



# Ovarian sex cord-stromal tumors: an update on clinical features, molecular changes, and management

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## ABSTRACT

Sex cord stromal-tumors are rare tumors of the ovary that include numerous tumor subtypes of variable histological features and biological behavior. Surgery is the main therapeutic modality for the management of these tumors, while chemotherapy and hormonal therapy may be used in some patients with progressive and recurrent tumors. Several studies investigated molecular changes in the different tumor types. Understanding molecular changes underlying the development and progression of sex cord-stromal tumors provides valuable information for diagnostic and prognostic biomarkers and potential therapeutic targets for these tumors. In this review, we provide an update on the clinical presentation, molecular changes, and management of sex cord-stromal tumors.

## INTRODUCTION

Sex cord-stromal tumors are rare tumors of the ovary that usually occur in the first two to three decades of life<sup>1,2</sup> and represent approximately 7% of all primary malignant ovarian tumors,<sup>3</sup> with the exception of adult granulosa cell tumors, which are characterized by later onset with a peak incidence between 50 and 55 years of age.<sup>1</sup> Sex cord-stromal tumors are usually diagnosed at an early stage, and may have late recurrence, as late as 30 years, after the initial diagnosis and treatment.<sup>4</sup> The longest period of recurrence of granulosa cell tumors after initial diagnosis reported was 41 years.<sup>5</sup> Sex cord-stromal tumors constitute a heterogeneous group of benign and malignant neoplasms and are formed by distinct cell types that arise from stromal cells or primitive sex cord cells.<sup>6,7</sup>

## CLASSIFICATION OF SEX CORD-STROMAL TUMORS

These tumors are classified into three main groups, according to the World Health Organization, as presented in [Table 1](#), and include pure stromal tumors, pure sex cord tumors, and mixed sex cord-stromal tumors.<sup>7</sup> Pure stromal tumors arise from mesenchymal cells of the ovarian stroma, and include fibromas, thecomas, sclerosing stromal tumors, microcystic stromal tumors, Leydig cell tumors, and steroid cell tumors.<sup>7</sup> Pure sex cord tumors, such as granulosa cell tumors, Sertoli cell tumors, and sex

cord tumors with annular tubules, arise from primitive sex cord cells.<sup>7</sup> Mixed sex cord-stromal tumors include Sertoli–Leydig cell tumors and sex cord-stromal tumors that have not otherwise been specified.<sup>7</sup>

Sex cord-stromal tumors may present with an adnexal mass, abdominal distention, and abdominal pain.<sup>1</sup> Unlike epithelial and germ cell tumors, some sex cord-stromal tumors have clinical signs of hormone production, including menstrual changes, precocious puberty, hirsutism, and/or virilization.<sup>1</sup> The most important prognostic factors for sex cord-stromal tumors are the International Federation of Gynecology and Obstetrics (FIGO) stage and tumor rupture.<sup>4</sup>

## PURE STROMAL TUMORS

### Fibromas

Fibromas are relatively common tumors and account for 4% of all ovarian tumors.<sup>8</sup> These solid, typically benign, tumors arise from spindle shaped stromal cells that form collagen.<sup>9</sup> These hormonally inactive tumors occur most often in perimenopausal and postmenopausal women.<sup>9</sup> Fibromas are commonly unilateral; however, bilateral cases may occur and may be associated with Gorlin syndrome.<sup>10</sup> Gorlin syndrome, also called nevoid basal cell carcinoma syndrome or basal cell nevus syndrome, is a rare hereditary disease and it is inherited in an autosomal dominant manner.<sup>11</sup> It affects multiple organ systems of the human body and is associated with an increased risk of developing several types of benign and malignant tumors.<sup>11</sup> This syndrome is caused by a germline mutation in the human homolog of the patched (*PTCH1*) gene, which is located on chromosome 9.<sup>12,13</sup> However, it is still unclear whether this germline mutation is also involved in the development of sporadic ovarian fibromas.<sup>14</sup> Molecular cytogenetics analysis by fluorescence in situ hybridization has shown the presence of trisomy 12 in fibromas.<sup>15</sup>

### Thecomas

Thecomas are very rare tumors and represent approximately 0.5–1% of all ovarian tumors.<sup>16</sup> They can occur at any age and can be seen in women

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**Table 1** World Health Organization classification of ovarian sex cord-stromal tumors

Tumor type	
Pure stromal tumors	
Fibroma	4% of all ovarian tumors <sup>8</sup>
Cellular fibroma	
Thecoma	0.5–1% of all ovarian tumors <sup>16</sup>
Luteinized thecoma associated with sclerosing peritonitis	
Fibrosarcoma	
Signet ring stromal tumor	
Sclerosing stromal tumor	5% of all sex cord stromal tumors <sup>7</sup>
Microcystic stromal tumor	
Leydig cell tumor	
Steroid cell tumor	
Steroid cell tumor, malignant	
Pure sex cord tumors	
Adult granulosa cell tumor	95% of all granulosa cell tumors <sup>68</sup>
Juvenile granulosa cell tumor	5% of all granulosa cell tumors <sup>68</sup>
Sertoli cell tumor	
Sex cord tumors with annular tubules	1.4% of all sex cord-stromal tumors <sup>81</sup>
Mixed sex cord stromal tumors	
Sertoli–Leydig cell tumors	<0.5% of all ovarian tumors <sup>84</sup>
Well differentiated	
Moderately differentiated	
With heterologous elements	
Poorly differentiated	
With heterologous elements	
Retiform	
With heterologous elements	
Sex cord-stromal tumor, not otherwise specified	

under 30 years of age.<sup>17</sup> These tumors are hormonally active and consist of lipid laden stromal cells that may or may not be luteinized. Cytogenetics analysis of thecoma has identified the presence of trisomies of chromosomes 12 and 4.<sup>18</sup> Trisomy 12 is the most frequent aberration in benign sex cord-stromal tumors, and it is suggested that trisomy 4 may be a later event in the tumorigenesis of thecoma.<sup>18</sup>

### Sclerosing Stromal Tumors

Sclerosing stromal tumors represent less than approximately 5% of all sex cord-stromal tumors,<sup>7</sup> and 70% are diagnosed in young women aged 14–29.<sup>19</sup> These tumors are usually unilateral and hormonally inactive. However, sclerosing stromal tumors may present with hormonal manifestations, primarily androgenic ones, and they occur more frequently during pregnancy.<sup>20</sup> On immunostaining, sclerosing stromal tumors show strong TFE3 expression, which is a transcription factor binding to the immunoglobulin heavy chain enhancer 3.<sup>21</sup> A study using whole exome, targeted capture, and RNA sequencing identified recurrent gene fusions of *FHL2-GLI2* in 65% and other *GLI2* rearrangements in 15% of sclerosing stromal tumors, but none of these fusion genes has been reported in other types of sex cord-stromal tumors.<sup>22</sup> *FHL2-GLI2* fusions activate the sonic hedgehog pathway in sclerosing stromal tumors and could, therefore, serve as an oncogenic driver of sclerosing stromal tumor.<sup>22</sup>

### Microcystic Stromal Tumors

Microcystic stromal tumors are very rare and present in patients between the ages of 20 and 60.<sup>23</sup> On immunostaining, microcystic stromal tumors have shown the expression of CD10, vimentin, and Wilms tumor 1, while sex cord-stromal markers ( $\alpha$ -inhibin and calretinin) and epithelial membrane antigen are negative.<sup>24</sup> Nuclear expression of  $\beta$ -catenin occurs in microcystic stromal tumors.<sup>25</sup> The somatic exon 3 missense *CTNNB1* mutation is a hallmark of most ovarian microcystic stromal tumors.<sup>25</sup> The *CTNNB1* gene encodes the  $\beta$ -catenin protein, and this mutation leads to the loss of a phosphorylation site in the  $\beta$ -catenin protein. Also, microcystic stromal tumors may be associated with familial adenomatous polyposis, which is an autosomal dominant inherited disease caused by germline mutations of the adenomatous polyposis coli gene on chromosome 5 (q21-22).<sup>26</sup> A case study of the molecular analysis of microcystic stromal tumors by Zhang et al identified two missense mutations, one in exon 1 of the *KRAS* gene and the other in exon 15 of the adenomatous polyposis coli gene.<sup>27</sup>

### PURE SEX CORD TUMORS

#### Granulosa Cell Tumors

Granulosa cell tumors are the most common subtype of sex cord-stromal tumors, accounting for 2–5% of all ovarian tumors.<sup>28–29</sup> Granulosa cell tumors originate from normally proliferating granulosa cells of late preovulatory follicles, with which they share similar biochemical, morphological, and hormonal characteristics, including the expression of inhibin, estrogen, and Müllerian inhibiting substance.<sup>28–30</sup> These hormones account for some of the clinical manifestations and provide valuable tumor markers for monitoring disease progression and treatment efficacy.<sup>28–30–31</sup>

Inhibin is a glycoprotein hormone produced by ovarian granulosa cells and plays an essential role in the negative feedback regulation of pituitary follicle stimulating hormone secretion from the pituitary.<sup>32</sup> Inhibin is composed of an alpha subunit and one of two beta subunits, either a beta A subunit (inhibin A) or a beta B subunit (inhibin B).<sup>33–34</sup> Serum inhibin A and B fall to very low or even undetectable levels in postmenopausal women due to the depletion of ovarian follicles.<sup>35</sup> In contrast, serum inhibin A and B levels rise with granulosa cell tumors.<sup>35</sup> Therefore, inhibin can be used as a tumor

marker for primary as well as recurrent granulosa cell tumors.<sup>36</sup> Studies using subunit specific enzyme linked immunosorbent assay showed inhibin B is the main form of inhibin produced by granulosa cell tumors and the serum inhibin B level is more effective than inhibin A level in reflecting disease status.<sup>35 37 38</sup>

Estradiol is the key steroid hormone secreted by granulosa cell tumors in the presence of theca cells and it is accountable for the clinical signs of hyperestrogenism, such as precocious puberty.<sup>39</sup> Approximately 70% of patients with granulosa cell tumor have elevated circulating levels of estradiol,<sup>40</sup> whereas about 30% of patients with granulosa cell tumor do not produce estradiol due to the lack of theca cells in the tumor stroma.<sup>39</sup> Therefore, although estradiol may be useful in monitoring the course of disease, it does not display a high degree of sensitivity to act as a reliable tumor marker for patients with granulosa cell tumors.<sup>39</sup> Serum concentrations of estradiol are initially elevated in the early course of the disease, but rapidly decrease within 3 months after surgical removal of the tumor.<sup>41</sup>

This rapid decline in serum estradiol concentration is confirmed by a very low level in 24 hour urinary total estrogen excretion, decreasing from 504 to 108 nmol per day (normal range 14–216) within the first 48 hours following surgery,<sup>41</sup> while the urinary estradiol level drops from 385 to 73 nmol per day (normal <250).<sup>41</sup>

Mullerian inhibiting substance, also known as anti-Mullerian hormone, is a glycoprotein hormone and a member of the transforming growth factor  $\beta$  family.<sup>42</sup> In women, anti-Mullerian hormone is secreted mainly by ovarian granulosa cells of small follicles and plays an important role in the control of follicular growth.<sup>43 44</sup> Women have undetectable serum anti-Mullerian hormone levels until the prepubertal period, whereas after puberty, serum anti-Mullerian hormone levels of 2–5 ng/mL remain constant until clinical menopause when the levels become undetectable.<sup>45</sup>

There are two types of granulosa cell tumors, which differ based on clinical signs and histopathological features: adult granulosa cell tumors and juvenile granulosa cell tumors.<sup>46</sup>

#### Adult Granulosa Cell Tumors

Adult granulosa cell tumors account for approximately 95% of all granulosa cell tumors, present in perimenopausal and postmenopausal women, with a peak incidence in women aged 50–55.<sup>47</sup> Adult granulosa cell tumors are the most common malignant ovarian tumors that secrete hormones, primarily estrogen, and lead to endometrial alterations, such as hyperplasia and endometrial cancer. Patients often exhibit one or more of the following symptoms: abnormal vaginal bleeding, abdominal pain, or abdominal distension.<sup>48 49</sup> These tumors are usually considered low grade malignant tumors with a tendency to remain localized and demonstrate an indolent clinical course and late relapse.<sup>50</sup> Several studies have reported that approximately 70–97% of adult granulosa cell tumors carry a somatic *c.402C>G* missense point mutation in the *FOXL2* gene.<sup>51–53</sup> The *FOXL2* gene encodes a transcription factor that is expressed in different tissue types, including the ovaries and pituitary gland. This gene plays an essential role in ovarian development and differentiation. This single missense mutation is a rather pathognomonic hallmark of adult granulosa cell tumors, and is rarely seen in other ovarian tumors.<sup>25 54 55</sup> This makes *FOXL2* a highly sensitive and relatively specific marker for adult granulosa cell tumors, as well as a useful diagnostic test for distinguishing

between adult and juvenile granulosa cell tumors types and other sex cord-stromal tumors.<sup>56</sup> *FOXL2* has been shown to interact directly with other genes involved in the pathogenesis of adult granulosa cell tumors, including *CCND2*, *GATA4*, and *SMAD3*.<sup>57</sup> Furthermore, *FOXL2* expression is a potential prognostic marker for adult granulosa cell tumors, where patients with higher *FOXL2* expression have a worse prognosis and worse overall rates of disease free survival than patients with negative or weak expression.<sup>58</sup>

Several studies have investigated copy number changes in adult granulosa cell tumors and reported that gains in chromosomes 12 and 14 are observed in about 30% of adult granulosa cell tumors, while chromosome 22 loss occurs in about 40% of adult granulosa cell tumors.<sup>59–61</sup> A molecular study using comparative genomic hybridization and transcriptomic analyses of adult granulosa cell tumors has shown the presence of highly recurrent chromosomal imbalances, such as trisomy 14 and monosomy 22, as well as preferential co-occurrences, such as trisomy 14/monosomy 22 and trisomy 7/monosomy 16q.<sup>61</sup> This study also showed copy number changes in other genes, including *LIMA1*, *RUNX1*, and *AKT1*.<sup>61</sup> These alterations may be involved in adult granulosa cell tumor development and progression, along with the confirmed *FOXL2* somatic mutation.<sup>61</sup>

Significant differences in gene expression have been identified between early (stage I) and advanced (stage III) adult granulosa cell tumors. Genes with the greatest fold change in expression included cytokine *CXCL14* (chemokine C-X-C-motif ligand 14) and *MFAP5* (microfibrillar associated protein 5 transcript variant 1). These two genes are prominently expressed in advanced stage adult granulosa cell tumors, while *INSL3* (insulin-like 3 transcript variant 2) is highly expressed in stage I adult granulosa cell tumors.<sup>56 62</sup>

Another study conducted by Alexiadis et al showed that a high frequency of promoter mutations in telomerase reverse transcriptase  $-124C>T$  in adult granulosa cell tumors is associated with more aggressive disease progression.<sup>59</sup> Kraus et al found that the presence of chromosome instability and *FOXL2* homozygous genotypes primarily appeared to predict early recurrence and aggressive tumors.<sup>63</sup> Furthermore, a case study of adult granulosa cell tumors performed by Wang et al revealed that a DNA replication error is detectable when analyzing lengths of cytosine–adenine–guanine (CAG) repeats in the androgen receptor gene.<sup>64</sup> They implied that the influence of deficient DNA mismatch repair is associated with malignant behavior in adult granulosa cell tumors, and that this deficiency is an early event in tumor development and progression.<sup>64</sup>

Using methylation specific polymerase chain reaction analysis, Xu et al examined the hypermethylation of Dickkopf WNT signaling pathway inhibitor *DKK3*, *CDH13*, and *FOXL2* promoters in 30 granulosa cell tumors and in follicular cyst tissue specimens used as controls.<sup>65</sup> The results showed that the frequency of *CDH13*, *DKK3*, and *FOXL2* promoter methylation was significantly higher in granulosa cell tumors compared with follicular cyst tissue.<sup>65</sup> Furthermore, immunostaining of EZH2, a histone H3K27 methyltransferase, showed that there was no expression of the EZH2 protein in the 30 follicular cyst samples, while EZH2 protein was expressed in 11 of the 30 granulosa cell tumors.<sup>65</sup> Another study of the methylation status of five gene promoters, including *FHIT*, *FNACF*, *Cyclin D2*, *BRCA2*, and *RUNX3*, in 25 granulosa cell tumors, showed that the methylation frequency was 28% for *FHIT*, 24% for *FNACF*, 12% for *Cyclin D2*, 4% for *BRCA2*, and 56% for *RUNX3*



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genes.<sup>66</sup> Furthermore, the correlation of clinical features with promoter methylation status showed that overall promoter methylation was higher in higher stage tumors.<sup>66</sup> Another study performed by Dhillon et al assessed the promoter hypermethylation of different tumor suppressor genes, including *MGMT*, *CDH1*, *RAR-beta*, and *SYK* in 43 adult granulosa cell tumors.<sup>67</sup> They observed the hypermethylation of *MGMT* in 32%, *CDH1* in 21%, *RAR-beta* in 19%, and *SYK* in 16% of tumors.<sup>67</sup>

### Juvenile Granulosa Cell Tumors

The juvenile granulosa cell tumor subtype represents about 5% of all granulosa cell tumors.<sup>68,69</sup> Juvenile granulosa cell tumors are usually found in women younger than age 30, with a mean age of 13 years.<sup>70</sup> Clinical presentations of juvenile granulosa cell tumors include precocious pseudopuberty, vaginal bleeding, irregular menstruation and, in rare cases, virilization or hirsutism.<sup>68</sup> Approximately 80% of juvenile granulosa cell tumors presenting in children result in isosexual precocity.<sup>71</sup> Generally, juvenile granulosa cell tumors have a relatively favorable prognosis and are almost always unilateral and confined to the ovary.

Unlike adult granulosa cell tumors, juvenile granulosa cell tumors have either low or absent *FOXL2* protein expression, providing a clear distinction between juvenile and adult types.<sup>72</sup> However, loss of *FOXL2* expression in juvenile granulosa cell tumors may be associated with aggressive disease progression and poorer prognosis, given that the expression of *FOXL2* is essential for establishing and maintaining granulosa cell identity in the adult ovary.<sup>73</sup> Mutations in the *GNAS* gene, which encodes the stimulatory G protein, have been implicated in the development of juvenile granulosa cell tumors.<sup>72</sup> *GNAS* mutations have not been documented in the adult type or in other ovarian tumors.<sup>72</sup> The *GSP* oncogene mutation is a constitutive activating mutation of the G $\alpha$ c subunit and has frequently been observed in approximately 30% of juvenile granulosa cell tumors. The exact role of *GSP* mutation in the malignant transformation of granulosa cells remains unknown, but its presence correlates with a poorer prognosis.<sup>74</sup> A study conducted by Bessiere et al showed that more than approximately 60% of juvenile granulosa cell tumors bear in-frame duplications in the oncogene *AKT1*.<sup>75</sup> Tumors without *AKT1* in-frame duplications often carried two or more point mutations that altered highly conserved residues.<sup>75</sup>

### Sertoli Cell Tumors

Sertoli cell tumors are rare, and are present in women of reproductive age and sometimes in children.<sup>76</sup> Sertoli cell tumors are hormonally active in approximately 40–60% of cases; usually estrogenic but occasionally androgenic, and rarely both.<sup>76</sup> Pejovic et al reported the presence of isochromosome 1q as the sole chromosomal abnormality in ovarian Sertoli cell tumors.<sup>77</sup> Occasionally, Sertoli cell tumors of the testis occur in patients who have Peutz–Jeghers syndrome,<sup>78</sup> which is an autosomal dominant hereditary syndrome caused by germline mutations in the *STK11/LKB1* gene.<sup>79</sup> The syndrome is characterized by hamartomatous gastrointestinal polyps and mucocutaneous pigmentation and a predisposition to development of tumors at different sites.<sup>80</sup>

### Sex Cord-Stromal Tumors with Annular Tubules

Sex cord-stromal tumors with annular tubules represent 1.4% of all sex cord-stromal tumors and usually present at a mean age of

22.6 years.<sup>81</sup> Sex cord-stromal tumors with annular tubules have two different clinical types: one is associated with Peutz–Jeghers syndrome and the other is sporadic. Approximately 36% of sex cord-stromal tumors with annular tubules cases are associated with Peutz–Jeghers syndrome.<sup>82</sup> Sex cord-stromal tumors with annular tubules associated with Peutz–Jeghers syndrome are mostly benign, bilateral, or multifocal, and very small, whereas sporadic sex cord-stromal tumors with annular tubules are usually unilateral, large, and may have malignant potential.<sup>83</sup> Somatic mutations in the *SKT11* gene have not been detected in sporadic sex cord-stromal tumors with annular tubules.<sup>82</sup>

### Mixed Sex Cord-Stromal Tumors

#### Sertoli–Leydig Cell Tumors

Sertoli–Leydig cell tumors are rare, representing less than 0.5% of all ovarian tumors.<sup>84</sup> About 75% of Sertoli–Leydig cell tumors present in women under the age of 30.<sup>85</sup> These tumors are hormonally active, usually producing androgens, but sometimes producing estrogen. Approximately 80% of patients with ovarian Sertoli–Leydig cell tumors present with virilizing manifestations.<sup>86</sup> Most of these tumors are unilateral and confined to the ovary, and approximately 90% of cases are diagnosed at stage I.<sup>86</sup> Sertoli–Leydig cell tumors are associated with both somatic and germline *DICER1* mutations, which encode an RNA endoribonuclease that cleaves microRNA precursors to generate mature microRNA.<sup>25</sup> However, tumors without *DICER1* hot spot mutations exhibit no androgenic manifestations and usually present in elderly patients.<sup>87</sup> A case study of metastasizing Sertoli–Leydig cell tumors showed the presence of trisomy 8 as the sole karyotypic abnormality in ovarian Sertoli–Leydig cell tumors.<sup>88</sup> A molecular–cytogenetic analysis of two cases of testicular Sertoli–Leydig cell tumors and one case of ovarian Sertoli–Leydig cell tumor with benign behavior showed DNA copy number changes in entire chromosomes or chromosome regions, including 1p, 8, 9p, 1q, 12, 16q, 19, 22, and X.<sup>89</sup>

### MANAGEMENT AND PROGNOSIS OF SEX CORD-STROMAL TUMORS

There are a variety of treatment options available, including surgery, chemotherapy, hormonal therapy, and targeted therapy. These therapies may be used either alone or in combination, depending on several factors, including age, type, and stage of the tumor. Surgery is generally considered the most effective treatment for sex cord-stromal tumors. As the majority of patients diagnosed with sex cord-stromal tumors usually present with stage I disease, surgery is the treatment of choice. Total abdominal hysterectomy and bilateral salpingo-oophorectomy are appropriate for postmenopausal women.<sup>90</sup> In contrast, a more conservative unilateral salpingo-oophorectomy is appropriate for women of reproductive age when the tumor is confined to one ovary.<sup>90</sup>

#### Surgery

As sex cord-stromal tumors tend to present generally in younger patients with early stage disease,<sup>91</sup> fertility sparing surgery (unilateral salpingo-oophorectomy with surgical staging) may be offered to young patients with early stage disease who wish to preserve fertility.<sup>46,91</sup> Subsequent completion surgery (total abdominal hysterectomy and removal of the other ovary) is a reasonable

consideration at an older age.<sup>92</sup> Moreover, it is recommended to perform an endometrial biopsy for patients who choose fertility sparing surgery to rule out endometrial hyperplasia or carcinoma.<sup>92</sup> A retrospective study of 36 FIGO stage I adult granulosa cell tumor patients reported that 17 (47%) patients presented with endometrial alterations, as atypical hyperplasia or endometrial carcinoma.<sup>93</sup> This emphasizes the importance of endometrial assessment and endometrial biopsy during the fertility and uterine preservation procedure in order to rule out a concomitant neoplasia.<sup>93</sup>

There are no standard therapies for the management of advanced or recurrent sex cord-stromal tumors. However, secondary cytoreductive surgery is the preferred option for the management of recurrent tumors.<sup>91</sup> The study by Karalok et al showed that patients with recurrent adult granulosa cell tumors who underwent maximal cytoreductive surgery had excellent survival outcomes.<sup>92</sup> However, the presence of postoperative residual tumor was associated with an increased risk of recurrence not only at initial surgery, but also in the secondary cytoreductive surgery. A retrospective study of 35 patients with recurrent adult granulosa cell tumors by Mangili et al found that among 32 patients who had a complete resection at the time of the initial surgery, 13 patients had relapsed, whereas recurrence occurred in all three patients with residual tumors.<sup>93</sup> In the same retrospective study, all six patients with residual tumors who underwent secondary cytoreductive surgery had a second recurrence, whereas recurrence occurred in only 11 of 28 patients who underwent complete surgical resection.<sup>93</sup> Therefore, it is very important to achieve complete resection of tumor in both the initial surgery and secondary cytoreductive surgery.

### Chemotherapy

In addition to surgery for sex cord-stromal tumors, chemotherapy is recommended for patients with advanced disease or recurrence. The most common chemotherapy regimens for sex cord-stromal tumors include bleomycin, etoposide, and cisplatin, cisplatin and etoposide, or carboplatin with paclitaxel.<sup>94</sup> Although there is no specific guideline for the use of chemotherapy regimens after surgery for recurrent granulosa cell tumors, bleomycin, etoposide, and cisplatin is the preferable chemotherapy regimen for patients with advanced or recurrent tumors.<sup>95</sup> For patients with recurrent granulosa cell tumors, the National Comprehensive Cancer Network guidelines recommend taxane with or without carboplatin.<sup>96</sup> Other chemotherapy regimens for recurrent adult granulosa cell tumors include bleomycin, etoposide, and cisplatin, paclitaxel plus platinum based regimens (such as paclitaxel plus cisplatin and paclitaxel plus carboplatin), and paclitaxel plus ifosfamide.<sup>97</sup>

Several studies have shown that postoperative chemotherapy is not associated with improved prognosis and prolonged disease free survival and possibly overall survival of granulosa cell tumor patients.<sup>97–99</sup> In a study of the impact of adjuvant chemotherapy on disease specific survival in patients with granulosa cell tumors, Oseledchik et al found that regardless of stage, there were no significant differences in 5 year disease specific survival between patients who received chemotherapy and those who did not.<sup>100</sup> A retrospective study by Wang et al which included 60 patients with stage IC adult granulosa cell tumors (32 in the adjuvant chemotherapy group and 28 in the no adjuvant chemotherapy group), reported that adjuvant chemotherapy in stage IC adult granulosa

cell tumors patients was not associated with improved disease free survival.<sup>99</sup>

### Hormonal Therapy

Hormonal therapy is considered another treatment option for patients with tumor recurrence or those with advanced disease. This approach could also be a promising therapeutic approach in the management of granulosa cell tumors, due to the steroidogenic nature of these tumors. Granulosa cell tumors are hormonally active tumors and, as such, generally express steroid hormone receptors.<sup>101</sup> Hormonal therapy may, therefore, inhibit the proliferation of granulosa cell tumors through several mechanisms.<sup>102</sup> There is a possibility of classifying these mechanisms as direct effects on the tumor via a local mechanism mediated by specific receptors in the tumor and indirect action on tumors via suppression of gonadotropins or endogenous steroids.<sup>102</sup> For instance, aromatase inhibitors are a class of hormone therapy drugs used in the management of granulosa cell tumors, which include anastrozole, letrozole, and exemestane.<sup>29</sup> Aromatase inhibitors produce a higher response rate compared with other hormonal therapies used in granulosa cell tumors.<sup>29</sup>

A study by Korach et al which included four patients with recurrent granulosa cell tumors who were treated with an aromatase inhibitor, two treated with letrozole, and two with anastrozole, showed clinical responses with both types of aromatase inhibitors and three of the four patients exhibited complete responses.<sup>103</sup> A cohort study of adult granulosa cell tumor patients treated with different hormone therapy drugs (aromatase inhibitors, gonadotropin releasing hormone agonists, steroidal progestins, and selective estrogen receptor modulators) by van Meurs et al reported only 18% objective response rate although the majority of patients (60%) had stable disease.<sup>104</sup> Another possible hormone therapy for granulosa cell tumors is activin A inhibitor. Activin A is a protein that belongs to the transforming growth factor  $\beta$  superfamily and is primarily produced by ovarian granulosa cells and pituitary cells.<sup>105</sup> This protein plays a key role in inducing granulosa cell proliferation during folliculogenesis.<sup>105</sup> A study of 12 patients with granulosa cell tumors treated with activin A inhibitor (STM434) reported that approximately 80% of patients had dose related metabolic effects and no antitumor response was observed.<sup>106</sup>

Another promising therapeutic approach for recurrent granulosa cell tumors is targeted therapy. One example of this therapy is tyrosine kinase inhibitors, which are potential therapeutic targets that have been used to target specific proteins in different types of solid tumors.<sup>107</sup> In 2019, a case study of recurrent adult granulosa cell tumor treated with imatinib monotherapy, which is a tyrosine kinase inhibitor, reported that this targeted drug was well tolerated and resulted in long term stabilization of recurrent tumors where there was no significant increase in the size of the tumor nodules.<sup>108</sup> In addition to tyrosine kinase inhibitor targeted therapy, inhibitors of apoptosis proteins might be a promising targeted therapeutic for granulosa cell tumors.<sup>109</sup> A study by Bagnjuk et al found that the analogs of the second mitochondria derived activator of caspases SMAC mimetic BV-6, which blocks the inhibitor of apoptosis proteins, is capable of inducing apoptosis in KGN cells (metastatic granulosa cell tumor cell line).<sup>109</sup>

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### Conclusion

In conclusion, surgery remains the most effective therapeutic approach for the management of both primary and relapsed tumors, while adjuvant chemotherapy may be used only for advanced or unresectable tumors due to the toxicity and limited efficacy of this therapy. Hormonal therapy appears promising for relapsed tumors, but further assessment is needed. There is still an unmet clinical need for the identification of therapeutic targets and the development of targeted therapeutic agents to be added to the management modalities for aggressive and recurrent sex cord-stromal tumors, which is a challenging task as these tumors generally seem to have a low gene mutation burden, and particularly in genes commonly involved in tumor development and progression.

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