FERTILITY

Infertility is an important consequence of the treatment of GCTs. Preexisting infertility or impaired fertility is often present. Azoospermia and/or oligospermia are present at diagnosis in at least 50% of patients with testicular GCTs. Ejaculatory dysfunction is associated with RPLND, and germ cell damage may result from cisplatin-containing chemotherapy. Nerve-sparing techniques to preserve the retroperitoneal sympathetic nerves have made retrograde ejaculation less likely in the subgroups of patients who are candidates for this operation. Spermatogenesis does recur in some patients after chemotherapy. However, because of the significant risk of impaired reproductive capacity, semen analysis and cryopreservation of sperm in a sperm bank should be recommended to all patients before treatment.

117 Gynecologic Malignancies

Michael V. Seiden

OVARIAN CANCER

INCIDENCE AND PATHOLOGY

Cancer arising in or near the ovary is actually a collection of diverse malignancies. This collection of malignancies, often referred to as "ovary cancer," is the most lethal gynecologic malignancy in the United States and other countries that routinely screen women for cervical neoplasia. In 2014, it was estimated that there were 21,980 cases of ovarian cancer with 14,270 deaths in the United States. The ovary is a complex and dynamic organ and, between the ages of approximately 11 and 50 years, is responsible for follicle maturation associated with egg maturation, ovulation, and cyclical sex steroid hormone production. These complex and linked biologic functions are coordinated through a variety of cells within the ovary, each of which possesses neoplastic potential. By far the most common and most lethal of the ovarian neoplasms arise from the ovarian epithelium or, alternatively, the neighboring specialized epithelium of the fallopian tube, uterine corpus, or cervix. Epithelial tumors may be benign (50%), malignant (33%), or of borderline malignancy (16%). Age influences risk of malignancy; tumors in younger women are more likely benign. The most common of the ovarian epithelial malignancies are serous tumors (50%); tumors of mucinous (25%), endometrioid (15%), clear cell (5%), and transitional cell histology or Brenner tumor (1%) represent smaller proportions of epithelial ovarian tumors. In contrast, stromal tumors arise from the steroid hormone–producing cells and likewise have different phenotypes and clinical presentations largely dependent on the type and quantity of hormone production. Tumors arising in the germ cell are most similar in biology and behavior to testicular tumors in males (Chap. 116).

Tumors may also metastasize to the ovary from breast, colon, appendiceal, gastric, and pancreatic primaries. Bilateral ovarian masses from metastatic mucin-secreting gastrointestinal cancers are termed *Krukenberg tumors*.

OVARIAN CANCER OF EPITHELIAL ORIGIN

Epidemiology and Pathogenesis A female has approximately a 1 in 72 lifetime risk (1.6%) of developing ovarian cancer, with the majority of affected women developing epithelial tumors. Each of the histologic variants of epithelial tumors is distinct with unique molecular features. As a group of malignancies, epithelial tumors of the ovary have a peak incidence in women in their sixties, although age at presentation can range across the extremes of adult life, with cases being reported in women in their twenties to nineties. Each histologic subtype of ovarian cancer likely has its own associated risk factors. Serous cancer, the most common type of epithelial ovarian cancer, is seen with increased frequency in women who are nulliparous or have a history of use of talc agents applied to the perineum; other risk factors include obesity and probably hormone replacement therapy. Protective factors include the use of oral contraceptives, multiparity, and breast-feeding. These protective factors are thought to work through suppression of ovulation and perhaps the associated reduction of ovulation associated inflammation of the ovarian epithelium or, alternatively, the serous epithelium located within the fimbriae of the fallopian tube. Other protective factors, such as fallopian tube ligation, are thought to protect the ovarian epithelium (or perhaps the distal fallopian tube fimbriae) from carcinogens that migrate from the vagina to the tubes and ovarian surface epithelium. Mucinous tumors are more frequent in women with a history of cigarette smoking, whereas endometrioid and clear cell tumors are more frequent in women with a history of endometriosis.

Considerable evidence now suggests that the precursor cell to serous carcinoma of the ovary might actually arise in the fimbria of the fallopian tube with extension or metastasis to the ovarian surface or capture of preneoplastic or neoplastic exfoliating tubal cells into an involuting ovarian follicle around the time of ovulation. Careful histologic and molecular analysis of tubal epithelium demonstrates molecular and histologic abnormalities, termed serous tubular intraepithelial carcinoma (STIC) lesions, in a high proportion of women undergoing risk-reducing salpingo-oophorectomies in the context of high-risk germline mutations in *BRCA1* and *BRCA2*, as well as a modest proportion of women with ovarian cancer in the absence of such mutations.

Genetic Risk Factors A variety of genetic syndromes substantially increase a woman's risk of developing ovarian cancer. Approximately 10% of women with ovarian cancer have a germline mutation in one of two DNA repair genes: *BRCA1* (chromosome 17q12-21) or *BRCA2* (chromosome 13q12-13). Individuals inheriting a single copy of a mutant allele have a very high incidence of breast and ovarian cancer. Most of these women have a family history that is notable for multiple cases of breast and/or ovarian cancer, although inheritance through male members of the family can camouflage this genotype through several generations. The most common malignancy in these women is breast carcinoma, although women harboring germline *BRCA1* mutations have a marked increased risk of developing ovarian malignancies in their forties and fifties with a 30–50% lifetime risk of developing ovarian cancer. Women harboring a mutation in *BRCA2* have a lower penetrance of ovarian cancer with perhaps a 20–40% chance of developing this malignancy, with onset typically in their fifties or sixties. Women with a *BRCA2* mutation also are at slightly increased risk of pancreatic cancer. Likewise women with mutations in the DNA mismatch repair genes associated with Lynch syndrome, type 2 (*MSH2, MLH1, MLH6, PMS1, PMS2*) may have a risk of ovarian cancer as high as 1% per year in their forties and fifties. Finally, a small group of women with familial ovarian cancer may have mutations in other *BRCA*-associated genes such as *RAD51*, *CHK2*, and others. Screening studies in this select population suggest that current screening techniques, including serial evaluation of the CA-125 tumor marker and ultrasound, are insufficient at detecting early-stage and curable disease, so women with these germline mutations are advised to undergo prophylactic removal of ovaries and fallopian tubes typically after completing childbearing and ideally before age 35–40 years. Early prophylactic oophorectomy also protects these women from subsequent breast cancer with a reduction of breast cancer risk of approximately 50%.

Presentation Neoplasms of the ovary tend to be painless unless they undergo torsion. Symptoms are therefore typically related to compression of local organs or due to symptoms from metastatic disease. Women with tumors localized to the ovary do have an increased incidence of symptoms including pelvic discomfort, bloating, and perhaps changes in a woman's typical urinary or bowel pattern. Unfortunately, these symptoms are frequently dismissed by either the woman or her health care team. It is believed that high-grade tumors metastasize early in the neoplastic process. Unlike other epithelial malignancies,