when first discovered, are single, and 70% are localized to the bladder.

Individuals with urothelial tumors, whatever their grade, have a tendency to develop new tumors after excision, and *recurrences* may show a higher grade. The risk of recurrence and progression is related to several variables, including tumor size, stage, grade, multifocality, prior recurrence rate, and associated dysplasia and/or CIS in the surrounding mucosa. Although the term recurrence is used, most of the subsequent tumors arise at different sites from the original lesion. In some instances the recurrences may be entirely independent new tumors, but in other cases they share the same clonal abnormalities as the initial tumor and represent a true recurrence caused (presumably) by shedding and implantation of the original tumor cells at a new anatomic site.

Prognosis depends on the histologic grade and the stage at diagnosis. Papillomas, papillary urothelial neoplasms of low malignant potential, and low-grade papillary urothelial cancer yield a 98% 10-year survival rate regardless of the number of recurrences; only a few patients (<10%) have progression of their disease to higher grade lesions. High-grade papillary urothelial carcinomas invade and lead to death in about 25% of cases. Patients with primary (de novo) CIS, as opposed to CIS associated with infiltrating urothelial carcinoma, are less likely to progress to muscle-invasive cancer (28% versus 59%) or die of disease (7% versus 45%). Invasive urothelial carcinoma is associated with a 30% mortality rate once tumor invades into the lamina propria. Overall, squamous cell carcinoma and adenocarcinoma are associated with a worse prognosis than urothelial carcinoma, yet stage for stage they are all similar.

The clinical challenge with these neoplasms is early detection and adequate follow-up. A significant issue is that 50% of invasive bladder cancers present with muscle-invasive disease and have a relatively poor prognosis despite therapy. For tumors detected at an earlier stage, cystoscopy and biopsy are the mainstays of diagnosis. Subsequently, patients are typically followed with additional surveillance cystoscopies to look for tumor recurrence. Additionally, cytologic examination of cells obtained from urine samples and tests performed on urine to detect chromosomal abnormalities (aneuploidy of chromosome 3, 7, and 17 and 9p deletions) by fluorescent in situ hybridization (FISH) are also helpful screening measures, particularly for CIS that might be missed by cytoscopy. The major limitation of both FISH and cytologic screening is that they often fail to identify low-grade neoplasms.

The selection of treatment for bladder cancer depends on the grade, stage, and whether the lesion is flat or papillary. For small, localized low-grade papillary tumors, the diagnostic transurethral resection is the only surgical procedure done. Patients are followed with cystoscopy and urine cytology for the rest of their lives to detect recurrence. Patients at high risk of recurrence and/or progression (CIS; papillary tumors that are high grade, multifocal, have a history of recurrence, or are associated with lamina propria invasion) receive intravesical instillation of an attenuated strain of *Mycobacterium bovis* called bacillus Calmette-Guérin (BCG). The bacteria elicit a local inflammatory reaction that destroys the tumor. Radical cystectomy is typically reserved for (1) tumor invading the muscularis propria, (2) CIS or high-grade papillary cancer refractory to BCG, and (3) CIS extending into the prostatic urethra and into the prostatic ducts, where BCG will not come into contact with the neoplastic cells. Metastatic bladder cancer responds to chemotherapy, but is not curable with current agents.

Mesenchymal Tumors

Benign Tumors. A great variety of benign mesenchymal tumors may arise in the bladder, having the histologic features of their counterparts elsewhere. Collectively, they are rare. The most common is *leiomyoma.* They all tend to grow as isolated, intramural, encapsulated, oval-to-spherical masses, varying in diameter up to several centimeters.

Sarcomas. True sarcomas are distinctly uncommon in the bladder. Inflammatory myofibroblastic tumors and various carcinomas may assume sarcomatoid growth patterns and be mistaken histologically for sarcomas. As a group, sarcomas tend to produce large masses (varying up to 10 to 15 cm in diameter) that protrude into the vesicle lumen. Their soft, fleshy, gray-white gross appearance suggests their sarcomatous nature. The most common sarcoma in infancy or childhood is *embryonal rhabdomyosarcoma.* In some of these cases they manifest as a polypoid grapelike mass *(sarcoma botryoides).* The most common sarcoma in the bladder in adults is leiomyosarcoma (Chapter 26).

Secondary Tumors

Secondary malignant involvement of the bladder is most often by direct extension from primary lesions in nearby organs, cervix, uterus, prostate, and rectum. Lymphomas may involve the bladder as a component of systemic disease, but also, rarely, as primary bladder lymphoma.

KEY CONCEPTS

Bladder Tumors

- Bladder cancer is more common in males than in females and cigarette smoking constitutes one of the most important risk factors.
- Painless hematuria is a common presenting symptom of bladder cancer and requires clinical investigation by cystoscopy and/or urine cytology specimens to rule out urothelial neoplasia.
- There are two different noninvasive precursor lesions to invasive urothelial carcinoma: papillary urothelial carcinoma (which may be low- or high-grade) and flat urothelial carcinoma in situ (uniformly high grade).
- Noninvasive high-grade urothelial carcinoma (either papillary or flat) is associated with loss of the *TP53* and *RB* tumor suppressor genes and frequently progresses to muscle-invasive disease with the potential for systemic spread.
- Noninvasive low-grade papillary urothelial carcinoma is associated with gain of function *FGFR3* and *HRAS* mutations. While these tumors are infrequently life-threatening, they may locally recur and a subset may progress to high grade disease.