Chapter 3 ■ Germ Cell Tumors

Ⅰ Introduction

At the Japan Society of Obstetrics and Gynecology and the Japanese Society of Pathology (1990), ovarian germ cell tumors are distinguished on the basis of the World Health Organization (WHO) classification, which is further subdivided into benign, borderline, or malignant tumors (Tables 15, 16). Malignant tumors are rare and account for less than 5% of all cases of ovarian cancer,[1] but there are more important clinical facts regarding malignant tumors than their frequency. First, malignant tumors have a occur predominantly in a younger population, in women in their teens and 20s (approximate median age 18–20years). Malignant tumors are sometimes detected during pregnancy and at an early post-partum stage.[2) 3)] Second, malignant tumors are mostly unilateral and the rate of occurrence of bilateral tumors is approximately 10% for dysgerminoma. If detected at an early stage and treated appropriately, malignant tumors can be cured. In young patients, conservative surgery is performed as a standard and there has been a rapid improvement in prognosis by performing concomitant chemotherapy after the initial surgery. However, it is important to start early treatment after early diagnosis, because the progression of this type of tumor is fast.

The most frequent dysgerminoma is equivalent to seminoma in males and is sensitive to radiation. The immaturity of teratoma, including immature nerve tissues, is classified according to the grading system proposed by Thurlbeck and Scully and revised by Norris and the risk of recurrence correlates with grade.[4)] According to the report of Norris *et al.*, the recurrence rate for dysgerminoma is 18% for grade 1, 37% for grade 2, and 70% for grade 3.[5)] Other tumors, such as yolk sac tumor, embryonal carcinoma, and choriocarcinoma, are even more rare, but they have a high degree of malignancy. In many cases, multiple histological types are mixed. It has been reported that the tumor diameter and histological type are important prognostic factors in these mixed germ cell tumors. An accurate histological diagnosis must be made from a sufficient number of histological tissue sections.[5) 6)] The prognosis is poor for large tumors in which more than one-third of the tumor composition is yolk sac tumor and choriocarcinoma, or grade 3 immature teratoma. Conversely, if the diameter of the tumor is < 10 cm, then the prognosis is considered to be favorable, regardless of tumor composition.[6)]

A typical initial clinical symptom is a palpable intrapelvic or abdominal mass with frequent abdominal pain. Approximately 10% of yolk sac tumors and mixed germ cell tumors have acute abdominal symptoms owing to capsular rupture, hemorrhage, or adnexal torsion. These symptoms may be misdiagnosed as being caused by other acute conditions, such as appendicitis, and, in some cases, during surgery for the misdiagnosed condition, a correct diagnosis is made.[7)]

With regard to tumor markers, α-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) are characteristically high in these types of tumors. Levels of AFP are characteristically high in yolk sac tumors and the increase is also seen in immature teratoma and embryonal carcinoma. Levels of hCG are characteristically high in choriocarcinoma and lactate dehydrogenase is frequently increased in dysgerminoma, although it is not specific for this type of tumor. However, it is important that AFP be at normal levels when a diagnosis is made. The continuation of positive AFP and hCG after surgery reflects the presence of residual tumor. Because the changes in these tumor markers correlate with the state of the disease, they become important indices for the therapeutic effects of treatment and for

follow-up examinations.

Determination of clinical staging is as for epithelial ovarian cancer. Retroperitoneal lymph nodes and peritoneal areas are the main sites of dissemination in cases where the cancer has progressed beyond the ovary.

Because this is a rare cancer, it is impossible to perform a randomized controlled study. Therefore, management based on a high evidence level cannot be established. For this reason, present standard management is based on a qualitatively evaluated evidence level over III and a recommendation level A or B from research paper reviews.

Table 15 Histological Classification of Germ Cell Tumors

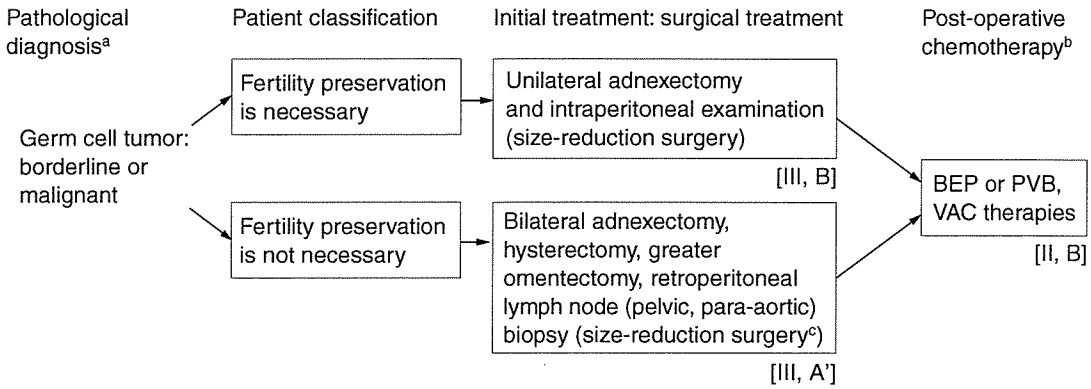
1. Dysgerminoma
2. Yolk sac tumor/endodermal sinus tumor
3. Embryonal carcinoma
4. Polyembryoma
5. Choriocarcinoma
6. Teratoma
a. Mature teratoma
b. Immature teratoma (Grade 1–3)
c. Monodermal and highly specialized teratoma
7. Mixed germ cell tumor

Table 16 Clinical Pathological Classification of Germ Cell Tumors

Benign tumors	Borderline tumors	Malignant tumors
Mature cystic teratoma	Immature teratoma (G1, G2)	Dysgerminoma
Mature solid teratoma	Carcinoid	Yolk sac tumor
Struma ovarii	Stromal carcinoid	Embryonal carcinoma
		Polyembryoma
		Choriocarcinoma
		Mature cystic teratoma with malignant transformation
		Immature teratoma (G3)

II Treatment of Germ Cell Tumors: Flowchart and Explanations

A. Treatment Flowchart



BEP, bleomycin + etoposide + cisplatin; PVB, cisplatin + visblastine + bleomycin; VAC, vincristine + actinomycin D + cyclophosphamide.

B. Explanation of Flowchart

a. Tumor marker (AFP, hCG, and LDH) measurements are necessary.

b. Can be omitted for immature teratoma (grade 1) stage I and dysgerminoma stage Ia.

c. The correlation between residual tumor diameter and prognosis is not clearly known.

Ⅲ Surgical Treatment

A. Initial Surgical Treatment

1. For cases in which fertility preservation is necessary, unilateral salpingo-oophorectmy is performed [**III, B**].
2. For cases in which fertility preservation is not necessary, hysterectomy and bilateral salpingo-oophorectmy are performed [**III, A'**].

Remarks

1. Determination of stage is as for epithelial ovarian cancer.
2. Evaluation of lymph nodes is as for epithelial ovarian cancer. However, because complete lymph node dissection is not necessary, the procedure is limited to biopsy and sampling. Greater omentectomy is also performed, but is limited to partial resection or biopsy.
3. Unnecessary biopsy of the contralateral ovary should be avoided.
4. It is necessary to perform a rapid intra-operative pathological examination as a standard. However, this has limited diagnostic accuracy and, in order to prevent excessive surgery, the possibility of reoperation should be included in the thorough informed consent obtained prior to surgery.
5. If the uterus is preserved even with bilateral adnexectomy, future conception is possible by egg donation, *in vitro* fertilization, and embryo transfer. However, this procedure is not a recognized practice in Japan.

Additional Statements:

Surgery to preserve organ function is not considered to affect the prognosis.[5)~11)] Surgery to preserve ovarian function and fertility should be actively selected for young patients.

(1) Stages I and II.

Unilateral salpingo-oophorectmy is performed for stage Ia dysgerminoma and stage I, grade 1 immature teratoma.[12)] If no abnormality is detected by visual inspection, unnecessary biopsy should be avoided to prevent possible infertility due to postoperative adhesion and ovarian dysfunction.[8) 12)] For stage I of all other histological types (including cases with incomplete staging) and all stage II cases, hysterectomy and bilateral adnexectomy are normally performed. However, if fertility preservation is necessary, surgery is limited to unilateral salpingo-oophorectmy.

(2) Stages III and IV.

Hysterectomy, bilateral salpingo-oophorectmy, and resection of metastatic lesions are standard surgical procedures. However, for cases in which fertility preservation is required, the surgery is limited to unilateral salpingo-oophorectmy.[8) 11)~13)] It is necessary to start postoperative chemotherapy early and to avoid invasive procedures, such as systematic lymph node dissections, ureterectomy, and intestinal resection.[12)]

B. Second-Look Operation

The SLO is not performed as a standard procedure **[III, B]**.

Remarks

Independent of the stage, the usefulness of SLO is not recognized.[12) 14)]

There are different opinions regarding the significance of secondary debulking surgery for recurrent and intractable advanced cases.[14) 15)]

Ⅳ Chemotherapy

A. Initial Chemotherapy

1. BEP therapy (bleomycin + etoposide + cisplatin) is the standard treatment **[II, B]**.
2. Cisplatin is used as the platinum agent **[II, B]**.
3. There is no established consensus regarding the number of cycles of administration. Generally, if the tumor marker result is negative, three cycles are administered for cases with complete resection; an additional one to two cycles can be given for incomplete resection after negative tumor marker results **[IV, E]**.

Remarks

1. Initial chemotherapy can be omitted for dysgerminoma stage Ia and immature teratoma (grade 1) stage I.
2. It is necessary to modify the doses and number of cycles of bleomycin to prevent lung damage.
3. Radiation therapy is limited to cases of dysgerminoma in which chemotherapy cannot be performed.

Additional Statements:

Changes in chemotherapy (Table 17).

In the early 1970s, the effectiveness of VAC therapy (vincristine + actinomycin D + cyclophosphamide) was demonstrated in the postoperative chemotherapy of germ cell tumor.[15)~20)] Since then, PVB therapy (cisplatin + visblastine + bleomycin), used for testicular tumors, has become the standard treatment.[21)~24)] However, BEP therapy, in which vinblastine is replaced by etoposide, became the most common standard regimen owing to its favorable results in terms of DFS rate and peripheral neuropathy.[25)~28)] The positive progression of chemotherapy for this tumor is due largely to good therapeutic results for testicular germ cell tumors, which occur approximately 10 times more frequently than their ovarian counterparts. According to the results of randomized, controlled studies of testicular germ cell tumors, BEP has favorable results over PVB[25)] or EP.[29)] Although there was no difference in efficacy rate between concomitant cisplatin and concomitant carboplatin therapies in a comparative study, the DFS rate of the group receiving concomitant cisplatin was better. Therefore, the standard platinum agent for germ cell tumors is cisplatin, which is different from that for epithelial ovarian cancer.[30)]

Table 17 Changes in Chemotherapy for Germ Cell Tumors

Reference	Year reported	Subjects	No. cases	Regimen	Results
Slayton[16]	1978	Non-dysgerminoma (advanced and recurrent)	16	VAC	Efficacy rate 50%
Gershenson[17]	1983	Endodermal sinus tumor	22	VAC	Efficacy rate 73%
Slayton[18]	1985	Germ cell tumor (with residual tumor)	22	VAC	Recurrence rate 68%
Gershenson[19]	1985	Non-dysgerminoma	80	VAC	Efficacy rate 70%; stage I 86%, stage II 57%, stage III 50%, and stage IV 0%
Gershenson[20]	1986	Immature teratoma	21	VAC	Efficacy rate 86%
Einhorn[21]	1977	Disseminated testicular germ cell tumor	50	PVB	Efficacy rate 100%
Taylor[22]	1985	Germ cell tumor (including mixed type)	14	PVB	Efficacy rate 100%
Williams[23]	1989	Non-dysgerminoma (with residual tumor)	35	PVB (+ VAC/EP)	Efficacy rate 74%
Kumar[24]	1993	Germ cell tumor (advanced and recurrent)	17	PVB	Efficacy rate 70.5%
Williams[25]	1987	Disseminated testicular germ cell tumor	261	PVB vs. BEP	BEP has low toxicity; DFS rate is favorable (61% vs. 77%)
Gershenson[26]	1990	Germ cell tumor	26	BEP	DFS rate 96%
Williams[27]	1991	Dysgerminoma	20	PVB/BEP (+ VAC)	Efficacy rate 91%
Williams[28]	1994	Germ cell tumor	93	BEP	DFS rate 98%
Wit[29]	1997	Testicular non-seminoma	395	EP vs. BEP	Efficacy rate 87% vs. 95%

BEP, bleomycin + etoposide + cisplatin; PVB, cisplatin + visblastine + bleomycin; VAC, vincristine + actinomycin D + cyclophosphamide; EP, etoposide + cisplatin; DFS, disease-free survival.

B. Chemotherapy for Recurrent Cases

The selection of chemotherapy is the concomitant administration of cisplatin with two other agents (ifosfamide, etoposide, paclitaxel, or vinblastine), and high-dose chemotherapy with bone marrow transplant or PBSCT **[III, C]**.

Remarks

Some studies have examined recurrent cases of germ cell tumors that have recurred after initial treatment. Most of these cases started as primary testicular tumors, which were treated by VeIP therapy or VIP therapy (see Table 18) and cytoreductive surgery. The results showed a 20%–30% increase in the long-term DFS rate.[31) 32)] Other studies have reported a 20%–50% increase in the long-term DFS rate achieved in cases where carboplatin, etoposide, cyclophosphamide, and/or ifosphamide were used in high-dose chemotherapy with bone marrow transplant or PBSCT.[33)~35)]

For recurrence after 6 weeks following the completion of initial chemotherapy (sensitive tumor), additional cisplatin-based chemotherapy, VeIP therapy, is recommended.[8)] High-dose therapy is one of the treatment choices for cases in which chemotherapy is ineffective or recurrence (resistant tumor) is seen within 6 weeks of the start of chemotherapy. However, the efficacy rate of high-dose therapy is low.[8)] In recent years, first-line or second-line salvage chemotherapy using paclitaxel has been performed, and the effectiveness of TIP therapy has been reported.[36)] Studies with TIP + high-dose chemotherapy (carboplatin and etoposide) are also being conducted.[37)]

The chemotherapies are summarized in Table 18.

Table 18 Chemotherapies of Germ Cell Tumors (Including Recurrent Cases)

Regimen/agents	Dose	Administration schedule
BEP therapy		
Bleomycin	30 mg/body	i.v., Days 2, 9, 16
Etoposide	100 mg/m^2	i.v., Days 1–5
Cisplatin	20 mg/m^2/normal saline solution 500 mL	i.v., Days 1–5 (drip infusion)
		Every 3 weeks
VAC therapy		
Subjects ≥ 14 years of age*		
Vincristine	1.5 mg/m^2 (maximum 2.0 mg)	i.v., weekly, 8–12 weeks
Actinomycin D	300 μg/m^2	i.v., Days 1–5
Cyclophosphamide	150 mg/m^2	i.v., Days 1–5
		Every 4 weeks
Subjects ≤ 13 years of age*		
Vincristine	2.0 mg/m^2	i.v., weekly, 8–12 weeks
Actinomycin D	400 μg/m^2	i.v., Days 1–5
		Every 4 weeks
PVB therapy		
Cisplatin	20 mg/m^2/normal saline solution 500 mL	i.v., Days 1–5 (drip infusion)
Vinblastine	0.15 mg/kg	
Bleomycin	20 mg/m^2	i.v., Days 1–2
		i.v., Days 2, 9, 16
		Every 3 weeks
VIP therapy		
Etoposide	75 mg/m^2	i.v., Days 1–5 (drip infusion)
Ifosfamide	1.2 g/m^2	i.v., Days 1–5
Cisplatin	20 mg/m^2/normal saline solution 500 mL	i.v., Days 1–5 (drip infusion)
		Every 3 weeks
VeIP therapy		
Vinblastine	0.11 mg/kg	i.v., Days 1–2
Ifosfamide	1.2 g/m^2	i.v., Days 1–5
Cisplatin	20 mg/m^2/normal saline solution 500 mL	i.v., Days 1–5 (drip infusion)
		Every 3 weeks
TIP therapy		
Paclitaxel	175–250 mg/m^2	i.v., Day 1 (drip infusion)
Ifosfamide	1.2 g/m^2	i.v., Days 2–6
Cisplatin	20 mg/m^2/normal saline solution 500 mL	i.v., Days 2–5 (drip infusion)
		Every 3 weeks

*Note, these doses are from Europe and the US.

C. After-Effects of Chemotherapy

1. Ovarian function and fertility.

A minimal amount of dysfunction is caused by three to four cycles of initial chemotherapy **[III, B]**.

Remarks

Histological findings have shown that many anticancer agents cause ovarian cortical fibrosis, reduction in follicular numbers, and impaired follicular maturity.[38)]

Clinically, cyclophosphamide is known for its high ovarian toxicity. Generally, the important factors affecting ovarian functions are considered to be a patient's age at the start of treatment, the chemotherapeutic agents used, cumulative doses, and the duration of administration. It has been reported that ovarian dysfunction is rare with VAC therapy and cisplatin-containing regimens, such as PVB and BEP therapy, at initial therapy. Reports of cases in which the patients conceived and gave birth to a healthy child post-treatment are not rare.[39)~45)]

2. Secondary cancer

There is an increase in the occurrence rate of acute leukemia and myelodysplasia due to etoposide administration **[III, B]**.

Remarks

There is no report regarding the development of leukemia based experiences in many cases of ovarian germ cell tumor. However, two of 348 testicular germ cell tumor cases, receiving three to four cycles of BEP therapy with 2000 mg/m^2 etoposide as initial chemotherapy, developed leukemia. Conversely, no case of leukemia was reported in 67 cases receiving three cycles of etoposide 1500 mg/m^2. [46)] In another study, four cases developed acute leukemia and one case developed myelodysplasia of 212 cases of testicular germ cell tumor receiving BEP therapy.[47)] There was no report of such complications in 127 cases receiving PVB therapy. Because such effects were not observed in 130 cases receiving less than 2000 mg/m^2 etoposide, 2000 mg/m^2 etoposide is considered to be the threshold value for the onset of secondary cancer.[47)]

Additional Statements:

(1) The risk of the secondary onset of cancer has also been reported for cases of epithelial ovarian cancer following chemotherapy.[48)]

(2) Owing to the progress in assisted reproductive technology, in the future, there will be an increase in the number of cases in which the gametes of patients (sperm or ova) are cryopreserved before the treatment of malignant tumors and conception is attempted post-treatment. As a reference, the anticancer agents that adversely affect the ova and ovarian functions are classified according to the risks they pose in Table 19.

Table 19 Anticancer Agents That Adversely Affect the Ova and Ovarian Functions

Frequency of risk occurrence	Anticancer agents
Common	Cyclophosphamide
Possible	Cisplatin Carboplatin Vinblastine Etoposide Actinomycin D
Rare	Doxorubicin Vincristine Methotrexate 5-Fluorouracil Bleomycin
No data	Paclitaxel Docetaxel Ifosfamide Gemcitabine

Data taken from Perry.[x]

Chapter 4■Appendix

Ⅰ Abbreviations

AGO	Arbeitsgemeinschaft Gynaekologische Onkologie
AGO-GINECO OVAR7	Arbeitsgemeinschaft Gynakologische Onkologie-Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens
AUC	area under the concentration-time curve
CAP	cyclophosphamide, doxorubicin (adriamycin) and cisplatin
cCR	clinical complete response
CJ	cyclophosphamide and JM-8 (carboplatin)
CP	cyclophosphamide and cisplatin
CR	complete response
CSF	colony stimulating factor
CT	computed tomography
DFI	disease-free interval
DJ	docetaxel and JM-8 (carboplatin)
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization Research of Treatment of Cancer
FIGO	International Federation of Gynecology and Obstetrics
FN	febrile neutropenia
Ga scintigram	gallium scintigram
G-CSF	granulocyte-colony stimulating factor
GFR	glomerular filtration rate
GINECO	Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens
GOG	Gynecologic Oncology Group
GONO	Gruppo Oncologico Nord-Ouest
HSR	hypersensitive reaction
ICON	International Collaborative Ovarian Neoplasm Study
IDS	interval debulking surgery
ip	intraperitoneal
IRB	Institutional Review Board
iv	intravenous
IVP	intravenous pyelography
JP	JM-8 (carboplatin) and cisplatin
M-CSF	macrophage-colony stimulating factor
MRI	magnetic resonance imaging
MS	median survival
MST	median survival time
NAC	neo-adjuvant chemotherapy
NCCN	National Comprehensive Cancer Network

NIH	National Institutes of Health
NS	not significant
OS	overall survival
PALA	para-aortic lymphadenectomy
PBSCT	peripheral blood stem cell transplantation
pCR	pathological complete response
PFI	progression-free interval
PFS	progression-free survival
PLA	pelvic lymphadenectomy
PR	partial response
PS	performance status
PtFI	platinum-free interval
QOL	quality of life
RR	response rate
SCOTROC	Scottish Randomized Trial in Ovarian Cancer
SDS	secondary debulking surgery
SEER	Surveillance, Epidemiology, and End Results (National Cancer Institute)
SLO	second look operation
SLO/SDS	second look operation/secondary debulking surgery
SWOG	Southwest Oncology Group
TJ	taxol (paclitaxel) and JM-8 (carbopaltin)
TP	taxol (paclitaxel) and cisplatin
WHO	World Health Organization
51Cr EDTA	51Cr ethylenediaminetetraacetic acid
95%CI	95% confidential interval

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Chapter 2: Epithelial Ovarian Tumors

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