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## Detailed overview on rare malignant ovarian tumors

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### *Les tumeurs rares de l'ovaire*

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## Abstract

The group of rare malignant ovarian tumors includes the group of germ cell tumors, sex cords stromal ovarian tumors, small cell carcinoma, malignant Brenner tumors, rare epithelial tumors such as mucinous carcinoma, clear cell carcinoma, or low-grade serous carcinoma, as well as ovarian carcinosarcoma. Together they comprise about 10% of all ovarian tumors. Due to their low prevalence and their heterogeneity, data and treatment recommendations are limited. Even though all ovarian tumors are staged according to the FIGO staging of epithelial ovarian tumors, treatment differs especially in germ cell tumors and sex cords stromal ovarian tumors. Non-epithelial ovarian tumors can arise from a variety of ovarian precursor cells such as germ cells, granulosa cells, theca cells, or stromal fibroblasts. As can be expected already due to their divergent precursor lesions, these malignancies are substantially different but united by their rarity. This overview article gives a comprehensive summary on the pathology and clinical presentation, as well as therapy recommendations of a selection of those rare ovarian tumors, based on the latest national guidelines and related important publications.

**Keywords:** germ cell tumors, sex cords stromal tumors, mucinous carcinoma, clear cell carcinoma

## Résumé

Le groupe des tumeurs ovariennes malignes rares comprend le groupe des tumeurs germinales, des tumeurs des cordons sexuels et du stroma, le carcinome à petits cellules, la tumeur de Brenner maligne, des tumeurs épithéliales rares telles que le carcinome à cellules claires, le carcinome mucineux, et le carcinome séreux de bas grade, et également le carcinosarcome ovarien. Au total, elles représentent environ 10% de l'ensemble des tumeurs ovariennes. En raison de leur faible prévalence et de leur hétérogénéité, les données et les recommandations de traitement sont limitées. Bien que toutes les tumeurs ovariennes soient classées selon la classification FIGO des tumeurs épithéliales de l'ovaire, le traitement diffère en particulier dans les tumeurs germinales et les tumeurs de l'ovaire des cordons sexuels et du stroma. Les tumeurs ovariennes non épithéliales peuvent provenir d'une variété de cellules précurseurs de l'ovaire telles que des cellules germinales, des cellules de la granulosa, des cellules thécales ou des fibroblastes stromaux. Comme on peut s'y attendre déjà en raison de la diversité de leurs lésions précurseurs, ces tumeurs malignes sont substantiellement différentes – mais unies par leur rareté. Cet article donne un résumé complet de l'histopathologie et de la présentation clinique, ainsi que des recommandations thérapeutiques de certaines de ces tumeurs rares de l'ovaire, sur la base des dernières recommandations nationales et des publications importantes.

**Mots-clés:** tumeurs germinales, tumeurs des cordons sexuels et du stroma, carcinome mucineux, carcinome à cellules claires

## Rare ovarian tumors

A tumor is defined as rare, if an incidence of less than six per 100 000 per year is documented in the respective population. Due to their rarity, diagnosis might be difficult and a histological review by an expert pathologist is recommended, including a comprehensive molecular characterization to guide further treatment. Outcome significantly improves if rare tumors are treated in a referral center [1]. To provide a national-wide access to dedicated experts in the field of rare ovarian tumors and to improve the clinical management of those rare malignancies, a comprehensive website ([www.ovaire-rare.org](http://www.ovaire-rare.org)) and associated network was developed in France in 2004. Due to its constantly growing activity, the national network for rare ovarian/gynecological cancers (TMRG) was officially labeled in 2011, comprising a 3-site national expert center and 22 regional reference centers. The website “[www.ovaire-rare.org](http://www.ovaire-rare.org)” enables clinicians an easy access to accurate treatment recommendations with regular updates. Additionally, clinicians can discuss patient management by integrating them in a regional referral multidisciplinary tumor board specialized on rare ovarian tumors. This expert-based tumor board is held in a weekly basis and also provides a structure to facilitate the organization of a respective histological review by a listed pathological expert. Recommendations are based on therapy guidelines publicly available on the website and additionally allow the proposition of clinical trials to enable access to targeted therapies if applicable. Creating a national network with a dedicated system for referral, the management of rare ovarian tumors can be monitored and an equal national-wide access to medical expertise provided [2, 3]. This article will present an overview on malignant germ cell tumors, sex cords stromal ovarian tumors, rare epithelial tumors such as mucinous carcinoma and clear cell carcinoma but also ovarian metastases of non-ovarian origin as they need to be considered in differential diagnosis. A detailed decision-path for each tumor entity can be accessed at [www.ovaire-rare.org](http://www.ovaire-rare.org) [4].

## Germ cell tumors

Malignant germ cell tumors (GCT) are diagnosed in approximately 5% of all malignant ovarian tumors. They are distinguished from epithelial ovarian cancers by several factors such as diagnosis in younger women, often rapid tumor growth and thus respective related symptoms leading to a diagnosis in early stages and a significantly better prognosis, as well as a different set of relevant biomarkers (serum human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP), and lactate dehydrogenase (LDH) [5]). It has to be noted, that malignant GCTs represent 80% of the preadolescent malignant ovarian tumors. Thereof, dysgerminoma, immature teratoma, and yolk sac tumor are the most important representatives. The complete list of GCTs is depicted in Table 1 and the detailed respective treatment recommendations can be downloaded from [www.ovaire-rare.org](http://www.ovaire-rare.org) [6].

**Dysgerminomas** are the most common malignant GCTs and can be seen as the equivalent to male testicular seminoma. Incidence is highest in the second and third decade. Bilateral tumors can occur in up to 15% [7]. Elevated serum LDH is characteristic; rarely elevation of serum b-HCG and AFP can also be present. The immunohistochemical profile of those large solid tumors comprises CD117 (strong, membranous expression in approximately 80% of cases), SALLA-4 (diffuse, nuclear expression), OCT3/4 (nuclear expression), and D2-40 (membranous and cytoplasmic expression) [8].

In young dysgerminoma patients presenting with primary amenorrhea, an XY gonadal dysgenesis has to be excluded by chromosomal analysis as subsequently, the confirmation of an XY gonadal dysgenesis would lead to a bilateral adnexectomy.

**Malignant Teratoma:** Immature Teratomas only represent about 1% of all teratomas and contain immature cells derived from the three germ-cell layers (ecto-, endo-, and mesoderm as well as immature neural elements) [7, 9]. Immature teratomas are usually unilateral, lobulated tumors with hemorrhagic and necrotic areas. Microscopically, a variety of cells representing those three germ-cell layers can be identified in different stages of differentiation. The grade is determined by the respective amount of immature neuroepithelium.

Most patients with early-stage immature teratoma are managed with fertility sparing surgery (whereby the respective surgical staging criteria have to be fulfilled), chemotherapy, and close follow up and have an excellent prognosis [10].

**Yolk sac tumors (endodermal sinus tumors)** are rapidly growing, aggressive tumors usually diagnosed in younger women and characterized by elevated serum AFP levels. Microscopically, they comprise a multiplicity of histological patterns and diagnosis can be difficult. Immunohistochemically, the expression of SALLA4 (a marker of primitive germ cell differentiation) as well as AFP or Glypican 3 is observed (SOX2 and OCT3/4 negative). In contrast to other GCTs, the standard treatment comprises adjuvant chemotherapy after surgery even in stage I disease [11]. Although in selected optimally staged (pediatric) patients with stage I disease and negative post-operative AFP levels, surveillance might be considered [12].

Taking into account that the majority of patients with GCTs are diagnosed in stage I and at a young age with excellent long-term survival results, fertility preservation is of high importance. Fertility sparing unilateral salpingo-oophorectomy is thus generally recommended and can be considered even in advanced stages in pre-menopausal women because of the high chemotherapy sensitivity of GCTs. In women of childbearing age, specific information on infertility risks and on fertility preservation options should be implemented [13]. The initial surgery has the aim to determine the exact tumor stage by comprehensive exploration of the abdominal cavity, followed by a complete surgical staging after cytology has been taken. Systematic biopsy of the contralateral ovary is not recommended, neither systematic lymphadenectomy. Given the high chemotherapy-sensitivity, nodal metastases should be cured by adjuvant treatment. But even in stage I disease where no adjuvant chemotherapy is planned, lymphadenectomy only needs to be performed if bulky nodes are present during surgery or on pre-operative imaging.

Malignant germ cell tumors of the ovary are highly sensitive to cisplatin-containing combination chemotherapies. The therapy of choice represents the combination chemotherapy with bleomycin, etoposide and cisplatin (BEP scheme). In principle, the majority of patients with malignant GCTs in stages  $\geq 2$  will receive chemotherapy whereby the number of cycles depends on specific criteria (e.g. complete surgical resection and tumor marker levels post-surgery). In stage I disease the option of an adjuvant chemotherapy should be discussed with the patient in grade 2 and 3 as well as all IB/IC immature teratoma, stage IC dysgerminoma if an adequate surveillance can't be guaranteed, and in all stage I yolk sac tumors (besides rare cases of stage IA disease with adequate AFP and LDH levels after surgery if an active and intensified surveillance will be performed) [6, 14].

The BEP scheme has not negligible adverse effects (of importance the pulmonary toxicity for bleomycine) and an associated risk of consecutive second malignancies. An international clinical trial (AGCT1531; ClinicalTrials.gov identifier: NCT03067181) is thus currently evaluation the outcome of surgery alone followed by BEP chemotherapy at time of tumor recurrence patients with stage I grade 2, 3 ovarian immature teratoma and all low-risk stage I malignant germ cell tumors [15].

Early stage, young age (<45years), low grade and complete staging surgery are positive prognostic factors [16]. Adequate therapy of malignant germ cell tumors leads to an excellent overall survival, especially in stage I disease. In advanced stages after completing adjuvant chemotherapy treatment, failure is nevertheless observed in about 25% of patients [14]. More than two third of recurrences are diagnosed already within the first year after initial management. Recurrence occurs mainly locally in the peritoneal cavity.

A rare particularity in patients that had been treated for immature teratoma is the development of a benign “**growing teratoma syndrome**”. As recurrence is not common, alternative benign diagnoses should be considered in the case of progressing intra-abdominal masses without associated elevated tumor markers. In this context, histological findings comprise benign mature teratoma, sometimes associated with peritoneal gliomatosis [17]. In complementary imaging, mature elements such as fat or areas of calcification might be present within those masses. The growing teratoma syndrome has first been described in male patients after treatment of nonseminomatous germ cell tumor [18] and occurs seldom in women. Due to its rarity, a growing teratoma could thus easily be misinterpreted as disease progression or recurrence. Chemotherapy and radiation are not effective and only cause side effects; a reasonable, surgery-based treatment and observation thus has to be implemented [19].

## **Sex cords stromal ovarian tumors (SCSTs)**

Tumors of the stromal (Leydig cells) and/or sex cords (Granulosa or Sertoli cells) as depicted in Table 2 represent approximately 7% of ovarian neoplasms and develop from the stromal tissue that surrounds the oocytes (interstitial and nurse cells). Tumors arising from a sex cord component such as granulosa or Sertoli cells are rare and diagnosed in about 5% of malignant ovarian tumors [20]. An important difference to germ cell tumors is the fact that SCSTs have no particular age dependency and that they are diagnosed in all age groups. Nevertheless, the mean age at the time of diagnosis is lower than in epithelial ovarian cancer. In addition, they are essentially more often endocrine active (in about 66% of cases) and occur usually unilateral. The most common representative of malignant SCSTs are granulosa cell tumors. Sertoli-Leydig cell tumors, steroid cell tumors, gynandroblastoma and SCST with annular tubules are extremely rare.

**Granulosa cell tumors** are typically large unilateral adnexal masses with heterogeneous solid, cystic, as well as hemorrhagic components. Granulosa cell tumors are often endocrine active and lead to increased estrogen production that may result in various clinical symptoms such as a hyperplastic or malignant transformation of the endometrium or in young women the appearance of a pseudo-precocious puberty.

Two forms of granulosa cell tumors are to be distinguished: the juvenile type and the adult type, whereby the later accounts for 95% of all granulosa cell tumors. Tumors of the **adult type** are characterized by a slow progression and occurrence of late recurrences, surveillance thus has to be adequate. FOXL2 mutation is virtually present in almost all granulosa cell tumors of the adult type

and the determination of FOXL2 (402C→G) mutation distinguishes this type from other SCSTs [21]. Immunostaining for FOXL2 on the other hand is present in the majority of SCSTs and thus together with  $\alpha$ -inhibin and calretinin a general marker for SCSTs [22].

On the other hand, the **juvenile type** account for only about 5% of all granulosa cell tumors and is typically found before puberty – especially in the first life decade. Tumor recurrences are rare as tumors are usually diagnosed in early stage with good prognosis. In advanced stages relapse is frequently observed and associated with poor outcome [23].

As granulosa cells produce inhibin, serum levels rise with the growth of granulosa cell tumors. Inhibin B as well as AMH can thus be used as markers to monitor disease recurrence and progression in both, adult and juvenile type.

Fertility sparing surgery is the standard **treatment** for granulosa cell tumors of the **juvenile type**. These tumors are usually confined to one ovary and recurrence is seldom observed after simple unilateral salpingo-oophorectomy. In the rare cases of advanced stage or tumor recurrence, chemotherapy needs to be considered. Platinum-based chemotherapy is considered the therapy of choice [11]. Still, it has to be noted that data on adjuvant treatment regimens are limited. Surgery is likewise the cornerstone in treatment of tumors from the **adult type**. Debulking surgery remains the most effective treatment not only in early but also in advanced stage. Even in recurrence, debulking surgery should be considered whenever feasible [24]. An endometrial curettage needs to be performed in fertility sparing approaches to rule out concomitant endometrial pathologies. In advanced stage or recurrence, if not completely resected, adjuvant platinum-based therapy (either BEP or Carboplatin/Paclitaxel) is recommended. Hormonal anti-estrogen therapy seems to be a potential alternative in recurrent adult granulosa cell tumors.

**Sertoli-Leydig cell tumors** (SLCT) are usually diagnosed in young women as unilateral, early stage tumors. They comprise three grades according to the degree of differentiation of the Sertoli cell component of the tumor (well, intermediate and poorly differentiated tumors). Additionally, the presence of heterologous elements as well as a retiform pattern have a prognostic significance. Associated virilization signs are present in about 80% of patients due to an increased androgen production. Macroscopically, they appear as solid tumors with a smooth surface. Mutation in DICER1 occurs in a subset of SLCTs and might be prognostic relevance [25]. If a germline DICER1 mutation is diagnosed, subsequently screening of family members has to be considered.

Fertility sparing surgery is the standard treatment as the majority of tumors are diagnosed in early stage. A currently published analysis of The U.S National Cancer Data Base, including 286 patients with Sertoli-Leydig cell carcinoma, there was no difference in overall survival in patients receiving adjuvant chemotherapy (n=180) versus no adjuvant treatment (n=150) in stage I disease (5-year OS rates 85.1% and 85.7%, respectively) or stage II disease (n=25), correct surgery might thus be sufficient in early stage. In advanced stage, a significantly better OS was observed for patients treated with chemotherapy [26]. As stage and grade are important prognostic parameters, adjuvant chemotherapy should be considered in tumors with poor differentiation or heterologous elements regardless of the FIGO stage [11].

**Stromal tumors** (such as fibromas, thecomas, and Leydig cell tumors) are usually benign, nevertheless they should be mentioned as they need to be considered as differential diagnosis.

Thereof, **fibromas** are the most common histological type. They usually occur unilateral in postmenopausal women and are not hormonally active. **Thecomas** are very rare and mostly benign. Likewise, they occur usually unilateral but can produce both, estrogen as well as androgens – clinically related to varying endocrine symptoms. Leydig cell tumors are rare, usually unilateral but appear in contrast to the other germline stroma tumors in young women. In the majority of cases an increased androgen production is present but estrogen production can likewise be observed.

## Rare malignant epithelial tumors

Rare ovarian carcinomas comprise low-grade serous, endometrioid, mucinous or clear cell carcinomas. We will further discuss the subgroups of mucinous and clear cell carcinomas. Compared to high grade serous epithelial ovarian cancer (HGSOC) they are more often diagnosed in earlier stage and considered to be less chemotherapy responsive. Additionally the classical epithelial marker CA-125 is not a reliable marker in non-HGSOC.

Mucinous ovarian carcinomas are of particular interest. The exact incidence of **mucinous ovarian carcinomas** is probably even lower than estimated as differential diagnosis from digestive metastatic tumors can be difficult and thus diagnosis might not be accurate in all cases. Systematic realization of digestive endoscopies is at least required when the tumor is bilateral or less than 10 cm, or with peritoneal involvement. In low grade stage I disease, the differential diagnosis between invasive- and borderline tumors might likewise be difficult. In intra-operative frozen section analysis the determination of malignancy is complicated by the fact of different histologic components comprised in mucinous carcinomas, including benign cystadenoma as well as borderline aspects and intra-epithelial carcinoma.

Contrary to HGSOC, mucinous ovarian carcinoma occurs in younger age and is often diagnosed in early stage. However, if diagnosed in an advanced stage prognosis is inferior to HGSOC and these cases a metastasis from gastrointestinal or pancreatic primary should be ruled out. On the molecular level, KRAS is mutated in over 40% and P53 mutation is rarely detected (20%).

The pathology report should include the sub-classification of a mucinous carcinoma according to their growth pattern into either an **expansile** or a destructive-**invasive** type. This approach was proposed in 2014 by the WHO as prognosis differs according to the respective morphologic differences. Thereof, the expansile type has the better prognosis and treatment needs thus to be adapted to the respective classification [27].

In total, a staging surgery should be considered, regardless of the sub-type. The role of systematic lymphadenectomy has been under discussion for long as generally literature was in favor of a rare incidence of lymph node metastases in mucinous ovarian carcinomas. Recently, a comprehensive analysis of mucinous ovarian carcinomas (stratified into the respective morphologic subtypes) showed that lymph node metastases are present in >10% (17%) of carcinomas of the invasive type. This might justify restaging surgery for lymph node-excision in this subtype for diagnostic implications but if a therapeutic benefit can be obtained remains still an open question [28]. Additionally the role of appendectomy (particularly related to the question of restaging surgery) needs to be questioned if the appendix is macroscopically normal appearing [29].

Adjuvant treatment recommendations differ according to the histological subtype. For stage I tumors the indication of adjuvant treatment is under discussion and thus either observation, platinum-based Chemotherapy or a protocol derived from gastrointestinal tumors are proposed in literature. The 2019 ESMO guidelines recommend adjuvant chemotherapy in the infiltrative type already in stage I disease (thereof optional in IA) [30]. Platinum-based chemotherapy is recommended for all patients with stage II to IV disease. A detailed decision-path can be accessed at [www.ovaire-rare.org](http://www.ovaire-rare.org) [4]. Given the lower response rate to platinum-based chemotherapy in mucinous carcinoma compared to HGSOC, a gastrointestinal-type regimen can likewise be considered. Targeted treatments in tumors with KRAS mutation or HER2 amplification could be an interesting approach in mucinous carcinomas but given the rarity, performing clinical trials rests difficult [31, 32].

Similar to mucinous ovarian carcinoma, **Clear cell carcinoma** is often diagnosed in early stage. The incidence of this epithelial tumor differs according to the studied population, considered a rare ovarian tumor in Western countries (about 5% of ovarian carcinomas), occurrence is significantly higher in East-Asia (up to 27% of EOC in Japanese women) [33]. Clear cell carcinoma may be associated with endometriosis or Lynch syndrome and has an interesting molecular profile. PIK3CA and ARID1A mutation co-occur frequently [34]. Associated paraneoplastic symptoms such as hypercalcemia are another characteristic of this rare tumor. Despite diagnosed often in early stage, clear cell histology is a negative prognostic factor. Relapse is frequently observed already in stage IC disease (37%) [33].

The basis of treatment is surgery, whereby the standard surgical approach of staging and debulking surgery is the same as in other EOCs. For rare epithelial carcinoma such as clear cell carcinoma, platin-based chemotherapy remains the standard treatment even though the efficiency observed in HGSOC is not reached. Certainly, drug-resistance to conventional chemotherapy is contributing to the poor prognosis of clear cell carcinoma [35]. Several clinical trials are ongoing comparing different therapeutic approaches, such as targeting the PI3K/AKT/mTOR pathway, tyrosine kinase inhibitors or immunotherapy to determine alternative therapeutic approaches in this aggressive and commonly platin-resistant tumor. Although the benefit of platin-based chemotherapy remains uncertain, adjuvant treatment is to be discussed and evaluated individually even in stage I disease (thereof optional in stages IA, IB and ICI) [30].

## **Ovarian metastases from non-ovarian origin**

The primary site of disease has an important impact on prognosis and treatment of cancer. Thus, it needs to be considered that a small number of ovarian malignancies are metastases of primary tumors with non-ovarian origin. These include metastases from gastro-intestinal carcinomas (stomach, colon, and appendix), but also breast cancer, or rarely pancreatic, gallbladder or urinary bladder cancer [36]. Gastric cancer probably accounts for the predominant primary tumor with ovarian metastases, accounting for an increased incidence of so called Krukenberg tumors in Asian women. These tumors often occur bilateral, consistent with a metastatic origin, and are normally limited to the ovaries. As previously discussed, mucinous ovarian carcinomas can be difficult to distinguish immunohistochemically from ovarian metastases of tumors harboring a gastrointestinal origin – thus especially in bilateral tumors a comprehensive clinical gastro-intestinal evaluation has to be performed. Surgical and (neo) adjuvant treatment relies on the guidelines of the respective primary tumor.

## Beyond standard treatment

Patients with rare tumors need an adequate treatment. Respective therapy recommendations can only improve if clinicians work together, national-wide and internationally. Integrating rare tumor cases in respective networks and organizations (e.g. the European Reference Networks on rare cancers EURACAN) not only enhances our general understanding of those diseases but also enables the conduction of clinical trials and the future development of new treatment strategies.

## Conflict of interest

none

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**Table 1** Classification of germ cell tumors

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<b>Germ cell tumors</b>
Dysgerminoma
Yolk sac tumor (Endodermal sinus tumor)
Embryonal carcinoma
Polyembryoma
Non-gestational choriocarcinoma
Mature teratoma
Immature teratoma
Monodermal teratoma (struma ovarii, Carcinoid, neuroectodermal tumor)
Mixed germ cell tumors

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**Table 2** Classification of sex cord-stromal tumors

<b>Ovarian sex cord tumors</b>	<b>Pure ovarian stromal tumors</b>
Adult granulosa cell tumor	Fibroma and thecoma
Juvenile granulosa cell tumor	Fibrosarcoma
Sertoli cell tumors	Sclerosing stromal tumor
Gynandroblastoma	Signet ring stromal tumor
Sex cord tumor with annular tubules	Microcystic stromal tumor
	Ovarian myxoma
	Stromal-Leydig cell tumor
<b>Mixed sex cord-stromal tumors</b>	
Sertoli-Leydig cell tumor	