additional genes, including those encoding PI3K and PP2A (a tumor suppressive phosphatase that is the target of the certain viral oncoproteins), in a significant number of serous carcinomas. Mutations in the genes encoding these two proteins are also found in serous endometrial intraepithelial carcinoma, suggesting that (like *TP53* mutations) they occur early in the development of this aggressive type of endometrial carcinoma.

MORPHOLOGY

Generally, serous carcinomas arise in small atrophic uteri and are often large bulky tumors or deeply invasive into the myometrium. The precursor lesion, **serous endometrial intraepithelial carcinoma,** consists of malignant cells identical to those of serous carcinoma that are confined to the epithelial surfaces (Fig. 22-26*A* and *B*). The invasive lesions may have a papillary growth pattern composed of cells with marked cytologic atypia including high nuclear-to-cytoplasmic ratio, atypical mitotic figures, hyperchromasia, and prominent nucleoli (Fig. 22-26*C* and *D*). However, they can also have a predominantly glandular growth pattern; in such cases they are distinguished from endometrioid carcinoma by the marked cytologic atypia. All of the tumors in this category are classified as grade 3 irrespective of histologic pattern. Serous carcinoma, despite relatively superficial endometrial involvement, may be associated with extensive peritoneal disease, suggesting spread by routes (i.e., tubal or lymphatic transmission) other than direct invasion.

Clinical Features. Carcinoma of the endometrium is uncommon in women younger than 40 years of age; the peak incidence is in postmenopausal women 55 to 65 years of age. There is no currently available screening test for carcinoma of the endometrium. Although it may be asymptomatic for a period of time, it usually produces irregular or postmenopausal vaginal bleeding with excessive leukorrhea. Fortunately, postmenopausal bleeding often leads to early detection, and cures are possible in most patients. Uterine enlargement may be absent in the early stages. The diagnosis of endometrial cancer must be established by histologic examination of tissue obtained by biopsy or curettage.

As would be anticipated, the prognosis depends heavily on the clinical stage at diagnosis, as well as histologic grade and subtype. In the United States, most tumors (about 80%) are stage I well-differentiated or moderately differentiated endometrioid carcinomas. Surgery, alone or in combination with irradiation, gives about 90% 5-year survival in stage I (grade 1 or 2) disease. This rate drops to approximately 75% for grade 3/stage I tumors and to 50% or less for stage II and III endometrial carcinomas.

As mentioned, serous carcinoma has a propensity for extrauterine (lymphatic or transtubal) spread, even when apparently confined to the endometrium or its surface epithelium. For unknown reasons, serous carcinoma occurs more frequently in women of African American descent, a difference that accounts for a two fold higher mortality rate in African American women compared with Caucasian women. Overall, the 5-year survival for women with serous carcinoma is 18% to 27% and even when it is confined to the uterus the recurrence rate is as high as 80%. Adjuvant radiation is often used to reduce local recurrence and chemotherapy is given to women with endometrioid carcinoma when it has spread beyond the uterus. However, because of the aggressive nature of serous carcinoma, women may be treated with chemotherapy even in the absence of detectable extrauterine spread. Inhibitors of the PI3K/AKT pathway are being tested in clinical trials and the continued identification of biologic targets is likely to expand the roster of rational therapies in the future.

Malignant Mixed Müllerian Tumors

Malignant mixed müllerian tumors (MMMTs) (also referred to as *carcinosarcomas*) are endometrial adenocarcinomas with a malignant mesenchymal component. The mesenchymal component can take a number of forms. Some contain tumor cells resembling uterine mesenchymal elements (stromal sarcoma, leiomyosarcoma), while others contain heterologous malignant cell types (rhabdomyosarcoma, chondrosarcoma). The epithelial and stromal components appear to be derived from the same founding cell, a concept supported by molecular studies showing the presence of shared mutations. Both clinicopathologic and molecular studies suggest that the vast majority of these tumors are carcinomas with sarcomatous differentiation. Mutations found in MMMTs tend to involve the same genes that are mutated in endometrial carcinoma, such as *PTEN*, *TP53,* and *PIK3CA*, while alterations typical of those found in sarcomas are absent. At present, the mechanisms underlying the sarcomatous transformation are unknown, but some abnormality of epigenetic regulation seems likely.

MORPHOLOGY

MMMTs are often bulky and polypoid, and may protrude through the cervical os. On histology, the tumors usually consist of adenocarcinoma (endometrioid, serous, or clear cell) mixed with the malignant mesenchymal (sarcomatous) elements (Fig. 22-27*A*); alternatively, the tumor may contain two distinct and separate epithelial and mesenchymal components. Sarcomatous components may also mimic extrauterine tissues (e.g., striated muscle, cartilage, adipose tissue, and bone). Metastases usually contain only epithelial components (Fig. 22-27*B*).

MMMTs occur in postmenopausal women and present with bleeding. Outcome is determined primarily by depth of invasion and stage. The only other known prognostic factor is the differentiation of the mesenchymal component; patients with tumors that have heterologous mesenchymal components do worse than those whose tumors do not. Overall 5-year survival rates are 25% to 30% for patients with high-stage disease.

KEY CONCEPTS

Endometrial Carcinoma

- Endometrial carcinoma is the most common malignancy of the female genital tract.
- There are two major types of endometrial carcinoma: type I and type II. Type I tumors are low-grade and usually indolent; type II tumors are high-grade aggressive tumors and have a poor prognosis.