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Izabela Pilarska[1], Kinga Grabska[1], Marta Fudalej[2], Andrzej Deptała[2], Anna Badowska-Kozakiewicz[2]

[1]Students' Scientific Organization of Cancer Cell Biology, Department of Cancer Prevention, Medical University of Warsaw, Warsaw, Poland
[2]Department of Cancer Prevention, Medical University of Warsaw, Warsaw, Poland

What is new about germ cell ovarian tumors?

Address for correspondence:
Marta Fudalej, MD
Department of Cancer Prevention,
Medical University of Warsaw,
ul. 27 Erazma Ciołka St.,
01–445 Warsaw, Poland

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ABSTRACT

Germ cell tumors of the ovary are the second most frequently found ovarian neoplasms following epithelial ovarian cancers. It is a heterogeneous group with an origin in a primitive germ cells. Therefore, germ cell tumors arise typically in the gonads- ovaries, and testicles. Neoplasms that develop from germ cells in other parts of the body are very rare. Among ovarian germ cell tumors, the most common is a mature teratoma. Tumors such as immature teratoma, dysgerminoma, embryonal carcinoma, or yolk sac tumor appear less frequently. Surgical treatment and chemotherapy, especially a protocol BEP (bleomycin, etoposide, cisplatin) play the most crucial role in the treatment of germ cell malignancies. Before the introduction of systemic chemotherapy, treatment of malignant germ cell tumors of the ovary tended to be poor. The prognosis has improved recently and fertility-conserving surgeries are being performed to enable patients to become pregnant. Additionally, it reduces the risk of late side effects. However, more and more emphasis is placed on developing new methods of treatment and on improving current methods. Some studies showed a therapeutic potential of SOX2 silencing for embryonal carcinoma. The aim of our study was to review the literature to analyze the latest and most effective treatments for embryonic ovarian tumors.

Key words: germ cell tumors, ovary, teratoma, dysgerminoma, embryonal carcinoma

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Introduction

Non-epithelial neoplasm is a rare malignancy and consists of germ cell tumors (GCT), sex-cord stromal tumors, and the most infrequent tumors of mesenchymal origin [1]. Germ cell neoplasms, besides epithelial ovarian cancers, are the second most common group — they account for approximately 10% of all ovarian malignancies [2]. GCTs include a broad set of histologic subtypes, such as teratoma, seminoma (known as dysgerminoma in the ovary and germinoma in the pineal gland), yolk sack tumor, choriocarcinoma, embryonal cell carcinoma, and mixed GCT [3].

Germ cell tumors are a distinctive group originating from the primitive germ cell. They usually arise in gonads – ovaries and testicles (over 90% of cases) — but may also arise in the anterior mediastinum, retroperitoneum, brain, pineal gland, and neurohypophysis [4–6]. The extragonadal GCTs might be derived from the primitive germ cells, which are separated during their migration to the primitive gonadal glands in the urogenital ridge [6].

Malignant germ cell tumors occur mainly in women and are usually found in younger patients [7].

Among ovarian germ cell tumors, the most common is a mature teratoma. Malignant tumors such as immature teratoma, dysgerminoma, embryonal carcinoma, or yolk sac tumor appear less frequently [8]. Malignant ovarian GCTs (MOGCTs) are subdivided into dysgerminomatous tumors (the most frequent type) and non-dysgerminomatous tumors [5] (Tab. 1).

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Table 1. Classification of malignant embryonic tumors of the ovary, based on the classification of tumors of the World Health Organization [4, 6]

Germ Cell Tumors	Tumor Type
Primitive germ cell tumors	Dysgerminoma
	Yolk sac tumor
	Polyvescicular vitelline tumor
	Glandular variant
	Hepatoid variant
	Embryonal carcinoma
	Polyembryoma
	Non-gestational choriocarcinoma
	Mixed germ cell tumor
Biphasic or triphasic teratoma	Immature teratoma
	Mature teratoma

Surgical treatment and chemotherapy [bleomycin, etoposide, cisplatin (BEP)] play the most critical role in the case of germinal and gonadal neoplasms. Avoiding surgery is often possible because most diagnoses are at an early stage. In recent years, however, more and more effort is put into modernizing ways of treating ovarian malignancies.

The study aimed to analyze and discuss the latest methods of treatment of germ cell tumors. The articles published from 1976 to 2020 in the Pubmed and Elsevier databases were analyzed. The authors concentrated on the analysis of possible neoplasm therapies, and methods of improving the quality of life (including preserving fertility after treatment). The focus of the article was in particular: immature teratoma, dysgerminoma, and embryonal carcinoma of the ovary (ECO).

Immature teratoma

Immature teratoma (IT) accounts for approximately 1% of all ovarian tumors. IT can occur in both children and adults (range 1.5–60 years of age) [9]. Immature teratoma consists of all the embryonic tissues: endoderm, mesoderm, and ectoderm [10]. The five-year survival rate of patients with stage I immature teratoma is 98.3%, but in stage IV of the disease, the survival drops to 72%, thus early detection seems significant [11]. Due to the small number of patients (especially among adults), there are obstacles with an extensive follow-up and research, so it appears challenging to find the best IT therapy.

The treatment of choice for immature teratoma is surgical tumor excision. In the situation of incomplete tumor resection, 3 BEP cycles are recommended. Chemotherapy is also used in most adult patients with stages II or III or in the case of IT relapses, which, however, do not happen commonly [9, 12].

Shinkai et al. [13] reported, based on the experience of treating their patients between 2000 and 2016, that pediatric patients should be treated only surgically and chemotherapy should be mainly used in case of relapse. Therefore, children's situation is entirely different from adult women's, in whom adjuvant chemotherapy is recommended if the tumor advancement level exceeds stage I. Although adjuvant chemotherapy is prescribed routinely among adult women, no data have confirmed its responsiveness. Additionally, Imran et al. [9] pointed out that using chemotherapy in recurrent IT may lead to the transformation of IT into a mature teratoma [growing teratoma syndrome (GTS)]. Mature teratoma is, undoubtedly, a disease that can be cured by surgery alone; however, we must be aware of the further enlargement of the mass that might make surgery difficult. Since mature teratoma shows high expression of the retinoblastoma protein (cyclin-dependent kinase 4/6), it opens a new, non-operable treatment for GTS [9, 14].

GTS is a rare condition that may occur in patients with IT who had already undergone surgery. It is characterized by normal tumor marker levels, while tumor mass or implants can be observed on imaging studies or during laparoscopy [15]. The incidence of GTS is unknown, but it is more common among patients with testicular germ cell tumors than with ovarian ones [16]. The benefit of radical intervention in asymptomatic cases of GTS has not been proven. The disease can be stable for a long period of time [17]. One of the longest and most well-documented studies about GTS was conducted by Rathod et al. [18] from 2000 to 2020. During this period, 303 cases of germ cell tumor ovarian cancers were treated, and 8 cases recurred as GTS. All the cases were managed with optimal surgical cytoreduction, some of the cases more than once. The study claims that prolonged survival and possible recovery in patients with GTS depend on optimal cytoreduction [18].

Dysgerminoma

Dysgerminoma is a malignant germ cell tumor that accounts for less than 1% of all ovarian tumors [19]. Dysgerminoma most commonly occurs in children and young women. Bleomycin, etoposide, and platinum are the main chemotherapy drugs for germ cell tumors, including dysgerminomas [20]. Almost all patients with stage IA dysgerminoma are treated only by surgery, while potential relapses respond well to the chemotherapy [21]. Additionally, chemotherapy is also given in the case of incomplete tumor resection [21, 22].

Duhil de Benaze et al. [23] described 45 patients treated for dysgerminoma over 20 years. Pediatric

patients were treated with unilateral ovariectomy. Over the years, the strategy for managing lymph nodes has changed. Patients were treated with strategies like prophylactic lymph nodes removal, the strategy for the prophylactic radiation of the lymph nodes, or platinum-based chemotherapy in advanced cases. Unfortunately, the common side effect of the treatment is reduced fertility, associated with ovary removal or chemotherapy. As a result of long-term observation, the authors concluded that dysgerminoma presents an excellent prognosis, even in advanced cases, thanks to the treatment combination of surgery and platinum-based chemotherapy.

In 2019, an article presenting the observation of 180 patients diagnosed with dysgerminoma was published. This study confirmed the difference in 5-year survival between the optimal and suboptimal groups receiving cytoreduction. The groups receiving optimal cytoreduction benefit most. Factors associated with optimal cytoreduction at all stages of the disease were higher levels of lactate dehydrogenase, higher levels of CA125, receiving adjuvant chemotherapy, or the patient being under treatment in a specialized facility. Authors of the study also underlie the importance of maintaining fertility, especially among young women [22, 24]. Although surgical treatment is still the basis for treating dysgerminoma, chemotherapy also plays a crucial role in therapy (among others in cases like: incomplete resection, relapses, lymph node metastases) [22].

Kilic et al. [25] conducted a retrospective study that analyzed 18 patients diagnosed with pure ovarian dysgerminoma, who underwent staging surgeries with retroperitoneal lymph node dissection between 1993 and 2019. Adjuvant therapy was added according to the guidelines of the tumor board. It consisted of chemotherapy or radiotherapy or combined chemotherapy with radiotherapy. All patients were followed up. The number of patients was low; however, the study group was homogeneous. That led to the conclusion that the treatment of choice in patients with pure dysgerminoma should be fertility-sparing surgery. Additionally, besides staging surgery, retroperitoneal lymph node dissection is obligatory for identifying stage IA patients, who are exempt from adjuvant therapy [25].

Embryonal carcinoma of the ovary (ECO)

In 1976, Kurman and Norris described embryonal carcinoma of the ovary (ECO) as a separate entity that often occurs together with other types of germ cell tumors. The most common cancer symptoms are hormonal disorders, such as premature puberty or irregular periods [26]. ECO can be managed with fertility-preserving treatments, such as a staging laparotomy and unilateral adnexectomy, followed by chemotherapy [27]. In embryonal carcinoma, 3 cycles of BEP are used for chemotherapy. Chemotherapy with surgery has been the gold standard in the treatment of embryonal carcinoma of the ovary for years [27–29].

Although the majority of patients with advanced ovarian germ cell cancer are successfully treated by platin-based chemotherapy, one-third of patients relapse and half of them develop resistance to platin-based therapy. The treatment of this group of patients is challenging, and the disease is often fatal [5]. Some studies showed a therapeutic potential of SOX2 silencing for embryonal carcinoma [30]. SOX2 is a core transcription factor, that controls embryonal stem cells' self-renewal and pluripotency [31]. Silencing of SOX2 with SOX2-siRNA in a mouse model resulted in cell cytotoxicity and growth inhibition. However, the authors of the study claim that SOX2-siRNA delivery to the tumor should be improved [30].

Conclusions

Even though GCTs constitute an extremely rare group of neoplastic diseases in women, most patients can be successfully cured. Treatment in germ cell tumors has not changed much over the years — surgery, possibly with chemotherapy, is still the gold standard in treatment. Maintaining fertility and reducing the risk of late side effects must also be an important treatment goal.

Conflict of interest

The authors declare no conflict of interest.

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