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Review Article

Malignant germ cells tumor of the ovary

Francesca De Maria,[1] **Frédéric Amant**,[2,3] **Valentina Chiappa**,[1] **Biagio Paolini**,[1] **Alice Bergamini**,[4,5] **Robert Fruscio**,[6,7] **Giovanni Corso**,[8,9] **Francesco Raspagliesi**,[1] **Giorgio Bogani**[1]

[1]Gynecological Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milano, Italy
[2]Center for Gynecological Oncology Amsterdam (CGOA), Antoni van Leeuwenhoek - Netherlands Cancer Institute, Amsterdam, The Netherlands
[3]Unit of Gynecologic Oncology, UZ Leuven, Leuven, Belgium
[4]Faculty of Medicine and Surgery, Vita-Salute San Raffaele University, Milano, Italy
[5]Unit of Obstetrics and Gynaecology, IRCCS San Raffaele Scientific Institute, Milano, Italy
[6]UO Gynecology, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy
[7]Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy
[8]Division of Breast Surgery, European Institute of Oncology (IEO), IRCCS, Milan, Italy
[9]Department of Oncology and Hemato-Oncology, University of Milano, Milan, Italy

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Correspondence to
Francesca De Maria
Gynecological Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Via Giacomo Venezian 1, Milano 20133, Italy.
Email: francesca.demaria@istitutotumori.mi.it

ORCID iDs
Francesca De Maria
https://orcid.org/0009-0008-0388-1540
Frédéric Amant
https://orcid.org/0000-0002-5452-4905
Valentina Chiappa
https://orcid.org/0000-0002-1811-209X
Biagio Paolini
https://orcid.org/0000-0001-7535-7715
Alice Bergamini
https://orcid.org/0000-0002-1915-8313
Robert Fruscio
https://orcid.org/0000-0001-5688-2194
Giovanni Corso
https://orcid.org/0000-0002-9269-0146

ABSTRACT

Malignant ovarian germ cell tumors are rare and diverse malignancies, accounting for approximately 5% of all ovarian cancers. Primarily affecting young women, these tumors present unique challenges, particularly in balancing effective treatment with fertility preservation. Early diagnosis is common due to the rapid tumor growth and symptoms such as abdominal pain and distension, leading to favorable prognoses when combined with the high chemosensitivity of platinum-based regimens. Fertility-sparing surgery is the cornerstone of treatment for stage I disease, often followed by close surveillance to minimize the long-term toxicities of chemotherapy. Pathology is pivotal for diagnosis, incorporating immunohistochemical markers to differentiate malignant ovarian germ cell tumors subtypes, including dysgerminomas, yolk sac tumors, and immature teratomas. Advanced imaging modalities like ultrasound, magnetic resonance imaging, and computed tomography are essential for staging, monitoring treatment response, and detecting recurrences. Despite high cure rates, long-term follow-up is crucial to manage late toxicities, such as gonadal dysfunction and secondary malignancies. Recurrent malignant ovarian germ cell tumors present significant therapeutic challenges. High-dose chemotherapy with stem-cell transplantation offers promise in select cases, while the role of secondary cytoreductive surgery and radiotherapy is limited to specific indications. Emerging targeted therapies and novel approaches, such as KIT inhibitors for dysgerminomas with KIT mutations, remain experimental, with limited success reported so far. The rarity and heterogeneity of malignant ovarian germ cell tumors impede large-scale research efforts, underscoring the need for greater understanding of their molecular and genetic landscape to develop more effective and personalized therapies.

Keywords: Ovarian Neoplasms; Surgery; Fertility; Chemotherapy

INTRODUCTION

Non-epithelial ovarian tumors constitute approximately 10% of all ovarian cancers, with malignant ovarian germ cell tumors accounting for about 5% [1]. Malignant ovarian germ cell

Francesco Raspagliesi
https://orcid.org/0000-0001-8953-1657
Giorgio Bogani
https://orcid.org/0000-0001-8373-8569

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tumors originate from primitive germ cells in the embryonic ovary, mirroring developmental stages from undifferentiated germ cells to adult tissues [1-3]. Unlike epithelial ovarian cancers, malignant ovarian germ cell tumors are more prevalent in women under 30 years of age and are extremely rare in older women, with only a few case reports in the literature [4,5]. These cases are often associated with a poor prognosis [4,5].

Given the young age of most patients, gynecologic oncologists face significant challenges in managing these tumors, particularly in balancing the need for effective treatment with fertility preservation. As such, issues of fertility preservation and prognosis are critical considerations. The majority of malignant ovarian germ cell tumors are diagnosed at an early stage (60%–70%), and fertility-sparing treatments have proven to be safe and associated with excellent long-term survival outcomes [1]. Survival rates are strongly correlated with International Federation of Gynecology and Obstetrics (FIGO) stage (5-year overall survival [OS] 91% for stage I and 59% for stage IV disease) [6].

Histological subtypes also significantly influence survival outcomes. A 2011 MITO retrospective study reported 5-year OS rates of 100%, 97.9%, 69.6%, and 62.9% for immature teratomas, dysgerminomas, yolk sac tumors, and mixed germ cell tumors, respectively [7]. Similarly, a recent SEER analysis identified embryonal carcinoma as the histotype with the poorest prognosis (5-year OS 33.3%) [8]. In the MITO-9 study, major prognostic factors for survival included age >45 years, stage >I disease, incomplete surgical resection, and yolk sac tumor histology [1,7,8]. Due to the rarity of germ cell tumors, the current body of evidence is limited, and high-quality data from international prospective studies are urgently needed. This comprehensive review aims to summarize the current state of knowledge regarding the clinical features, diagnostic work-up, treatment options, and emerging approaches for germ cell tumors, with a focus on the most critical issues surrounding their management.

EPIDEMIOLOGY AND CLINICAL CHARACTERISTICS

The overall incidence of malignant ovarian germ cell tumors is low. According to the 2023 Cancer Statistics, the incidence rate is approximately 5.7 cases per million among 14-year-old patients, increasing to 27 cases per million among women aged 15–19 years. Despite this difference, survival rates are comparable between these groups [9].

The incidence of malignant ovarian germ cell tumors varies across populations, with a higher prevalence observed in Asian and African societies (15%) compared to Western countries (5%). Specifically, the Saudi Arabian population has one of the highest reported incidences at 13.8%, highlighting the need for further research into the potential influence of lifestyle and dietary habits on this disparity [4,10]. A likely genetic component is suggested by the higher incidence observed in Eastern Asia, as well as among Asian/Pacific Islanders within the United States and in Central America and in Hispanic children in the United States. Nevertheless, in some regions the data is scarce so a conclusion cannot be drawn.

Currently, the most widely used classification is the one established by the 2014 World Health Organization but the 2020 classification is also used, as detailed in **Table 1** [11-13]. Since dysgerminoma is the most common malignant histological subtype, ovarian germ cell tumors are often categorized in clinical practice into 2 main groups: dysgerminomas and non-dysgerminomatous tumors [4,10]. Malignant ovarian germ cell tumors are typically

Table 1. World Health Organization 2020 classification ovarian germ cell tumors [13]

Ovarian germ cell tumors
Dysgerminoma
Yolk sac tumor
Embryonal carcinoma
Choriocarcinoma, NOS
Teratoma, benign
Immature teratoma
Mixed germ cell tumor
Monodermal teratomas and somatic type tumors from dermoid cyst (struma ovarii NOS, struma ovarii malignant, strumal carcinoid, teratoma with malignant trasformation)
Germ cell sex cord stromal tumors (gonadoblatoma, mixed germ cell-sex cord stroma tumor)

NOS, not otherwise specified.

Table 2. Serum markers associated with malignant ovarian germ cell tumors [15]

Serum tumoral markers	Tumor type
β-hCG	▪ Embryonal carcinoma ▪ Choriocarcinoma ▪ Mixed germ cell tumor ▪ Dysgerminoma*
AFP	▪ Yolk sac tumor ▪ Embryonal carcinoma ▪ Mixed germ cell tumor ▪ Immature teratoma
LDH	▪ Dysgerminoma ▪ Mixed germ cell tumor ▪ Yolk sac tumor* ▪ Immature teratoma* ▪ Embryonal carcinoma* ▪ Choriocarcinoma*

AFP, α-fetoprotein; LDH, lactate dehydrogenase; β-hCG, beta-human chorionic gonadotropin.
*Not always elevated.

unilateral, large, and grow rapidly. Common presenting symptoms include abdominal pain and a palpable pelvic-abdominal mass. Acute abdominal pain due to tumor torsion or rupture is also not uncommon [10]. A small percentage of pure dysgerminomas (10%–15%), mixed malignant ovarian germ cell tumors with a predominant dysgerminoma component, and metastasized germ cell tumors from one ovary to the other can be bilateral [2,14]. Unlike other non-dysgerminomatous germ cell tumors, embryonal carcinoma is frequently associated with signs of hormone production, particularly human chorionic gonadotropin (β-hCG), which may present clinically as uterine bleeding [15]. The initial diagnostic workup for malignant ovarian germ cell tumors should include serum tumor marker evaluation, pelvic ultrasound (US), and computed tomography (CT) of the abdomen and pelvis. Magnetic resonance imaging (MRI) of the abdomen and pelvis is preferred over CT to minimize radiation exposure and to provide better characterization of the mass. Serum tumor markers are critical for initial diagnosis and for monitoring the disease during and after treatment. **Table 2** highlights the specificity of these serum markers [12,15]. Yolk sac tumors frequently exhibit elevated cancer antigen 125 levels. The serum markers for mixed germ cell tumors depend on the specific composition and quantity of tumor elements.

PATHOLOGICAL FEATURES

The diagnosis of ovarian germ cell neoplasms is mainly based on the morphological characteristics of the surgical specimens: generally, morphology alone is sufficient to

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Table 3. Immunohistochemistry of primitive malignant ovarian germ cell tumors [15,16]

Dysgerminoma	Embryonal carcinoma	Yolk sac tumor	Non-gestational choriocarcinoma	Immature teratoma
PLAP	PLAP	PLAP	β-hCG	SALL4
SALL4	SALL4	SALL4	SALL4	SOX2
OCT-3/4	OCT-3/4	AFP	Inhibin	Glypican-3
ALP	SOX2	Glypican-3	GATA-3	GFAP
D2-40	AFP	LIN28		S100
NANOG	CD 30			Synaptophysin
SCFR				CD99

differentiate the main histotypes (dysgerminoma, yolk sac tumor, embryonal carcinoma, teratoma and choriocarcinoma) from each other and from other types of ovarian neoplasms (epithelial or sex-cord). Immunohistochemical (IHC) markers are invaluable for achieving a definitive diagnosis, particularly in challenging cases. Research has demonstrated that delayed germ cell maturation and malignant germ cells share OCT3/4 expression. Additionally, the oncogenic activity of OCT3/4 has been shown in vitro using germ cell tumor lines in mice [3]. Several IHC markers are commonly used to differentiate between various malignant ovarian germ cell tumors subtypes. Dysgerminoma is frequently positive for SALL4, OCT3/4, alkaline phosphatase, placental-like alkaline phosphatase (PLAP), D2-40, NANOG, and SCFR. Yolk sac tumor, commonly, is positive for SALL4, PLAP, α-fetoprotein, LIN28, and glypican-3, whereas typically negative for estrogen receptor, progesterone receptor, epithelial membrane antigen, PAX8, CK7, OCT3/4, D2-40, SOX2, and CD30. Embryonal carcinoma expresses SALL4, SOX2, OCT3/4 and CD30. As well as generic epithelial markers such as CK pool. Lastly, non-gestational choriocarcinoma is positive for CK pool, Gata-3, β-HCG, SALL4 (only in mononucleated trophoblast cells) and inhibin, and negative for OCT3/4 [15,16].

Table 3 provides a summary of the differential IHC diagnoses for malignant ovarian germ cell tumors. Among these markers, PLAP staining is particularly valuable in differentiating malignant ovarian germ cell tumors from non-germ cell malignancies. The diagnosis of immature teratomas relies on the presence of immature or embryonic tissues, with neuroepithelium being the most common immature element. The extent of primitive neuroepithelial tissue is critical for diagnosis, grading, and prognosis determination. Histological grading is based on the number of microscopic low-power fields (LPF) containing immature neuroepithelial tissue on a single slide: G1 (low grade): foci of immature neuroepithelial tissue occupy ≤1 LPF. G2 (high grade): foci occupy 2–3 LPFs. G3 (high grade): foci occupy ≥4 LPFs. Due to the focus on histological criteria, IHC has a limited role in diagnosing immature teratomas [1,15].

Fig. 1 shows some of the pathological characteristics of ovarian germ cell tumors.

MOLECULAR AND GENETIC LANDSCAPE

The onset of malignant ovarian germ cell tumors appears to be primarily influenced by genetic alterations, combined with external factors such as exposure to maternal hormones, external endocrine disruptors, or adverse lifestyle-related factors that disrupt normal cellular biochemistry [17]. However, the clinical significance of genetic abnormalities remains unclear, and a deeper understanding of the molecular and genetic landscape is urgently needed [2]. Certain subgroups of patients with disorders of sex development are

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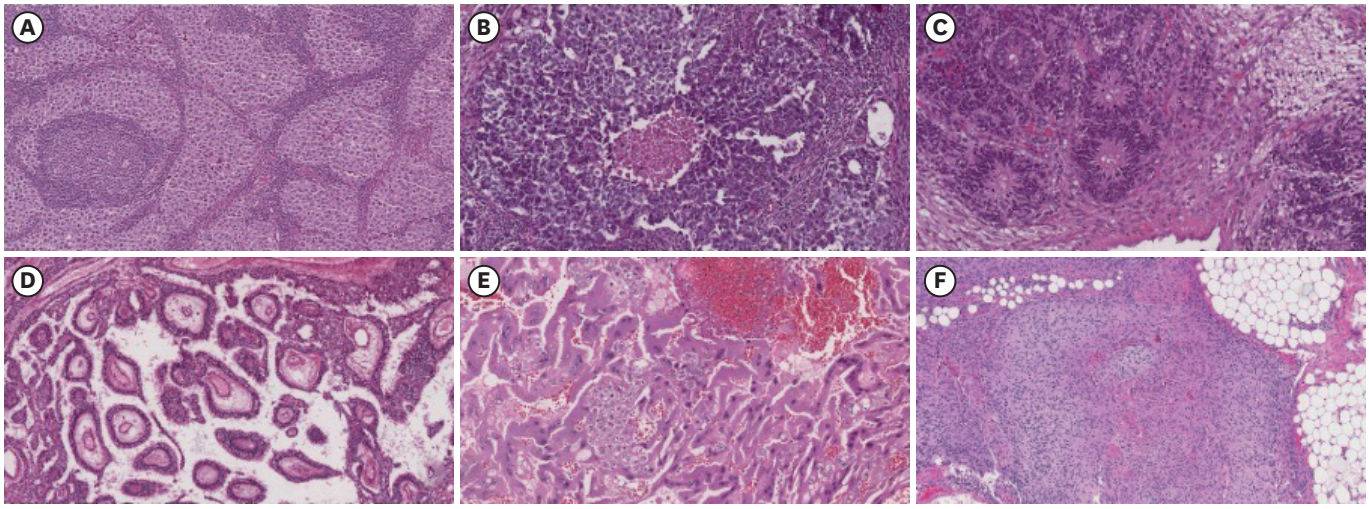

Fig. 1. Pathological characteristics of ovarian germ cell tumors. (A) Dysgerminoma. (B) Embryonal carcinoma. (C) Immature teratoma. (D) Yolk sac tumor. (E) Non-gestational choriocarcinoma. (F) Gliomatosis peritonei.

at a higher risk of developing malignant ovarian germ cell tumors. Key genes involved in gonadal development include WT1, SF1, and DAX, and mutations in any of these genes can result in gonadal dysgenesis, which is associated with specific pathologies. Gonadal dysgenesis is linked to an increased risk of malignant ovarian germ cell tumors, with risk levels varying depending on the specific syndrome (ranging from 0%–60%, average risk of 12% approximately). For patients with high-risk syndromes, such as Turner's syndrome and Swyer's syndrome, prophylactic gonadectomy may be a reasonable recommendation [3,18]. A preoperative karyotype is ideally recommended for all premenarchal girls. The most frequent genetic alteration across all malignant ovarian germ cell tumors subtypes, except for pure immature teratomas, is a gain in chromosome 12p. Additional genetic changes include frequent KIT and KRAS mutations. Specifically: *KIT* mutations are commonly observed in ovarian dysgerminomas and *KRAS* mutations, along with *PIK3CA* and *AKT1* amplifications, are frequently found in yolk sac tumors [2].

THE ROLE OF IMAGING IN MALIGNANT OVARIAN GERM CELL TUMORS

Imaging plays a vital role in the diagnosis, characterization, staging, and management of malignant ovarian germ cell tumors. As these tumors primarily affect young women and exhibit rapid growth, imaging modalities such as US, CT, and MRI are indispensable for early detection, monitoring response to therapy, and detecting recurrence. US is often the first imaging tool utilized due to its accessibility and ability to evaluate adnexal masses. Malignant ovarian germ cell tumors, including dysgerminomas, yolk sac tumors, and mixed germ cell tumors, frequently present as large, solid, or multilocular-solid tumors with heterogeneous echogenicity and prominent vascularization on color Doppler imaging [19,20]. **Fig. 2** shows US features of malignant ovarian germ cell tumors.

MRI complements US by providing superior soft tissue contrast and detailed characterization of tumor components. Dysgerminomas appear as solid, lobulated masses with T2 hyperintense stromal edema and prominent flow voids due to vascularity. Yolk sac tumors, on the other

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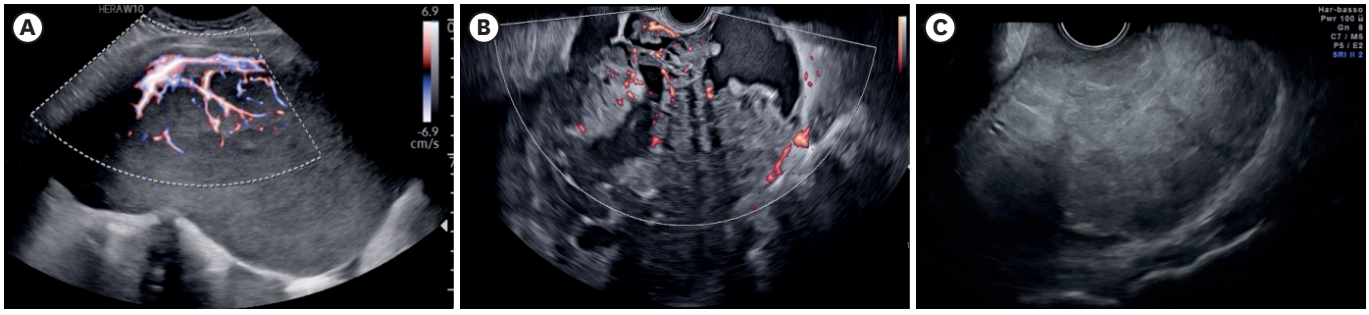

Fig. 2. Ultrasound features of malignant ovarian germ cell tumors. (A) Dysgerminoma. (B) Immature teratoma. (C) Yolk sac tumor.

hand, demonstrate multiloculated cystic regions with T1 hyperintense hemorrhage and T2 hypointense solid components. MRI is also valuable for identifying complications such as capsular rupture, peritoneal spread, and gliomatosis peritonei associated with immature teratomas [19,20].

CT imaging is integral to staging and assessing metastatic disease. It helps evaluate tumor size, local invasion, and distant metastases. For instance, choriocarcinomas often metastasize to the lungs and liver, and CT is ideal for assessing these regions. Dysgerminomas occasionally involve bilateral ovaries and adjacent structures, while yolk sac tumors may spread peritoneally, appearing as hypervascular implants on contrast-enhanced CT. Despite advancements in imaging technology, challenges persist in distinguishing certain subtypes of malignant ovarian germ cell tumors [19,20].

STANDARD TREATMENT

The staging system for malignant ovarian germ cell tumors is generally adapted from the system used for epithelial ovarian cancers, as defined by the FIGO [21]. Currently, fertility-sparing surgery is the standard surgical treatment for malignant ovarian germ cell tumors, followed by either close follow-up or chemotherapy, depending on the tumor's histotype, grade, and stage of disease. The precise role of staging procedures in this context remains a topic of debate. Outcomes are consistently better when patients are treated at specialized cancer centers.

SURGERY

The staging procedure for malignant ovarian germ cell tumors includes infracolic omentectomy, biopsies of the peritoneum (diaphragmatic, para-colic gutters, and pelvic), as well as peritoneal washing in cases of macroscopic stage I disease. The standard surgical approach remains an open route; however, in selected cases, minimally invasive techniques (laparoscopy or robotic surgery) can be considered if performed by an experienced surgeon to avoid tumor rupture during surgery. Evidence suggests that omission of surgical staging increases the risk of recurrence, though it does not compromise OS given the high chemosensitivity of these tumors [1,22]. According to European Society for Medical Oncology (ESMO) guidelines, in early-stage disease that does not require adjuvant chemotherapy, lymph node dissection is recommended only for suspicious lymph nodes

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detected intraoperatively or lymphadenopathies identified on preoperative imaging [1]. In a large retrospective study by Mahdi et al. [23], lymphadenectomy was not found to be an independent predictor of survival, with similar survival outcomes reported regardless of lymphadenectomy or lymph node status. Among germ cell tumors, dysgerminomas have the highest risk of lymphatic metastases. Despite this, lymphadenectomy is not recommended due to their high chemosensitivity and high likelihood of remission with adjuvant chemotherapy or at recurrence. Additionally, staging procedures, particularly lymphadenectomy, are associated with complications such as lymphocele, lymphorrhea, and deep vein thrombosis, which may delay the initiation of chemotherapy when indicated. Although ovarian carcinomas frequently metastasize to the omentum, the incidence of omental metastases in early-stage malignant ovarian germ cell tumors is generally low [24].

Given the young age of most patients, the standard surgical treatment is unilateral salpingo-oophorectomy with preservation of the contralateral adnexa and uterus [25]. A 2017 retrospective study found no significant difference in oncologic outcomes between conservative and non-fertility sparing surgeries, reporting 5-year disease-free survival (DFS) rates of 92.3% and 94.3%, respectively [26].

Biopsy of the contralateral ovary is not recommended as it increases the risk of fertility impairment due to adhesions or ovarian failure. In cases of macroscopic bilateral ovarian involvement, which is rare in yolk sac tumors, unilateral salpingo-oophorectomy with contralateral cystectomy is advised. For patients with gonadal dysgenesis, removal of the remaining ovary is recommended. Fertility-sparing surgery is not indicated in postmenopausal women, who should undergo hysterectomy with bilateral salpingo-oophorectomy and complete surgical staging. In young patients, fertility-sparing surgery may still be performed in cases of advanced disease due to the high chemosensitivity of malignant ovarian germ cell tumors, with the goal of achieving no residual tumor [1,27]. Extensive surgical procedures with high complication risks should be avoided to prevent delays in chemotherapy and the risk of tumor regrowth.

In cases of residual disease following adjuvant chemotherapy and normalization of serum tumor markers, second-look surgery may be considered, especially for patients with suspected growing teratoma syndrome. Growing teratoma syndrome is often associated with immature teratoma at diagnosis [1,28]. Lymph node dissection is indicated in cases of residual lymph node disease post-chemotherapy. When advanced disease is suspected, gliomatosis peritonei should be excluded. Gliomatosis peritonei is a rare condition often associated with immature teratoma and characterized by the presence of mature glial tissue in extra-ovarian sites, such as the omentum and peritoneum, without immature components. While gliomatosis peritonei is benign, large and multiple biopsies of extra-ovarian sites are essential to confirm the mature and glial nature of the tissue. In rare cases where immature glial components are present, medical treatment is recommended [27,29].

ADJUVANT TREATMENT

The indication for chemotherapy in malignant ovarian germ cell tumors depends on the tumor grade, histology, and molecular features of the disease. Over the past 40 years, the introduction of chemotherapy has significantly improved survival rates for these patients. The development of combination chemotherapy regimens for malignant ovarian germ cell

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tumors originated from studies on testicular carcinoma, transitioning from the vincristine, actinomycin D, cyclophosphamide (VAC regimen) to the current standard bleomycin, etoposide, cisplatin (BEP regimen) [10,28]. According to the ESMO guidelines, Stage IA dysgerminomas and properly staged Stage IA Grade 1 immature teratomas should be treated with surgery alone, followed by postoperative surveillance. Stage IB and IC dysgerminomas can be closely monitored. The treatment of immature teratomas in Stage IA Grade 2–3 and Stage IB–IC remains controversial [1,2]. Bergamini et al. [30] in 2020 published one of the largest series of Stage I pure immature teratomas showing as surveillance did not decrease survival compared to adjuvant chemotherapy even in patients at higher risk of recurrence properly staged and with negative postoperative tumor markers (IC Grade 2–3 immature teratomas). Encouraging data have arisen from the 2021 prospective observational study by Mangili et al. [31] as well. They reported a low relapse rate (3.2%) in Stage IA–C dysgerminomas, Stage IA–C Grade 1–3 immature teratomas and Stage IA mixed malignant germ cell tumors well-staged who underwent surveillance alone underlining the importance of surgical restaging too.

Yolk sac tumors have been shown to be a poor prognostic indicator [7,32]. All yolk sac tumors and mixed histologies with yolk sac elements should be treated with adjuvant chemotherapy after surgery. Only properly staged Stage IA–IB yolk sac tumor patients with negative postoperative tumor markers may be considered for close surveillance, but robust data on this histology are lacking [1,22]. Since salvage chemotherapy reserved for cases of recurrence has an excellent chance of therapeutic success, the balance lies in overtreatment of many young patients versus treatment for recurrent disease in the group of patients at risk. For all other advanced stages and malignant ovarian germ cell tumors histotypes, such as embryonal carcinoma, the standard treatment is 5-day adjuvant BEP chemotherapy. The 2020 European Society of Gynaecological Oncology-European Society of Paediatric Oncology guidelines recommend that the standard chemotherapy regimen for Stage III–IV disease in adolescents and young adults follows adult protocols with bleomycin, etoposide, and platinum for 3 to 4 cycles. For pediatric patients, carboplatin may be substituted for cisplatin [27]. An alternative regimen used for high-risk patients is cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide, and etoposide (POMB/ACE). The number of chemotherapy cycles should be tailored according to residual tumor and postoperative tumor markers [1].

Due to the high pulmonary toxicity of bleomycin, it is generally omitted after 3 cycles, reaching a maximum total cumulative dose of 270 IU. Bleomycin should also be avoided in patients with pre-existing pulmonary conditions and in those over 40 years old due to a drug-related mortality rate of 3% [1,27].

FOLLOW-UP AND QUALITY OF LIFE

Strict and active surveillance should be proposed when adjuvant chemotherapy is not indicated. Patient adherence to the surveillance program is crucial for successful monitoring. The follow-up schedule should extend for 10 years, with gradually increasing intervals between clinical appointments. Since approximately 75% of malignant ovarian germ cell tumors recurrences occur within the first 2 years after initial diagnosis, visits and exams should be more frequent during this period. It is also essential to advise patients against pregnancy during the first 2 years after the initial diagnosis [1].

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Table 4. Follow-up strategy of malignant ovarian germ cell tumors for those undergoing strict surveillance [1,27,33]

Year	Description
1 yr	Physical exam + tumor markers* + pelvic or abdominal US every 2 mo Chest-abdomen imaging† every 2–6 mo
2 yr	Physical exam + tumor markers* + pelvic or abdominal US every 2–3 mo Chest-abdomen imaging† every 3–6 mo
3–5 yr	Physical exam + tumor markers* + pelvic or abdominal US every 3–6 mo Chest-abdomen imaging† every 6–12 mo
After 5 yr	Physical exam + tumor markers* + pelvic or abdominal US every 12 mo Chest-abdomen imaging† every 12 mo or if needed

According National Comprehensive Cancer Network (NCCN) Guidelines Ovarian Cancer 2024, follow-up visits for non-dysgerminoma histotypes should be more frequent.
US, ultrasound.
*Specific tumor markers (lactate dehydrogenase, human chorionic gonadotropin, α-fetoprotein) depending on the type of tumor; †Chest-abdomen computed tomography scan, abdomen-pelvis magnetic resonance imaging, chest X-ray.

Different protocols have been proposed for active surveillance [30]. The surveillance schedule should include clinical examinations, radiological imaging (such as abdominal-pelvic US, chest X-ray, or CT of the chest, abdomen, and pelvis) at regular intervals, and tumor marker monitoring (as outlined in **Table 4** as an example) [1,27,33]. After adjuvant chemotherapy, serum tumor markers and radiological imaging are key tools for evaluating the response to treatment. Due to the excellent prognosis associated with malignant ovarian germ cell tumors, evaluating the long-term effects of treatment is essential. Chemotherapy-related side effects can be categorized into acute and long-term effects. The most common acute side effects include pulmonary toxicity, neutropenia, thrombocytopenia, mucocutaneous toxicity, neuropathy, ototoxicity, and nephrotoxicity. In contrast, late toxicities include cardiovascular disease, hypertension, gonadal dysfunction, and second malignancies [34]. Among these, the onset of secondary tumors is particularly concerning, especially in young survivors [25]. Therefore, the potential for long-term side effects must be carefully considered when evaluating adjuvant chemotherapy for stage I tumors.

The long-term effects of anti-neoplastic chemotherapy on ovarian function have been extensively studied in other types of cancer. The risk of chemotherapy-induced ovarian insufficiency cannot be underestimated. It appears that the chemotherapy agent, age at administration, cumulative dose, and duration of therapy all influence the incidence of ovarian dysfunction. In general, cisplatin is considered moderately gonadotoxic, however fertility seems not impaired in 2 recent studies [1,35-37]. It should also be noted that the likelihood of fertility preservation and resumption menses is higher in these women due to their greater ovarian reservoir. Furthermore, the Norwegian group found that the likelihood of pregnancy was lower in patients who received more than 3 cycles of chemotherapy or non-platinum-based chemotherapy [25]. The infertility rate reported after treatment for malignant ovarian germ cell tumors is 5%–10%, which is similar to the rate in the general population [36,37].

RECURRENCE TREATMENT

Patients who experience a recurrence of malignant disease after primary chemotherapy for malignant ovarian germ cell tumors are associated with a poorer prognosis. As mentioned earlier, most relapses occur within the first few years. Relapses are typically detected through an increase in serum tumor markers and/or radiologic changes during follow-up visits [1].

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The most appropriate therapeutic approach should be determined by a multidisciplinary team and may include chemotherapy, high-dose chemotherapy (HDCT) with stem-cell rescue, surgery, radiotherapy, or a combination of these modalities [2].

SECONDARY CYTOREDUCTIVE SURGERY

Unlike epithelial ovarian cancers, the role of secondary surgery in recurrent germ cell tumors remains uncertain and should be considered only for selected patients. Factors such as the site, extent, and localization of the disease, as well as the patient's performance status, must be considered when determining the most appropriate treatment approach. It appears that recurrent immature teratomas, growing teratoma syndrome, or recurrent mixed malignant germ cell tumors may benefit from cytoreductive surgery [38]. Growing teratoma syndrome is characterized by a rapid increase in tumor size during chemotherapy, despite normalized tumor markers, due to the proliferation of a benign mature teratoma component. In these cases, surgery is the sole required treatment, aimed at alleviating compression symptoms and disease-related morbidity. In this category of patients, a diagnostic biopsy to exclude a malignant lesion may be helpful.

As with primary surgery, the goal of secondary surgery is complete gross resection, combined with chemotherapy in the presence of any residual mass [38]. A retrospective Chinese study found that patients with chemo-refractory ovarian germ cell tumors and residual tumors ≤1 cm after salvage surgery were able to achieve long-term survival, which contrasts with the outcomes seen in epithelial ovarian cancer. The authors suggested that this difference may be attributed to the high chemosensitivity of germ cell tumors, even when a small residual tumor remains. However, the 5-year survival rates were 60.95% and 14.04% for optimal and suboptimal cytoreduction, respectively [39].

STANDARD-DOSE CHEMOTHERAPY REGIMEN

The current data on second-line treatment for malignant ovarian germ cell tumors have been largely extrapolated from the treatment protocols used for testicular germ cell tumors [40]. In cases of platinum-sensitive recurrence, a second-line regimen involving ifosfamide/platinum, with or without paclitaxel, should be considered. Other chemotherapy combinations that may be used include vinblastine/ifosfamide/cisplatin, etoposide/ifosfamide/cisplatin, and cisplatin/vinblastine/bleomycin [1,28]. Repeating the first-line BEP regimen is generally not recommended due to the poor response, unless the initial disease was treated with surgery alone. Furthermore, due to toxicity concerns, bleomycin cannot be repeated in subsequent lines of treatment if it was administered during the first-line therapy. Unfortunately, there are no current trials comparing second-line chemotherapy regimens specifically for malignant ovarian germ cell tumors, and the overall response rate to salvage chemotherapy in germ cell tumors patients is approximately 50% [28]. Response rates reported in phase II studies vary between 17% and 51%, with the highest responses observed when paclitaxel is included in the regimen [41,42]. Despite this, long-term progression-free survival remains low [43]. Therefore, the choice of chemotherapy regimen should be tailored based on the patient's previous treatments, toxicities, comorbidities, and the specific characteristics of the recurrence.

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HIGH-DOSE SALVAGE CHEMOTHERAPY (HDCT) WITH STEM-CELL RESCUE

In the context of therapeutic options for recurrent malignant ovarian germ cell tumors, HDCT with stem cell transplant has been proposed with curative intent following the promising results in testicular cancer [44]. **Table S1** shows the most relevant studies about recurrence treatments of malignant ovarian germ cell tumor [45-66]. For recurrent testicular germ cell tumors, 2 main regimens are utilized: Carboplatin combined with etoposide prior to peripheral blood stem cell (PBSC) administration, followed by 2 tandem cycles (CE). Paclitaxel combined with ifosfamide every 2 weeks for 2 cycles, followed by high-dose carboplatin and etoposide with stem-cell support (TI-CE). Due to the high toxicity associated with these regimens, PBSC rescue and the use of granulocyte colony-stimulating factor were introduced to reduce toxicity. Despite the higher toxicity, retrospective studies have shown promising results, with a complete response rate of 31% in platinum-refractory patients and a 2-year OS of 37% [45,67]. In cases of second recurrences, HDCT is strongly recommended. Given the promising outcomes, the role of HDCT in treating first recurrences is currently under investigation. In 2017, De Giorgi et al. [45] reported encouraging results with a long-term DSF rate of 59% when HDCT was used as first-line salvage therapy. To further evaluate its effectiveness, a randomized phase III trial (TIGER NCT02375204) is underway to compare conventional-dose chemotherapy (paclitaxel, ifosfamide, cisplatin [TIP]) with HDCT using TI-CE as the first salvage treatment for relapsed or refractory germ cell tumors.

RADIOTHERAPY

Radiotherapy was the most common treatment for malignant ovarian germ cell tumors before 1980. However, despite the high radiosensitivity of dysgerminomas, its use today is limited to rare cases, such as adjuvant therapy or for recurrences after multiple lines of prior treatment [1,68]. Radiotherapy may still be considered in a multimodal approach for treating brain metastases and persistent disease [69]. Additionally, radiotherapy can play a role in palliative care, helping to control symptoms related to bone metastases.

NOVEL THERAPEUTIC AGENTS AND FUTURE PERSPECTIVES

In the era of targeted therapy, greater clarity and new proposals in the field of malignant ovarian germ cell tumors are urgently needed. The rarity of the disease remains a major limitation for designing prospective trials and making treatment comparisons. Most evidence on novel therapeutic approaches is derived from studies on testicular germ cell tumors.

One such approach, known as “accelerated chemotherapy,” proposes administering standard chemotherapy every 2 weeks instead of every 3 weeks (NCT02582697). This treatment may prove effective, with OS and biomarker correlations set as primary endpoints in phase III trials [70]. High aberrant expression of programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) has been observed in testicular germ cell tumors, prompting phase II trials with anti-PD-L1 agents but yielding disappointing results [71,72]. Other targeted therapies have been tested (inhibitors of epidermal growth factor receptor, CD30, c-KIT, MET, CDK4/6, tyrosine kinase, and mammalian target of rapamycin, but none have shown promise in male

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germ cell tumors [73-75]. Several other targeted therapies are under investigation, including the tyrosine kinase inhibitor cabozantinib (NCT04876456), olaparib (NCT02533765), and the monoclonal antibody targeting CLDN6, ASP1650 (NCT03760081). As the understanding of the molecular and genetic landscapes of germ cell tumors improves, certain mutations have been identified as potential targets for clinical trials as KIT mutations in dysgerminoma. Tumors with this mutation are more likely to be at an advanced stage. In these cases, KIT might be a promising therapeutic target [76]. Other potential gene targets include ARID1A mutations, PI3KCA mutations, and a high tumor mutational burden [77].

CONCLUSIONS

Malignant ovarian germ cell tumors are rare and encompass a diverse group of tumors, primarily affecting young women. As fertility-sparing treatment is a priority, even in advanced stages, early diagnosis contributes to an excellent prognosis. Platinum-based chemotherapy is highly effective due to the tumor chemosensitivity. For patients with adequately staged stage I disease, close surveillance is increasingly recommended to avoid the acute and long-term toxicities associated with chemotherapy. Pathology plays a pivotal role in diagnosis, which should be confirmed by expert pathologists. Follow-up should be intensive during the first few years and extend for up to 10 years. The management of recurrence, which involves a combination of chemotherapy, HDCT, surgery, and radiotherapy, remains a major challenge for clinicians and researchers. However, data on novel therapeutic agents are limited, with most findings being extrapolated from studies on testicular germ cell tumors, often with modest results. The low incidence and tumor heterogeneity are significant barriers to research in new therapeutic approaches and targeted therapies. A deeper understanding of the molecular and genetic landscape of malignant ovarian germ cell tumors could provide valuable insights for developing more effective treatments.

SUPPLEMENTARY MATERIAL

Table S1

Most relevant studies about recurrence treatments of OGCTs

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