Diagnosis and Management of Nonepithelial Ovarian Cancer

Erin A. Blake, Saketh Guntupalli, and Koji Matsuo

Abstract

Nonepithelial ovarian cancers represent a small fraction of ovarian cancers. Malignancies in this category include sex cord-stromal tumors (SCST) and ovarian malignant germ cell tumors (OMGCT), and each of these classifications encompasses multiple histologic subtypes. The most common SCST include granulosa cell and Sertoli-Leydig cell tumors. Dysgerminomas, yolk sac tumors, and immature teratomas are the most frequently encountered OMGCT. The prognosis for these tumors is good; however, the survival outcome is dependent on factors such as tumor subtype and stage at diagnosis. Most patients with nonepithelial ovarian cancers present with low stage disease due to symptoms that occur early in the disease process. Surgery is the mainstay of treatment for all nonepithelial ovarian cancers. If desired, fertility sparing surgery is typically an appropriate management option for both SCST and OMGCT. Postoperative adjuvant chemotherapy is dependent on disease type and stage; however, due to the exquisite chemosensitivity of malignant germ cell tumors of the ovary, platinum-based combination chemotherapy is used for almost all cases. The most commonly used initial regimen for both SCST and OMGCT is combination of bleomycin, etoposide, and cisplatin. Surveillance for recurrent disease is mandated for all SCST and OMGCT, even those that present in early stages.

Keywords

Nonepithelial ovarian cancer • Sex cord-stromal tumors • Malignant germ cell tumors of the ovary • Granulosa • Sertoli-Leydig • Fibroma-thecoma • Gynandroblastoma • Dysgerminoma • Yolk sac • Teratoma

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D. Shoupe (ed.), *Handbook of Gynecology*,
DOI 10.1007/978-3-319-17798-4_35

1 Introduction

Ovarian cancers are classified by their histological origin, and the majority of ovarian malignancies are of epithelial origin. Primary nonepithelial ovarian cancers most commonly include those originating from germ cells or sex cord-stromal cells, and there are extremely rare instances of alternative histological subtypes such as carcinosarcomas or lipoid cell tumors. Metastases from other primary sites can also be found on the ovaries; the most well-known example of this phenomenon is Krukenberg tumors. Nonepithelial ovarian cancers are relatively rare entities, composing only five to ten percent of all ovarian cancers (Quirk and Natarajan 2005). There are many similarities between different subtypes of nonepithelial ovarian cancer in epidemiologic presentation and treatment pattern; however, each specific type of tumor has individual clinical characteristics that are important to recognize. Nonepithelial ovarian cancers are often caught at an earlier stage than epithelial type because of more noticeable early symptoms; however, overall prognosis remains mainly dependent on histological subtype, tumor grade, and stage at presentation.

2 Sex Cord-Stromal Tumors

2.1 Pathogenesis

Sex cord-stromal tumors (SCSTs) are cancers that originate from the embryonal stromal or mesenchymal elements of the ovary. These matrix cell elements of the ovary are typically capable of producing sex hormones; so, patients with SCST often present with evidence of excessive estrogen or androgen phenotypes. The SCST subtypes consist of granulosa cell tumors, Sertoli-Leydig cell tumors, fibroma-thecoma tumors, steroid cell tumors, sex cord tumor with annular tubules, gynandroblastoma, and otherwise unclassified tumors. Mixed cell type tumors are relatively common. Refer Table 1 for SCST subtype classification. The typical age of presentation varies according to the subtype.

2.2 Granulosa Cell Tumors

Granulosa cell tumors (GCT) are the most common type of SCST, comprising approximately 75% of SCST (Chen et al. 2003). There are two types of granulosa cell tumor: adult type and juvenile type. Demographically, the age at

Table 1 World Health Organization histologic classification for sex cord-stromal tumors

WHO histologic classification	Pathology
Granulosa cell tumor	
Adult	Malignant
Juvenile	Malignant
Sertoli cell tumors	Malignant potential
Sertoli-Leydig cell tumors	
Well differentiated	Malignant potential
Intermediate differentiation	Malignant
Poorly differentiated	Malignant
Heterologous elements	Malignant
Leydig cell tumors	Benign
Stromal-Leydig cell tumors	Benign
SCTAT[a] without Peutz-Jaghers syndrome	Malignant
SCTAT[a] with Peutz-Jaghers syndrome	Benign
Gynandroblastoma	Malignant/malignant potential
Thecoma	
Typical	Benign
Luteinized	Malignant potential
Increased mitotic figures	Malignant potential
Fibroma	
Cellular	Malignant potential
Cellular with increased mitotic figures	Malignant potential
Fibrosarcoma	Malignant
Stromal tumor with minor sex cord elements	Benign
Sclerosing stromal tumor	Benign
Signet ring stromal tumor	Benign
Unclassified	Malignant potential
Steroid cell tumors	Malignant
Unclassified SCST[b]	Malignant potential

[a]Sex cord tumor with annular tubules
[b]Sex cord-stromal tumor

presentation for GCT is bimodal, with over 90% of juvenile type presenting prior to puberty, while the average age of presentation for adult type is 50 years (Schumer and Cannistra 2003).

2.3 Adult Type GCT

The presentation of a patient with adult type granulosa cell tumor often presents with signs of hyperestrogenization including heavy abnormal uterine bleeding or postmenopausal vaginal bleeding. Notably, due to the excess estrogen exposure encountered with these tumors, there is an increased risk of coincident endometrial hyperplasia, endometrial carcinoma, and breast cancer (Colombo et al. 2007). Endometrial adenocarcinoma is diagnosed in approximately 5–10% of patients with adult type GCT (Schumer and Cannistra 2003). Additionally, these tumors sometimes present with symptoms of torsion including acute visceral abdomino-pelvic pain and pressure, nausea, and vomiting. Adult GCT expand rapidly and are often 10–15 cm in diameter at the time of presentation; so, patients can also present with symptoms of mass effect including increasing abdominal girth, early satiety, decreasing appetite, nausea, vomiting, and vague abdominal or pelvic pain. It is not uncommon for women with adult type GCT to present with hemoperitoneum after rupture of one of these large vascular masses.

The most important prognostic factor for adult type GCT is stage at diagnosis. Although adult GCT is considered to be malignant, clinical aggressiveness is not defined by mitotic activity or nuclear atypia (Aboud 1997). The majority, 70–90%, of GCT is unilateral and diagnosed at stage I disease. For FIGO stage I disease, 5-year survival rate is reported to be 75–95%; however, that decreases to 55–75% for stage II disease. Stage III/IV disease has poor 5-year survival rates at 20–50% (Gurumurthy et al. 2014). Long-term recurrence is relatively high for patients with all stages of disease. Approximately 25% of patients experience a recurrence, with 30% recurrences occurring greater than 5 years after treatment and 20% after 10 years (Gurumurthy et al. 2014).

2.4 Juvenile Type GCT

Juvenile granulosa cell tumor also typically presents with the effects of hyperestrogenization. In prepubertal girls, these tumors can present with signs of isosexual precocious pseudopuberty, including premature breast and pubic hair development and other secondary sexual

characteristics. Amenorrhea or menstrual irregularities can present in young women who are closer to the expected chronologic age of puberty. Like adult type GCT, juvenile type can present with mass effect as described above or hemoperitoneum. Additionally, since these tumors potentially present in reproductive age women, they should be considered in the differential diagnosis of an adnexal mass during pregnancy. GCT are especially concerning as rupture during pregnancy can be catastrophic, with one review finding a 10% rate of rupture with resulting hemoperitoneum requiring emergent intervention during pregnancy (Blake et al. 2014).

Prognosis for juvenile type GCT is also dependent on stage at presentation, and these tumors exhibit more aggressiveness and worse outcome if initially diagnosed at an advanced stage. The juvenile form of GCT is also typically diagnosed early, with over 90% of cases being unilateral and stage I disease at diagnosis (Young et al. 1984). Survival has been noted to be approximately 25% for patients diagnosed with stage II–IV disease, and recurrences of juvenile type disease typically occur early, within 3 years or less from treatment (Young et al. 1984).

2.5 Diagnosis of GCT

Diagnosis of both types of GCT is similar. Clinical suspicion might be aroused by presentations as described above, specifically evidence of hyperestrogenization, mass effects, torsion, or more acute presentation of hemoperitoneum and hypotension indicating a surgical emergency. On physical exam, these clinicians will often encounter a palpable mass on bimanual pelvic exam. Other physical exam findings would be contingent on the patient's age at diagnosis, such as breast and pubic hair development in young girls or postmenopausal vaginal bleeding in older women.

Ultrasonography often demonstrates a large adnexal mass with semisolid or echogenic features, sometimes with septations. Additionally, thickened endometrial stripe is a concerning sign in postmenopausal women (Schumer and Cannistra 2003). Cystic adult GCT, a rare variant, can appear sonographically like a benign, simple cyst, thus causing delays in management and diagnosis. Cystic adult GCT are typically thin walled and can be loculated. There is no definitive diagnostic imaging modality for these or any other type of ovarian tumor.

Tumor markers are also not diagnostic but can contribute to clinical suspicion for and subsequent surveillance of GCT. Estradiol has not been found to be a reliable marker of disease progression. Inhibin A and B have been found to be useful markers for both adult and juvenile type disease; however, they are nonspecific and can also be elevated in epithelial ovarian cancers as well as other conditions (Colombo et al. 2007).

Other important diagnostic considerations include performing an endometrial biopsy and performing breast exam and imaging due to potential sequelae from elevated levels of serum estrogen.

Definitive diagnosis requires final pathological analysis. Gross analysis typically yields a large tumor measuring 10–15 cm with dense vascular solid components. Hemorrhage and necrosis are common macroscopic findings. The most characteristic microscopic features are the "coffee bean" nuclei within granulosa cells and the Call-Exner bodies, an eosinic cystic center surrounded by rosettes of cells. Microscopic images of granulosa cell and other ovarian sex cord-stromal tumors can be found in Fig. 1a. Microscopic nodular growth patterns can also be observed in juvenile type GCT (Fig. 1b).

2.6 Genetic Alteration of GCT

Recent advances have allowed for better elucidation of the molecular components of these rare tumors. A missense point mutation in a gene encoding a transcription factor, FOXL2, has been identified in adult granulosa cell tumors, and it is thought that this mutation is likely present

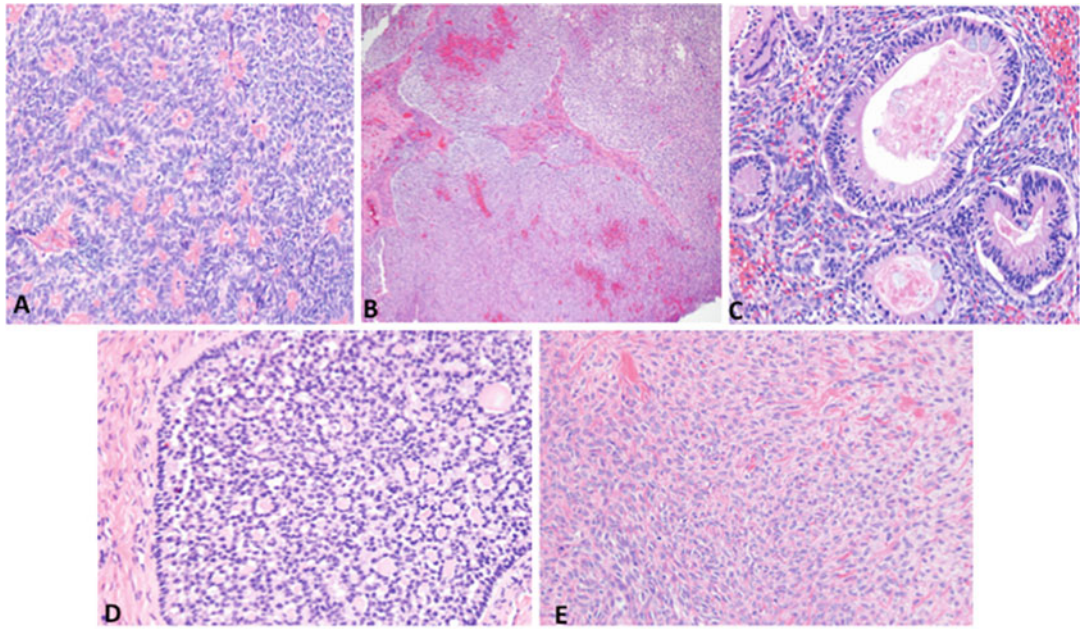

Fig. 1 Microscopic findings in sex cord-stromal tumors of the ovary ((**a**). Adult granulosa cell tumor with Call-Exner bodies (**b**). Juvenile granulose cell tumor with nodular growth (**c**). Sertoli-Leydig cell tumor with heterologous elements (**d**). Sex cord tumor with annular tubules (**e**). Fibrothecoma (Courtesy of Drs. Abby M Richmond and Miriam D Post, Department of Pathology, University of Colorado, Aurora, Colorado))

in all adult granulosa cell tumors (Gershenson 2012).

2.7 Sertoli-Stromal Cell Tumors

Sertoli-stromal cell tumors, or androblastomas, comprise approximately 5–10% of all diagnosed SCSTs. There are several subtypes of tumor that fall into this category, Sertoli cell tumors and Sertoli-Leydig cell tumors, which are then characterized by the degree of tumor differentiation. These tumors typically present in reproductive age women and are almost universally unilateral. Over 90% of Sertoli-stromal cell tumors are stage I at diagnosis (Colombo et al. 2007).

2.8 Sertoli-Leydig Cell Tumors

Sertoli-Leydig cell tumors are typically found in premenopausal women with an average age of presentation of 25. Histologically, they are formed of cells resembling stromal and epithelial testicular cells. They are frequently hormonally active, most commonly producing androgenic sex steroid hormones. Due to this, approximately 75% of patients present with clinical evidence of virilization including temporal balding, hirsuitism, voice changes, and even clitoromegaly in rare cases (Colombo et al. 2007).

There are five histological subtypes of Sertoli-Leydig tumor based on degree of differentiation: well, intermediate, poor, retiform, and heterologous. Sertoli-Leydig cell tumors are most likely to fall into the pathological category of low malignant potential; however, those that are poorly differentiated can demonstrate aggressive behavior. Multiple review articles have examined outcome based on histological subtype. Well-differentiated tumors have uniformly benign behavior, but poorly differentiated tumors have been shown to have malignant characteristics such as metastasis or invasion in up to 60% of

the time (Young 2005; Zaloudek and Norris 1984). Grading is based on cellular differentiation; cytologic atypia, mitotic activity, and necrosis are markers of increased risk. Survival of patients with stage I disease is greater than 90% (Colombo et al. 2007). However, outcome is extremely poor for patients that present with disease beyond stage I with mortality being more than 90% (Chen et al. 2003).

2.9 Genetic Alteration of Sertoli-Leydig Cell Tumors

The recent identification of an important genetic alteration called the DICER1 somatic missense mutation will allow for future research on the molecular biology of these tumors. The DICER1 codes for a domain on a component of the RNase III family, and this mutation was identified on 60% of patients with Sertoli-Leydig cell tumors in one recent study (Gershenson 2012). The DICER1 mutation has also been identified in familial nontoxic multinodular goiter and pleuropulmonary blastoma, and both of these pathologies have been associated with increased frequency of Sertoli-Leydig cell tumors (Rio Frio et al. 2011).

2.10 Sertoli Cell Tumors

Sertoli cell tumors are formed from cellular proliferations that resemble the rete ovarii and rete testis and lack the Leydig component. The average age of presentation is 30 years. Only a quarter of these tumors demonstrate hormonal activity, which, if present, can be either estrogenic or androgenic. Sertoli cell tumors have been associated with Peutz-Jaghers syndrome (PJS) (Oliva et al. 2005). They are usually unilateral and stage I at presentation (Chen et al. 2003). Most of these tumors are well differentiated and clinically benign; however, those with atypical cytologic features are more likely to be clinically malignant (Young 2005). Pure Sertoli cell tumors are rare and there is little data on survival in patients with more advanced disease; however, there is much higher risk for distant metastasis in tumors exhibiting cytologic atypia (Oliva et al. 2005).

2.11 Diagnosis of Sertoli-Stromal Cell Tumors

Clinical suspicion for Sertoli cell tumors should be aroused if an adnexal mass is detected in a young reproductive age woman with evidence of virilization. If evidence of masculinization is present, elevated serum testosterone-to-androstenedione ratio is concerning for Sertoli-Leydig tumor. Other serum markers for an androgenically active tumor includes serum testosterone levels >150 ng/dL or dehydroepiandrosterone sulfate (DHEAS) levels >8000 μg/L (Carmina et al. 2006). However, only one half of patients will present with evidence of androgenic change; presenting symptomatic complaints in most patients will be related to mass effects of a tumor. Inhibin A and B can be useful clinical markers to follow for Sertoli-stromal cell tumors if elevated prior to surgical management.

Pathological analysis of the excised tumor is the only way to definitively diagnose these tumors. Many of these tumors have notable eosinophilic cytoplasm that is sometimes strikingly vacuolated, similar to a seminoma (Young 2005). The predominant microscopic pattern noted is tubular cells. Immunohistochemical staining is important for correctly identifying different histologic subtypes of Sertoli cell tumors as they can appear visually similar (Young 2005). Sertoli-Leydig cell tumors, which are subclassified into five levels of differentiation, have significant overlap amongst these levels of differentiation (Fig. 1c). Sertoli-Leydig tumors are sometimes described as having a distinct retiform pattern (Young 2005).

2.12 Sex Cord Tumor with Annular Tubules

Sex cord tumors with annular tubules (SCTAT) are rare, encompassing only 5% of SCST. SCTAT

are morphologically described as having components of both granulosa and Sertoli cell tumors (Fig. 1d). There are two distinct subtypes of SCTAT. Approximately one-third of SCTAT are associated with Peutz-Jaghers syndrome (PJS); these masses are typically small, bilateral, multifocal, and clinically benign.

SCTAT not associated with PJS tend to be larger and unilateral; approximately half of these tumors present with evidence of hyperestrogenization including postmenopausal vaginal bleeding, menstrual irregularities, or isosexual precocious puberty. Another distinctive characteristic is an association of SCTAT with adenoma malignum of the cervix. Adenoma malignum of the cervix, or minimal deviation adenocarcinoma, is an extremely rare well-differentiated adenocarcinoma of the cervix; this finding is only associated with SCTAT not found in conjunction with PJS. Although adenoma malignum of the cervix is a very rare finding, a review article of SCTAT found that of the four patients with this condition two of them died from it (Young et al. 1982). Approximately 20% of these tumors are malignant.

Diagnosis of SCTAT associated with PJS is typically incidental as they are not hormonally active nor large enough to cause mass effects. Diagnosis of SCTAT not associated with PJS is similar to that of other SCST. If there are signs of hyperestrogenism, endometrial sampling is recommended to evaluate for a coincident malignant process. Also, carefully evaluate the cervix prior to surgery due to the associated with adenoma malignum.

2.13 Fibroma-Thecomas

Fibromas are typically benign masses found incidentally as they are rarely hormonally active. They originate from collagen producing cells in the ovarian stroma. They typically present in women around the age of perimenopause. They are sometimes associated with ascites. Even more rarely, they present with a clinical triad including pleural effusion, typically right sided, ascites, and a solid ovarian mass. This triad is called Meigs syndrome and is present on only 1% of fibromas (Riker and Goba 2013). The mechanism surrounding Meigs syndrome is unclear; however, it is likely due to a large volume transudative process involving the tumor which exceeds the pertinoeum's ability to resorb the fluid (Carson and Mazur 1982). While the vast majority of these tumors are benign, approximately 10% have nuclear characteristics, such as cytologic atypia or increased mitotic patterns, that characterize them as tumors of low malignant potential, and 1% show evidence of transformation into fibrosarcoma and therefore warrants further treatment.

Thecomas are called such due to their characteristic appearance which resembles the theca lutein cells surrounding ovarian follicles (Chen et al. 2003). They can present at any age but present most often in postmenopausal women. These tumors are often hormonally active and present with signs of hyperestrogenization. Much like granulosa cell tumors, patients presenting with signs of excess estrogen exposure are also at risk for endometrial hyperplasia or adenocarcinoma (Aboud 1997). Less commonly these tumors are either not hormonally active or androgenic luteinizing elements are present with resulting signs of masculinization. Notably, these are benign masses and are typically unilateral.

Sclerosing stromal tumors are rare masses that also fall under the classification of fibroma-thecomas. Their characteristic presentation is that of a unilateral mass in a woman under the age of 30. They are clinically benign. Sclerosing stromal tumors are typically hormonally inactive but can present with menstrual irregularities and pelvic pain (Marelli et al. 1998).

2.14 Diagnosis of Fibroma-Thecoma

Like other ovarian masses, fibromas and thecomas are definitely diagnosed histologically after surgical management (Fig. 1e). After initial clinical evaluation with a thorough history and physical, at which time an adnexal mass might be palpated, ultrasonography can be performed. Thecomas are uniformly solid appearing masses on ultrasound and can be mistaken as an extrauterine leiomyoma (Burandt and Young 2014). For fibromas, if the Meigs triad is present, a thoracentesis can help to

evaluate for malignant pleural effusion prior to operative management. There are no specific serum markers that are relevant for fibromathecomas. However, cancer antigen 125 (CA125) is sometimes elevated, which can initially raise suspicion for epithelial ovarian carcinoma in the context of an adnexal mass. As with any patient presenting with postmenopausal vaginal bleeding, it is recommended that the endometrium be sampled prior to surgery if there is any concern for endometrial pathology.

2.15 Steroid Cell Tumor

Steroid cell tumors are rare, representing less than 5% of SCST. Histologically, they resemble either testicular Leydig cells (Leydig cell tumors), adrenal cells (stromal luteomas), or steroid cell tumors not otherwise specified (NOS). Both Leydig cell tumors and stromal luteomas typically present in older, postmenopausal women. Leydig cell tumors often present with evidence of virilization, while stromal luteomas are more likely to present with postmenopausal vaginal bleeding or other evidence of hyperestrogenization. These tumors are almost universally benign; however, as with other SCSTs that are hormonally active, evaluation of the endometrium is recommended if there is concern for excess estrogen exposure.

Steroid cell tumors NOS typically present in a younger demographic and are more likely to secrete adrenal hormones such as cortisol. Women with steroid cell tumors NOS might present with a clinical characteristics mimics to Cushing syndrome, signs of which include increased abdominal adiposity, violaceous striae, moon facies, and labile mood. Approximately one-fifth of these tumors behave in a malignant fashion (Chen et al. 2003).

2.16 Gynandroblastoma

Gynandroblastomas are extremely rare. Like many SCSTs they do not demonstrate uniform cellular patterns; they typically are composed of granulosa and Sertoli components. These tumors can also present with signs of hormonal excess, and either evidence of hyperandrogenism or hyperestrogenism are possible depending on the histologic components of the tumor. The prognosis for gynandroblastoma is very good, although evidence regarding outcome is limited due to the extremely rare nature of this tumor.

2.17 Unclassified Sex Cord-Stromal Tumors

An additional category of SCST is otherwise unclassified. These are composed of an indistinct mixture of granulosa and Sertoli cells. Because they can have either ovarian or testicular cell predominance, their presentation is varied. Much like pure granulosa or Sertoli cell tumors, unclassified SCST can present with signs of virilization or hyperestrogenism. However, many of these tumors do not demonstrate hormonal activity. They behave clinically like their primary components, and outcome is typically based on the degree of morphological differentiation.

2.18 Management of Sex Cord-Stromal Tumor

Surgical resection is the foundation of treatment for SCST. However, while surgical management is the best method treatment and is often curative, it is important to tailor the treatment plan based on the patient and the specific tumor cell type. Typically, neoadjuvant chemotherapy does not have a role in treatment of SCST as these tumors are typically identified at an early stage and often aren't recognized as malignancies until intraoperative frozen section identifies them as such, especially in those tumors that are hormonally inactive.

2.19 Preoperative Management

Considerations prior to surgery include standard preoperative work-up. Serum labs, such as complete blood count, complete metabolic panel, and

Table 2 Tumor markers for sex cord-stromal tumor and malignant germ cell tumor of the ovary[a]

Serum marker	Associated nonepithelial ovarian tumor
Inhibin A and B	Granulosa cell tumor, Sertoli-Leydig cell tumor
Serum testosterone	Sertoli-Leydig cell tumor
Lactate dehydrogenase (LDH)	Dysgerminoma
Beta human chorionic gonadotropin (beta-hCG)	Choriocarcinoma, embryonal carcinoma
Alpha-fetoprotein (AFP)	Yolk sac tumor, embryonal carcinoma, immature teratoma
Serum squamous cell cancer antigen (SSCA)	Mature teratoma with malignant squamous transformation
Cancer antigen 25 (CA125)	Fibroma, struma ovarii, teratoma

[a]Markers will not be elevated in all cases of the associated malignancy

type and screen, are recommended. While the blood loss is typically minimal, a type and cross ought to be considered if granulosa cell tumor is suspected due to the possibility of highly vascular nature of these tumors and associated risk for rupture and hemoperitoneum. Other preoperative considerations include systemic imaging. If there is concern for metastasis beyond the ovary alone, chest radiography or computed tomography of the chest, abdomen, and pelvis can provide more insight regarding the presence of metastatic disease. Tumor markers can be drawn prior to resection, as these can be used in surveillance and can be predictive of increased risk for recurrent disease. See Table 2 for suggested tumor markers. CA125, which is a useful marker for many epithelial ovarian cancers, has no clinical utility for SCST (Stine et al. 2013). If the patient has multiple medical comorbidities, consider referral to a primary care physician and preanesthesia services to achieve the best medical optimization possible prior to surgery.

Another integral aspect of treatment planning that can be discussed with the patient and family preoperatively is desire for future fertility. Approximately, 15% of all ovarian cancers present in women of reproductive age, and, while the majority of SCST are diagnosed in postmenopausal women, these tumors do present frequently in young women (Gershenson 2005). As detailed above, the vast majority of SCST present unilaterally at an early stage. In this context, it is possible to consider conservative surgery in those that desire future parity. While some fertility sparing options would require assisted reproductive technology, they would allow for the potential of future biological children. Oocyte cryopreservation can also be considered since recurrence in the contralateral ovary or premature ovarian failure following adjuvant chemotherapy can occur. A consultation with a specialist in oncofertility can be offered to young women wishing to discuss options for future fertility. While management of the malignancy must supersede considerations of future fertility, it is integral to discuss the subject of future fertility with younger women prior to proceeding with surgery. In addition, benefits of ovarian sex hormone for cardiovascular, bone, and cognitive health aspects in young premenopausal women need to be considered.

If a malignancy is suspected, a consultation with a gynecologic oncologist prior to operative management is suggested. Due to the rare nature of SCST and the fact that they are often not hormonally active, there are a significant number of these tumors that are identified intraoperatively or on pathology postoperatively. It is beneficial to have the potential for frozen pathology analysis if concerning tumor characteristics are encountered intraoperatively.

2.20 Surgical Management

Surgical management with complete cytoreduction if metastases are present will provide the patient with the best outcome (Gershenson 2012). Surgical approach will vary based on patient and disease characteristics. Minimally invasive approaches are often appropriate for presumed stage I disease; however, if there is tumor rupture this will result in upstaging and potentially necessitate further treatment. Open approaches allow more access for complete cytoreduction in more advanced stage

disease, which can be anticipated based on clinical exam and imaging findings.

The decision to proceed with surgical staging will be based on frozen section results and intraoperative findings. If the tumor is not a malignant SCST, comprehensive staging can be omitted. Thus, if the pathology is positive for a benign lesion, then the surgery can be completed without further staging. However, it must be remembered that frozen pathology is not infallible, and accuracy may be decreased in the setting of rare tumors such as SCST (Covens et al. 2012). If staging was not performed at the time of an initial surgery, an additional staging procedure may be completed if indicated by malignancy results on permanent pathology and systemic imaging suggests suspicion for metastasis. Figure 2 provides recommendations for the initial surgical management of SCST.

Surgical staging can be completed via minimally invasive approach or open laparotomy. Staging consists of a thorough exploration of the abdomen and pelvis, collection of pelvic washings, peritoneal biopsies and partial omentectomy as well as cytoreduction any visible tumor including hysterectomy and bilateral salpingo-oopherectomy in women not wishing to maintain reproductive potential. The role of routine lymphadenectomy in staging SCST has been debated. Lymphadenectomy has not been shown to improve survival in SCST, and the procedure can be associated with increased postoperative complications including lymphocele or lymphedema (Gershenson 2012). The National Comprehensive Cancer Network (NCCN), which articulates treatment guidelines for malignancies in the United States, specifies that routine lymphadenectomy can be omitted during the staging of SCST (Morgan 2015).

As above, the desire for future fertility can be discussed prior to proceeding with operative management. In the absence of advanced disease,

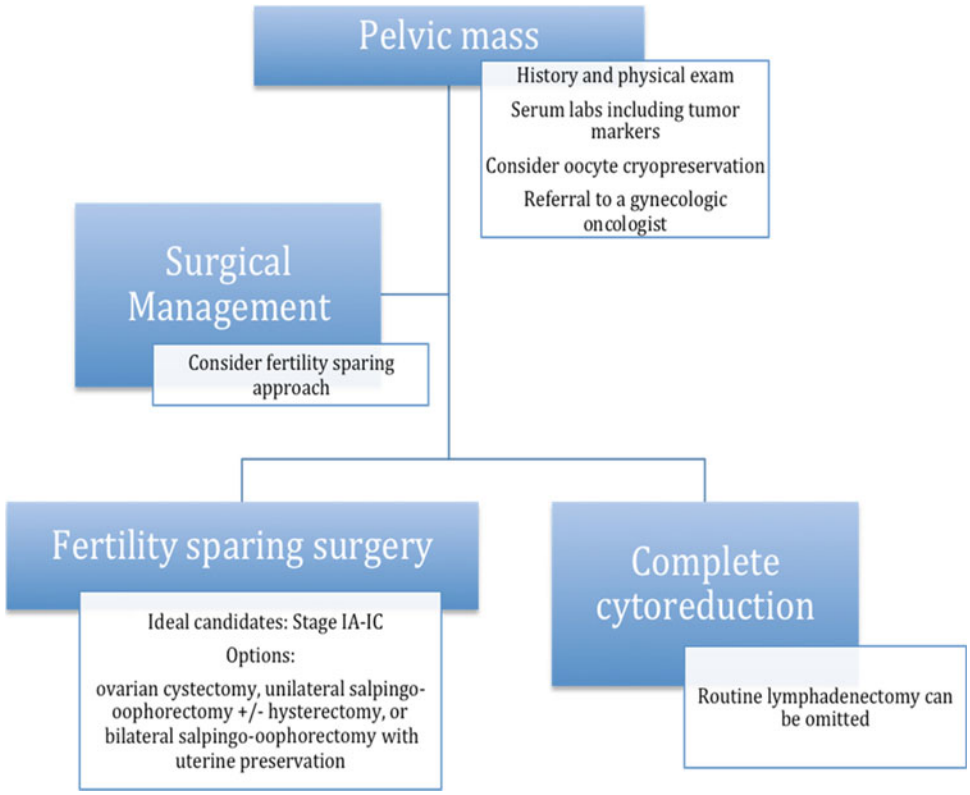

Fig. 2 Principles of surgical management for sex cord-stromal tumors of the ovary

fertility sparing surgery is an acceptable management option for women with stage IA to IC disease (Morgan 2015). Procedures considered fertility sparing include ovarian cystectomy, unilateral salpingo-oopherectomy with or without coincident hysterectomy, or bilateral salpingo-oopherectomy with uterine preservation (Gershenson 2005).

2.21 Postoperative Management

The decision to proceed with additional treatment versus expectant management is dependent on stage and, sometimes, tumor characteristics. Guidance on postoperative treatment is shown in Fig. 3. The most common postoperative treatment options utilized are either observation or platinum-based chemotherapy. Tumor markers, if elevated at the time of presentation, are a relatively noninvasive way to monitor for recurrence. Radiotherapy is of limited use for SCST but can be used for palliative purposes.

As with surgical management, fertility desires can be discussed prior to initiation of chemotherapy. Cryopreservation can be considered before starting chemotherapy, especially since platinum-based modalities are known to be especially toxic to oocytes. Cryopreservation also allows for fertility in the context of recurrent disease on the contralateral ovary if fertility sparing surgery has been performed.

2.22 Low-Risk Disease

For stage IA disease, the prognosis is excellent; so, no further treatment is recommended (Morgan 2015). Surveillance, consisting of pelvic exams and serum tumor marking testing if initially elevated, should occur every 2–4 months for the first 2 years following surgery, then every 6 months thereafter (Salani et al. 2011). Systemic imaging is indicated if recurrence is suspected.

2.23 Intermediate-Risk Disease

For disease diagnosed at a higher stage, there is still debate over optimal management. Intermediate-risk

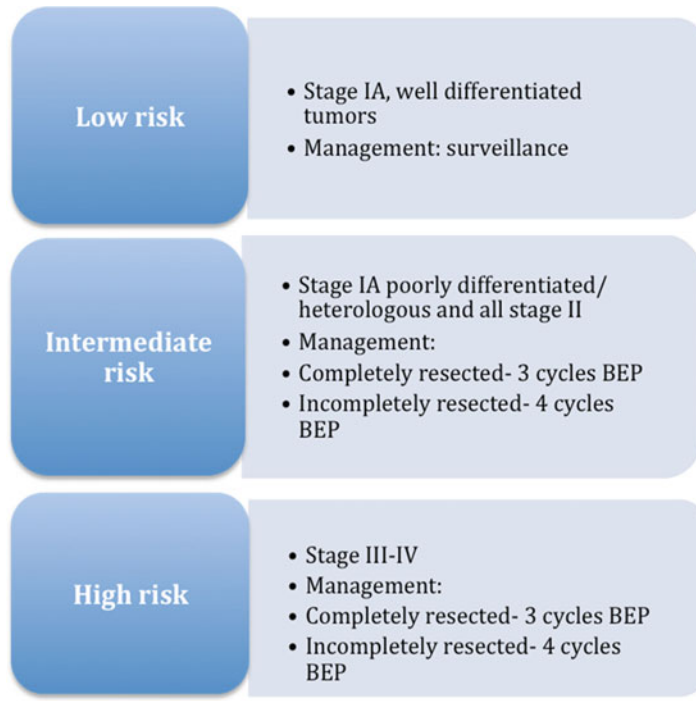

Fig. 3 Adjuvant therapy for sex cord-stromal tumors

stage I disease is classified based on characteristics such as tumor rupture, large tumor size, high mitotic rate, positive cytology, heterologous elements, poorly differentiated tumor, or incompletely staged disease (Morgan 2015). Any stage II disease also falls into the category of intermediate risk. The current consensus recommends either observation, with surveillance as detailed above, or platinum-based chemotherapy (Morgan 2015). The preferred adjuvant regimen is either platinum plus taxane or bleomycin, etoposide, and cisplatin (BEP). The most commonly used first line regimen is the 5-day BEP course because it has the highest known response rate (Homesley et al. 1999). Three cycles administered every 3 weeks is recommended for completely resected disease, but one additional cycle is recommended for patients with incompletely resected disease (Homesley et al. 1999).

2.24 High-Risk Disease

Adjuvant chemotherapy is definitely recommended for higher risk patients including stage III to IV disease. The same regimen of BEP as that detailed for intermediate-risk disease is recommended. Thus, for completely resected disease, three cycles is adequate treatment, while administering four cycles is recommended for incompletely resected disease.

2.25 Surveillance

Risk of recurrence remains high even years after surgical resection and adjuvant treatment. According to the NCCN guidelines, surveillance consists of office visits every 2–4 months for 2 years following completion of treatment. These visits will include a pelvic exam and serum tumor markers if initially elevated. Imaging can be performed in the context of a suspected recurrence. There is no role for routine serum tumor markers or imaging without suspicion for recurrence. After 2 years, surveillance visits should occur every 6 months (Morgan 2015).

2.26 Recurrent Disease

Disease can recur after long periods of remission, which is why continued surveillance at 6-month intervals is recommended after the initial 2-year period. Currently, there are no definitive guidelines for recurrent disease. Secondary cytoreduction is considered in cases with limited disease volume. Combination platinum-based chemotherapeutic regimens are typically considered first-line therapy whether or not secondary debulking is performed; BEP is administered most frequently due to its high response rate (Homesley et al. 1999). Other acceptable recurrence therapy options as designated by the NCCN include aromatase inhibitors, bevacizumab (for GCT), taxane, taxane plus ifosfamide, taxane plus carboplatin, tamoxifen, vincristine plus dactinomycin plus cyclophosphamide, radiation, or supportive care only (Morgan 2015). Possible novel strategies include hormonal therapy, such as aromatase inhibitors or the gonadotropin-releasing hormone agonist, leuprolide, for granulosa cell tumors (Morgan 2015). While promising, these treatment methodologies are still under investigation. The identification of germline mutations, such as FOXL2 mutations, may allow for exploration of targeted therapeutics. Thus far, there has been investigation of ketoconazole, the cytochrome P17 (CYP17) inhibitor, as a treatment modality for recurrent granulosa cell tumors due to the recognition that FOXL2 downregulates CYP17 (Garcia-Donas et al. 2013). Because this is based on case report, further studies are warranted. The antiangiogenic bevacizumab has been shown to have moderate activity against recurrent OSCST; more studies involving vascular endothelial growth factor inhibitors are currently underway (Gershenson 2012).

2.27 SCST in Pregnancy

Although a rare phenomenon, SCST does occur coincident with pregnancy. Mirroring the incidence of SCST outside of pregnancy, the most commonly encountered histological subtype is

granulosa cell. Notably, a rate of serious adverse events including hemoperitoneum and maternal shock was observed to be greater than 40% in a recent review of pregnancies complicated by SCST (Blake et al. 2014). Therefore, pregnancy complicated by suspected SCST is characterized as a high-risk pregnancy and managed in conjunction with gynecologic oncology and maternal-fetal medicine specialists. Survival of patients with SCST diagnosed within the context of a pregnancy seems comparable to those diagnosed not related to pregnancy, even when managed conservatively (Blake et al. 2014). Management of pregnancy complicated by SCST is not standardized; however, fetal preservation surgery, especially if undertaken in the second trimester, is a reasonable option associated with good maternal and fetal outcomes.

3 Ovarian Malignant Germ Cell Tumors

3.1 Pathogenesis

Germ cell tumors are cancers that originate from primordial germinal cells. Germ cell tumors of the ovary are most often benign, with malignant tumors representing only 5% of germ cell diagnoses. Malignant germ cell tumors comprise only about 2–3% of all ovarian malignancies (Quirk and Natarajan 2005). Ovarian germ cell tumors can be further classified into primitive germ cell tumors, differentiated germ cell tumors, and mixed tumor types as described in Table 3. This chapter will address malignant variations of germ cell tumors including dysgerminoma, immature teratoma, yolk sac tumor, polyembryoma, choriocarcinoma, embryonal carcinoma, and mixed germ cell tumor. The most common germ cell tumor is the mature cystic teratoma, or dermoid cyst, and, while typically benign, cellular components of the dermoid can undergo malignant transformation. In general, ovarian malignant germ cell tumors (OMGCT) present in women under age 30. Depending on the subtype, malignant germ cell tumors can demonstrate hormonal activity.

Table 3 World Health Organization histologic classification for germ cell tumors of the ovary

Primitive germ cell tumors
Dysgerminoma
Yolk sac tumor
Embryonal carcinoma
Polyembryoma
Nongestational choriocarcinoma
Teratomas
Immature
Mature solid
Mature cystic (dermoid)
Monodermal
Mixed forms

The molecular pathogenesis of OMGCT is currently under investigation. Specific microRNA clusters were noted to be overexpressed in all OMGCT. Notably, after a patient with yolk sac tumor was successfully treated, these clusters returned to a normal level (Gershenson 2012). Additionally, the KIT oncogene, a tyrosine kinase receptor recognized as a proto-oncogene in multiple malignancies, has been identified in dysgerminomas, especially those at advanced stage (Gershenson 2012).

3.2 Dysgerminoma

Dysgerminomas are traditionally the most common malignant germ cell neoplasm, but incidence is reported to be decreasing proportionally to other germ cell malignancies in recent years (Smith et al. 2006). These tumors are the "prototypical" germ cell tumors, meaning they are composed of cells that resemble primordial germ cells and appear histologically very similar to seminomas originated from testicular cells. Unlike other types of germ cell tumors, dysgerminomas cannot further differentiate (Chen et al. 2003). These tumors present bilaterally in approximately 15% of cases.

Historically, the prognosis for dysgerminoma was dismal; however, due to their chemosensitivity, overall survival is now greater than 99% (Chan et al. 2008). Over two-thirds of patients present at stage I; however, even later

stage disease has an excellent prognosis. Notably, dysgerminomas often spread lymphatically, and approximately one quarter of dysgerminomas are found to have metastasized to regional lymph nodes at the time of diagnosis (Kumar et al. 2008).

3.3 Diagnosis of Dysgerminoma

If an adnexal mass is identified in a young woman, malignant germ cell tumors can be considered in the differential diagnosis. Since these tumors occur bilaterally in approximately 15% of cases, careful attention during the exam of the contralateral ovary after a mass is appreciated. The most common presenting symptom is vague abdominal or pelvic pain due to mass effect. However, acute presentations can occur if the mass torses or ruptures causing hemoperitoneum.

Notably, dysgerminomas are found disproportionately in the context of gonadal dysgenesis. Females with karyotypically abnormal gonads, such as those with Turner syndrome (45X/46XY) or Swyer syndrome (46XY), are at risk for developing a gonadoblastoma. While gonadoblastomas are benign lesions, approximately 40% of these masses undergo malignant transformation, often into dysgerminomas (Pena-Alonso et al. 2005). Young women presenting with abnormal bleeding patterns and pelvic masses should be carefully evaluated for the presence of gonadal dysgenesis. If there is concern for gonadal dysgenesis, a karyotype can be performed.

Imaging via ultrasonography is another important component of the evaluation of a patient with an adnexal mass. Typically these present as solid masses on imaging. Ultrasound characteristics include a well-defined mass divided into component lobules with color Doppler demonstrating rich vascularization (Shaaban et al. 2014). Computed tomography (CT) also demonstrates a mass that is solid and potentially septated with scattered calcifications (Shaaban et al. 2014). CT can also demonstrate sequelae of advanced disease including ascites or evidence of distant metastases or lymphadenopathy.

Tumor markers can also be elevated in the presence of dysgerminoma. Typically these tumors are not hormonally active; they can contain syncytiotrophoblasts which cause serum beta-human chorionic gonadotropin (beta-hCG) elevations. Additionally, serum levels of lactate dehydrogenase (LDH) can also be elevated in the presence of dysgerminoma. While LDH is not specific, it can be a useful serum marker for recurrence if elevated initially.

As with any malignancy, definitive diagnosis cannot be made until final pathology is reviewed. These tumors are typically solid and white or gray in macroscopic appearance. Microscopically, these tumors resemble testicular cancers. Cells are round and uniform, usually surrounded by fibrous stranding or T lymphocyte infiltration (Fig. 4a).

3.4 Yolk Sac Tumors

Yolk sac tumors, previously called endodermal sinus tumors, are composed of remnants of the primitive yolk sac or vitelline elements. These tumors characteristically grow rapidly, and they typically present at a young age, rarely occurring in women over the age of 40. While yolk sac tumors are generally unilateral, they are more aggressive than most other germ cell tumors. Not only do yolk sac tumors demonstrate rapid growth, distant disease is often noted at presentation. The most common sites of metastasis include the lungs and local peritoneal spread (Chen et al. 2003).

Due to their aggressive characteristics, yolk sac tumors have the worst prognosis of all germ cell malignancies. Almost half of the cases of yolk sac tumor present after advancing beyond stage I disease. Even with appropriate treatment, survival rate for patients with stage III-IV disease is 50–75%. However, 5-year survival rate for patients with only stage I disease is greater than 90% (Chan et al. 2008). According to recent data, recurrences usually present within a year following treatment and are typically not responsive to further therapy (Cicin et al. 2009).

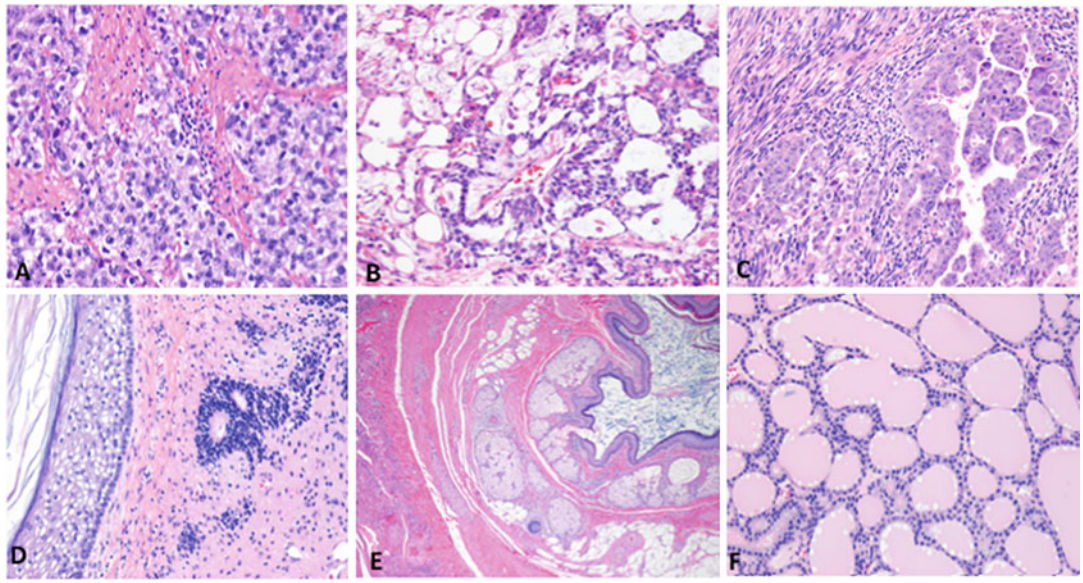

Fig. 4 Microscopic findings of malignant germ cell tumors of the ovary ((**a**). Dysgerminoma (**b**). Yolk sac tumor with Schiller-Duval bodies (**c**) Embryonal carcinoma (**d**). Immature teratoma with rosette (**e**). Mature cystic teratoma (**f**). struma ovarii (Courtesy of Drs. Abby M Richmond and Miriam D Post, Department of Pathology, University of Colorado, Aurora, Colorado))

3.5 Diagnosis of Yolk Sac Tumor

Since yolk sac tumors typically grow rapidly, women with these tumors often complain of relatively acute onset abdominal or pelvic pain. Review articles have noted several cases with growth of masses measuring greater than 20 cm over the course of weeks to months (Kurman and Norris 1976). Capsular rupture is fairly common, likely because of the rapid expansion of these tumors. These patients can also present with hemoperitoneum as these rapidly growing lesions are highly vascularized. If a large mass is palpable on pelvic exam, especially in a young premenopausal woman, suspicion for a yolk sac tumor is increased.

Imaging can be obtained after appreciation of a mass on exam. Ultrasound findings can include a unilateral mass with heterogenous echogenicity and septations. Computed tomographic images are often significant for enhancing foci in the tumor wall attributable to dilated blood vessels. Capsular tears can also sometimes be appreciated on imaging. None of these findings is pathognomonic for yolk sac tumors; however, they can help contribute to heightened preoperative suspicion for this entity (Shaaban et al. 2014).

Serum tumor markers can also be helpful in both preoperative evaluation for yolk sac tumors and for postoperative surveillance. These tumors produce alpha-fetoprotein (AFP). AFP is not specific for yolk sac tumors as other germ cell malignancies can produce this protein that is typically found in fetal circulation; however, yolk sac tumors will almost universally have elevated AFP level.

Pathological analysis is required for definitive diagnosis. Gross pathology will be significant for a large mass, on average measuring 15 cm, with mixed solid and cystic components. There are often focal areas of hemorrhage and necrosis in macroscopic appearance. Microscopically, these tumors can vary significantly in appearance; however, by definition they resemble the cellular structure of the primitive yolk sac. The appearance of an isolated papillary body containing a centralized vessel and surrounded by embryonic epithelial cells, called a Schiller-Duval body, is pathognomonic for yolk sac tumor but is not required for diagnosis (Fig. 4b).

3.6 Embryonal Carcinoma, Polyembryona, and Mixed Germ Cell Tumor

Other rare subtypes of primitive germ cell tumors include embryonal carcinoma, polyembryona, and mixed germ cell tumor. While all of these variants are likely to present in somewhat mixed form, they each have specific characteristics that allow them to be classified as individual entities.

Embryonal carcinoma is another malignant variant that can evolve from dysgenetic gonads. These tumors typically present in girls in their teenage years. Embryonal carcinoma typically produces beta-hCG and often produces AFP. On pathology, these tumors are noted to have solid sheets of anaplastic cells and distinctive papillary projections (Ulbright 2005; Fig. 4c).

Polyembryonas are extremely rare. These tumors have features of both primitive and differentiated germ cell tumor types, so are sometimes considered to be extremely immature teratomas (Ulbright 2005). Serum AFP and beta-hCG are often elevated in the presence of these tumors. Polyembryonas almost exclusively present as components of mixed germ cell tumor. Microscopically, these tumors have central "germ discs" surrounded by two cavities, one resembling the amniotic cavity and the other resembling the yolk sac cavity (Ulbright 2005).

Ovarian mixed germ cell tumors contain aspects of multiple types of germ cell tumors without one predominant component. Dysgerminoma is the most common component of mixed germ cell tumors, but they can contain elements of any histological subtype. The presence of higher risk malignant elements, such as high-grade immature teratoma, increases the likelihood of aggressive behavior.

3.7 Nongestational Choriocarcinoma

Nongestational choriocarcinoma in pure form is very rare, accounting for less than 5% of malignant germ cell tumors (Smith et al. 2006). These are aggressive tumors which can be confused with metastatic gestational choriocarcinoma. Gestational choriocarcinoma is associated with a proximate pregnancy and can metastasize to the ovaries. This distinction is important due to the poorer prognosis of nongestational choriocarcinoma (Corakci et al. 2005). The distinction between these two entities is made based on pathology findings; nongestational choriocarcinoma will be found in the presence of other germ cell components (Ulbright 2005).

These tumors are typically found in patients less than 20 years. Information on prognosis is limited due to the extremely rare nature of this tumor; however, prognosis is typically poor due to the frequency of distant metastasis at presentation (Corakci et al. 2005). Beta-hCG is often markedly elevated in these patients. The elevated beta-hCG can result in prominent symptoms such as isosexual precocious puberty or menstrual abnormalities in women who have undergone menarche.

3.8 Teratoma

All teratomas consist of components from all three germ cell layers: endoderm, mesoderm, and ectoderm. The malignant variation of teratoma is termed immature, but the majority of these tumors are classified as mature. Although rare, malignancy can develop within a mature cystic teratoma. The term dermoid is often used interchangeably with teratoma; however, there is a histological distinction between the two entities. Dermoids are composed of epidermal and dermal elements, while teratomas contain mesodermal and endodermal components. Teratomas can also be classified as monodermal or specialized when they consist predominantly of endodermal or ectodermal elements.

3.9 Immature Teratoma

Immature teratomas account for 30% of deaths from ovarian malignancy in women under age 20. They are now the most commonly detected malignant germ cell tumor (Smith et al. 2006). In

addition to endodermal, mesodermal, and ectodermal components, they also contain embryonic tissue, thus qualifying them as immature. These tumors typically present in women in their teenage years and rarely occur in postmenopausal women. Immature teratomas are typically unilateral but often have spread via local peritoneal seeding or via lymphatics at the time of diagnosis. If bilateral, which occurs in about 10% of cases, the contralateral tumor is generally a mature teratoma. The typical size at presentation is 14–25 cm (Wisniewski and Deppisch 1973).

Despite immature teratomas having a propensity to disseminate early, approximately three-quarters of these tumors are detected at stage I. The 5-year overall survival for stage I disease is greater than 95%. Survival for later stage disease is associated with poorer prognosis, but overall survival is still relatively high, ranging from 73% to 88% (Chan et al. 2008). Recurrence is not uncommon, but recurrent disease typically remains chemosensitive.

A phenomenon specific to immature teratoma is that of growing teratoma syndrome, which refers to postoperative growth of mature teratoma elements implanted in the peritoneum. These implants are typically benign and chemoresistant and can continue enlarging so resection is required to exclude recurrent malignancy. The incidence is relatively low, approximately 12% (Zagame et al. 2006). Prognosis is generally not affected by the presence of growing teratoma syndrome.

3.10 Mature Teratoma with Malignant Transformation

Mature cystic teratomas are the most common benign ovarian neoplasm and typically present in women age 20–40. These masses typically measure approximately 7 cm at presentation (Wisniewski and Deppisch 1973). Malignant transformation occurs very rarely in mature cystic teratomas, and it typically presents in postmenopausal women. The incidence of malignant transformation is approximately 1–2% (Smith et al. 2006). The most commonly identified malignancy is squamous cell carcinoma, which accounts for about 80% of malignant transformations. There is no clear mechanism of malignant transformation identified; however, it is notable that the average age of presentation is approximately 50 years, while most mature cystic teratomas are diagnosed in women several decades younger (Dos Santos et al. 2007). This finding has led to the hypothesis that prolonged presence of teratomas in situ increases the likelihood of malignant transformation; therefore, even though typically benign, it is important to surgically remove these masses. Unfortunately, the prognosis for squamous cell carcinoma within mature cystic teratoma is low as 48% overall; 5-year survival for stage IV disease is reported as 0% in one study (Chen et al. 2008). Other malignancies that have been reported within mature cystic teratomas include melanoma, basal cell carcinoma, thyroid carcinoma, carcinoid, chondrosarcoma, leiomyosarcoma, angiosarcoma, and intestinal adenocarcinoma (Chen et al. 2003).

3.11 Malignant Struma Ovarii

Struma ovarii refers to a type of monodermal teratoma that is composed of at least 50% thyroid tissue. Struma ovarii accounts for approximately 3% of mature teratomas (Roth and Talerman 2007). These tumors are typically benign, but a malignant component presents in less than 5% of cases of struma ovarii. Carcinomas that can occur within malignant struma ovarii include follicular or papillary variants. Additionally, struma ovarii can contain nonthyroid type neoplasms including carcinoid, Brenner tumor, or mucinous cystadenoma. These tumors typically present in postmenopausal women.

3.12 Paraneoplastic Encephalitis

Although not a malignancy, *N*-methyl-D-aspartate (NMDA) receptor antibody encephalitis is an important phenomenon associated with ovarian teratomas. NMDA receptor antibody encephalitis is a paraneoplastic neurologic

syndrome characterized by psychiatric symptoms, seizures, amnesia, and semirepetitive dystonic movement abnormalities. While a mass is not always present, the syndrome is most classically associated with teratomas in young women. Positive serum NMDA receptor antibody titers in the presence of this constellation of symptoms is diagnostic, and typically a higher antibody titer correlates with more severe symptoms (Irani and Vincent 2011). The pathogenesis of this condition is not fully understood; however, it is thought that impaired immunomodulation in the context of a disrupted blood–brain barrier could be responsible for the paraneoplastic syndrome (Irani and Vincent 2011). Treatment is centered on decreasing antibody levels both via surgical resection and pharmacologic agents including corticosteroids, plasma exchange, and intravenous immunoglobulins. Early resection and treatment are noted to have the best outcomes; death or permanent neurological sequelae can occur in the absence of prompt recognition and treatment (Irani and Vincent 2011).

3.13 Diagnosis of Teratoma

Most teratomas will be diagnosed either incidentally or after palpation of an adnexal mass as there are typically few systemic sequelae. Some patients will present complaining of vague abdominal or pelvic pain. Mature teratomas also commonly present with symptoms of torsion including intermittent visceral abdominal pain or pressure and nausea or vomiting. Patients with struma ovarii present with clinical hyperthyroidism in approximately 5% of cases (Roth and Talerman 2007). Additionally, struma ovarii presents with ascites in one-third of cases and with Meigs syndrome in rare cases (Roth and Talerman 2007). Meigs syndrome is a clinical triad consisting of ascites, pleural effusion, and pelvic mass.

On imaging, teratomas appear as heterogenous solid adnexal masses, often described as a cystic mass with intratumoral fat. Classically, mature teratomas are described as having a "dot-dash" pattern on ultrasound. Small areas of cystic calcifications or fatty elements can be appreciated on ultrasound. In immature teratomas, these calcified areas appear small, irregular, and scattered, while calcifications appear more well-defined or even tooth-like in mature teratomas (Shaaban et al. 2014). Another common ultrasound finding in mature teratomas is the Rokitansky nodule or dermoid plug, which is a nodule containing hair, teeth, and fat. If present, malignant transformation can occur in the region of the Rokitansky nodule and is seen as a heterogenous irregular solid mass that might demonstrate invasion into surrounding tissue (Shaaban et al. 2014). Cystic components have attenuation and signal intensity similar to that of simple fluid in immature teratomas but will appear more as fatty sebaceous material in mature teratomas on CT imaging (Shaaban et al. 2014).

Although no tumor marker is characteristic for teratomas, there are several that can be present depending on the predominant cell types contained within the teratoma. Serum markers such as AFP, CA125, cancer antigen 19-9 (CA19-9) can be elevated in immature teratomas (Li et al. 2002). If elevated, these markers can assist in postoperative surveillance. Another useful tumor marker evaluating for the presence of malignant transformation of a mature teratoma is serum squamous cell carcinoma antigen (SSCA). SSCA has been shown to be elevated in greater than 80% of patients that have foci of squamous cell carcinoma (Chen et al. 2008). Elevated CA125 can be found in the context of struma ovarii. While most patients with struma ovarii are chemically and clinically euthyroid, there can be abnormalities in thyroid hormone levels.

While the above factors can help assist in diagnosis and surveillance, final pathology is required for definitive diagnosis. Microscopically, components of all three germ cell layers can be observed in both immature and mature teratomas (Fig. 4d). Immature teratomas typically appear as disordered mixed tissue (Fig. 4e). Tumor grade or aggressiveness is dependent on the amount of immature neural tissue contained within the tumor. Teratomas grossly contain hair, fatty or sebaceous material, and calcifications or teeth; immature teratomas tend to be larger in diameter

than mature teratomas. Struma ovarii is formed of mature thyroid tissue and grossly appears as brown- or amber-colored colloidal material with thick septations (Fig. 4f).

3.14 Management of Ovarian Malignant Germ Cell Tumors

Historically, malignant germ cell tumors were associated with an abysmal prognosis. However, the development of modern chemotherapeutic techniques has drastically improved outcomes for these tumors. Initial surgical cytoreduction remains the cornerstone of management for malignant germ cell tumors. Surgery and resulting pathology findings are both therapeutic and diagnostic. Neoadjuvant chemotherapy has little clinical utility in OMGCT.

3.15 Preoperative Evaluation

Thorough preoperative assessment includes a consideration of preoperative imaging to evaluate for evidence of distant metastasis and thus aid in surgical planning. Preoperative labs including complete blood count, complete metabolic panel, and type and screen can be drawn prior to any potential major abdominal surgery. Tumor markers including LDH, b-HCG, AFP, CA125, CA19-9, and SSCA can be considered. Appropriate tumor markers are to be selected based on presentation and clinical suspicion for specific subtypes of OMGCT. The age of incidence for OMGCT is typically younger than that of other malignancies, so medical comorbidities necessitating preoperative anesthesia clearance are less common in this demographic; however, preanesthesia evaluation can be taken into consideration.

It is important to discuss implications of surgery and subsequent chemotherapy with patients and their families prior to undertaking the procedure. Since OMGCT often presents in women of reproductive age, a discussion of future fertility desires is recommended. Although management of the present malignancy must take precedence over future fertility desires, current literature indicates that patients and their families appreciate this discussion and may even be unaware prior to the procedure that loss of fertility or changes in future hormonal status could be a result of treatment (Loren et al. 2013). Due to excellent outcomes, fertility sparing surgery is now considered standard of care for OMGCT (Gershenson 2012). Oocyte cryopreservation is also a potential option for patients wishing to preserve future fertility. Adjuvant chemotherapy and risk of relapse in the remaining ovary are concerns to potential future fertility; as such, oocyte harvesting can help to ensure better reproductive outcomes in the future. There are multiple options available for young women wishing to preserve their future fertility in the context of malignancy, and, if available, referral to a specialist in oncofertility can be offered.

There is a high rate of relapse after inadequate staging and follow-up of OMGCT (Gershenson 2012). Therefore, for cases in which there is high suspicion for one of these malignancies, a referral to a gynecologic oncologist for staging and management is recommended.

3.16 Surgical Management

Surgical approach is dictated based on tumor and patient characteristics. Whenever possible, surgical spill should be avoided in order to prevent iatrogenic upstaging of disease. Many OMGCT are large at the time of presentation and thus preclude minimally invasive surgical options. However, if possible, the reduced postoperative morbidity of laparoscopic surgery compared to laparotomy is favorable if adequate staging is allowed through this approach. Surgeons consider low threshold to convert from laparoscopy to laparotomy when surgical spill is concerned for the tumor grossly confined in the ovary. See Fig. 5 for recommendations regarding surgical management for OMGCT.

The exact extent of appropriate surgical staging for apparent early stage OMGCT remains somewhat contentious. Procedures considered fertility sparing include ovarian cystectomy,

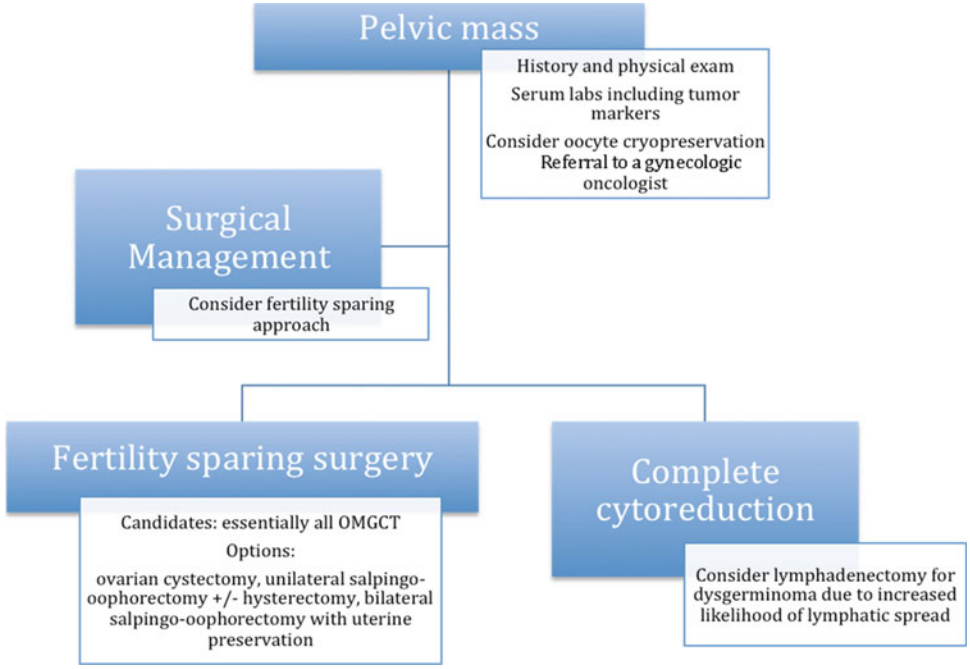

Fig. 5 Principles of surgical management for malignant germ cell tumors of the ovary

unilateral salpingo-oopherectomy with or without coincident hysterectomy, or bilateral salpingo-oopherectomy with uterine preservation (Gershenson 2005). Pediatric literature recommends conservative staging consisting of examination of peritoneal surfaces and collection of washings, palpation of retroperitoneal lymph nodes, and biopsy of abnormal appearing areas following resection of the affected ovary and visible mass (Billmire et al. 2004). A longitudinal review of oncologic and fertility outcomes for pediatric patients that underwent fertility sparing surgery and adjuvant chemotherapy found favorable outcomes regardless of histologic subtype and FIGO stage (Park et al. 2015). Additionally, fertility sparing surgery in the aforementioned study was conservatively defined as preservation of the unaffected ovary and uterus.

Bilateral tumors are present in less than 10% of OMGCT; however, they present a challenge to those wishing to preserve fertility. Although literature for the rare presentation of bilateral malignancies is minimal, available studies indicate that these tumors have a good prognosis and that fertility preservation can be considered, especially in the setting of bilateral dysgerminoma (Sigismondi et al. 2015). In a small study examining outcomes of bilateral OMGCT of various subtypes, a unilateral salpingo-oophorectomy was performed along with either a biopsy or cystectomy on the contralateral ovary followed by treatment with chemotherapy. The small subset of four patients treated with ovarian preservation demonstrated resultant preservation of future fertility and similar survival outcomes to those patients that were completely staged (Sigismondi et al. 2015). This data is based on very limited case numbers and risks and benefits ought to be considered carefully before deciding to leave an affected ovary in situ.

Traditional practice endorses that, similar to those with epithelial ovarian cancers, patients receiving complete cytoreduction improves survival outcome (Suita et al. 2002). However, as supported by the data above, accumulating evidence endorses a less aggressive staging procedure even if fertility preservation is not a priority of management. A careful inspection of all intraabdominal and pelvic surfaces is necessary. If tumor histology is identified on frozen pathology, characteristic patterns of dissemination are to

be taken into consideration. Dysgerminomas demonstrate lymphatic spread more frequently than other types of OMGCT, and this can be taken into consideration when deciding whether or not to perform staging with lymphadenectomy. Yolk sac tumors and immature teratomas are more likely to spread locally and have metastases present on the peritoneum and omentum. In advanced disease, the aim of surgery is maximally cytoreducing all accessible tumors.

4 Postoperative Management

4.1 Adjuvant Chemotherapy

OMGCT are typically notably chemosensitive. The responsiveness to chemotherapy allows surgical treatment to be less aggressive and allows for fertility sparing treatment as above. OMGCT, especially dysgerminoma, are often radiosensitive, and radiation was used in the past to treat these tumors but is no longer standard of care. Combination chemotherapy regimens including vincristine, dactinomcycin, cyclophosphamide (VAC) or cisplatin, vinblastine, bleomycin (PVB) were introduced in the 1970s with marked improvement in outcomes for patients diagnosed with OMGCT. Currently, all histologic subtypes of these tumors are treated with a combination of bleomycin, etoposide, and cisplatin (BEP), as this regimen was found to be more active and had an acceptable toxicity in patients (Gershenson et al. 1990). BEP is now first line for adjuvant therapy. Figure 6 outlines basic principles of postoperative management of OMGCT.

Current standard of care includes postoperative chemotherapy for all patients except those with well staged stage IA, grade 1 pure immature teratoma or stage I pure dysgerminoma. BEP is typically administered every 3 weeks. Randomized control trials have demonstrated that three cycles is adequate to prevent recurrence in nearly all patients who have undergone staging with complete cytoreduction (Williams et al. 1994). NCCN guidelines recommend three cycles for patients considered low risk for recurrence and four cycles for higher risk disease (Morgan 2015). Pulmonary function tests are recommended prior to starting bleomycin. Alternatively, the NCCN specifies that three courses of carboplatinum and etoposide can be used to reduce toxicity if the diagnosis is stage IB-III dysgerminoma (Morgan 2015). This regimen is administered every 4 weeks for 3 cycles.

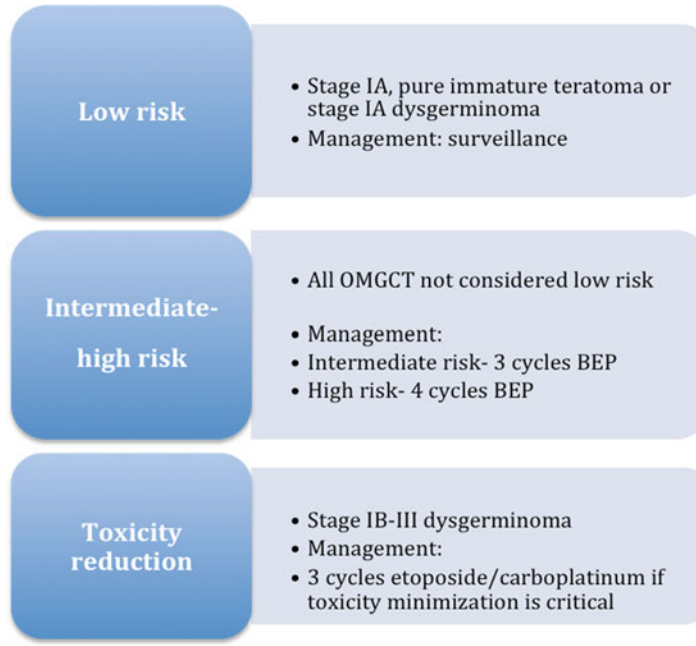

Fig. 6 Adjuvant therapy for malignant ovarian germ cell tumors

Many patients and families will express concern about the effects of chemotherapy on future fertility. Unlike radiation treatment, the majority of patients receiving the standard BEP regimen resume normal menses and have successful future fertility outcomes (Weinberg et al. 2011). As above, oocyte cryopreservation will allow for improved fertility outcomes for the minority patients that experience premature ovarian failure following BEP.

4.2 Surveillance

Risk of recurrence is highest in the first few years following surgical resection. According to the NCCN guidelines, surveillance consists of office visits every 2–4 months for 2 years following completion of treatment (Morgan 2015). These visits include a pelvic exam and serum tumor markers if initially elevated. Imaging can be performed in the context of a suspected recurrence. There is no role for routine serum tumor markers or imaging without suspicion for recurrence. After 2 years, annual exams can be performed (Salani et al. 2011).

4.3 Recurrence

Rates of recurrence vary depending on histological subtype, disease stage, and extent of the initial cytoreduction. As above, there remains controversy about the extent of surgical staging that is recommended with the initial tumor reduction surgery. Fortunately, even in the event of recurrent disease, the overwhelming majority of patients are salvageable.

The NCCN guidelines recommend referral to a tertiary center for management of recurrent disease (Morgan 2015). There are multiple options for recurrent disease, but there are no definitive guidelines. The NCCN recommends either high-dose chemotherapy, the specifics of which can differ among institutions, or another choice of combination regimens, most of which include a platinum agent (Morgan 2015). Platinum agents are not recommended if the tumor is platinum resistant or recurrent within 6 months of completing initial treatment. There is negligible role for secondary cytoreduction if disease recurs unless it demonstrates growth or persistence following chemotherapy, thus demonstrating chemoresistance (Williams et al. 1994). Radiotherapy is another option for recurrent disease. KIT targeting in dysgerminoma has not been well studied and future studies are expected. Alternatively, for patients with advanced disease or otherwise poor prognosis, supportive care alone is an option.

4.4 Ovarian Malignant Germ Cell Tumor in Pregnancy

Although a rare event, the propensity for OMGCT to present in young reproductive aged women results in them accounting for 18–26% of all ovarian cancers recognized in pregnancy. Dysgerminoma is the most frequently encountered OMGCT in pregnancy. OMGCT diagnosed in pregnancy are usually unilateral and stage I, mirroring the typical presentation in nongravid women (Kodama et al. 2014). These tumors can sometimes be recognized in the context of a persistent adnexal mass due to markedly elevated tumor markers; however, this can sometimes be obscured by the expected presence of markers such as AFP during pregnancy.

Review of the literature indicates that, although rates of preterm birth are higher than those in the general population, the majority of these cases result in delivery of viable infants. Pregnancy preservation is in general a reasonable option. However, due to the tendency of OMGCT to disseminate rapidly, intervention should not be delayed until delivery. Surgical staging can be performed if suspicion for an ovarian malignancy is raised even during pregnancy. Although there are no randomized control trials to provide guidance, observational studies indicate that BEP is safe in pregnancy (Karimi Zarchi et al. 2008). Furthermore, advanced stage disease diagnosed during pregnancy has been identified as an independent predictor of decreased survival (Kodama

et al. 2014). Therefore, although identification of a suspected OMGCT does not necessitate pregnancy termination, early intervention consistent with the standard of care is recommended if the patient desires continuation of the pregnancy.

5 Conclusion

Nonepithelial cell ovarian cancers are rare entities. Sex cord-stromal tumors and malignant germ cell tumors are the most common nonepithelial ovarian cancers. Although not encountered often, it is important to consider these tumors in differential diagnoses of adnexal masses. These tumors often, but not always, present with the sequelae of overproduction of either androgens or estrogens. It is important to diagnose these masses early, as overall prognosis is typically very good for early stage disease in all histological subtypes. Both sex cord-stromal tumors and malignant germ cell tumors of the ovary are treated with initial surgical resection. Fertility sparing surgery can be considered for both sex cord-stromal and malignant germ cell tumors of the ovary. Depending on the pathological diagnosis and disease stage, postoperative management consists of either expectant management or adjuvant chemotherapy. It is recommended that all patients with nonepithelial ovarian cancer be monitored for evidence of disease recurrence on a standardized schedule.

References

Aboud E. Adult granulosa cell tumours of the ovary. Eur J Gynaecol Oncol. 1997;18(6):520–2.

Billmire D, Vinocur C, Rescorla F, Cushing B, London W, Schlatter M, et al. Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. J Pediatr Surg. 2004;39(3):424–9.

Blake EA, Carter CM, Kashani BN, Kodama M, Mabuchi S, Yoshino K, et al. Feto-maternal outcomes of pregnancy complicated by ovarian sex-cord stromal tumor: a systematic review of literature. Eur J Obstet Gynecol Reprod Biol. 2014;175:1–7.

Burandt E, Young RH. Thecoma of the ovary: a report of 70 cases emphasizing aspects of its histopathology different from those often portrayed and its differential diagnosis. Am J Surg Pathol. 2014;38(8):1023–32.

Carmina E, Rosato F, Janni A, Rizzo M, Longo RA. Extensive clinical experience: relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. J Clin Endocrinol Metab. 2006;91(1):2–6.

Carson SA, Mazur MT. Atypical endometrioid cystadenofibroma with Meigs syndrome: ultrastructure and S phase fraction. Cancer. 1982;49(3):472–9.

Chan JK, Tewari KS, Waller S, Cheung MK, Shin JY, Osann K, et al. The influence of conservative surgical practices for malignant ovarian germ cell tumors. J Surg Oncol. 2008;98(2):111–6.

Chen VW, Ruiz B, Killeen JL, Cote TR, Wu XC, Correa CN. Pathology and classification of ovarian tumors. Cancer. 2003;97(10 Suppl):2631–42.

Chen RJ, Chen KY, Chang TC, Sheu BC, Chow SN, Huang SC. Prognosis and treatment of squamous cell carcinoma from a mature cystic teratoma of the ovary. J Formos Med Assoc. 2008;107(11):857–68.

Cicin I, Saip P, Guney N, Eralp Y, Ayan I, Kebudi R, et al. Yolk sac tumours of the ovary: evaluation of clinicopathological features and prognostic factors. Eur J Obstet Gynecol Reprod Biol. 2009;146(2):210–4.

Colombo N, Parma G, Zanagnolo V, Insinga A. Management of ovarian stromal cell tumors. J Clin Oncol. 2007;25(20):2944–51.

Corakci A, Ozeren S, Ozkan S, Gurbuz Y, Ustun H, Yucesoy I. Pure nongestational choriocarcinoma of ovary. Arch Gynecol Obstet. 2005;271(2):176–7.

Covens AL, Dodge JE, Lacchetti C, Elit LM, Le T, Devries-Aboud M, et al. Surgical management of a suspicious adnexal mass: a systematic review. Gynecol Oncol. 2012;126(1):149–56.

Dos Santos L, Mok E, Iasonos A, Park K, Soslow RA, Aghajanian C, Kaled A, Barakat RR, Abu-Rustum NR. Squamous cell carcinoma arising in mature cystic teratoma of the ovary: a case series and review of the literature. Gynecol Oncol. 2007;105(2):321–4.

Garcia-Donas J, Hurtado A, Garcia-Casado Z, Albareda J, López-Guerrero JA, Alemany I, Grande E, Camara JC, Hernando S. Cytochrome P17 inhibition with ketoconazole as a treatment for advanced granulosa cell ovarian tumor. J Clin Oncol. 2013;31:165–6.

Gershenson DM. Fertility-sparing surgery for malignancies in women. J Natl Cancer Inst Monogr. 2005;34:43–7.

Gershenson DM. Current advances in the management of malignant germ cell and sex cord-stromal tumors of the ovary. Gynecol Oncol. 2012;125:515–7. United States.

Gershenson DM, Morris M, Cangir A, Kavanagh JJ, Stringer CA, Edwards CL, et al. Treatment of malignant germ cell tumors of the ovary with bleomycin, etoposide, and cisplatin. J Clin Oncol. 1990;8(4):715–20.

Gurumurthy M, Bryant A, Shanbhag S. Effectiveness of different treatment modalities for the management of

adult-onset granulosa cell tumours of the ovary (primary and recurrent). Cochrane Database Syst Rev. 2014;4:Cd006912.

Homesley HD, Bundy BN, Hurteau JA, Roth LM. Bleomycin, etoposide, and cisplatin combination therapy of ovarian granulosa cell tumors and other stromal malignancies: a Gynecologic Oncology Group study. Gynecol Oncol. 1999;72(2):131–7.

Irani S, Vincent A. NMDA receptor anitbody encephalitis. Curr Neurol Neuosci Rep. 2011;11:298–304.

Karimi Zarchi M, Behtash N, Modares Gilani M. Good pregnancy outcome after prenatal exposure to bleomycin, etoposide and cisplatin for ovarian immature teratoma: a case report and literature review. Arch Gynecol Obstet. 2008;277(1):75–8. Gynecol Oncol. 1999;72:131–7.

Kodama M, Grubbs BH, Blake EA, Cahoon SS, Murakami R, Kimura T, et al. Feto-maternal outcomes of pregnancy complicated by ovarian malignant germ cell tumor: a systematic review of literature. Eur J Obstet Gynecol Reprod Biol. 2014;181:145–56.

Kumar S, Shah JP, Bryant CS, Imudia AN, Cote ML, Ali-Fehmi R, et al. The prevalence and prognostic impact of lymph node metastasis in malignant germ cell tumors of the ovary. Gynecol Oncol. 2008;110(2):125–32.

Kurman RJ, Norris HJ. Endodermal sinus tumor of the ovary: a clinical and pathologic analysis of 71 cases. Cancer. 1976;38(6):2404–19.

Li H, Hong W, Zhang R, Wu L, Liu L, Zhang W. Retrospective analysis of 67 consecutive cases of pure ovarian immature teratoma. Chin Med J (Engl). 2002;115(10):1496–500.

Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31(19):2500–10.

Marelli G, Carinelli S, Mariani A, Frigerio L, Ferrari A. Sclerosing stromal tumor of the ovary. Report of eight cases and review of the literature. Eur J Obstet Gynecol Reprod Biol. 1998;76(1):85.

Morgan et al. [Internet]. NCCNOCV, updated Feb 2015, cited 15 Oct 2015. Available at http://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

Oliva E, Alvarez T, Young RH. Sertoli cell tumors of the ovary: a clinicopathologic and immunohistochemical study of 54 cases. Am J Surg Pathol. 2005;29(2):143–56.

Park JY, Kim DY, Suh DS, Kim JH, Kim YM, Kim YT, et al. Outcomes of pediatric and adolescent girls with malignant ovarian germ cell tumors. Gynecol Oncol. 2015;137(3):418–22.

Pena-Alonso R, Nieto K, Alvarez R, Palma I, Najera N, Erana L, et al. Distribution of Y-chromosome-bearing cells in gonadoblastoma and dysgenetic testis in 45, X/46,XY infants. Mod Pathol. 2005;18(3):439–45.

Quirk JT, Natarajan N. Ovarian cancer incidence in the United States, 1992–1999. Gynecol Oncol. 2005;97(2):519–23.

Riker D, Goba D. Ovarian mass, pleural effusion, and ascites: revisiting Meigs syndrome. J Bronchology Interv Pulmonol. 2013;20(1):48–51.

Rio Frio T, Bahubeshi A, Kanellopoulou C, Hamel N, Niedziela M, Sabbaghian N, Pouchet C, Gilbert L, O'Brien PK, Serfas K, Broderick P, Houlston RS, Lesueur F, Bonora E, Muljo S, Schimke RN, Bouron-Dal Soglio D, Arseneau J, Schultz KA, Priest JR, Nguyen VH, Harach HR, Livingston DM, Foulkes WD, Tischkowitz M. DICER1 mutations in familial multinodular goiter with and without Sertoli-Leydig cell tumors. JAMA. 2011;305(1):68–77.

Roth LM, Talerman A. The enigma of struma ovarii. Pathology. 2007;39(1):139–46.

Salani R, Backes FJ, Fung MF, Holschneider CH, Parker LP, Bristow RE, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: society of Gynecologic Oncologists recommendations. Am J Obstet Gynecol. 2011;204(6):466–78.

Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. J Clin Oncol. 2003;21(6):1180–9.

Shaaban AM, Rezvani M, Elsayes KM, Baskin Jr H, Mourad A, Foster BR, et al. Ovarian malignant germ cell tumors: cellular classification and clinical and imaging features. Radiographics. 2014;34(3):777–801.

Sigismondi C, Scollo P, Ferrandina G, Candiani M, Angioli R, Vigano R, et al. Management of bilateral malignant ovarian germ cell tumors: a MITO-9 retrospective study. Int J Gynecol Cancer. 2015;25(2):203–7.

Smith HO, Berwick M, Verschraegen CF, Wiggins C, Lansing L, Muller CY, et al. Incidence and survival rates for female malignant germ cell tumors. Obstet Gynecol. 2006;107(5):1075–85.

Stine JE, Suri A, Gehrig PA, Chiu M, Erickson BK, Huh WK, et al. Pre-operative imaging with CA125 is a poor predictor for granulosa cell tumors. Gynecol Oncol. 2013;131(1):59–62.

Suita S, Shono K, Tajiri T, Takamatsu T, Mizote H, Nagasaki A, et al. Malignant germ cell tumors: clinical characteristics, treatment, and outcome. A report from the study group for Pediatric Solid Malignant Tumors in the Kyushu Area, Japan. J Pediatr Surg. 2002;37(12):1703–6.

Ulbright TM. Germ cell tumors of the gonads: a selective review emphasizing problems in differential diagnosis, newly appreciated, and controversial issues. Mod Pathol. 2005;18 Suppl 2:S61–79.

Weinberg LE, Lurain JR, Singh DK, Schink JC. Survival and reproductive outcomes in women treated for malignant ovarian germ cell tumors. Gynecol Oncol. 2011;121(2):285–9.

Williams S, Blessing JA, Liao SY, Ball H, Hanjani P. Adjuvant therapy of ovarian germ cell tumors with cisplatin, etoposide, and bleomycin: a trial of the Gynecologic Oncology Group. J Clin Oncol. 1994;12(4): 701–6.

Wisniewski M, Deppisch LM. Solid teratomas of the ovary. Cancer. 1973;32(2):440–6.

Young RH. Sex cord-stromal tumors of the ovary and testis: their similarities and differences with consideration of selected problems. Mod Pathol. 2005;18 Suppl 2:S81–98.

Young RH, Welch WR, Dickersin GR, Scully RE. Ovarian sex cord tumor with annular tubules: review of 74 cases including 27 with Peutz-Jeghers syndrome and four with adenoma malignum of the cervix. Cancer. 1982;50(7):1384–402.

Young RH, Dickersin GR, Scully RE. Juvenile granulosa cell tumor of the ovary. A clinicopathological analysis of 125 cases. Am J Surg Pathol. 1984;8(8): 575–96.

Zagame L, Pautier P, Duvillard P, Castaigne D, Patte C, Lhomme C. Growing teratoma syndrome after ovarian germ cell tumors. Obstet Gynecol. 2006;108(3 Pt 1): 509–14.

Zaloudek C, Norris HJ. Sertoli-Leydig tumors of the ovary. A clinicopathologic study of 64 intermediate and poorly differentiated neoplasms. Am J Surg Pathol. 1984;8(6):405–18.