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Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence and epidemiology

Non-epithelial malignancies of the ovary account for ∼10% of all ovarian cancers [1]. Germ cell tumors (GCTs) are diagnosed principally in the first two decades of life, whereas sex cord-stromal tumors (SCSTs) are more common in adult women (granulosa adult type has an average age at diagnosis of 50 years, 90% of juvenile type occurs in pre-pubertal girls and Sertoli-Leydig occurs mainly in women younger than 40 years). The yearly adjusted incidence rate is 3.7/1 000 000 and 2.1/1 000 000 women for GCTs and SCSTs, respectively [2].

diagnosis and pathology/molecular biology

The initial symptoms and signs of non-epithelial ovarian tumors are usually a subacute pelvic pain and feeling of pelvic pressure because of a pelvic mass and menstrual irregularities. Diagnostic work-up should include pelvic ultrasound, abdomino-pelvic computed tomography (CT-scan) and chest X-ray. In young patients, serum human chorionic gonadotropin (hCG), α-fetoprotein (AFP) titers and lactate dehydrogenase (LDH), complete blood count and liver and renal function tests should be carried out. Inhibin is secreted by granulosa cell tumors and could be a useful marker for this disease [3]. In case of suspected gonadoblastomas, a preoperative karyotype should be obtained on all pre-menarche girls because of the propensity of these tumors to arise in dysgenetic gonads [4].

Primary non-epithelial tumors of the ovary arising from the cells specific to the ovary (germ cells, granulosa cells, theca cells, stromal fibroblasts and steroid cells) are the most typical ovarian tumors; other gonadal tumors arise from non-specific ovarian cells.

Classification of GCTs is well established (Table 1). These tumors recapitulate the steps of development, from undifferentiated germ cells to adult tissues. The primitive GCTs, composed of undifferentiated germ cells and tumors with extra-embryonic differentiation, are all malignant. Teratomas are the most common GCTs; most of them are composed of mature tissues and are benign (dermoid cysts). In immature teratomas, embryonic tissues represent the malignant potential and grading is prognostically relevant. Other rare malignant GCTs represent a heterogeneous group including somatic cancers arising in dermoids and some monodermal teratomas [5].

Primitive GCTs and immature teratomas are chemosensitive and susceptible to fertility-sparing surgery. Because of their chemosensitivity and of the increasing adoption of fertility-sparing surgery, the correct pathological diagnosis is essential. Owing to the rarity of these ovarian tumors, a histological second opinion of expert pathologist/s should always be considered [level III]. Diagnosis can be made on conventional histologic material; given the multiplicity of morphological features, immunohistochemical markers (Table 2) and chromosome 12p fluorescence *in situ* hybridization can be used to confirm the diagnosis in difficult cases. Salla4 and OCT3/4 are widely used and more recently expression of SOX2 in embryonal carcinoma and primitive neuroectoderm of teratoma has been recognized [6].

Sex cord-stromal and steroid cell tumors constitute a heterogeneous group of tumors (Table 3) and vary in their capacity to produce clinically significant amounts of steroid hormones. Those with sex cord elements are malignant, with granulosa cell tumors being the most frequent histological type.

Neoplasms of pure ovarian stroma are mostly benign, >50% of them being fibromas. Unlike GCTs, SCSTs and steroid cell tumors occur over a wide range of age and many are found in peri and post-menopausal women; however, for specific tumor types, the age range is often more limited. Since patients are

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Table 1. Classification of germ cell tumor (GCTs)

Primitive GCTs
Dysgerminoma
Yolk sac tumor
Embryonal carcinoma
Others
Mixed GCTs (specify components)
Biphasic or triphasic teratoma
Immature teratoma
Mature teratoma
Monodermal teratoma and somatic-type tumors associated with teratoma

Table 2. Immunohistochemistry of primitive germ cell tumor (GCTs)

	Salla4	OCT3/4	SOX2
Dys	+	+	−
YST	+	−	−
EC	+	+	+

Dys, Dysgerminoma; YST, yolk sac tumor; EC, embryonal carcinoma.

Table 3. Classification of sex cord-stromal tumors (SCSTs) and steroid cell tumors

Ovarian stromal tumors with sex cord elements
Adult granulosa cell tumor
Juvenile granulosa cell tumor
Sertoli-Leydig cell tumors
Gynandroblastoma
Sex cord tumor with annular tubules
Others
Pure stromal tumors
Fibroma and thecoma, typical, cellular and mitotically active
Malignant tumors (fibrosarcoma)
Other ovarian stromal tumors
Ovarian stromal tumor with minor sex cord elements
Sclerosing stromal tumor
Signet-ring stromal tumor
Microcystic stromal tumor
Ovarian myxoma
Stromal-Leydig cell tumor
Steroid cell tumors
Stromal luteoma, Leydig cell tumor
Steroid cell tumor, not otherwise specified

frequently young and the majority of cases are unilateral, an accurate diagnosis is necessary for deciding the treatment and the maintenance of fertility, wherever desirable. Combination chemotherapy has only modestly improved the prognosis for malignant diseases. In morphologically ambiguous cases, an immunopanel of a-inhibin, calretinin and FOXL2, together with mutational analysis of FOXL2 (402C-G) in a subset of cases, is useful to confirm granulosa cell tumor of adult type. Recent reports demonstrated that mutation of FOXL2 (402C-G) is virtually present in all granulosa cell tumors of adult type [7, 8].

A subset of SCSTs is typically negative for FOXL2 on immunostaining (retiform or poorly differentiated SLCTs), but these tumors usually express a-inhibin and/or calretinin.

Among rare tumors including non-specific tumors of the ovary, the most frequent is small-cell carcinoma of hypercalcemic type; it is the most common form of undifferentiated carcinoma <40 years of age and the most common ovarian tumor associated with hypercalcemia. This tumor is typically unilateral and should be differentiated from primitive GCTs and granulosa cell tumor.

staging and risk assessment

The staging system for non-epithelial ovarian cancers is generally adopted from that of epithelial ovarian cancer as originally defined by the International Federation of Obstetrics and Gynecology. Surgical approach can be carried out through an open route or, in selected cases, by laparoscopy and robotics. A careful examination of the abdominal cavity is required. The staging procedure includes infracolic omentectomy, biopsy of the diaphragmatic peritoneum, paracolic gutters, pelvic peritoneum and peritoneal washings. There is no consensus about the role of systematic lymphadenectomy [9, 10].

Node dissection should be carried out only in those cases with evidence of nodal abnormality. For SCSTs, retroperitoneal evaluation is not mandatory because of the very low incidence of retroperitoneal metastases in the early stage [III, A]. An endometrial curettage must be carried out to rule out concomitant uterine cancers in patients with granulosa cell tumor. Sertoli-Leydig cells tumors are frequently low grade malignancies, although occasionally a poorly differentiated variety may behave more aggressively. These tumors typically produce androgens, and clinical virilization is noted in 70–85% of patients.

Unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus is now considered the adequate surgical treatment for patients with GCTs. This surgical approach should be considered, even in the case of advanced disease, because of the sensitivity of the tumor to chemotherapy. No systematic ovarian biopsy needs to be carried out when the contralateral ovary is macroscopically normal [III, A]. Conservative surgery seems to be the appropriate approach in young patients also for stage I disease SCSTs. In postmenopausal women and in patients with advanced stage disease or with bilateral ovarian involvement, abdominal hysterectomy and bilateral salpingo-oophorectomy should be carried out with careful surgical staging.

Younger age and early-stage disease are the most important predictors for improved disease-specific survival for SCSTs; studies with a long-term follow-up showed a 10-year survival rate difference between stage I to II and III to IV of 84% to 95%, 50% to 65% and 17% to 33%, respectively. Tumor size has been proposed as another prognostic factor: in a multi-institution series of 83 patients, Chan et al. showed that tumor size ≥10 cm contributed to decreased survival rates in both univariate and multivariate analyses [11, 12]. Stage is an important prognostic factor for CGTs; however, because of the

sensitivity to chemotherapy, also advanced stage diseases can have good prognosis.

treatment plan

early stages

GCTs. The majority of GCTs (60%–70%) are diagnosed at an early stage. Stage I patients have an excellent prognosis with long-term disease free status in >90% of cases. Stage IA pure dysgerminoma can be treated with surgery only. The recurrence rate in this group of patients is relatively low (15%–25%) and they can be successfully treated at the time of relapse with a high likelihood of cure (Figure 1).

Patients with Stage IA grade 1 immature teratoma do not require further adjuvant chemotherapy after adequate surgical staging [13]. The need for adjuvant chemotherapy in stage IA G2-G3 and IB-IC is still controversial. Some published data indicate that all grades of immature teratoma can be managed with close surveillance after fertility-sparing surgery (III, A), reserving chemotherapy for those cases in which post-surgery recurrence is documented [14]. However, this policy is not universally accepted.

Overall, the role of chemotherapy in stage IA to B non-dysgerminomatous ovarian GCTs remains controversial: a surveillance policy has been proposed by Charing Cross Hospital and Mount Vernon Hospital groups in this subset of patients [15]. Data from the English literature show that the most used combination is bleomycin, etoposide and cisplatin (BEP) [III, A].

advanced stages and recurrences

GCTs. Fertility-sparing surgery should be considered also in advanced stage disease with a cure rate of > 95%. Patients should undergo debulking surgery to remove as much gross tumor as possible, but without major extensive procedures because of the high chemo-sensitivity of these tumors. Platinum-based regimens have been the treatment of choice over the past decade and the BEP regimen is the most widely used platinum-based chemotherapy [16, 17]. The optimal duration of therapy is still under debate; generally, three cycles of BEP in completely resected disease and four to five cycles (bleomycin should be omitted to reduce the risk of lung toxicity) for patients with macroscopic residual disease seem appropriate [III, A]. Dysgerminomas are very sensitive to radiotherapy; however, its use is limited to selected cases because of the negative impact on fertility.

In patients, previously treated with platinum, who have relapsed after a disease-free interval >6 months (platinum-sensitive relapse), ifosfamide/platinum (IP) with or without paclitaxel (P; Taxol) should be considered as second-line treatment. Further active chemotherapy regimens include: vinblastine–ifosfamide–cisplatinum (VeIP), cisplatin, vinblastine and bleomycin (PVB). Patients resistant to a cisplatin-based combination may receive vincristine–actinomycin D–cyclophosphamide (Cytoxan) [VAC] or paclitaxel–gemcitabine as salvage therapy [16].

The role of secondary cytoreductive surgery in patients with recurrent or progressive ovarian GCTs remains controversial. It may have some benefits for a selected group of patients,

Management of Germ Cell Tumors of the ovary

Stage	Surgery (fertility-sparing surgery when indicated)	Chemotherapy	Surveillance policy
Dysgerminoma			
Stage IA	X	-	X
Stage IB-IC	X	X	(X)
Stage IIA-IV	X	X	
Immature teratoma			
Stage IA G1	X	-	X
Stage IA G2-G3	X	X	(X)*
Stage IB-IC	X	X	(X)
Stage IIA-IV	X	X	
Yolk sac tumor			
Stage IA-IB	X	X	X
other stages	X	X	

X=suggested

(X) = suggested by some authors

- = no therapy

* Properly surgical staged

Figure 1 Management of germ cell tumors (GCTs) of the ovary. X = suggested, * Properly surgical staged, (X) = suggested by some authors, – = no therapy.

particularly those with immature teratoma and a growing teratoma syndrome.

The role of the new targeted agents in GCTs is yet to be demonstrated. Target agents already investigated in testicular tumors and of potential interest include tyrosine kinase inhibitors (imatinib and sunitinib) and antiangiogenic agents (bevacizumab).

Targeted agents either alone or in combination could represent therapeutic options, but their role must be evaluated in prospective studies [II–IV] [18].

treatment plan

early stages

SCSTs. The majority of SCSTs (60%–95%) are diagnosed at an early stage. Stage IA granulosa cell tumor disease has an excellent prognosis after surgery alone and does not require adjuvant therapy [4]. The selection of early-stage SCST patients for any postoperative treatment is controversial. To date, the relative benefit of adjuvant chemotherapy has yet to be demonstrated. Some authors would suggest adjuvant therapy for stage IC patients with high mitotic index, in this case platinum-based chemotherapy is the treatment of choice [II–III] (Figure 2).

The most commonly used regimen is the BEP combination [19]. Alternative chemotherapy options include: etoposide plus cisplatin; cyclophosphamide, doxorubicin (Adriamycin) and cisplatin; paclitaxel and carboplatin; or platinum agent alone [level II–III] [20].

For Sertoli-Leydig cell tumors, postoperative adjuvant chemotherapy should be considered for those patients with stage I poorly differentiated or with heterologous elements [level II–III].

advanced stages and recurrences

SCSTs. Debulking surgery, whenever feasible, remains the most effective treatment of metastatic or recurrent granulosa cell tumors. Platinum-based chemotherapy is currently used for patients with advanced stage SCSTs or recurrent disease, with an overall response rate of 63%–80% [21]. Unfortunately, the majority of patients with advanced disease do not have durable remissions. BEP regimen for at least three cycles or carboplatin/paclitaxel is currently recommended for adjuvant postoperative chemotherapy and for patients with recurrent SCSTs (III-A) [22].

Patients with steroid cell tumors, who have tumors that are pleomorphic, have an increased mitotic count, are large or are at an advanced stage should be treated with additional postoperative platinum-based chemotherapy; either BEP if not previously used or a taxane–platinum combination may be the most appropriate chemotherapeutic regimen [23].

The Gynecologic Oncology Group is currently conducting a randomized phase II trial of BEP versus the combination of paclitaxel and carboplatin for patients with newly diagnosed and chemo-naïve recurrent metastatic SCSTs of the ovary [24]. Alternative chemotherapy options include: PVB, etoposide–cisplatin, cyclophosphamide–doxorubicin–cisplatin, and VAC. There are limited data regarding the utility of chemotherapy in patients with persistent Sertoli-Leydig tumors, but responses in patients with measurable disease have been reported [25]. Given the functional hormonal nature of granulosa cell tumors which express steroid hormone receptors, there must be some rationale for a hormone-based approach [26]. Response to gonadotropin-releasing hormone agonists, tamoxifen, progestins and aromatase inhibitors has been reported.

Antiangiogenic agents have also been investigated in patients with recurrent adult granulosa cell tumor, due to the overexpression of vascular endothelial growth factor and vascularity of these tumors [27]. A recent experience at the MD Anderson Cancer Center seems to confirm the potential activity of bevacizumab even though this was in a very limited number of patients. The Gynecologic Oncology Group is currently conducting a phase II trial of bevacizumab for women with recurrent sex cord-stromal ovarian tumors [III–IV].

response evaluation and follow-up

Serum tumor markers (hCG, AFP, LDH, CA 125 and inhibin) can correlate with tumor response during chemotherapy. In

Management of Sex Cord Stromal Tumor of the ovary

Stage	Surgery	Chemotherapy	Surveillance policy
Granulosa cell tumor			
Stage IA-IC	X	-	X
Stage IIA-IV	X	X	
Sertoli-Leydig cell tumors			
Stage IA	X	-	X
All Stages with poorly differentiated or heterologous elements	X	X	

X = suggested

- = no therapy

Figure 2 Management of sex cord stromal tumors (SCSTs) of the ovary. X = suggested, – = no therapy.

Table 4. Summary of recommendations

Diagnosis and pathology/molecular biology	• Diagnostic work-up should include pelvic ultrasound, abdomino-pelvic computed tomography (CT-scan) and chest X-ray • In young patients, human chorionic gonadotropin (hCG), α-fetoprotein (AFP) titers and lactate dehydrogenase (LDH), complete blood count, and liver and renal function tests should be carried out • In case of suspected gonadoblastomas, a preoperative karyotype should be obtained on all pre-menarche girls • In primitive germ cell tumors (GCTs) and immature teratomas, histological second opinion by expert pathologist(s) should always be considered. Diagnosis can be made on conventional histologic material • Neoplasms of pure ovarian stroma: in morphologically ambiguous cases, an immunopanel of a-inhibin, calretinin and FOXL2, plus mutational analysis for FOXL2 (402C-G), is useful to confirm granulosa cell tumor of adult type
Staging and risk assessment	• Surgical approach can be carried out through open route or, in selected cases, by laparoscopy and robotics • A careful examination of the abdominal cavity is required • Staging procedure includes infracolic omentectomy, biopsy of the diaphragmatic peritoneum, paracolic gutters, pelvic peritoneum and peritoneal washings • Node dissection should be carried out only in the cases with evidence of nodal abnormality • For SCSTs retroperitoneal evaluation is not mandatory • An endometrial curettage must be carried out to rule out concomitant uterine cancers in patients with GCTs • Unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus is considered an adequate surgical treatment for patients with GCTs. This should be considered even in advanced disease because of the sensitivity of the tumor to chemotherapy. No systematic ovarian biopsy is necessary when the contralateral ovary is macroscopically normal • Conservative surgery seems to be the appropriate approach in young patients also for stage I disease SCSTs • In postmenopausal women and in patients with advanced stage disease or with bilateral ovarian involvement, abdominal hysterectomy and bilateral salpingo-oophorectomy should be carried out with careful surgical staging
Early-stage GCTs: treatment plan	• Stage IA pure dysgerminoma can be treated with surgery only • Patients with Stage IA grade 1 immature teratoma do not require further adjuvant chemotherapy after adequate surgical staging (14) • The need for adjuvant chemotherapy in stage IA G2-G3 and IB-IC is still controversial. Some data indicate that all grades of immature teratoma can be managed with close surveillance after fertility-sparing surgery, reserving chemotherapy for cases in which post-surgery recurrence is documented
Advanced stage and recurrent GCTs: treatment plan	• Patients should undergo debulking surgery to remove as much gross tumor as possible, but without major extensive procedures • Platinum-based regimens are the treatment of choice with bleomycin, etoposide and cisplatin (BEP) regimen the most widely used, generally, three cycles of BEP in completely resected disease and four to five cycles (bleomycin should be omitted to reduce the risk of lung toxicity) for patients with macroscopic residual disease • In patients, previously treated with platinum, relapsed after a disease-free interval >6 months (platinum-sensitive relapse), combinations with platinum should be considered • Patients resistant to a cisplatin-based combination may receive VAC or paclitaxel–gemcitabine as salvage therapy • Targeted agents either alone or in combination could represent therapeutic options, but their role must be evaluated in prospective studies
Early-stage SCSTs: treatment plan	• Stage IA granulosa cell tumor disease has an excellent prognosis after surgery alone and does not require adjuvant therapy. Some authors would suggest adjuvant therapy for stage IC patients with high mitotic index, in this case platinum-based chemotherapy is the treatment of choice • BEP is the most commonly used regimen. Alternative chemotherapy options include: etoposide plus cisplatin; cyclophosphamide, doxorubicin and cisplatin; paclitaxel and carboplatin; or platinum agent alone • Sertoli-Leydig cell tumors: postoperative adjuvant chemotherapy should be considered for patients with stage I poorly differentiated or heterologous elements
Advanced stage and recurrent SCSTs: treatment plan	• Debulking surgery remains the most effective treatment of metastatic or recurrent granulosa cell tumor. Platinum-based chemotherapy is currently used for patients with advanced stage SCSTs or recurrent disease • BEP regimen for ≥3 cycles or carboplatin/paclitaxel is recommended for adjuvant postoperative chemotherapy and patients with recurrent SCSTs • Patients with steroid cell tumors, with tumors that are pleomorphic, have an increased mitotic count, are large, or are at an advanced stage should be treated with additional postoperative platinum-based chemotherapy; either BEP if not previously used or a taxane–platinum combination • Response to gonadotropin-releasing hormone agonists, tamoxifen, progestins and aromatase inhibitors has been reported

Response evaluation and follow-up	• Serum tumor markers (hCG, AFP, LDH, CA 125 and inhibin) can correlate with tumor response during chemotherapy • A CT–scan of the abdomen, pelvis and chest (in case of suspected lung metastases) and pelvic ultrasound are the most common and useful imaging techniques to evaluate the response to chemotherapy • Follow-up visits must include history, physical examination with pelvic examination and tumor markers every 3 months for the first 2 years, then every 6 months during the third, fourth and fifth year or until progression • A pelvic ultrasound should be carried out every 6 months in those patients who have undergone fertility-sparing surgery, whereas a CT-scan of the abdomen and pelvis is carried out according to clinical indication • PET-scan for tumor response evaluation or follow-up is not yet well established

particular, inhibin is secreted by granulosa cell tumors and is a useful tumor marker that falls after tumor removal and is also a marker for tumor recurrence. CA125 is not increased in GCTs, but sometimes it is useful in detecting relapse in those with values of AFP/BHCG within the normal range. CT-scan of the abdomen, pelvis and chest (in case of suspected lung metastases) and pelvic ultrasound are the most common and useful imaging techniques used to evaluate the response to chemotherapy in patients with measurable disease (Table 4).

Approximately 75% of GCT recurrences occur within the first year after initial treatment; the most common site is the peritoneal cavity, more rarely retroperitoneal lymph nodes. Conversely, the indolent nature of SCSTs with the tendency for late recurrence (the median time to relapse is ~4 to 6 years) requires long-term follow-up. Several reports describe relapses occurring >20 years (up to 37 years) after diagnosis. The common sites of recurrence are the upper abdomen (55%–70%) and the pelvis (30%–45%). Follow-up visits must include history, physical examination with pelvic examination and tumor markers every 3 months for the first 2 years, then every 6 months during the third, fourth and fifth year or until progression. A pelvic ultrasound should be carried out every 6 months in those patients who have undergone fertility-sparing surgery, whereas a CT-scan of the abdomen and pelvis is usually carried out according to clinical indication. The use of PET-scan for tumor response evaluation or follow-up is not yet well established.

conflict of interest

The authors have reported no potential conflicts of interest.

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