Indications for cystectomy include muscle-invading tumors not suitable for segmental resection; non–muscle-invasive tumors unsuitable for conservative management (e.g., due to multicentric and frequent recurrences resistant to intravesical instillations); high-grade T1 tumors especially if associated with CIS; and bladder symptoms (e.g., frequency or hemorrhage) that impair quality of life.

Radical cystectomy is major surgery that requires appropriate preoperative evaluation and management. It involves removal of the bladder and pelvic lymph nodes and creation of a conduit or reservoir for urinary flow. Grossly abnormal lymph nodes are evaluated by frozen section. If metastases are confirmed, the procedure is often aborted. In males, radical cystectomy includes the removal of the prostate, seminal vesicles, and proximal urethra. Impotence is universal unless the nerves responsible for erectile function are preserved. In females, the procedure includes removal of the bladder, urethra, uterus, fallopian tubes, ovaries, anterior vaginal wall, and surrounding fascia.

Several options are frequently used for urinary diversion. Ileal conduits bring urine directly from the ureter to the abdominal wall. Some patients receive either a continent cutaneous reservoir constructed from detubularized bowel or an orthotopic neobladder. Approximately 25% of men receive a neobladder, leading to 85–90% continence during the day. Cutaneous reservoirs are drained by intermittent catheterization. Contraindications to a neobladder include renal insufficiency, an inability to self-catheterize, or CIS or an exophytic tumor in the urethra. Diffuse CIS in the bladder is a relative contraindication based on the risk of a urethral recurrence. Concurrent ulcerative colitis or Crohn's disease may hinder the use of bowel.

A partial cystectomy may be considered when the disease is limited to the dome of the bladder, a ≥2 cm margin can be achieved, there is no associated CIS, and the bladder capacity is adequate after resection. This occurs in 5–10% of cases. Carcinomas in the ureter or in the renal pelvis are treated with nephroureterectomy with a bladder cuff to remove the tumor.

The probability of recurrence following surgery is based on pathologic stage, presence or absence of lymphatic or vascular invasion, and nodal spread. Among those whose cancers recur, the recurrence develops in a median of 1 year. Long-term outcomes vary by pathologic stage and histology (Table 114-1). The number of lymph nodes removed is also prognostic, whether or not the nodes contained tumor.

Chemotherapy (described below) has been shown to prolong the survival of patients with muscle-invasive disease when combined with definitive treatment of the bladder by radical cystectomy or radiation therapy. Presurgical (or neoadjuvant) chemotherapy has been the most thoroughly explored, and increases the cure rate by 5–15%, whereas postsurgical (adjuvant) chemotherapy has not been proven definitively beneficial. For the majority of patients, chemotherapy alone is inadequate to eradicate the disease. Use of neoadjuvant chemotherapy is increasing, although it still remains underused. Experimental studies are evaluating bladder preservation strategies by combining chemotherapy and radiation therapy in patients whose tumors were endoscopically removed.

METASTATIC DISEASE

The primary goal of metastatic disease treatment is to achieve complete remission with chemotherapy alone or with a combined-modality approach of chemotherapy followed by surgical resection of residual disease. One can define a goal in terms of cure or palliation on the basis of the probability of achieving a complete response to chemotherapy using prognostic factors, such as Karnofsky performance status (KPS) (<80%) and whether the pattern of spread is nodal or visceral (liver, lung, or bone). For those with zero, one, or two risk factors, the probability of complete remission is 38, 25, and 5%, respectively, and median survival is 33, 13.4, and 9.3 months, respectively. Patients who have low KPS or who have visceral disease or bone metastases rarely achieve long-term survival. The toxicities also vary as a function of risk, and treatment-related mortality rates are as high as 3–4% using some combinations in these poor-risk patient groups. For most patients, treatment is palliative, aimed at delaying or relieving cancer-related symptoms, because few patients experience durable complete remissions.

CHEMOTHERAPY

A number of chemotherapeutic drugs have activity as single agents; cisplatin, paclitaxel, and gemcitabine are considered most active. Standard therapy consists of two-, three-, or four-drug combinations. Overall response rates of >50% have been reported using combinations such as methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC); gemcitabine and cisplatin (GC); or gemcitabine, paclitaxel, and cisplatin (GPC). MVAC was considered standard, but the toxicities of neutropenia and fever, mucositis, diminished renal and auditory function, and peripheral neuropathy led to the development of alternative regimens. At present, GC is used more commonly than MVAC based on the results of a comparative trial of MVAC versus GC that showed less neutropenia and fever and less mucositis for the GC regimen with similar response rates and median overall survival. Anemia and thrombocytopenia were more common with GC. GPC is not more effective than GC.

Chemotherapy has also been tested in the neoadjuvant and adjuvant settings. In a randomized trial, patients receiving three cycles of neoadjuvant MVAC followed by cystectomy had a significantly better median (6.2 years) and 5-year survival (57%) compared to cystectomy alone (median survival 3.8 years; 5-year survival 42%). Similar results were obtained in an international study of three cycles of cisplatin, methotrexate, and vinblastine (CMV) followed by either radical cystectomy or radiation therapy. The decision to administer adjuvant therapy is based on recurrence risk after cystectomy. Studies of adjuvant chemotherapy have been underpowered, and most closed for lack of accrual. One underpowered study using the GPC regimen suggested that adjuvant treatment improved survival, although many patients never received chemotherapy for metastases. Another underpowered study did not show a benefit for GC chemotherapy. Therefore, preoperative chemotherapy is preferred when medically appropriate. Indications for adjuvant chemotherapy in patients who did not receive neoadjuvant treatment include nodal disease, extravesical tumor extension, or vascular invasion in the resected specimen.

The management of bladder cancer is summarized in Table 114-2.

CARCINOMA OF THE RENAL PELVIS AND URETER

About 5000 cases of renal pelvis and ureter cancer occur each year; nearly all are transitional cell carcinomas similar to bladder cancer in biology and appearance. This tumor is associated with chronic phenacetin abuse and aristolochic acid consumption in Chinese herbal preparations; aristolochic acid also seems to be associated with Balkan nephropathy, a chronic interstitial nephritis endemic in Bulgaria, Greece, Bosnia-Herzegovina,

TABLE 114-1 SURVIVAL FOLLOWING SURGERY FOR BLADDER CANCER

Pathologic Stage	5-Year Survival, %	10-Year Survival, %
T2,N0	89	87
T3a,N0	78	76
T3b,N0	62	61
T4,N0	50	45
Any T,N1	35	34

TABLE 114-2 MANAGEMENT OF BLADDER CANCER

Nature of Lesion	Management Approach
Non–muscle-invasive disease	Endoscopic removal, usually with intravesical therapy
Muscle-invasive disease	Cystectomy ± systemic chemotherapy (before or after surgery)
Metastatic disease	Curative or palliative chemotherapy (based on prognostic factors) ± surgery