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Supplement to ***Cancer***

Pathology and Classification of Ovarian Tumors

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Knowledge of the embryology and microscopic anatomy of the ovary is fundamental to the understanding of the various cancer types that originate in this organ. A complete description of the embryology and anatomy of the ovary is beyond the scope of this monograph; however, comprehensive reviews are available for those who seek more detail.[1–7] The current discussion focuses on key developmental events and anatomic features that shed light on the natural history of ovarian cancers.

At approximately five weeks of gestation, thickenings of the lining of the posterior embryonic body cavity, the *coelomic epithelium*, form the *genital ridges*. Continued proliferation of the coelomic epithelium into the underlying primitive connective tissue, known as the *mesenchyme,* leads to the formation of the primordial *indifferent gonads*. Cells from adjacent transient embryonic structures, known as *mesonephros,* concurrently invade the mesenchyme, and the primordial *germ cells* arrive after a long journey that starts at their place of origin in the yolk sac and takes the cells along the distal embryonic intestine and the posterior wall of the embryonic body cavity. The different tumor types that arise in the ovary are linked to the different cell types that are present at this stage of development: coelomic epithelial, mesenchymal, mesonephric, and germ cells.

Ovaries and testes develop in similar fashion until approximately the fourth month of embryonic life. This finding explains the origin of tumors that are commonly associated with testicular tissue but appear in the ovaries and vice versa. At two months gestation, the primitive gonad is recognized as an ovary because of the lack of development of the well-defined testicular sex cords. Instead, mesonephric cells and germ cells remain closely associated, forming ill-defined ovarian sex cords embedded in the primitive mesenchyme. The coelomic epithelium remains at the periphery, enwrapping the developing ovary.

In the adult, the ovaries are flat, nodular, oval structures that measure between 3 and 5 cm in their greatest dimension and weigh between 2 and 4 g. They are suspended by peritoneal folds and ligaments on either side of the uterus and attached to the back of the broad ligament of the uterus, behind and below the uterine tubes. A single layer of cells, the *surface epithelium*, which is derived from the coelomic epithelium, lines their external surface. A dense, fibrous tissue, the *stroma*, which is derived from the mesenchyme, makes up most of their internal substance. The germ cells, also known as *oocytes*, are located near the periphery of the stroma. The *granulosa cells*, specialized cells of probable mesonephric origin that are derived from the sex cords, surround the germinal cells that form the *follicles*. The stroma immediately surrounding the follicles differentiates into plum elongated cells known as *theca cells*. When stimulated, theca

cells accumulate abundant lipids in their cytoplasm by a process known as *luteinization*. The ovary also contains *hilus cells* (which are identical to a type of testicular cells known as *Leydig cells*) that specialize in hormone production. The *rete ovarii*, a network of cellular cords and tubes, is similar to a testicular structure known as the *rete testis*.

PATHOLOGY OF OVARIAN TUMORS

Most tumors of the ovary can be placed into one of three major categories—*surface epithelial-stromal* tumors, *sex cord-stromal* tumors, and *germ cell* tumors (Fig. 1)—according to the anatomic structures from which the tumors presumably originate. Each category includes a number of subtypes. Combinations of different subtypes, either intimately intermixed or side-by-side within a single tumor, are found with some frequency. Tumors that combine two or more subtypes are designated as *mixed*, with the contributing subtypes specified in the designation. By convention, for classification purposes, tumor subtypes making up $< 10\%$ of the total tumor mass are ignored.

The ovarian surface epithelium is histologically similar to the mesothelium, which is the epithelium that lines the interior of the pelvic and abdominal cavities. This similarity, as well as the close morphologic resemblance of ovarian epithelial-stromal tumors to some epithelial tumors arising elsewhere within the pelvis and abdomen, may be explained by the shared origin (i.e., the primitive coelomic epithelium) of the ovarian surface epithelium and the mesothelium.

The sex cord-stromal group includes tumors of mesenchymal and mesonephric origin. Some of these tumors, namely fibromas and thecomas, have a fibrous appearance, and some appear to be derived from the granulosa cells or their testicular sex cord counterparts, the Leydig and Sertoli cells.

The ovarian germ cells are the origin of a number of tumors that are identical to testicular germ cell tumors. Germ cells that are stranded or have gone astray during their migration between the yolk sac and the developing gonads may develop into germ cell tumors outside the gonads.

The three main types of ovarian cancer and their subtypes are discussed briefly in the current article, with special consideration of key aspects related to tumor registration and epidemiology. A more comprehensive and detailed discussion of the pathology of ovarian tumors can be found in specialized publications[8–11] that were used to prepare the current summary.

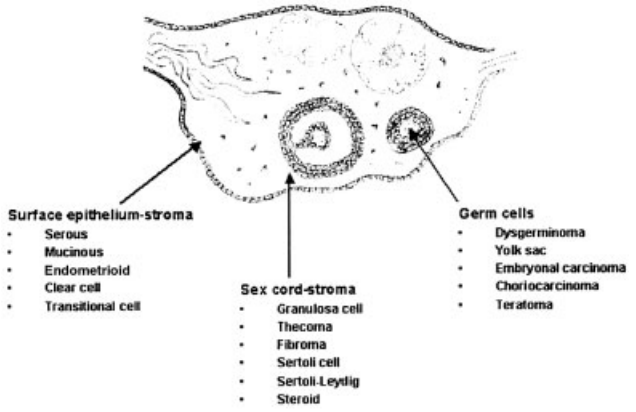

FIGURE 1. Origins of the three main types of ovarian tumors.

Surface Epithelial-Stromal Tumors

Surface epithelial-stromal tumors are believed to originate from the surface epithelium of the ovary. They are classified as *benign* if they lack exuberant cellular proliferation and invasive behavior; as *borderline* (also known as *atypically proliferating* or *of low malignant potential*) if there is exuberant cellular proliferation but no invasive behavior; and as *malignant* if there is invasive behavior. Surface epithelial-stromal tumors account for approximately 60% of all ovarian tumors and approximately 90% of malignant ovarian tumors. Most borderline tumors behave clinically as benign tumors and have good prognosis, but some may recur after surgical removal and some may seed extensive *implants* within the abdominal cavity. Surface epithelial-stromal tumors occur primarily in women who are middle-aged or older and are rare in young adults, particularly before puberty.

Five major subtypes are included within the surface epithelial-stromal group. They are designated as follows: *serous, mucinous, endometrioid, clear cell,* and *transitional cell* (or *Brenner* type). Highly malignant epithelial-stromal tumors lacking any specific differentiation are classified as *undifferentiated*. Epithelial-stromal tumors that are not designated as having a specific subtype commonly are recorded as *adenocarcinomas not otherwise specified* (*NOS*).

Serous or mucinous tumors identical to those occurring in the ovary may arise in multiple locations within the pelvic and abdominal cavities. They sometimes coincide with ovarian tumors of identical type. When they do so, it may be difficult to establish whether the extraovarian sites represent seedlings or implants originating from the ovarian tumor or de novo malignancies. By convention, when the ovaries appear to be incidentally involved and do not appear to be the primary origin of the tumor, the tumor is recorded as an *extraovarian peritoneal carcinoma*.

Serous tumors

Serous tumors are epithelial-stromal tumors formed by cells that resemble those of the internal lining of the fallopian tube. Benign serous tumors are thin-walled cysts formed by a single chamber filled with a watery, straw-colored fluid. The internal lining of the cyst is usually flat but may display a few coarse papillary projections. Benign serous tumors account for approximately one-quarter of all benign ovarian neoplasms and two-thirds of all ovarian serous tumors. Benign serous tumors most frequently occur between the fourth and fifth decades of life. In up to 20% of patients, benign serous tumors are bilateral, occurring simultaneously in both ovaries. Surgical removal is curative.

Compared with benign tumors, borderline serous tumors have more exuberant and finer papillary projections within the cyst cavity. Similar projections also may occur on the external surface of the tumor. Small tumorlets with similar features may be found elsewhere on the internal lining of the pelvic and abdominal cavities in up to 40% of patients. In most cases, these tumorlets do not progress, but they occasionally display invasive behavior. Borderline serous tumors account for 10–15% of all ovarian serous tumors. Most studies show that on average, borderline serous tumors are diagnosed in the fifth decade of life.[8,10,11] Up to one-third of these tumors are bilateral. Treatment is surgical. Reported 5-year survival rates are 70–95%. Recurrences may develop many years after the initial diagnosis, with intervals of 20–50 years reported. These recurrences usually are limited to the pelvic and abdominal cavities. It is estimated that 30–40% of patients with extragonadal spread die of progressive disease or other complications.

Most malignant serous tumors are at least partially cystic. They may contain multiple cyst chambers, or loculations, and also solid areas. Most display an abundance of delicate papillae that project into the cyst cavities and, in some cases, outward from the external surface of the tumor. Malignant serous tumors make up one-third of all ovarian serous tumors and approximately half of all malignant ovarian neoplasms. This histologic type most frequently occurs in the sixth decade of life.[8,10,11] In the current analysis, the mean age at diagnosis is 59.4 years. Two-thirds of malignant serous tumors are bilateral. Treatment includes surgery and chemotherapy. Most tumors are widely disseminated at the time of diagnosis. Five-year survival rates are 76% for patients with Stage I tumors, 56% for patients with Stage II tumors, 25% for patients with Stage III tumors, and 9% for patients with Stage IV tumors.

Mucinous tumors

Mucinous tumors are epithelial ovarian tumors formed by cells that resemble either those of the endocervical epithelium (*endocervical* or *müllerian type*) or, more frequently, those of the intestinal epithelium (*intestinal type*).

Benign mucinous tumors are multiloculated cysts that are filled with opaque, thick, mucoid material. They account for up to one-fourth of all benign ovarian neoplasms and 75–85% of all mucinous ovarian tumors. Benign mucinous tumors most frequently occur between the third and fifth decades of life[8,10,11] and rarely are bilateral. Surgical removal is curative.

Upon gross pathologic examination, borderline mucinous tumors are similar to benign mucinous tumors but may have solid regions and exhibit papillae projecting into the cyst chambers. They make up 10–14% of all ovarian mucinous tumors. Borderline mucinous tumors most frequently occur between the fourth and sixth decades of life.[8,10,11] About 40% of borderline tumors of endocervical type are bilateral. In contrast, $< 10\%$ of borderline tumors of the intestinal type are bilateral. Borderline mucinous tumors of the endocervical type may be associated with mucinous tumorlets or implants in the pelvic and abdominal cavities. Tumors of the intestinal type may be associated with *pseudomyxoma peritonei*, an accumulation within the pelvis and abdomen of large amounts of mucoid material with few intermixed tumor cells. Most cases of pseudomyxoma peritonei involve the cecal appendix and are thought to originate in mucinous tumors that are primary to the appendix with secondary involvement of the ovaries. Pseudomyxoma peritonei also may be associated with malignant ovarian mucinous neoplasms, and its presence does not indicate dissemination. Treatment of borderline mucinous tumors is surgical. Tumor recurrence and metastatic disease are rare. Five-year survival rates are reported to be between 51% and 92%, depending on disease stage. Pseudomyxoma peritonei follows a relentless and protracted course. Treatment involves the removal of as much tumor as possible followed by abdominal taps to remove fluid and alleviate symptoms.

Compared with borderline tumors, malignant mucinous tumors may contain more papillary projections within the cyst cavities, larger solid areas, and larger areas of necrosis and hemorrhage. Malignant mucinous tumors represent 5–10% of all malignant ovarian neoplasms. Between 6% and 20% of malignant mucinous tumors are bilateral. On average, diagnosis occurs in the sixth decade of life;[8,10,11] in the current analysis, the mean age at diagnosis was 54.7 years.

Five-year survival rates are 83% for patients with Stage I tumors, 55% for patients with Stage II tumors, 21% for patients with Stage III tumors, and 9% for patients with Stage IV tumors.[12] Late extraperitoneal recurrences, particularly in the lungs, are characteristic of malignant mucinous tumors.

Endometrioid tumors

Endometriod tumors are epithelial ovarian tumors formed by cells that resemble those of the internal lining of the uterus (the *endometrium*). They may be associated with the aberrant presence of endometrium outside the uterus (*endometriosis*) and with overgrowth (*hyperplasia*) or cancer of the endometrium.

Benign endometrioid tumors occur infrequently and are predominantly cystic and unilateral. Surgical removal is curative. Borderline endometrioid tumors also are predominantly cystic and unilateral, but they often exhibit internal papillary projections. They represent one-fifth of all endometrioid ovarian neoplasms. Treatment of these tumors is surgical, and prognosis is excellent. On average, both benign and borderline endometrioid tumors are diagnosed in the sixth decade of life.

Malignant endometrioid ovarian tumors may be cystic or predominantly solid. These tumors, which make up the second most common malignant ovarian surface epithelial-stromal tumor type, account for approximately 80% of all ovarian endometrioid tumors and 10–25% of all ovarian carcinomas. On average, diagnosis occurs in the sixth decade of life.[8,10,11] Approximately 13–28% of these tumors are bilateral. Most malignant endometrioid tumors are confined to the ovaries and adjacent pelvic structures; 20–25% are associated with endometrial carcinoma, which is commonly regarded as an independent primary tumor. Malignant ovarian endometrioid carcinomas are considered to have a better prognosis than either mucinous or serous carcinomas. However, this finding may be due to a reluctance to diagnose less well-differentiated tumors as endometrioid type. The reported 5-year survival rates are 78% for patients with Stage I tumors, 63% for patients with Stage II tumors, 24% for patients with Stage III tumors, and 6% for patients with Stage IV tumors.[12]

Clear cell tumors

Clear cell tumors are epithelial ovarian tumors that are formed by clear, peglike or hobnail-like cells. Benign and borderline clear cell tumors are quite rare. Most clear cell ovarian tumors are malignant. They can be predominantly solid or cystic with one or more polypoid masses protruding into the lumen. Clear cell tumors represent 4–5% of all malignant ovarian epithelial tumors. On average, diagnosis occurs in the fifth decade of life.[8,10,11] Two-thirds of all women with malignant clear cell tumors have never given birth, and 50–70% have endometriosis. One-fourth of all clear cell tumors arise in the lining of benign endometrioid cysts, 15–20% are bilateral, and 60% are Stage I tumors at diagnosis. Most borderline clear cell tumors behave in a benign manner. Survival rates for clear cell carcinomas are poorer than for other surface epithelial carcinomas. The reported 5-year survival rates are 69% for patients with Stage I tumors, 55% for patients with Stage II tumors, 14% for patients with Stage III tumors, and 4% for patients with Stage IV tumors.[12]

Transitional cell (Brenner) tumors

Transitional cell tumors are epithelial ovarian tumors formed by cells that resemble those of the internal lining of the urinary bladder (the *transitional epithelium* or *urothelium*). These tumors presumably are derived from surface ovarian epithelium that undergoes urotheliumlike transformation (e.g., *urothelial metaplasia, Walthard nests*). They may occur in association with similar tumors in the urinary bladder. Transitional cell tumors rarely occur and are often reported within the category of *other specified* epithelial-stromal tumors.

Most benign transitional cell ovarian tumors are very small, asymptomatic, incidentally discovered, and clinically irrelevant. They are solid and nodular, and most are unilateral. Benign transitional cell ovarian tumors often arise in association with endocervical-type mucinous and serous tumors, and they most frequently occur between the fifth and sixth decades of life.[8,10,11] Surgical excision is curative. Borderline transitional cell tumors characteristically contain solid and cystic areas, with papillary or polypoid projections within the cyst lumen. Borderline transitional cell tumors, most of which are unilateral, most often occur between the sixth and seventh decades of life. They are believed to behave in a benign manner and seldom recur after surgical treatment.

Malignant transitional cell tumors also contain solid areas and cystic areas with internal papillary or polypoid projections. Approximately one-tenth of these tumors are bilateral. They are referred to as *transitional cell carcinomas* when they lack benign transitional cells and as *malignant Brenner tumors* when benign transitional areas are identified. Whereas most (70–100%) transitional cell carcinomas present at an advanced stage, only 10–20% of malignant Brenner tumors do so. Malignant Brenner tumors have excellent prognosis when they are confined to the

ovary, and, stage-by-stage, they may have better prognosis than transitional cell carcinomas; however, it has been reported that metastatic transitional cell carcinomas respond much better to chemotherapy than do any other type of surface epithelial-stromal tumors.[8]

Undifferentiated carcinomas

Undifferentiated carcinomas are ovarian epithelial tumors formed by cells that show highly malignant features, including high nuclear grade and no cytoplasmic differentiation. Approximately 5% of all ovarian cancers and 14% of all surface epithelial-stromal tumors are classified within this category. On average, diagnosis occurs in the sixth decade of life.[8,10,11] Half of all undifferentiated carcinomas are bilateral. More than three-quarters have extended beyond the pelvis at the time of diagnosis. The 5-year survival rates are 68% for patients with Stage I tumors, 40% for patients with Stage II tumors, 17% for patients with Stage III tumors, and 6.3% for patients with Stage IV tumors.[12]

Adenocarcinomas NOS

As mentioned earlier, when malignant epithelial-stromal tumors are diagnosed without designation of any specific tumor subtype, they often are recorded as adenocarcinomas NOS.

Sex Cord-Stromal Tumors

Sex cord-stromal tumors are ovarian tumors that are believed to originate in theca cells, other stromal cells, and granulosa cells and their testicular sex cord counterparts, the Sertoli and Leydig cells. These tumors often are associated with endocrine manifestations. They account for approximately 8% of all ovarian tumors and approximately 7% of all malignant ovarian tumors.

Granulosa cell tumors

Granulosa cell tumors are rare sex cord ovarian tumors that are formed by cells believed to be derived from those that surround the germinal cells in the ovarian follicles. Two major forms of granulosa cell tumors are recognized: the *adult* form, which primarily occurs in middle-aged and older women, and the *juvenile* form, which typically occurs in children and younger women.

Most adult granulosa cell tumors are partially cystic, with multiple fluid-filled or blood-filled loci and solid areas. They represent approximately 95% of all granulosa cell tumors. These tumors, the majority of which are unilateral, most often occur in postmenopausal women. Adult granulosa cell tumors are the ovarian tumor type most commonly associated with manifestations that are caused by the overproduction of female sex hormones (*estrogenic manifestations*). These manifestations include endometrial hyperplasia and endometrial cancer, which are present in 5–25% of cases. Adult granulosa cell tumors are considered to be tumors of low grade or low malignant potential. Ninety percent are Stage I at diagnosis, with a reported 10-year survival rate of 86–96%; the corresponding reported survival rate for patients with tumors found at more advanced stages is 26–49%. Treatment is primarily surgical. Rupture of the tumor during surgery adversely affects prognosis. Recurrences can occur 30 years or more after removal.

Juvenile granulosa cell tumors are grossly similar to those of the adult subtype. They account for only 5% of all granulosa cell tumors. Most are unilateral, and approximately half occur before puberty. Because of their estrogenic hormone production, many of these tumors result in precocious sexual development. Most juvenile granulosa cell tumors are limited to the ovary at the time of diagnosis. Surgical excision is curative in most cases. Recurrences are rare and typically occur within three years.

Thecomas

Thecomas are rare, solid ovarian tumors formed by stromal cells that resemble the theca cells that normally surround the ovarian follicles. Most thecomas are unilateral and occur in postmenopausal women. They are uncommon before age 30 years. These tumors commonly have estrogenic manifestations, including postmenopausal uterine bleeding, endometrial hyperplasia, and endometrial cancer. Most thecomas are benign, and surgical excision is curative.

Fibromas

Fibromas are rare, solid ovarian tumors arising from the spindled stromal cells that form *collagen*. On the rare occasions when these tumors are bilateral, they may be associated with *nevoid basal cell carcinoma syndrome,* also known as *Gorlin syndrome*. Fibromas are most common during middle age and rare before age 30 years; the mean age at diagnosis is in the late forties.[8,10,11] Unlike other sex cord-stromal tumors, fibromas rarely are associated with hormone production. In almost all cases, they are benign and curable by surgical excision. Fibromas with increased cellularity and cell proliferation (*mitotic activity*) are rare and may follow a malignant course; fibromas of this kind are known as *fibrosarcomas*.

Sertoli cell tumors

Sertoli cell tumors are rare sex cord-stromal ovarian tumors formed by cell proliferations that resemble the rete ovarii and rete testis, which characteristically are

arranged in hollow or solid tubules. The mean age at diagnosis is 30 years. These tumors usually do not function, but they may produce hormones that can induce precocious sexual development or, in rare cases, the development of male features (*virilization*) in girls. Most of these tumors are unilateral and Stage I. They form solid, yellow or brown, lobulated masses and rarely metastasize. Surgical treatment often is curative.

Sertoli-Leydig cell tumors

Sertoli-Leydig cell tumors are rare sex cord-stromal ovarian tumors that are formed by variable proportions of cells that resemble epithelial and stromal testicular cells. They can be solid, partially cystic, or completely cystic, and they may or may not have polypoid or vesicular structures in their interior. Most are unilateral and occur in young women. The mean age at diagnosis is in the mid-twenties.[8,10,11] Most patients with Sertoli-Leydig cell tumors are younger than age 30 years. These tumors cause virilization in approximately one-third of patients, but they also can lead to estrogenic manifestations in some patients. Five subtypes have been identified: *well-differentiated, of intermediate differentiation, poorly differentiated, retiform,* and *mixed*. Most patients present with Stage I disease. Very few Sertoli-Leydig cell tumors have spread beyond the ovary at the time of diagnosis; however, the death rate for patients presenting with greater than Stage I disease is close to 100%. Whereas no well-differentiated tumors and few tumors of intermediate differentiation display malignant behavior, most poorly differentiated tumors do so.

Steroid cell tumors

Steroid cell tumors are rarely occurring, solid, yellow, ovarian sex cord-stromal tumors formed by cells that resemble adrenal gland cells (*stromal luteomas*) or the testicular Leydig cells (*Leydig cell tumors*). Most stromal luteomas occur in postmenopausal women and are associated with estrogenic manifestations, the most common of which is uterine bleeding. The majority of Leydig cell tumors also occur in postmenopausal women but cause virilization (an *androgenic manifestation*) rather than estrogenic manifestations. Steroid cell tumors that cannot be classified as stromal luteomas or Leydig cell tumors are found in younger women (mean age in the early forties) and can occur before puberty. These tumors are larger, can be associated with androgenic or estrogenic changes, and may secrete adrenal cortex steroid hormones that can induce *hypercortisolism,* also known as *Cushing syndrome*. Whereas almost all stromal luteomas and Leydig cell tumors are benign, between one-fifth and one-fourth of other steroid cell tumors have spread beyond the ovary at diagnosis and clinically behave like malignant tumors.

Germ Cell Tumors

Germ cell tumors are ovarian tumors formed by cells that are believed to be derived form primordial germ cells. These tumors make up approximately one-fourth of all ovarian tumors but only 3–7% of malignant ovarian tumors. In parts of Asia and Africa where the prevalence of surface epithelial-stromal tumors is relatively low, germ cell tumors constitute a larger proportion of all ovarian neoplasms.[13] More than half of the ovarian neoplasms that develop in children and adolescents are of germ cell origin, with one-third of these being malignant. Conversely, in adults, germ cell tumors are relatively infrequent, and the great majority of them are benign, with most being *mature cystic teratomas (dermoid cysts)*.

The prototypical germ cell tumors are the *dysgerminomas*. *Embryonal carcinomas* are germ cell tumors composed of poorly differentiated, multipotential germ cells. Germ cell tumors with differentiation in an embryonal or *somatic* direction result in *teratomas*. Those that differentiate in an extraembryonic (*placental* or *trophoblastic*) direction result in *yolk sac tumors* or *choriocarcinomas*. Mixed subtypes of germ cell tumors also occur frequently.

Dysgerminomas

Dysgerminomas are tumors composed of cells that are similar to primordial germ cells. They display a striking similarity to their testicular counterpart, the *seminoma*. Dysgerminomas are solid, white or grayish-white tumors. Unilateral tumors are more common in the right ovary, and 10–20% of dysgerminomas are bilateral. Most cases occur in the second and third decades of life. Dysgerminomas account for $\leq$ 2% of all ovarian tumors and only 3–5% of all malignant ovarian tumors; nevertheless, they represent the most common type of malignant ovarian germ cell neoplasm. High prevalence has been reported in Japan and India.[8] Dysgerminomas are among the most common malignant neoplasms during adolescence and early adulthood. A high level of serum *lactic dehydrogenase* is associated with dysgerminoma and can be used as a tumor marker. Dysgerminomas spread late and do so primarily through the lymphatic system. These tumors respond very well to radiation therapy. The overall prognosis for patients with dysgerminomas is excellent; the 5-year survival rate approaches 100% for patients with Stage I disease and is 75–90% for patients with other stages of malignancy. Poor prognosis is associated with large tumor size, bilater-

alism, age < 20 years or > 40 years, and the presence of other neoplastic germ cell elements.

Yolk sac tumors

Yolk sac tumors, also known as *endodermal sinus tumors*, are germ cell tumors displaying cellular structures that resemble those of the primitive yolk sac (the *vitelline elements*). These tumors are mainly solid but frequently have cystic spaces. They are highly malignant, frequently invading the surrounding structures and exhibiting extensive spread within the abdominal cavity. Yolk sac tumors metastasize early and do so primarily through the lymphatic system. Most of these tumors are unilateral; involvement of the opposite ovary often is considered a manifestation of metastatic spread. Yolk sac tumors most frequently occur in the second and third decades of life and are exceptionally rare in postmenopausal women. Yolk sac tumors produce alpha-fetoprotein, a major component of the normal fetal serum; serum levels of alpha-fetoprotein may be used as a tumor marker. Yolk sac tumors are second only to dysgerminomas as the most common type of malignant ovarian germ cell neoplasm, and they often occur mixed with other germ cell tumor types. Radiotherapy is ineffective in the treatment of yolk sac tumors; however, most cases can be cured with a combination of conservative surgery and multiagent chemotherapy. The survival rate for patients with Stage I–II disease is 60–100%, and the rate for patients with Stage III–IV disease is 50–75% after appropriate chemotherapy.

Embryonal carcinoma

Embryonal carcinomas are germ cell tumors formed by primitive cells that resemble those of very early embryonic development. They are considered to be the least differentiated type of germ cell tumor. They often are combined with other forms of germ cell tumors, most commonly yolk sac tumors. Embryonal carcinomas are large, predominantly solid tumors with a variegated appearance, and most are unilateral. Involvement of the opposite ovary is commonly considered a manifestation of metastatic spread. Embryonal carcinomas occur primarily in children and young adults. These tumors can produce alpha-fetoprotein or *human chorionic gonadotropin*, the latter may be associated with precocious puberty and abnormal uterine bleeding. Embryonal carcinomas are highly malignant tumors that usually have spread extensively within the abdominal cavity by the time of presentation. They metastasize early and do so primarily through the lymphatic system. These tumors are not radiosensitive, but treatment with surgery and combination chemotherapy is sufficient to cure most patients completely. Survival rates are similar to those for patients with yolk sac tumors.

Choriocarcinoma

Choriocarcinomas are germ cell tumors formed by placental (namely, trophoblastic) cellular elements. They typically are solid and have a hemorrhagic appearance. Most of these tumors are unilateral. The large majority of primary ovarian choriocarcinomas are not related to pregnancy (*nongestational*). Some originate after a pregnancy (i.e., they are *gestational*), in which case, most are metastatic, primarily from the uterus. Choriocarcinomas are rare and often are admixed with other germ cell tumors. Primary ovarian choriocarcinomas occur in children and young adults. Secretion of human chorionic gonadotropin may cause precocious puberty and abnormal uterine bleeding; serum levels of this hormone may be used as a tumor marker. Choriocarcinomas are highly malignant and locally invasive, spread extensively throughout the abdominal cavity, and metastasize early. Nongestational choriocarcinomas spread mainly via lymphatics, whereas gestational choriocarcinomas spread primarily via the bloodstream. Survival has improved considerably since the implementation of combination chemotherapy. Sustained remission is achieved in most patients, but it is less common in those with nongestational choriocarcinomas.

Teratoma

Teratomas are germ cell tumors that are formed by cells derived from more than one of the three primitive embryonic layers (*ectoderm, mesoderm,* and *endoderm*). Teratomas can be *mature* (benign) or *immature* (benign or malignant). Teratomas formed predominantly by endodermal or ectodermal elements are referred to as *monodermal* or *specialized*.

Mature teratomas can be solid or cystic. Mature solid teratomas are rare, as most solid teratomas are at least partially immature. Mature teratomas occur mostly in children and young adults. These tumors, most of which are unilateral, grow slowly and usually are large at the time of diagnosis. Surgical excision is curative.

Mature cystic teratomas are the most common kind of ovarian germ cell tumor. In most studies, they are reported to represent at least 10% of all ovarian tumors. In most mature cystic teratomas, the ectodermal elements predominate; when this is the case, these teratomas are designated as dermoid cysts. Mature cystic teratomas commonly have a single cyst cavity filled with sebaceous material, and they often have a focal internal protuberance that may contain hair, teeth, bone, and/or cartilage. Mature cystic teratomas most commonly occur during the reproduc-

tive years. In most cases, surgical excision is curative. Rupture of the tumor may result in peritoneal implants.

In rare cases, mature cystic teratomas may undergo malignant transformation, most often in postmenopausal patients, that most commonly results in squamous cell carcinoma. Other malignant tumor types, including *carcinoid, thyroid carcinoma, basal cell carcinoma, intestinal adenocarcinoma, melanoma, leiomyosarcoma,* and *chondrosarcoma,* may arise. Prognosis is generally unfavorable; reported 5-year survival rate are only 15–31%. Better prognosis is observed if the malignant component is squamous cell carcinoma and if the tumor is confined to the ovary.

Immature teratomas contain primitive, immature, or embryonal structures in addition to well-developed or mature tissues. These tumors usually are unilateral, large, and predominantly solid. Immature cystic teratomas are rare and most frequently occur in the first two decades of life. Immature teratomas exhibit malignant behavior, grow rapidly, spread by implantation throughout the peritoneal cavity, and metastasize primarily through the lymphatic system. Excision usually is followed by local recurrence, but combination chemotherapy often leads to permanent remission.

CLASSIFICATION OF OVARIAN TUMORS

The primary purpose of a tumor classification system is to provide a standardized, reproducible communication tool that reflects the variations in the natural history of the disease and can be readily used by everyone involved in the management of cancer. Development of such a system for ovarian tumors is a work in progress. In the past, a number of approaches were advanced, but all fell short of the stated goal. Some systems were purely clinical, based on the hormonal effects of ovarian tumors; however, different ovarian tumors may give rise to similar hormonal effects, similar tumors may have different hormonal effects, and hormonal products may be derived in some cases from nonneoplastic (e.g., stromal) sources rather than from the tumor itself. Systems based on the gross appearance of the tumors (solid or cystic) also were inadequate. A classification system based on tumor histogenesis would be a logical alternative, although the histogenesis of some ovarian tumors is controversial.

A significant stride in the direction of a histogenesis-based classification system was made in 1973 with the publication of the World Health Organization (WHO) *Classification of Ovarian Tumors.*[14] This classification system was updated in 1999[10] and was approved by the International Society of Gynecological Pathologists (Table 1). A summarized version of the WHO classification system was proposed in 1998 by the International Agency for Research on Cancer[15] for use in comparative studies; this system was used to classify histologic types of ovarian cancer in the current monograph (Table 2). Two coding systems, the WHO International Classification of Diseases for Oncology[16] and the College of American Pathologists Systematized Nomenclature of Medicine,[17] are commonly used to code the histology/morphology of tumors.

TABLE 1
WHO Histologic Classification of Ovarian Tumors[a]

1 Surface epithelial-stromal tumors
1.1 Serous tumors: benign, borderline, malignant
1.2 Mucinous tumors, endocervical-like and intestinal-type: benign, borderline, malignant
1.3 Endometrioid tumors: benign, borderline, malignant, epithelial-stromal and stromal
1.4 Clear cell tumors: benign, borderline, malignant
1.5 Transitional cell tumors: Brenner tumor, Brenner tumor of borderline malignancy, malignant Brenner tumor, transitional cell carcinoma (non-Brenner type)
1.6 Squamous cell tumors
1.7 Mixed epithelial tumors (specify components): benign, borderline, malignant
1.8 Undifferentiated carcinoma
2 Sex cord-stromal tumors
2.1 Granulosa-stromal cell tumors: granulosa cell tumors, thecoma-fibroma group
2.2 Sertoli-stromal cell tumors, androblastomas: well-differentiated, Sertoli-Leydig cell tumor of intermediate differentiation, Sertoli-Leydig cell tumor poorly differentiated (sarcomatoid), retiform
2.3 Sex cord tumor with annular tubules
2.4 Gynandroblastoma
2.5 Unclassified
2.6 Steroid (lipid) cell tumors: stromal luteoma, Leydig cell tumor, unclassified
3 Germ cell tumors
3.1 Dysgerminoma: variant-with syncytiotrophoblast cells
3.2 Yolk sac tumors (endodermal sinus tumors): polyvesicular vitelline tumor, hepatoid, glandular
3.3 Embryonal carcinoma
3.4 Polyembryoma
3.5 Choriocarcinoma
3.6 Teratomas: immature, mature, monodermal, mixed germ cell
4 Gonadoblastoma
5 Germ cell sex cord-stromal tumor of nongonadoblastoma type
6 Tumors of rete ovarii
7 Mesothelial tumors
8 Tumors of uncertain origin and miscellaneous tumors
9 Gestational trophoblastic diseases
10 Soft tissue tumors not specific to ovary
11 Malignant lymphomas, leukemias, and plasmacytomas
12 Unclassified tumors
13 Secondary (metastatic) tumors
14 Tumorlike lesions

WHO: World Health Organization.

[a] Source: Scully R, Sobin L. Histological typing of ovarian tumours, volume 9. New York: Springer Berlin, 1999.[10]

TABLE 2
IARC Histologic Groups of Ovarian Tumors[a]

Histologic type	WHO ICD-O morphology code
1. Carcinoma	8010–8570,[b] 9014–9015, 9110
1.1 Serous carcinoma[c]	8441–8462, 9014
1.2 Mucinous carcinoma[c]	8470–8490, 9015
1.3 Endometrioid carcinoma	8380–8381, 8560, 8570
1.4 Clear cell carcinoma	8310–8313, 9110
1.5 Adenocarcinoma NOS	8140–8190, 8211–8231, 8260, 8440
1.6 Other specified carcinomas	
1.7 Unspecified carcinoma	8010–8034
2. Sex cord-stromal tumors	8590–8671
3. Germ cell tumors	8240–8245, 9060–9102
4. Other specified cancers (including malignant Brenner tumor, müllerian mixed tumor, and carcinosarcoma)	
5. Unspecified cancer	8000–8004

IARC: International Agency for Research on Cancer; WHO: World Health Organization; ICD-O: International Classification of Diseases for Oncology; NOS: not otherwise specified.

[a] Source: Parkin DM, Shanmugaratnam K, Sobin L, Ferlay J, Whelan SL. Histological groups for comparative studies, volume 31. IARC technical report. Lyon: International Agency for Research on Cancer, 1998.[15]

[b] Excludes 8240–8245.

[c] Includes tumors of borderline malignancy (low malignant potential). Unlike borderline tumors of other types, borderline tumors of serous and mucinous types are included with carcinomas by ICD-O. This approach remains to be validated fully.

STAGING OF OVARIAN CANCER

The extent of tumoral spread, also known as *stage of disease,* at diagnosis is typically established by radiologic evaluation and surgical excision. Surgical management may include debulking of the tumor resection of one or both ovaries, fallopian tubes, and uterus, as well as sampling of lymph nodes, liver, and suspicious sites within the abdomen. Staging of ovarian surface epithelial-stromal tumors is performed according to the TNM system,[18] the set of guidelines established by the American Joint Committee on Cancer, which is comparable to an alternative staging system approved by the International Federation of Gynecology and Obstetrics (FIGO) (Table 3).[19]

HISTOLOGIC GRADING AND PROGNOSTIC FACTORS

Microscopic examination is critical for predicting tumor behavior and deciding the best therapeutic approach. Such examination includes the assessment of specific histologic type and extent of disease and the grading of tumor differentiation (i.e., the extent to which the tumor resembles the normal tissue). Tumors are graded as well-differentiated (G1), moderately differentiated (G2), poorly differentiated (G3), or undifferentiated (G4). As discussed above, surface epithelial-stromal tumors also can be classified as borderline malignancy (GB). Attempts to identify prognostically relevant pathologic features in ovarian cancers are hindered by the diversity of tumors that are encountered. Most reported prognostic information addresses surface epithelial-stromal tumors.

The two most important prognostic factors for surface epithelial-stromal tumors are tumor stage and the presence or absence of residual disease after treatment intervention.[18] Specific histologic typing and grading may have prognostic significance as well; however, the independent contribution of each of these factors after adjusting for tumor stage has not been well established. Assessment of their contribution is hampered by interobserver variability among pathologists, lack of standardization of grading schemes, and differences in treatment among published series. Most grading schemes analyze architectural and cellular characteristics of tumors and delineate three or four groups with increasing risks of aggressive behavior. Unfortunately, it is difficult to apply a single grading system consistently to all histologic types of ovarian cancer. Recently, modified grading systems that can be applied to all epithelial ovarian cancers have been proposed.[20,21] Early confirmatory studies are encouraging, as they indicate that histologic grading may finally establish itself as an important prognostic factor for patients with ovarian carcinoma.[22]

The grading of sex cord-stromal tumors has been frustrating. This is not unexpected, given that the histogenesis of several subtypes still is unclear. For some subtypes, definitive histologic criteria for making the distinction between benign and malignant tumors are lacking. Histologic features that relate to the potential for aggressive behavior appear to be subtype-specific; for example, all granulosa cell tumors are considered to have malignant potential. Attempts to grade these tumors using nuclear characteristics or mitotic activity counts have produced inconsistent results, whereas tumor size and stage appear to be more reproducible prognostic factors. Most stromal tumors are benign. The uncommon malignant variant, fibrosarcoma, is associated with an aggressive clinical course, but it lacks an established grading system. The steroid cell tumors (luteoma and Leydig cell tumor) also are difficult to classify as benign or malignant based on microscopic features alone. Pathologic features that are reported to be correlated with malignant behavior include large size, high mitotic rate, necrosis, hemorrhage, and prominent nuclear atypia. Other sex cord tumors (Sertoli cell tumor, Sertoli-Leydig cell tumor, sex cord tumor with annular tubules, and gynandroblastoma) have varied clinical behaviors that show some correlation with specific differentiation criteria

TABLE 3
Ovarian Surface Epithelial-Stromal Tumor Staging Protocols: AJCC TNM System[a] and FIGO Staging System[b]

AJCC	FIGO	Description
TX		Primary tumor cannot be assessed.
T0		No evidence of primary tumor.
T1	I	Tumor limited to ovaries (one or both).
T1a	IA	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface. No malignant cells in ascites[c] or peritoneal washings.
T1b	IB	Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings.
T1c	IC	Tumor limited to one or both ovaries, with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings.
T2	II	Tumor involves one or both ovaries with pelvic extension.
T2a	IIA	Extension and/or implants on uterus and/or tube(s). No malignant cells in ascites or peritoneal washings.
T2b	IIB	Extension to other pelvic tissues. No malignant cells in ascites or peritoneal washings.
T2c	IIC	Pelvic extension (2a/IIA or 2b/IIB) with malignant cells in ascites or peritoneal washings.
T3 and/or N1	III	Tumor involves one or both ovaries, with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis.[d]
T3a	IIIA	Microscopic peritoneal metastasis beyond pelvis.
T3b	IIIB	Macroscopic peritoneal metastasis (2 cm or less in greatest dimension) beyond pelvis.
T3c and/or N1	IIIC	Peritoneal metastasis (more than 2 cm in greatest dimension) beyond pelvis and/or regional lymph node metastasis.
M1	IV	Distant metastasis (excludes peritoneal metastasis).[e]

AJCC: American Joint Committee on Cancer, FIGO: International federation of Gynecology and Obstetrics.

[a] Source: Fleming ID, Cooper JS, Henson DE, Hutter RVP, Kennedy BJ. American Joint Committee on Cancer (AJCC) cancer staging manual. Philadelphia: Lippincott-Raven, 1997.[18]

[b] Source: Heintz AP, Odicino F, Maisonneuve P, et al. Carcinoma of the ovary. *J Epidemiol Biostat.* 2001;6:107–138.[19]

[c] *Ascites* is the accumulation of excessive fluid within the abdominal (peritoneal) cavity. The presence of nonmalignant ascites is not classified. The presence of ascites does not affect staging unless malignant cells are present.

[d] Lymph nodes located in the pelvis or in the back of the abdomen on either side of the aorta (*para-aortic*). Liver metastases confined to the capsule are T3/Stage III. Liver parenchymal metastases are M1/Stage IV.

[e] Pleural effusion must have positive cytology for M1/Stage IV malignancy.

that are well defined in the gynecologic pathology literature.[8]

Stage of disease at diagnosis is the most important prognostic factor for germ cell tumors. Determination of the specific histologic subtype has prognostic relevance, but grading within or across these categories generally is not performed. One exception is the immature teratoma, for which histologic grading is based on the amount of immature tissue (usually neuroectodermal) that is present.[11]

EXTRAOVARIAN PERITONEAL CARCINOMA

Beginning in the 1940s, several reports described the occurrence of an apparent ovarian cancer in women long after removal of their ovaries. The cause was hotly debated, but the microscopic resemblance of the malignancy to surface epithelial ovarian tumors (serous, mucinous, and endometrioid subtypes) was striking. Women with the disease experienced a clinical course similar to that of women with primary ovarian cancer. Some investigators believed that this was a latent manifestation of metastatic ovarian cancer that preceded removal of the ovaries. Others pointed to malignant transformation of ectopic endometrial tissue (e.g., endometriosis) as the source of these cancers, while another hypothesis was that the coelomic epithelium was shed throughout the peritoneum as it traveled along its migratory course through the embryonic female.

Whatever the cause, it is clear that a small proportion ($< 5\%$) of cancers that microscopically appear to be ovarian actually do not originate in the ovary and instead arise from the peritoneum. The morphologic subtypes of extraovarian peritoneal carcinomas (EOPC), now commonly referred to as *primary peritoneal carcinomas (PPC),* are limited to the more common subtypes of surface epithelial malignancies (serous, mucinous, and endometrioid), and the

distribution of subtypes in the peritoneum is similar to what is observed in the ovary itself—serous tumors are most common, whereas endometrioid tumors are relatively infrequent. In 1984, the Gynecologic Oncology Group advanced a clinicopathologic definition of PPC/EOPC and recommended that treatment be similar to treatments for more common ovarian malignancies with the same FIGO stage.

NEW DEVELOPMENTS IN OVARIAN CANCER PATHOLOGY

There is a growing effort to define the genetic and molecular makeup of ovarian malignancies. As the complex molecular events associated with ovarian cancer are uncovered, the hope is that in addition to providing insight into the pathogenesis of ovarian neoplasia, these events also will serve as prognostic factors, markers for treatment effectiveness (i.e., predictive factors), and targets for future therapies (e.g., immunotherapy).

Molecular and genetic studies have increased our understanding of the pathogenesis of some ovarian tumors, especially surface epithelial tumors. Loss of heterozygosity on chromosome 17q has been found specifically in serous tumors.[23,24] Allelic studies have shown that many (if not all) endometrioid and clear cell carcinomas may arise from preexisting endometriosis.[25] Molecular and immunohistochemical markers also can be valuable in determining whether mucinous carcinomas are primary ovarian tumors or secondary metastases from the colon or appendix.[26,27] Finally, identification of inherited germline mutations in BRCA1 and BRCA2 genes that lead to a high susceptibility to ovarian and breast cancer, has shed light on the pathogenesis of ovarian cancer and at the same time raised complex medical, social, economic, and ethical issues.[28,29]

Histopathologic grading of malignant ovarian tumors has had only modest prognostic application; however, the use of molecular markers shows some promise. Detection of proliferation markers, such as MIB-1, and mutant suppressor gene products, such as p53, has been shown to be correlated with prognosis,[30,31] as has detection of the cell cycle inhibitor p27.[32] A number of other cell proteins with various normal and aberrant functions are being investigated as potential prognostic tools.

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