
بسم الله الرحمن الرحیم

Ovarian Tumors in Adolescene

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Ovarian germ cell tumors

Derived from primordial germ cells of the ovary They may be benign or malignant. These neoplasms comprise approximately 20 to 25 percent of ovarian neoplasms overall, but account for only an approximate 5 percent of all malignant ovarian neoplasms .

OGCTs arise primarily in young women between 10 and 30 years of age and represent 70 percent of ovarian neoplasms in this age group

Differentiation

- OGCTs can be broadly divided into those that di∫erentiate toward embryo-like neoplasms (teratomas and their subtypes and dysgerminomas)
- and those that di∫erentiate primarily toward extraembryonic fetal-derived (placenta-like) cell populations or a mixture of both.

Teratoma

- Benign cystic mature teratomas (dermoid cysts) are the most common OGCTs. Some malignant OGCTs develop when components of dermoid cysts develop into a somatic malignant neoplasm (termed mature cystic teratoma with malignant degeneration) **Immature teratomas**
- **Dysgerminomas** – These are the female version of the male seminoma and are essentially comprised of immature germ cells.
- **Yolk sac tumors** – These are carcinomas (epithelial neoplasms) that di∫erentiate toward yolk sac/primitive placenta forms.
- **Mixed germ cell tumors** – These are typically combinations of a teratoma with yolk sac, dysgerminoma, and/or embryonal carcinoma.
- Rare OGCTs – Pure embryonal carcinomas, nongestational choriocarcinomas, and pure polyembryoma.

distribution

- Among malignant OGCTs, dysgerminoma, immature teratoma, yolk sac tumors, and mixed germ cell tumors account for 90 percent of cases
  Pure embryonal carcinomas and nongestational choriocarcinomas are rare, and pure polyembryomas are very rare.
  A study of ɹndings from a United States national cancer database from 1973 to 2002
- The distribution by histology was:
  - pure dysgerminomas (33 percent);
  - teratomas, immature plus mature with malignant transformation (39 percent);
  - nondysgerminoma or mixed cell types

Growth and Bilaterality

- OGCTs grow rapidly, unlike the more common epithelial ovarian neoplasms, yet most patients present with stage IA disease (limited to one ovary).
- Evidence of bilateral ovarian involvement suggests the presence of a tumor with a propensity for involvement of the contralateral ovary, including benign cystic teratoma, dysgerminoma, or a tumor with components of **dysgerminoma** (mixed germ cell tumor). These conditions are bilateral in 10 to 12 percent of cases, while the majority of other histologies present as unilateral

Clinical manifestations

Clinical manifestations overview

- ● **Abdominal enlargement** – From the mass itself, ascites, or both
  ● **Abdominal pain** – From rupture or torsion
  ● Precocious puberty, abnormal vaginal bleeding – Presumably from hCG production
  ● Symptoms of pregnancy – From hCG production

Diagnosis overview

Diagnosis overview
The diagnosis is **made by histology** at time of surgical excision.

The diagnosis is **strongly suggested preoperatively** by the presence of an
adnexal mass on pelvic imaging and an elevated level of an associated tumor marker (eg, hCG, AFP).
For **benign cystic mature teratomas**, the diagnosis can be made with reasonable concordence using pelvic ultrasonography; however, removal of
the cyst is still advised.

Tumor markers

- **hCG** – Embryonal cell carcinomas and ovarian choriocarcinomas, mixed germ cell tumors, and some dysgerminomas.
  AFP – Yolk sac tumors, embryonal cell carcinomas and polyembryoma carcinomas, mixed germ cell tumors, and some immature teratomas
  most dysgerminomas are associated with a normal AFP.

  - Lactate dehydrogenase (LDH) – Dysgerminomas.

TERATOMAS

- Teratomas are the most common type of germ cell tumor. Most, but not all, teratomas are benign. The designation teratoma refers to a neoplasm that di∫erentiates toward somatic-type cell populations (typically including cell populations that would normally derive from ectoderm, endoderm, and mesoderm) that can be typical of either adult or embryonic development. The component tissues in a teratoma range from immature to well di∫erentiated and are foreign to the anatomic site in which they are found. Teratomas are divided into four categories: mature (cystic or solid, benign), immature (malignant), malignant due to a component of another somatic malignant neoplasm, and monodermal or highly specialized.

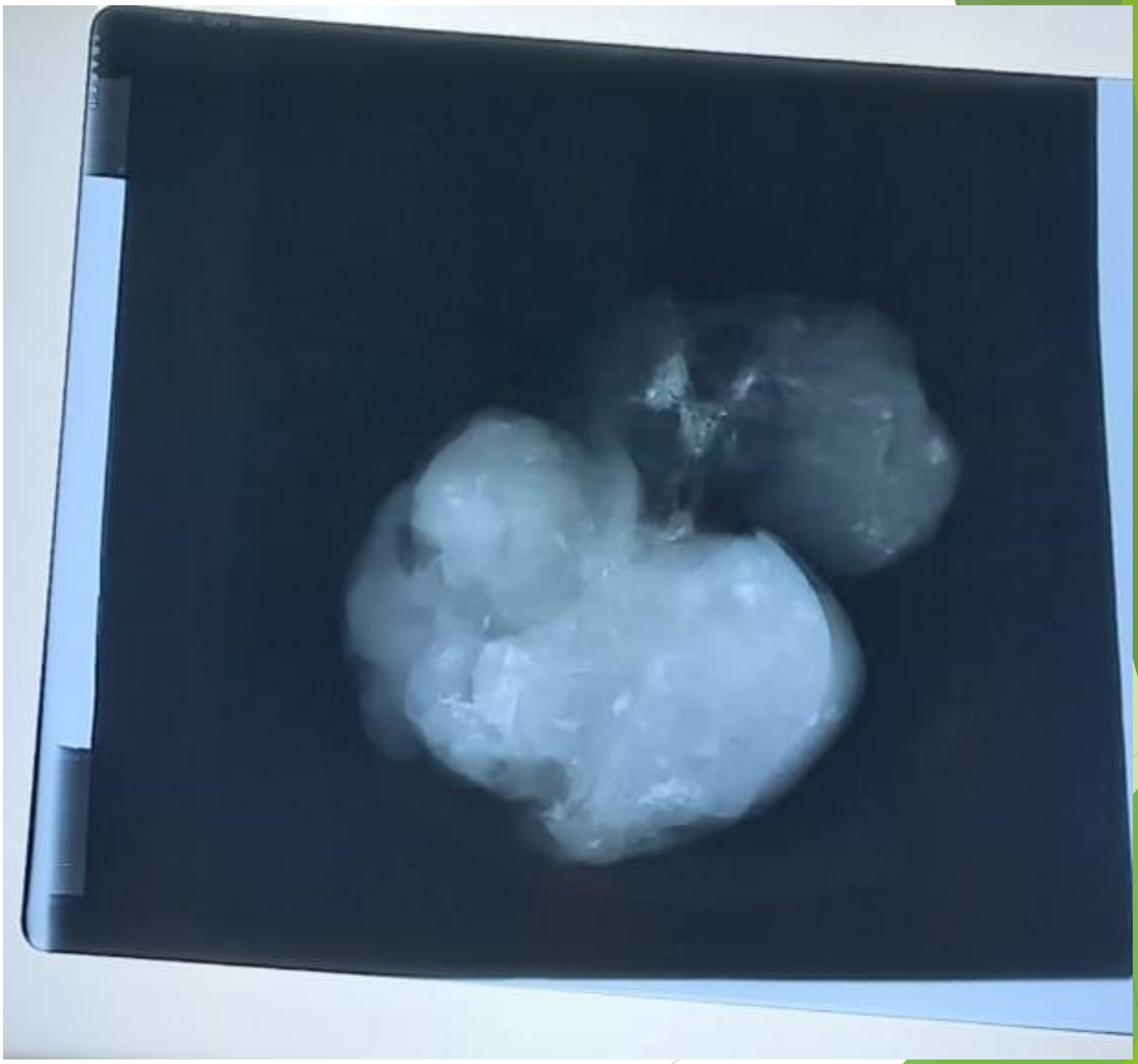
- Most teratomas are cystic and composed of mature di∫erentiated elements (mature); they are better known as dermoid cysts. The mature cystic teratoma accounts for more than 95 percent of all ovarian teratomas and is almost invariably benign .Dermoid cysts are the most common ovarian tumor in women in the second and third decade of life. In rare instances, a teratoma is solid but is composed entirely of benign-appearing heterogeneous collections of tissue and organized structures derived from all three cell layers. Most mature solid teratomas are unilateral and benign, although peritoneal implants have been described.
  Grossly, it may be di[cult/impossible to di∫erentiate these neoplasms from malignant solid immature teratomas, which are almost always solid,
  and they therefore may require sampling from multiple sites (see 'Immature teratoma' below). Management is as described above for mature
  cystic teratomas.

Treatment

- Ovarian cystectomy is suggested in order to make a definitive diagnosis, preserve ovarian tissue, and avoid potential problems such as torsion, rupture, or development of malignant components. For women who have completed childbearing, salpingo-oophorectomy is also acceptable treatment.
- Benign cystic teratomas do not recur if surgically resected. Dermoid cysts may be removed via either laparoscopy or laparotomy. With either approach, the abdomen should be copiously irrigated to avoid a chemical peritonitis from spillage of the sebaceous cyst fluid.

Case

- 19y girl ,pain, huge mass



توصیف ماکروسکوپی

نمونه ارسالی شامل شش ظرف می باشد .

ظرف اول با برچسب توده تخمدان راست شامل یک قطعه به ابعاد 18*17*9 سانتی متر ، سطح برش Solid cystic بوده . مناطق متعدد نکروز و Calcification و تعدادی ساقه مو مشاهده شد .

ظرف دوم با برچسب تخمدان و لوله راست شامل یک قطعه ، باقیمانده تخمدان راست ، به ابعاد 6.5*4.5*3 سانتی متر ، متصل به آن لوله به طول 7 سانتی متر و قطر 0.6 سانتی متر مشاهده شد .

ظرف سوم با برچسب حاشیه کیست تخمدان راست شامل 3 قطعه مجموعا به ابعاد 5*4*1.2 سانتی متر می باشد .

ظرف چهارم با برچسب اومنتوم ، شامل قسمتی از اومنتوم به ابعاد 26*6*1.5 سانتی متر می باشد .

ظرف پنجم با برچسب عدد لنفاوی ایلیاک راست شامل چند قطعه مجموعا به ابعاد 3*2*1 سانتی متر می باشد . در برش تعداد 6 عدد غده لنفاوی مشاهده شد.

ظرف ششم با برچسب لنف نود پاراآئورت شامل یک قطعه به ابعاد 2.5*1*0.6 سانتی متر، حاوی 1 عدد لنف نود ، به قطر 1.3 سانتیمتر می باشد .

توصیف میکروسکوپی :

1- توده تخمدان راست : در بررسی میکروسکوپی مقاطع متعدد تهیه شده از توده تخمدان ، ساختمان های mature از هر سه رده اکتودرم ، مزودرم و اندو درم در گستر توده مشاهده می شود که حجم عمده ای از توده را تشکیل می دهد . کانون های نورواکتودرمال بصورت توبول های عصبی مفروش از اپی تلیوم با نمای pseudostratified و با هسته های هیپر کروم مشهود است که با توجه به تعداد این کانون ها در گستر بافت در نمونه های frozen section و همچنین اسلایدهای permanent نمونه بیمار Grade I مطرح می باشد .

2- لوله راست : دارای نمای طبیعی است .

3- حاشیه کیست تخمدان راست : علاوه بر استرومای تخمدانی ، کانون هایی متشکل از نسج گلیال Mature مشاهده میشود. عناصر Imature مشهود نیست .

4- اومنتوم : در مقاطع اومنتوم ، کانون هایی از نسج گلیال mature gliomatosis peritonei در زمینه اومنتوم مشاهده میشود .

5- غدد لنفاوی ایلیاک راست : تعداد 6 عدد غده لنفاوی فاقد گرفتاری است (0/6)

6- غده لنفاوی پاراآئورت : تعداد 1 عدد غده لنفاوی فاقد گرفتاری است (0/1)

در مجموع تعداد 7 عدد غده لنفاوی فاقد گرفتاری است (0/7) .

Malignant transformation

- Malignant transformation occurs in 0.2 to 2 percent of mature cystic teratomas .
- Mature teratomas with malignant transformation comprise 2.9 percent of all malignant OGCTs
- Although any of the components of a mature cystic teratoma may undergo malignant degeneration, squamous cell carcinoma arising from the ectoderm is the most common secondary neoplasm

Risk factors for malignant neoplasm

- Risk factors for malignant neoplasm in a mature cystic teratoma include age over 45 years (mean age, 50 years versus 33 years for benign teratomas), tumor diameter **greater than 10 cm**, rapid growth, and findings on imaging (eg, low-resistance intratumor flow on Doppler)
  Other possible malignant neoplasms include (but are not limited to) basal cell carcinoma, melanoma, adenocarcinoma, sarcoma, and thyroid carcinoma. When malignant transformation has occurred within a teratoma, treatment must be tailored to the transformed histology.

Monodermal Teratomas

- **Monodermal highly specialized teratomas**
  The specialized or monodermal teratomas are a rare and remarkable subset of teratomas that consist of a predominant mature histologic cell type.
- The most common of these are struma ovarii and carcinoid (a well-di∫erentiated neuroendocrine neoplasm).
- They are usually unilateral, although a contralateral teratoma may be present.

Immature teratoma

- They comprise less than 1 percent of ovarian teratomas and are most common in the first two decades of life. They comprise 35.6 percent of all malignant OGCTs

DYSGERMINOMA

- Although dysgerminomas are relatively uncommon among all ovarian neoplasms (accounting for only an approximate 2 percent), they account for 32.8 percent of malignant OGCTs
- The majority of cases (75 percent) arise in adolescents and young adults, one-third of all ovarian malignant neoplasms
- of the more common ovarian malignant neoplasms detected during pregnancy. Nevertheless, dysgerminoma can occur at any age; case reports have described patients with dysgerminoma between 7 months and 70 years of age

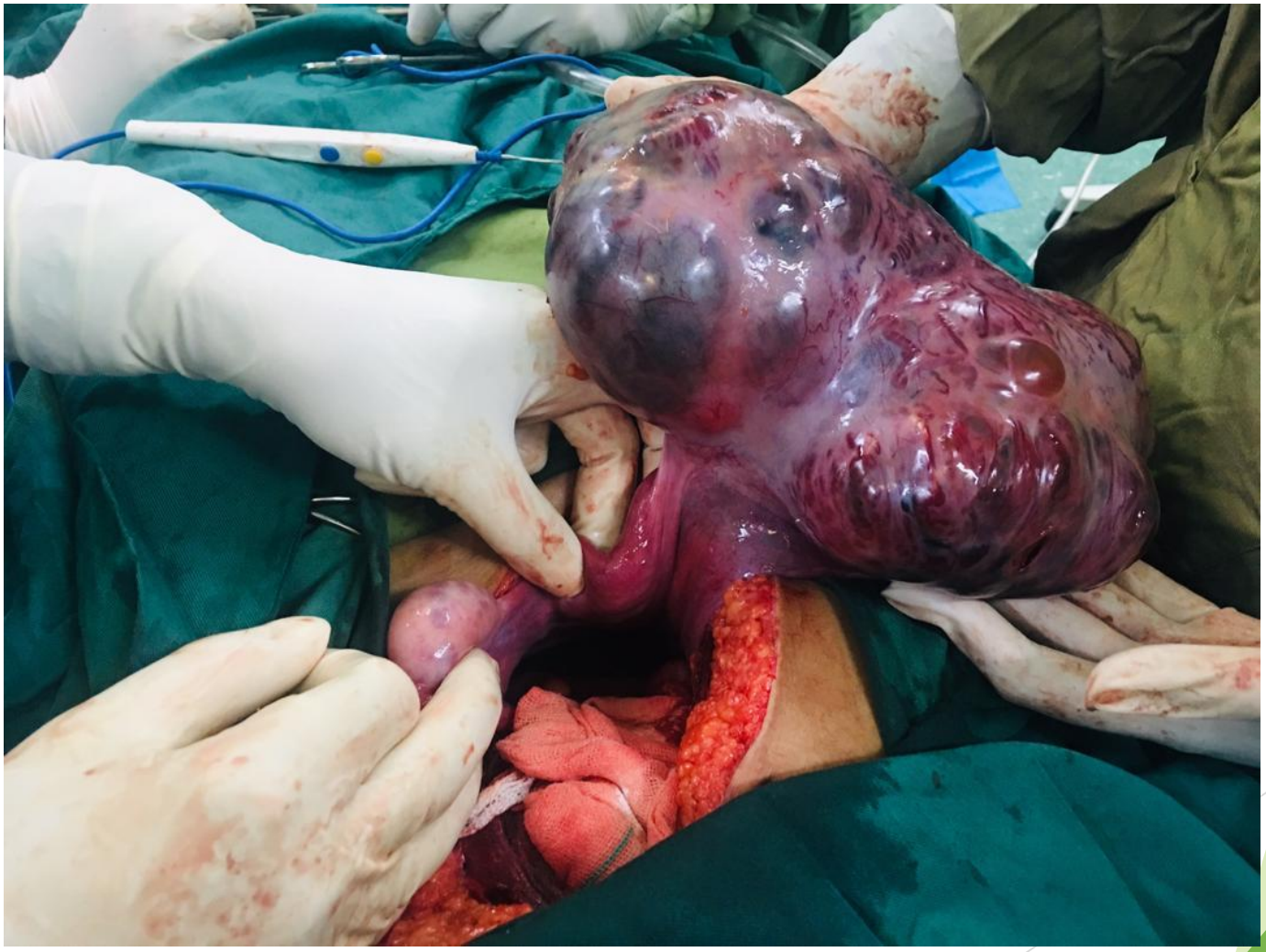
Clinical manifestations

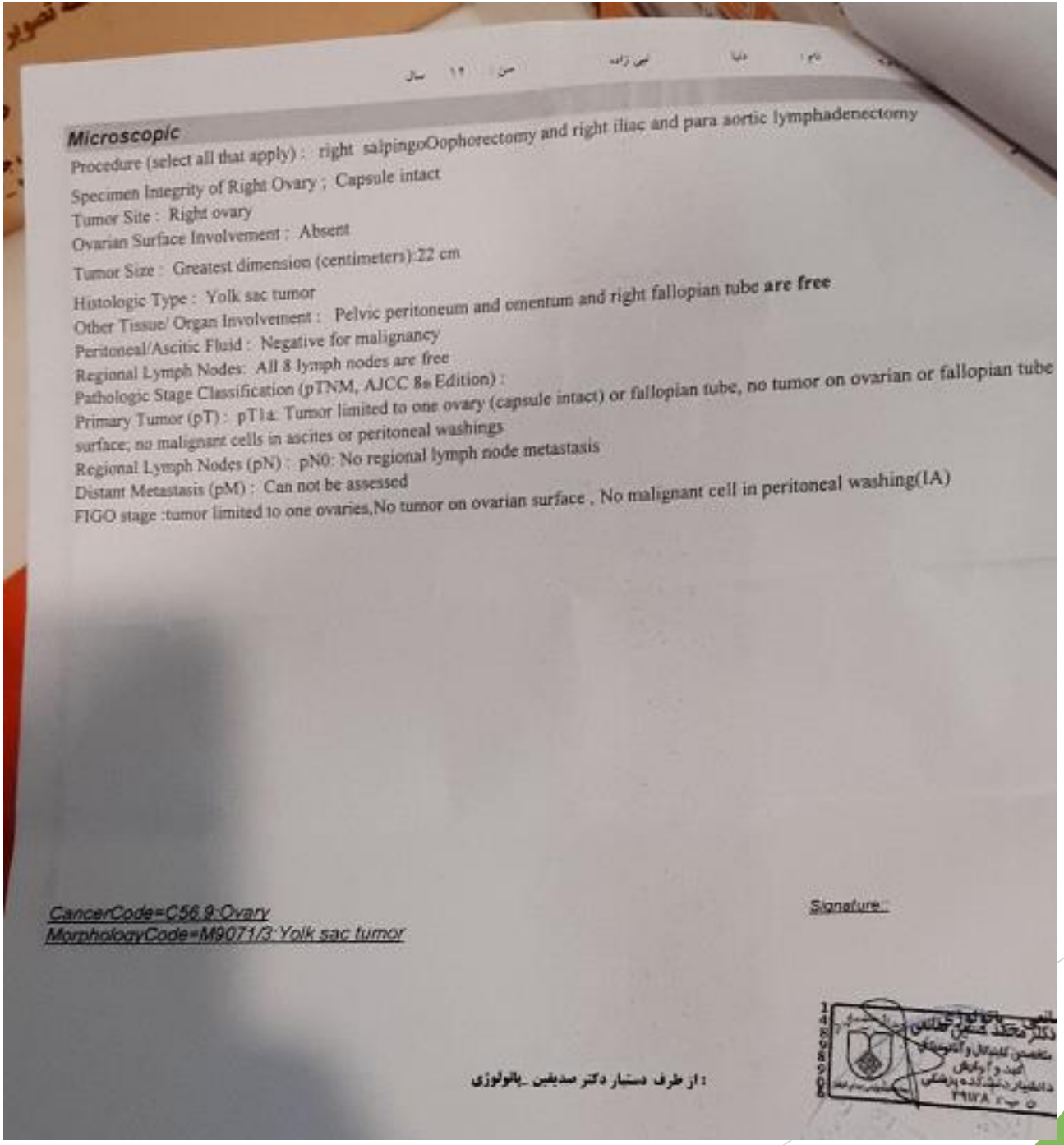
- The growth of dysgerminomas is usually rapid; as a result, patients often present with abdominal enlargement and pain due to rupture with hemoperitoneum or torsion. Menstrual abnormalities may occur
- Dysgerminomas can contain syncytiotrophoblastic giant cells that produce placental alkaline phosphatase, and lactate dehydrogenase (LDH)
- In general, dysgerminomas **do not produce alpha fetoprotein (AFP),**
- Seventy percent of women with dysgerminomas present with stage I disease the contralateral ovary is involved in 10 to 15 percent
- Bilateral ovarian disease is more common with dysgerminoma than with any other malignant OGCT.
  Surgery is performed for de‚nitive diagnosis, staging, and initial treatment.

Case2

- 12y premenarch girl
- Pain
- Huge mass and Alpha feto protein>1000

YOLK SAC TUMOR





Microscopic

Procedure (select all that apply) : right salpingoOophorectomy and right iliac and para aortic lymphadenectomy

Specimen Integrity of Right Ovary ; Capsule intact

Tumor Site : Right ovary

Ovarian Surface Involvement : Absent

Tumor Size : Greatest dimension (centimeters):22 cm

Histologic Type : Yolk sac tumor

Other Tissue/ Organ Involvement : Pelvic peritoneum and cementum and right fallopian tube **are free**

Peritoneal/Ascitic Fluid : Negative for malignancy

Regional Lymph Nodes: All 8 lymph nodes are free

Pathologic Stage Classification (pTNM, AJCC 8th Edition) :

Primary Tumor (pT) : pT1a: Tumor limited to one ovary (capsule intact) or fallopian tube, no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings

Regional Lymph Nodes (pN) : pN0: No regional lymph node metastasis

Distant Metastasis (pM) : Can not be assessed

FIGO stage :tumor limited to one ovaries,No tumor on ovarian surface , No malignant cell in peritoneal washing(IA)

CancerCode=C56.9:Ovary

MorphologyCode=M9071/3:Yolk sac tumor

Signature:

از طرف دستیار دکتر صدیقین ـ پاتولوژی :

YOLK SAC TUMOR

- Yolk sac tumors make up 14 to 20 percent of all malignant OGCTs
- The name was chosen because the tumor structure is similar to that of the endodermal sinuses of the rat yolk sac and is derived from the primitive yolk sac.
- These neoplasms usually occur in young girls and women; the median age at presentation is 23 years and one-third of patients are premenarchal

Clinical manifestations

- Patients with yolk sac tumors often present with abdominal pain and a pelvic mass, similar to dysgerminomas. The **pain may be acute** and is commonly misdiagnosed as appendicitis.
- Tumor growth can be very rapid and aggressive with extensive intraperitoneal dissemination.
- Serum alpha fetoprotein (AFP) levels are elevated in a signiıcant number of patients and, if elevated, are useful for monitoring the response to treatment

MIXED GERM CELL TUMORS

- Mixed germ cell neoplasms consist of two or more admixed types of OGCTs.
- They account for 5.3 percent of all malignant OGCTs (table 2)
- Components of dysgerminoma mixed with a yolk sac tumor are found most commonly.
- In cases in which a dysgerminoma component is present, the contralateral ovary is involved 10 percent of the time.
- The neoplasms may secrete tumor markers, such as lactate dehydrogenase (LDH), alpha fetoprotein (AFP), or human chorionic gonadotropin (hCG), depending upon the type of tissue present.

Treatment of malignant germ cell tumors of the ovary

- SURGICAL STAGING AND PRIMARY CYTOREDUCTION

Surgical management of OGCTs

- both diagnostic and therapeutic.
- In general, the scope of the operative procedure depends upon the surgical findings and the patient's desire to maintain fertility and/or avoid exogenous estrogen supplementation

Areas of controversy

- Areas of controversy include:
  - whether hysterectomy and bilateral salpingo-oophorectomy are required in apparent early-stage disease,
  - the extent of cytoreductive surgery in patients with advanced-stage disease,
  - role of minimally invasive surgery.

Staging procedure

- **Staging system**
  — The staging system used for OGCTs is identical to that used for epithelial ovarian cancer Malignant OGCTs spread via the
  lymphatics, bloodstream, or by peritoneal surface dissemination.

- **Staging procedure**
  — The staging procedure for adult women with OGCTs is the same as for EOC.

  OGCTs often a∫ect children, adolescents, or young women, and fertility-sparing surgery should be
  performed when possible. (See 'Children and adolescents' below and 'Fertility-sparing surgery' below.)

Staging procedure

- Peritoneal cytology is collected after the incision is made.
- Staging also includes omentectomy and cytology of the diaphragm. As with other intra-abdominal gynecologic malignancies
- , complete staging includes biopsy of any areas where metastases are suspected.
- Cytoreduction often is performed when metastases are evident. Laparotomy is generally used.
- **Laparoscopic or robot-assisted approaches are not considered prudent by some experts**, but some surgeons have reported success with these techniques

Lymphadenectomy

- The overall prevalence of lymph node involvement varies by histology
- Dysgerminoma (18 to 28 percent)
  - Mixed germ cell tumors (7 to 16 percent)
  - Malignant teratoma (3 to 8 percent)

Lymphadenectomy

- Lymphadenectomy is generally performed as part of the surgical procedure to guide postoperative treatment recommendations; however, it is associated with some morbidity (eg, increased intraoperative injury, lymphedema).

Initial cytoreduction

- **Initial cytoreduction for advanced disease**
  For patients with advanced tumors, optimal cytoreductive surgery is associated with improved outcomes, particularly for nondysgerminomatous tumors.
- the beneɹts and risks of aggressive cytoreductive maneuvers for metastatic disease must be carefully weighed for these chemotherapy-sensitive tumors.
- If advanced disease is encountered at initial exploration, cytoreductive surgery should be attempted, as is technically feasible and safe.

Initial cytoreduction

- Due to the rarity of malignant OGCTs, the benefit of cytoreductive surgery is less well-established than with EOC.
- surgical debulking of large tumor masses plays a central role in the upfront treatment of OGCTs. Despite the sensitivity of OGCTs to platinum-based chemotherapy, **tumor volume is one of the most important prognostic factors for outcome.**
-

ADJUVANT TREATMENT

- Bleomycin, etoposide, and cisplatin (BEP) (table 5)
  ● Etoposide and carboplatin (see 'Substitution of cisplatin with carboplatin' below)
  Etoposide and cisplatin (EP). While this regimen has very limited use given preference for BEP, it is an appropriate option for patients who
  cannot tolerate bleomycin. Based on data from the treatment of testicular GCTs, EP and BEP are likely to have equivalent activity

ADJUVANT TREATMENT

- Although there are no prospective data to inform the optimal number of cycles, three cycles of EP are usually administered for patients
  Although there are only limited data, carboplatin may be a reasonable alternative for women who cannot tolerate cisplatin for whatever reason.
  deemed to be at a lower risk of recurrence
-

ADJUVANT TREATMENT

- **Nondysgerminomas -** — Although the data are limited, adjuvant BEP (table 5) for three cycles appears to prevent recurrences, especially in well-staged patients. This was shown in a single-arm study conducted by the Gynecologic Oncology Group (GOG) where 93 women with stage I, II, or III nondysgerminomatous OGCTs were treated with three courses of BEP [15]. With a range of follow-up between 4 and 90 months, 91 were alive and free of recurrence. However, two patients developed a treatment-related hematologic secondary malignancy.

ADJUVANT TREATMENT

- **Dysgerminomas -** — As in the treatment of nondysgerminoma, the regimen of choice is BEP. The optimal number of cycles has not been established in randomized trials. In our practice, we administer three courses of adjuvant therapy for completely resected stage I disease and four courses for those with more advanced-stage disease. In one representative series of 26 patients with pure ovarian dysgerminoma (54 percent stage IIIC or IV (table 1)), 25 (96 percent) remained continuously disease-free following at least three cycles of BEP chemotherapy

Surveillance as an alternative option

- **Surveillance as an alternative option**
  — Although surveillance following primary surgery cannot be routinely recommended for adult patients with a malignant OGCT, there are some data that surveillance might be appropriate, especially for those patients with particular subtypes of stage IA nondysgerminoma (eg, yolk sac
  tumor, immature teratoma, mixed GCT, embryonal carcinoma) [28-31]. In one study, the outcomes of 31 patients with stage I disease (median age, 22; range 6 to 45 years) who underwent surgery followed by surveillance were reviewed [28]. With a median follow-up of 11.4 years, the
  relapse rate was 23 percent (7 of 31 patients). Of these seven patients, six went into remission with chemotherapy. An international trial of surveillance for children, adolescents, and adults with these stage IA malignant OGCTs is under development, and it is hoped that the results of
  this trial will clarify the role of surveillance

Radiation therapy

- **Radiation therapy**
  — We reserve RT for patients with a dysgerminoma who are not candidates for chemotherapy for whatever reason.
- RT is not e∫ective for nondysgerminomas, which tend to be radioresistant. Although adjuvant RT is e∫ective in the treatment of dysgerminomas it is not utilized due to the availability of chemotherapy because chemotherapy results in less long-term toxicity.

STAGE IV

- **TREATMENT OF DE NOVO STAGE IV DISEASE**
  — Patients who present with de novo stage IV disease should be oſered an attempt at maximal cytoreduction, including resection of metastatic
  disease if applicable. Following surgery, at least four courses of bleomycin, etoposide, and cisplatin (BEP) (table 5) should be given [39]. Of note,
  even for women with incompletely resected disease, long-term survival can be expected in over half of these patients [23,40,41]. For patients
  who are not surgical candidates at the time of presentation, we oſer neoadjuvant chemotherapy followed by interval debulking surgery [13,14].
  There are ongoing trials, principally for patients with high-risk testicular cancer, exploring the eſectiveness of more aggressive therapies,
  including accelerated BEP or a combination of paclitaxel and BEP.

FERTILITY PRESERVATION

- **FERTILITY PRESERVATION**
  — Because most women with OGCTs are young and wish to preserve future childbearing potential, fertility-sparing options should be explored.
  Fertility-sparing surgery
  — Unilateral salpingo-oophorectomy with preservation of a normal-appearing uterus and contralateral ovary is an option for women with clinically apparent early-stage disease. Even after chemotherapy, at least 80 percent of these women will resume normal menstrual function, and
  those who become pregnant appear to have no increase in pregnancy complications [42,43]. (See 'Premature menopause' below and 'Pregnant women' below.)
  The ipsilateral fallopian tube is removed because of the rich lymphovascular connections between the tube and ovary. Oncologic outcomes are
  not compromised by conservative surgery, even in the face of bulky metastatic disease elsewhere

occult contralateral ovarian involvement

- The risk of occult contralateral ovarian involvement appears to be greatest with dysgerminomas, although it is likely no higher than 5 to 10 percent
- For example, in one study of 98 patients with stage IA dysgerminoma, nine developed disease in the contralateral ovary
  These were presumably occult primaries undetected at the time of initial surgery.
- While some surgeons routinely perform a wedge biopsy of a normal-appearing contralateral ovary, this practice is not universally accepted, as these tumors are particularly sensitive to chemotherapy, and
  salvage rates are high.

Unnecessary surgery

- Unnecessary surgery on normal ovaries, even a biopsy, should be avoided because postoperative adhesions are common and can impair fertility.
  If bilateral salpingo-oophorectomy is required, women with a uterus but no ovaries can become pregnant using an egg donor or their own cryopreserved fertilized eggs/ovarian tissue/oocytes. In addition, women with an ovary but no uterus should be counseled about the potential for use of a gestational carrier.

Oocyte cryopreservation

- **Oocyte cryopreservation**
  — The most established method for preservation of child-bearing potential in women at risk of gonadal failure is embryo cryopreservation. For women who do not have a participating male partner and are not interested in using donor sperm, oocyte cryopreservation is also an option. The decision concerning use of assisted reproductive techniques prior to initiation of chemotherapy should be individualized and must be balanced against the delay in starting therapy. This topic is discussed in detail elsewhere.

PROGNOSIS

- **PROGNOSIS**
  Studies have addressed prognostic factors that might permit risk stratification for future treatment assignment in OGCTs [23,51-53]. As an
  example, the importance of stage and tumor markers was addressed in an analysis of 148 women with malignant OGCTs, 113 of whom received
  platinum-based chemotherapy [23]. Five-year survival rates were:

  - Stage IC disease– 100 percent
  - Stage II – 85 percent
  - Stage III – 79 percent
  - Stage IV – 71 percent

POST-TREATMENT SURVEILLANCE

- Tumor markers (alpha fetoprotein [AFP], human chorionic gonadotropin [hCG]) repeated regularly. In our practice, we repeat them every
month for a period of two years and then less frequently over time.
  -
  - Review of symptoms and physical examination every two to four months for the ɹrst two years, followed by annual visits every year.
  - Radiographic imaging every two to four months for the ɹrst two years only in patients whose initial tumor marker levels are not elevated.

Premature menopause

- — Although ovarian dysfunction or premature ovarian failure is a risk of chemotherapy, most women who receive platinum-based therapy for three to four cycles recover normal ovarian function [6,11,12,26,42-46]. For these patients, fertility is often spared. However, premature menopause has been reported in women who previously received chemotherapy as children, adolescents, or young adults [55,56]. As an example, one study reported that the incidence of nonsurgical premature menopause was higher among survivors of childhood cancer than control siblings (8 versus 0.8 percent). These data emphasize the importance of pretreatment counseling and planning to ensure the most appropriate treatment is rendered, taking into account the age of the patient and her desires regarding future fertility. (See "Ovarian failure due to anticancer drugs and radiation" and "Overview of infertility and pregnancy outcome in cancer survivors".)
The impact of platinum-based chemotherapy on adult women's gonadal function was demonstrated in a representative series of 71 patients treated with fertility-sparing surgery and combination chemotherapy (including cisplatin and bleomycin). Of these, 62 (87 percent) resumed normal menstruation, and 24 of these women subsequently had 37 o∫spring [43].

Secondary malignancies

- **Secondary malignancies**
— An important cause of late morbidity and mortality in patients undergoing treatment for germ cell tumors (GCTs) is the development of secondary malignancies, both solid tumors and leukemia. Etoposide in particular has been implicated in the development of treatment-related leukemias. The risk is dose-related. The incidence of leukemia is <0.5 percent in patients receiving a typical three- or four-cycle course of bleomycin, etoposide, and cisplatin (BEP; cumulative etoposide dose <2000 mg/m2) [57] compared with as high as 5 percent (representing a 336-fold increase in the likelihood of leukemia) in those receiving over 2000 mg/m2 [58].
Despite the risk of secondary leukemia, risk-benefit analyses have concluded that etoposide-containing chemotherapy regimens are beneficial in
advanced GCTs; one case of treatment-induced leukemia would be expected for every 20 additionally cured patients who receive BEP as compared with cisplatin, vinblastine, and bleomycin (PVB). The risk-benefit balance for low-risk disease, or for high-dose etoposide in the salvage setting, is less clear.

RELAPSED DISEASE

- Patients who were originally treated with surgery alone and then developed relapsed disease should meet with a gynecologic oncologist for consideration of secondary surgery. Regardless of whether surgery is performed, standard ɹrst-line chemotherapy should be administered. As in the adjuvant setting, the regimen of choice is bleomycin, etoposide, and cisplatin (BEP). (See 'Adjuvant treatment' above.)

RELAPSED DISEASE

- For patients who were previously treated with chemotherapy (as adjuvant therapy or ɹrst-line treatment of stage IV disease) and did not exhibit refractory disease (ie, no evidence of disease progression during or immediately after prior treatment), repeat treatment with a platinum-based regimen is indicated [61].●
For patients who relapse despite ɹrst-line treatment for recurrent disease and those with refractory disease, we utilize the approach to men with relapsed and refractory testicular cancer.

Role of surgery

- — The main utility of surgery for women with recurrent OGCTs is the ability to resect limited metastatic disease, which might alter the subsequent medical treatment. Although only low-quality data are available, they suggest that surgical resection may a∫ord a survival advantage in properly selected patients [63-65]. For example, one single-institution study included 34 women, all of whom progressed after initial chemotherapy and were treated with second-line chemotherapy followed by surgical resection [65]. Compared with women who had residual disease >1 cm, the ɹve-year survival rate was higher among those who were rendered macroscopically disease-free or who had residual tumor ≤1 cm (61 versus 14 percent, respectively). These data suggest that women with recurrent disease may beneɹt from surgical resection, especially if the disease appears to be resectable.

SPECIAL POPULATIONS

- **Children and adolescents**
  — The treatment approach to girls with a germ cell tumor (GCT) di∫ers from that for adult women. However, the optimal approach has not yet
  been characterized, primarily due to the rarity of these cancers. We agree with the position of the Children's Oncology Group Rare Tumors
  Disease Committee that further evidence is needed, which will only come through international collaborations in clinical research [66]. An
  example of how pediatric care di∫ers from management of these tumors in adults is that necessity for and extent of comprehensive surgical
  staging are controversial in children and adolescents, though not in adult women in whom staging is indicated.

Treatment after surgery

- **Treatment after surgery**
  — Although limited data are available, surveillance for girls with stage IA malignant OGCTs appears to be reasonable. Adjuvant chemotherapy is routinely oʃered to patients with higher-stage disease. The exception is for patients with metastatic immature
  teratoma, in whom postoperative chemotherapy has not been shown to decrease relapses, based on a combined data analysis of seven pediatric
  trials including 98 patients, of whom 90 were treated with surgery alone [67]. In general, we advocate for the use of bleomycin, etoposide, and
  cisplatin (BEP) if chemotherapy is indicated. However, limited data suggest that carboplatin can be used instead of cisplatin in an attempt to
  reduce toxicities while preserving eɽcacy

- Malignant ovarian germ cell tumors (OGCTs) include dysgerminomas (analogous to the male testicular seminoma) and nondysgerminomatous tumors. Nondysgerminomatous tumors include immature teratomas, embryonal cell carcinoma, yolk sac tumors, primary ovarian (nongestational) choriocarcinomas, polyembryoma, and mixed germ cell tumors. (See 'Introduction' above.)
- The treatment principles for all types of malignant OGCTs are generally similar and include surgery for diagnosis and staging, cytoreductive surgery if advanced disease is present, and adjuvant chemotherapy in most cases (table 6). (See 'Overview' above.)
- OGCTs occur predominantly in children and young women. For these patients, unilateral salpingo-oophorectomy with preservation of the uterus and the contralateral ovary may be performed if these organs appear normal. Standard surgical staging with total extrafascial hysterectomy and bilateral salpingo-oophorectomy is generally performed on women who have completed childbearing. (See 'Children and adolescents' above and 'Fertility-sparing surgery' above.)
- For most adult women with a newly diagnosed OGCT, we recommend adjuvant chemotherapy (**Grade 1B**). Our regimen of choice is bleomycin, etoposide, and cisplatin (BEP). Women with stage IA or IB dysgerminoma or stage IA, grade 1 immature teratomas have an excellent prognosis following surgical treatment alone, and therefore, we recommend against administering adjuvant chemotherapy (**Grade 1B**). (See 'Adjuvant treatment' above.)
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- All women should be followed by history and physical exam after the completion of treatment for OGCTs. Serum tumor markers should be followed serially as well. In keeping with the guidelines from the Society of Gynecologic Oncologists, we only perform radiographic surveillance within the first two years if tumor markers were not elevated initially. Given the risk for late relapse, dysgerminomas require annual follow-up for at least 10 years. (See 'Post-treatment surveillance' above.)
- For women who relapse and did not receive chemotherapy previously (ie, in the adjuvant setting), we recommend platinum-based chemotherapy (Grade 1A). As in the adjuvant setting, our regimen of choice is BEP. (See 'Relapsed disease' above.)
- The approach to treatment for women with relapsed disease despite prior treatment with chemotherapy is extrapolated from the approach to men with relapsed or refractory testicular germ cell tumors. (See "Diagnosis and treatment of relapsed and refractory testicular germ cell tumors".)
- ● For pediatric and adolescent girls (see 'Children and adolescents' above): We suggest postoperative surveillance for those with International Federation of Gynecology and Obstetrics (FIGO) stage IA and IB OGCTs (Grade 2C)

- With the exception of patients with immature teratomas regardless of grade, we suggest adjuvant chemotherapy for those with more advanced disease (stage IC to IV) (**Grade 2C**). For those with immature teratomas regardless of grade, we suggest observation rather than adjuvant chemotherapy (**Grade 2C**).
- As in adult women, our regimen of choice is BEP. However, carboplatin-based treatment appears to be a reasonable and less toxic regimen for use in this population, especially if there is a contraindication to cisplatin

- Most germ cell ovarian malignancies occur in young women and are limited to one ovary [3]. Maximal surgical cytoreduction is usually undertaken initially. (See "Treatment of malignant germ cell tumors of the ovary" and "Approach to surgery following chemotherapy for advanced testicular germ cell tumors".)
Despite being diagnosed at a relatively early stage, we recommend adjuvant chemotherapy for most women with completely resected malignant
ovarian germ cell tumors **except** those with stage IA dysgerminoma (table 1) or stage I grade one immature teratoma. When indicated, chemotherapy should be delayed at least until completion of the ɹrst trimester of pregnancy [18-20]. The most commonly used regimen is bleomycin, etoposide, and cisplatin (BEP (table 2)). (See "Ovarian germ cell tumors: Pathology, epidemiology, clinical manifestations, and diagnosis" and "Treatment of malignant germ cell tumors of the ovary".)
In other series, use of etoposide during pregnancy has been associated with growth restriction and neonatal bone marrow suppression [5,7]. Etoposide is teratogenic in mice and rats at doses much lower than the human dose and should not be used in the ɹrst trimester. A consensus report suggested paclitaxel-carboplatin or cisplatin-vinblastine-bleomycin as alternatives to BEP in pregnancy

- **Timing of chemotherapy**
  — Given that germ cell neoplasms are exquisitely sensitive to platinum-based chemotherapy, several investigators have published case reports addressing a treatment delay until after the completion of the pregnancy [22-24]. A summary of ɹndings is presented below:

- One case report documents a woman with a yolk sac (endodermal sinus) tumor that was surgically resected at 19 weeks of gestation [22].
  The pregnancy was allowed to continue and BEP was not initiated until after the baby was delivered at 36 weeks. At a follow-up of 27
  months, there was no evidence of recurrence disease.
  ●
  Another report described a patient with a yolk sac tumor resected at 22 weeks of gestation, after which the pregnancy was allowed to
  continue [23]. Unfortunately, at 34 weeks she was found to have tumor regrowth. After secondary debulking and delivery of the infant,
  the mother was successfully treated with BEP and was without evidence of disease 39 months after her last treatment with chemotherapy

- These reports suggest that delaying adjuvant chemotherapy may increase the risk of recurrence, although without an apparent risk to long-term recurrence free survival. Given the low quality of the data, however, a decision on the timing of adjuvant chemotherapy for women with a germ cell tumor should take into account the individual circumstances and preferences of the mother.

Final Message

- Ovarian germ cell tumors,5%of malignant,25% of all ovarian neoplasms
- Young women 10 -30y,70% of ovarian neoplasms in this age group
- Often produce tumor markers
- Most common ovarian germ cell tumor is mature cystic teratoma
- Dysgerminoma is he most common malignant ovarian germ cell tumor, more common bilateral ,less likely produce markers,LDH often elevated