clinical recommendations

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Non-epithelial ovarian cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

Non-epithelial malignancies of the ovary account for ~10% of all ovarian cancers. Germ cell tumors (GCTs) are diagnosed principally in young subjects whereas sex cord stromal tumors (SCSTs) are more common in adult women. GCTs represent 5% of all ovarian neoplasms and 80% of preadolescent malignant ovarian tumors. Sex cord stromal tumors are rare neoplasms that account for ~3–5 % of ovarian malignancies and for the majority are functioning tumors with clinical manifestations. The yearly adjusted incidence rate is 3.7/1000 000 and 2.1/1000 000 women for GCTs and SCSTs, respectively.

diagnosis

The initial symptoms and signs of non-epithelial ovarian cancers are usually characterized by subacute pelvic pain, feeling of pelvic pressure due to the presence of a pelvic mass and menstrual irregularities. Diagnostic work-up should include pelvic ultrasound, abdomino-pelvic computed tomography (CT scan), chest X-ray and PET scan for selected cases. In young patients serum human chrorionic gonadotropin (hCG), α-fetoprotein (AFP) titer and lactate dehydrogenase (LDH), a complete blood count, and liver and renal function tests should be determined. Inhibin is secreted by granulosa cell tumors and is a useful marker for the disease. 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.

The definitive diagnosis of non-epithelial ovarian cancer requires a surgical specimen. Pathological diagnosis should be made by a gynaecologic pathologist trained in ovarian cancer, according to the World Health Organization classification.

The histologic subtypes are listed in Tables 1 and 2.

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staging and risk assessment

The staging system for non-epithelial ovarian cancers is generally adopted from that used for epithelial ovarian cancer as originally defined by the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO). Surgery can be performed through the open route or, in selected cases, by laparoscopy. 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. Systematic lymphadenectomy is not required; there is no consensus about it. Only in cases of evidence of nodal abnormality is node dissection required. A thorough surgical staging for endodermal sinus tumor is not indicated because all patients need chemotherapy. For SCSTs the retroperitoneal evaluation is not mandatory because of the very low incidence of retroperitoneal metastases in early stage [III, A]. Endometrial curettage must be performed to rule out concomitant uterine cancers in patient with granulosa cell tumor. Sertoli–Leydig cell tumors are most frequently low-grade malignancies, although occasionally a poorly differentiated variety may behave more aggressively. The 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 adequate surgical treatment for patients with GCTs, even in cases of advanced disease, because of the sensitivity of the tumor to chemotherapy, and no systematic ovarian biopsy need be performed where the contralateral ovary is macroscopically normal. Conservative surgery also seems to be the appropriate approach in young patients with SCSTs at stage I disease. For postmenopausal women and in patients with advanced stage disease or with bilateral ovarian involvement, abdominal hysterectomy and bilateral salpingo-oophorectomy should be performed with careful surgical staging.

Stage is the most important prognostic factor established to date for SCSTs, in fact several article have reported that patients with advanced disease have a significantly poorer survival rate.

For GCTs stage is an important prognostic factor as well, though given their sensitivity to chemotherapy treatment even more advanced stage disease can have a good prognosis.

Table 1. Classification of germ cell ovarian tumors

Dysgerminoma
Teratoma
Immature
Mature
Monodermal and highly specialized
Endodermal sinus tumor
Embryonal carcinoma
Polyembryoma
Choriocarcinoma
Mixed forms

Table 2. Classification of sex cord stromal ovarian tumors

Granulosa-stromal cell tumors
Granulosa cell tumors
Adult type
Juvenile type
Tumors in the thecoma–fibroma group
Thecoma
Fibroma–fibrosarcoma
Sclerosing stromal tumor
Sertoli–Leydig cell tumors (androblastomas)
Sertoli cell tumors
Leydig cell tumor
Sertoli–Leydig cell tumors
Gynandroblastoma
Sex cord tumor with anular tubules
Unclassified

treatment plan

early stage disease, FIGO stage I–IIa

germ cell tumors. The majority of GCTs (60–70%) are diagnosed at an early stage. Stage I patients have an excellent prognosis (long-term disease-free status is ∼90%) and, after adequate surgical staging, very often further adjuvant treatment is not required. Therefore patients with stage Ia immature teratoma or stage I pure dysgerminoma can be treated with surgery only. All patients with stage I endodermal sinus are treated with adjuvant chemotherapy. Data from the English literature show that the most employed combination therapy is bleomycin, etoposide and cisplatin (BEP) [III, A].

sex cord stromal tumors. The majority of SCSTs (60–95%) are at stage I at the time of diagnosis. Patients with stage I have an excellent prognosis (long-term disease-free status is ∼90% of the cases). The selection of early stage SCSTs patients for any postoperative treatment is controversial. At present 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 SCST. In this case platinum-based chemotherapy is the treatment of choice [II–III].

advanced stage disease, FIGO stage IIb–IV

germ cell tumors. Patients with advanced stage disease should undergo debulking surgery to remove as much gross tumor as possible, but without major extensive procedures given the high chemosensitivity of these tumors. Platinum-based regimens have been the treatment of choice over the past decade for GCTs, with the BEP regimen becoming the most widely used. The optimal duration of therapy is still under debate, but generally many investigators believe that three cycles of BEP with completely resected disease and four cycles for patients with macroscopic residual disease seem appropriate [III, A]. Even though dysgerminomas are very sensitive to radiation therapy there is no evidence to support the use of adjuvant radiation therapy for advanced stage GCTs.

sex cord stromal tumors. Debulking surgery, whenever feasible, remains the most effective treatment for 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%. There are limited data regarding the utility of chemotherapy in patients with persistent Sertoli–Leydig tumor, but responses in patients with measurable disease have been reported. The BEP regimen for 3–6 cycles is currently recommended for adjuvant postoperative chemotherapy and for patients with recurrent SCSTs. Taxanes demonstrated an interesting activity in SCSTs with a favorable toxicity profile [III, A]. Taxane and platinum combination chemotherapy seems to be a reasonable candidate for future trials. Little evidence exists for the use of hormonal therapy or radiation therapy and these modalities should be restricted to selected cases.

response evaluation

Serum tumor markers (hCG, AFP, LDH, CA125 and inhibin) can accurately correlate with tumor response during chemotherapy. CT scan of the abdomen, pelvis and chest (in case of suspected lung metastases) and pelvic ultrasound are the most common and useful imaging methods to evaluate the response to chemotherapy in patients with measurable disease.

follow-up

Approximately 75% of GCT recurrences occur within the first year after initial treatment; the most common site is the peritoneal cavity and more rarely the retroperitoneal lymph nodes.

In contrast, the indolent nature of SCSTs with a tendency to late recurrence (median time to relapse is ∼4–6 years), requires long-term surveillance. Several reports describe relapses occurring >20 years (up to 37 years) after diagnosis. Common sites of recurrence are the upper abdomen (55–70%) and the pelvis (30–45%).

The follow-up visit must include history, physical examination with pelvic examination and tumor markers every 3 months for the first 2 years, and every 6 months during years 3–5 or until progression is documented. Pelvic ultrasound should be performed every 6 months in those patients who

underwent fertility sparing surgery, whereas CT scan of the abdomen and pelvic is usually performed yearly.

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty.

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