibitor, have been described [63].

Any residual changes after chemotherapy should be surgically removed [61].

Summary

Sex cord-stromal tumors are a rare group within testicular tumors, constituting approximately 5% of all gonadal tumors. While most of these tumors tend to be benign, some can be malignant. Over the years, the classification of sex cord-stromal tumors has evolved, presenting challenges due to some tumors remaining unclassified. Ultrasound of the testes and, in uncertain cases, MRI play a pivotal role in diagnosing these tumors, particularly Leydig cell tumors.

Given that a significant portion of these tumors exhibit a benign nature, TSS is recommended if the lesion is located peripherally or superficially on ultrasound. Followed by possible subsequent orchidectomy and continued patient observation. When malignancy is suspected, radical orchidectomy remains the standard treatment.

To assess metastasis, computed tomography is recommended for testicular tumors. Despite advancements, due to their rarity, there are no standard treatment protocols for sex cord-stromal tumors.

Table 2. Immunohistochemistry of sex cord-stromal tumors [56–58]

	Inhibin	S100	Calretinin	Vimentin	Keratin	SMA	FOXL2	MelanA	SF1
Leydig cell tumor	+	+/–	+	+/–	+/–	–	0	+	+
Sertoli cell tumor	+/–	+/–	+/–	+	+	+/–	0	–	+
Large cell calcifying sertoli cell tumor	+	+/–	+	+	+/–	0	0	+	+
Juvenile granulosa cell tumor	+	0	+	+	0	0	0	0	+
Adult granulosa cell tumor	+	+/–	+	+	+/–	+/–	+/–	–	+
Tumors in the fibroma thecoma group	+	+/–	0	+	+/–	+	0	0	0
Mixed sex cord-stromal tumor	+	+	+	0	0	0	0	0	+
Signet ring stromal tumor	+	+/–	–	+	0	0	0	0	–
Myoid gonadal stromal tumor	+/–	+	0	0	0	+	0	0	+
Sex cord-stromal tumor not otherwise specified	+/–	+	+/–	+	+/–	+	+	+/–	+

+ — positive; – — negative; 0 — no data available

Controversy still surrounds TSS in certain cases although increasing research supports its safety and efficacy.

Conclusions

1. Most sex cord-stromal tumors of the testis appear benign, with occasional malignancies.
2. Orchidectomy remains the standard treatment due to the rarity of these tumors, yet whenever feasible and the tumor nature suggests benignity, we recommend attempting TSS with frozen section analysis before considering orchidectomy. In cases with a peripheral or superficial tumor location, TSS is advised as the primary treatment.
3. Analyzing literature data, TSS appears to be a sufficient treatment for most sex cord-stromal tumors of the testis with benign nature.
4. Further research is needed to better understand this group of testicular tumors.

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Author contributions

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Conflict of interest

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Supplementary material

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