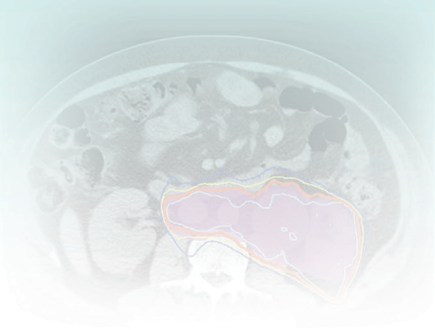
CHAPTER

54 Bladder Cancer



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INCIDENCE

Carcinoma of the urinary bladder is diagnosed in approximately 74,000 people each year in the United States, making it the fourth-most common cancer in men (56,000) and eleventh in women (18,000). Approximately one third will have muscle-invasive disease. About 16,000 (1,100 men, 4,500 women) will die from bladder cancer in 2015. Urothelial (transitional cell) carcinoma has strong etiologic connections with smoking. The less common squamous cancer is more closely associated with chronic inflammation such as *Schistosoma* infection or indwelling catheter.

BIOLOGIC CHARACTERISTICS

The most important predictors of progression from nonmuscle-invading stage to the muscle-invasive stage are high grade, penetration of the lamina propria, and the presence of carcinoma in situ. Once muscle invasion has occurred, the strongest predictors of metastasis and death are bulk of tumor and depth of invasion.

Expression studies and now large-scale sequencing efforts are providing new insights into the landscape of recurrent molecular alterations in bladder cancer and potentially targetable mutations and personalized treatment selection for patients undergoing selective bladder preservation. These include biomarkers prognostic and predictive of response and outcome involved in cell-cycle regulation, apoptosis, proliferation, DNA repair, chromatin regulation, kinase signaling pathways, and hypoxia. These biomarkers continue to be investigated and need further validation.

STAGING EVALUATION AND WORKUP

Painless hematuria is the classic and most common presentation, though irritative voiding symptoms may occur as well. Urine cytology commonly indicates cancer but cystoscopy and transurethral resection is necessary for definitive assessment of the primary tumor.

Magnetic resonance imaging (MRI) may define penetration of the bladder wall and either MRI or computed tomography (CT) scan can evaluate abdominopelvic lymph nodes. The upper tracts must also be evaluated with CT, intravenous pyelogram (IVP), or retrograde ureteroscopy because synchronous tumors are common. Chest x-ray (or CT of the chest) and bone scan are usually obtained to rule out metastatic disease when cancer invades the muscle.

PRIMARY THERAPY

Nonmuscle-invading tumors are managed by transurethral resection of the bladder tumor (TURBT) alone in the case of low-grade lesions and together with intravesical bacillus Calmette-Guérin (BCG) for high-grade, lamina propria invasion, or carcinoma in situ. Over 10 years as many as 50% of the latter group will progress to muscle invasion.

Radical cystectomy with urinary diversion is the United States standard for the management of muscle-invading cancers. There is 90% control within the pelvis, but up to 50% ultimately die of distant metastasis. Radical radiation alone provides only 30% to 40% local control though the use of salvage cystectomy keeps cure rates close to that of primary cystectomy. When limited surgery (TURBT) is combined with radiation and concurrent (often cisplatin-based) chemotherapy, more than 70% of patients keep their native bladders and cure rates are comparable to published cystectomy series. Quality-of-life studies show high levels of satisfaction with the retained bladder.

ADJUVANT THERAPY

Neoadjuvant chemotherapy downstages the primary tumor more than 50% of the time but only adds 5% to 10% to the chance for cure. Adjuvant chemotherapy is commonly used but has proven utility only in the case of node-positive disease.

Adjuvant radiation may be given after cystectomy for locally advanced disease but the benefits need to be better defined.

LOCALLY ADVANCED DISEASE AND PALLIATION

When there is hydronephrosis, extension into adjacent organs or nodal spread, the likelihood of cure is small. Cystectomy or radiation may be used for palliation of voiding symptoms or bleeding, but the mainstay of care for metastatic disease is combination chemotherapy.

Bladder cancer is a chemoresponsive disease. Cisplatin-based regimens give responses in more than 60% of patients and are often quite durable. Other active agents include Taxotere, gemcitabine, and 5-fluorouracil (5-FU)/mitomycin C.

Radiation therapy is effective in palliating painful bone metastases and in alleviating symptoms from brain metastases.

Approximately 70% of all new cases of bladder cancer are early stage and have not yet invaded the detrusor smooth muscle. In the absence of muscle invasion, endoscopic transurethral resection (TUR) with or without intravesical therapy is the therapy of choice, and the radiation oncologist plays only a limited and occasional role. For muscle-invading disease, the most appropriate treatment algorithm remains controversial. Although radical cystectomy has long been the standard treatment in the United States, organ-preserving regimens using radiation with concurrent chemotherapy are comparably effective alternatives in selected patients.

In this chapter, we separately discuss the treatment of nonmuscle-invading and muscle-invading disease. Special emphasis is placed on the development of combined-modality therapy in muscle-invading bladder cancer with and without bladder preservation.

ETIOLOGY AND EPIDEMIOLOGY

Bladder cancer is the most common malignancy involving the urinary system and the second-most common genitourinary cancer. It is the sixth-most common cancer overall; fourth-most common cancer among men and the eleventh-most common cancer among women. It is estimated that there will be approximately 74,000 new cases and 16,000 bladder cancer deaths in 2015.[1] The rates of new cancers and deaths have been fairly stable in men and have been dropping slightly in women in recent years. The reasons for the disparity between the sexes are not well understood. More than 500,000 people in the United States are bladder cancer survivors.

Internationally, incidence rates of bladder cancer vary almost 10-fold. Highest rates occur in western Europe and North America; relatively low rates are found in eastern Europe and several areas of Asia (China, India, Philippines).[2,3]

Cancer of the bladder occurs primarily in older men. Median age at diagnosis of is 73 years. More than two thirds of cases occur among persons age 65 and older. The incidence rate among African American and Hispanic men is about 50% of that among whites. The male-to-female ratio is at least 3:1, approaching 4:1 in whites.[4] Five-year survival rate for all patients is 77% (96% for in situ disease, 69% localized, 34% regional, and 5% distant). Overall incidence and death rates have been relatively stable over the past 10 years.

Risk Factors

Cigarette smoking and various environmental and occupational exposures are the major risk factors for bladder cancer. These substances concentrate in the urine, where the urothelial lining is exposed to their carcinogenic effects. Cigarette smoking is associated with up to 50% to 60% of bladder cancer diagnosed in men and 30% among women in the United States. Occupational exposure among white men accounts for 25% of bladder cancer diagnoses in men and 11% in women. Specific chemicals linked to bladder carcinogenesis include beta-naphthylamine, 4-aminobiphenyl, and benzidine. Evidence also suggests that chlorinated organic compounds formed as a by-product of drinking water chlorination may account for 10% to 15% of cases. Infection with *Schistosoma haematobium* is a well-documented risk factor and an important cause of bladder cancer in developing countries.

Cigarette smoking increases the risk of bladder cancer two- to fourfold. Risk estimates for moderate to heavy smokers range from 2 to 10 compared with nonsmokers.[5-9] Smokers with less functional polymorphisms of N-acetyltransferase-2 (known as slow acetylators) have a higher risk of bladder cancer than other smokers, presumably because of their reduced ability to detoxify carcinogens.

Some studies indicate a reduction in risk by more than 30% within the first year to 4 years after cessation of smoking, and more than 60% 25 years after cessation, but even after 25 years the risk still does not reach the background level of never smokers.[7,9] Smoking cessation may decrease recurrence rates for patients with nonmuscle-invasive disease.[10] Exposure to secondhand smoke in women may be a risk factor for the development of bladder cancer.[11]

In the 1950s, occupational exposures to aromatic amines in the British dyestuff and rubber industries were found to be associated with bladder cancer.[12,13] The mean time from start to exposure to death was 25 years, with the greatest risk for workers who started before age 25. Workers in the leather industry are at increased risk for bladder cancer.[14,15] The increased risk for painters seems to be the result of many known carcinogens in paint such as benzidine, polychlorinated biphenyls, formaldehyde, asbestos, and solvents such as benzene, dioxane, and methylene chloride.[16] Drivers of trucks, buses, or taxicabs are suspected to have an increased exposure to exhaust emissions containing polycyclic aromatic hydrocarbons (PAHs) and nitro-PAHs.[17]

It was first recognized in the 1970s that chlorination of drinking water generates a wide array of halogenated organic compounds. A number of epidemiologic studies investigated the possible association between exposure to these compounds and cancer. A 1992 meta-analysis of these studies found a significant association between exposure to chlorination by-products and bladder cancer.[18] Several studies published subsequently supported this conclusion.[19,20] High levels of arsenic in drinking water have also been linked to the subsequent development of bladder cancer.[21]

Aromatic amines are detoxified by *N*-acetylation. The *N*-acetyltransferase enzyme in the liver is polymorphic, displaying a slow and a rapid acetylator phenotype. The allele that confers a slow acetylator phenotype is assumed to be associated with an increased risk of bladder cancer (relative risk, 1.1 to 1.9).[22]

There are several other well-documents risk factors. Exposure to *S. haematobium* infection is associated with a predominantly increased risk of squamous cell carcinoma of the bladder.[23] Heavy consumption of phenacetin-containing analgesics was linked to cancer of the renal pelvis, ureter, and bladder.[24] Cyclophosphamide, an alkylating agent, and pelvic radiation have also been linked to the risk of bladder cancer.[25-27] Other risk factors include low total daily fluid intake, chronic cystitis, indwelling catheters, recurrent urinary tract infections, and consumption of Chinese herbs containing aristolochic acid.[28,29]

PREVENTION AND EARLY DETECTION

Primary prevention involves identification and avoidance of cancer-causing factors.[30] In public health terms, avoidance and cessation of cigarette smoking is the most effective means available for the prevention of bladder cancer. Decreasing exposure to workplace carcinogens and increasing fluid intake are other useful approaches.

Secondary prevention involves screening individuals at high risk for a particular cancer with the goal of early detection and treatment. Urine cytology as a screening test is low cost and low risk and has excellent specificity > 98% but relatively poor sensitivity, particularly for low-grade tumors (overall sensitivity 34%, with sensitivities for grades 1, 2 and 3 tumors of 12%, 26%, and 64%, respectively).[31] Furthermore, the prevalence of preclinical bladder cancer is probably too low in the general population for large-scale screening programs to be rewarding. Testing for asymptomatic hematuria does not appear to be a useful method for screening. A single test has a low sensitivity. Repeat testing at short intervals, such as weeks, has been advocated but yields unacceptably high rates of false-positive results.[32,33] Overall, screening has not been particularly useful in the detection of bladder cancer and the most recent statement from the U.S. Preventive Services Task Force concludes that the current data are insufficient to make a definitive recommendation on screening for bladder cancer in asymptomatic adults.[34] When urothelial cancer is suspected, noninvasive screening may be performed using cytology, nuclear matrix protein, telomerase, or fluorescence in situ hybridization (FISH) analysis, but the definitive diagnosis is made only by cystoscopy and biopsy.

Chemoprevention involves the administration of a natural or synthetic agent to healthy people (primary) or patients with precancerous conditions who are at high risk for bladder cancer (secondary) to prevent or retard the development or progression of cancer. Retinoids (vitamin A derivatives) as

well as high-dose multivitamins, pyridoxine (vitamin B6), alpha tocopherol (vitamin E), ascorbic acid, polyamine synthesis inhibitors, polyphenols (green tea extract), COX-2 inhibitors (celecoxib), EGFR tyrosine kinase inhibitors (erlotinib), and oltipraz have been or are under investigation as potential chemopreventive agents,[35-45] but nothing definitive has been established at present. Additional studies are under way.

PATHOLOGY AND PATHWAYS OF SPREAD

In the United States, more than 90% of cancers arising in the bladder are urothelial carcinoma (UC), also known as transitional cell carcinoma (TCC). Less common pathologies are squamous cell carcinoma (SCC), adenocarcinoma, and small cell carcinoma, comprising approximately < 10% of bladder tumors, respectively. In Egypt, SCC comprises 70% of all bladder cancers.

Macroscopically, papillary growth is more frequent than solid tumors (approximately 80% versus 20%). Solid tumors are more likely than papillary tumors to be high grade and invasive into the muscularis propria layer.

Although the collective term *superficial cancer* is still commonly used, it is a category that comprises several classes of transitional cell cancers with different rates of recurrence, different rates of progression to muscle invasion, and quite different treatments. The tumors that arise in the epithelium and develop in an exophytic (papillary) pattern are known as Ta tumors. They are usually low grade (I or II), and although they tend to recur, they are considered to be relatively benign lesions that closely resemble the normal urothelium. Although they have more than the normal seven layers of urothelium, they show normal nuclear polarity in more than 95% of tumors and no or only slight pleomorphism. When progression deeper into the submucosa or lamina propria occurs the tumor is described as T1 and carries a higher risk of progression and even of metastasis.

Grade is an important predictor of recurrence and progression for all categories of superficial disease. Pathologic grades I to III (low, intermediate, or high) are based on the number of mitoses, presence of nuclear abnormalities, and cellular atypia. High-grade tumors show loss of polarization of the nuclei and moderate to prominent pleomorphism. Muscle-invasive disease, however, is usually high grade, and depth of invasion is the more important prognostic factor for outcome.

Carcinoma in situ (Tcis) is defined as noninvasive, high-grade, flat cancer confined to the epithelium, which can be localized or diffuse, and it may occur in association with either superficial or muscle-invasive TCC. Tcis can also occur without a concurrent exophytic tumor. Endoscopically, Tcis presents as a friable red area indistinguishable from inflammation and spreads laterally, displacing normal epithelium. Urine cytology is positive in 90% of patients with Tcis because of a loss in the cohesiveness of cells.

In T2 lesions, muscle invasion is present and the probability of nodal and distant spread is increased. T2 disease is divided into superficial (T2a) or deep (T2b) invasion.[46]

SCCs are associated with chronic inflammation or infection with *Schistosoma* and tend to grow as large masses with a high degree of necrosis. In North America they are more commonly associated with chronic bladder irritation or stasis such as a lifelong indwelling catheter. The North American variant has the distinction of higher metastatic propensity.

TCC is often multifocal both in place and in time (polychronotropism). This is a striking characteristic of this disease but the etiology is uncertain. Two of the most commonly held explanatory theories are a genetic field defect with multiple new tumors spontaneously arising or, alternatively, the local reimplantation of tumor cells ("local metastasis). Evidence strongly suggests that tumor reimplantation or submucosal migration is the predominant mechanism. Multifocal tumors as well as upper tract and lower tract lesions arising in one individual demonstrate clonality.[47] Therefore, the entire urothelium needs to be evaluated if a tumor is found.

External and internal iliac chains as well as perivesical lymph nodes are first-echelon lymph nodes. Common iliac, paraaortic, and paracaval lymph nodes are considered second-echelon lymph nodes. Lymph node sampling in patients undergoing cystectomy should include excision of 12 or more lymph nodes.[47]

Bladder cancer can also spread by direct extension or hematogenous metastases. Direct extension can be to the prostate, pelvic side wall, anterior pelvic structures, symphysis pubis, rectum, or sigmoid colon. Hematogenous metastatic spread is most frequently seen to the lung, liver, and bone. Peritoneal metastases are another route of spread.

MOLECULAR BIOLOGY

Newly discovered cellular mechanisms and their associated proteins have become the subject of intense interest. This is partly for what they tell us about the biology of a tumor but also because of their potential role as prognostic markers or therapeutic targets. It has long been recognized that invasive bladder tumors are extremely heterogeneous in nature despite almost always being of high-grade transitional cell morphology because of complex genetic and epigenetic interactions that play a direct role in the initiation and progression of TCC. When the range of genetic alterations is considered, deletions (e.g., loss of tumor suppressor genes) generally arise in early stage disease, whereas gains and amplifications (e.g., activation of oncogenes) may be more frequent in advanced stages of disease. Genetic factors may also modify the risk associated with exogenous agents through activation or detoxification of potential carcinogens. The search to understand the heterogeneity and use it to therapeutic advantage is only just beginning. At the moment the best prognostic indicators we have in bladder cancer are clinical: stage, grade, tumor size, uni- or multifocality, and the presence or absence of either hydronephrosis or lymph node involvement (see later). No molecular biomarker has yet come close to improving on these clinical markers, but it is anticipated that they will in the near future.[48,49] Likely this will involve a combination of multiple independent markers and an individual tumor's gene expression pattern.

Apoptosis and Cell Cycle Receptors

These receptors provide malignant cells with an evolutionary selective advantage. These include cellular immortalization, escape from G1 checkpoint control, loss of DNA damage checkpoints (G2/M), loss of normal DNA repair mechanisms, loss of apoptotic response, and the development of invasive capabilities.[50-52] The *pRb* and *p53* pathways, which involve several common molecules, provide G1 checkpoint control and regulate the response to DNA damage. Though the *Rb* gene itself is only mutated in a few specific cancers it is thought that abnormalities of its function are far more common and transitional cell bladder cancer is one of these.[51,53-55] Disruption of its function is required to overcome the restraint it imposes on cell-cycle progression. The pro-apoptotic tumor suppressor gene eliminates cells with abnormalities in their *Rb* pathways. Thus, tumors commonly have abnormalities in p16 and p14ARF and abnormalities at these loci may also be required to overcome the checkpoints that protect the cell from aberrant stimuli. *p53* mutations, which may be detected by nuclear immunohistochemistry, are present in more than one half of bladder tumors and appear to be related to the progression of

bladder cancer and to outcome following treatment.[53,56-59] A meta-analysis of 168 studies assessing *p53* overexpression showed a weak, although significant, association with overall risk of relapse and mortality.[60] Cooperative group trials of either methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy or chemoradiation have not shown any clear association between *p53*, *pRb*, or *p16* or status and outcome.[61,62] Other genes that have been studied include *Bax*, *Bcl-2*, *p21*, survivin, and matrix metalloproteinases.[63-70]

Researchers from Germany have suggested that one does not have to analyze the molecular pathways relating to apoptosis to predict response; a measure of the baseline spontaneous apoptotic rate of the tumor may be easier and quite sufficient. High-apoptotic index and high Ki-67 index correlated with improved complete response, local control, and cause-specific survival with a preserved bladder following chemoradiation. The inability to undergo spontaneous apoptosis whether the result of overexpression of *Bcl-2* or survivin appears to predict local failure after irradiation and chemotherapy.[71]

The RAS family of transforming genes is often overexpressed in bladder cancer. Their presence may be related to the original development of the tumor. In a mouse model, farnesyltransferase inhibitors, which inhibit the posttranslational modifications of H-ras, worked synergistically with radiation in reducing tumor relapse.[72]

Growth Factor Receptors

The epidermal growth factor (EGFR) family of receptor tyrosine kinases is known to initiate a complex program of signal transduction events that modulate cell survival, invasion, migration, proliferation, and differentiation. This family has a number of members of which *erb-1* (EGFR) and *erb-2* (Her-2) are characterized the best. The role of these receptors has been studied extensively in recent years in a variety of malignancies and there is evidence that increased activity through this pathway is common.

Both EGFR and Her-2 are commonly overexpressed in urothelial tumors. Numerous studies have investigated expression of Her-2 in bladder cancer using immunohistochemistry and have found overexpression in 30% to 80% of tumors.[60,73-76] There are, however, conflicting data on the relationship between the expression of these receptors with response to treatment and clinical outcome.

An RTOG study evaluated the clinical relevance of EGFR and Her-2 expression as measured by immunohistochemical staining on slides from 73 patients treated on four of the RTOG bladder preservation trials and pointed to a more favorable prognosis in those who overexpress EGFR but a lower complete response rate in patients with TCC who overexpress Her-2.[62] EGFR positivity (EGFR-1 expression identified in 19% of patients) correlated with improved overall survival (OS, $p = 0.044$), disease-specific survival (DSS, $p = 0.042$), and survival with an intact bladder ($p = 0.021$). A trend toward decreased incidence of distant metastases was also associated with EGFR expression. On multivariate analysis, adding tumor stage, tumor grade, whether or not a visibly complete TURBT was done, and patient age to the model, EGFR positivity remained significantly associated with improved DSS. Her-2 overexpression correlated with reduced complete response rates to chemoradiation (50% versus 81%, $p = 0.026$), which remained significant on multivariate analysis. *p53* and *p16* had no prognostic significance. These patients had all been treated with chemotherapy and radiation, and it may be that EGFR has a more direct involvement in improving the response of TCC to these agents than it does other tumors. It will be crucial to elucidate this relationship clearly as a growth factor receptor may be either a favorable or an unfavorable marker depending on the proposed therapy. The RTOG data suggested that targeting the Her-2 pathway may be more profitable than EGFR in the initial therapy of muscle-invasive bladder cancer. There is certainly experimental evidence that Her-2 has an antiapoptotic effect and that tumor radiosensitization can result from targeting this mechanism.[77] RTOG trial 05-24 evaluated the addition of trastuzumab (Herceptin) to paclitaxel and daily radiation following TURBT in the treatment of noncystectomy candidates with muscle-invasive bladder cancer. The protocol was completed with 70 patients accrued in 2013. Thirty-one percent of patients overexpressed Her-2. Among patients with evaluable data, overall complete response rate was 62% (trastuzumab group) versus 58%.[78] This response rate was higher than expected from historical controls.

Another RTOG study evaluated VEGF pathway biomarkers and outcomes following chemoradiation for patients managed with selective bladder preservation.[79] No correlations of ligands VEGF A-D or receptors VEGF R1-2 were found with response to induction chemoradiation or with local tumor recurrence. However, VEGF-B overexpression did predict for distant failure and worse OS. Therefore, VEGF-B might prove useful in identifying patients more likely to benefit from early cytotoxic therapy or anti-VEGF–targeted therapies.

Alterations in fibroblast growth factor receptor (FGFR) expression and signaling have emerged as recurring and potentially important events in bladder urothelial carcinoma. In bladder cancer, these alterations primarily occur in one of the following ways: (1) activating mutations in the extracellular ligand-binding domain of FGFR3 that lead to ligand-independent signaling, (2) overexpression of the receptor, or (3) fusions primarily with TACC3 or BAIAP2L1. In addition, FGFR3 gene copy number alterations occur but are rare.[79a-79e] Data suggests that the presence of mutations in fibroblast growth factor receptor 3 (FGFR3) identifies a subgroup of patients with nonmuscle-invasive disease who may have a favorable prognosis.[80] Further investigation into the potential diagnostic and therapeutic implications of such findings is warranted and may lead to the rational development of targeted therapies.

DNA Repair

Biomarkers involved in DNA repair may also be prognostic and even predictive following radiation-based therapy.

Excision repair cross-complementing 1 (ERCC1) is vital for nucleotide excision repair (NER) and may predict efficacy of chemoradiation. Cisplatin-DNA adducts can by removed by NER, thus high levels of ERCC1 expression have been correlated with cisplatin resistance. ERCC1 also may participate in double-stranded break (DSB) repair and cells deficient in ERCC1 are highly sensitive to ionizing RT. ERCC1 down-regulation in high-expressing cells results in sensitization to RT but not cisplatin. Expression levels of ERCC1 in human tumors correlate with treatment response and survival to platinum-based chemotherapy and chemoradiation. Clinical complete response (CR) rate for patients with negative ERCC1 was 86% (12 of 14), compared to 25% (2 of 8) for patients with positive ERCC1.[81] Five-year OS was 31.2% for those with positive ERCC1 and 69.2% for those with negative ERCC1. Therefore, ERCC1 expression levels may predict for patients unlikely to respond to a chemoradiotherapy-based approach. Another recent effort found that tumors with ERCC2 mutations were enriched among muscle invasive bladder tumors that responded well to cisplatin-based combination cytotoxic chemotherapy.[80a]

X-ray repair cross-complement group 1 (XRCC1) and human AP endonuclease 1 (APE1) are both proteins vital for base excision repair (BER) in DNA repair. Increased expression

A cooperative group trial tested the role of three cycles of combination MVAC chemotherapy in patients with negative nodes but mutated *p53* given that *p53* alteration was thought to be prognostic for relapse in patients with urothelial bladder cancer and predictive for benefit from combination MVAC adjuvant chemotherapy.[61] Accrual was halted on the basis of a futility analysis. Overall 5-year probability of relapse was 0.20 (95% CI, 0.16 to 0.24) with no difference on the basis of *p53* status. Although the study was underpowered, neither the prognostic value of *p53* nor the benefit of MVAC chemotherapy in patients with *p53*-positive tumors was confirmed. These data emphasize the importance of careful validation of any biomarker before proceeding on with Phase III analysis. Work from the Radiation Therapy Oncology Group (RTOG) on patients who were treated with chemotherapy and radiation have also not shown any clear association between either *pRb*, *p16*, or *p53* status and outcome.[62]

Other genes regulating apoptotic function or involved in the initiation of bladder carcinogenesis and its progression have been studied, such as *Bax*, *Bcl*-2, *p21*, survivin, and matrix metalloproteinases.[63-70] In examining a large database containing bladder cancer of different stage all treated by a variety of methods it did seem that those who had Bax or CD40L tumors lived longer. Bcl-2 positivity appeared to predict worse survival. The caveat, however, is that most of these were not prospective studies balanced for other prognostic variables.

The FDA has approved the use of ZD1839, an inhibitor of EGFR1, for patients with lung cancer and of trastuzumab, a monoclonal antibody against EGFR2 or Her-2, for appropriate patients with breast cancer. In breast cancer, overexpression of Her-2 is associated with poor prognosis, and the activity of trastuzumab unequivocally correlates with overexpression of Her-2.

of XRCC1 and APE1 were both associated with improved DSS, but only when both were present ($p = 0.0003$).[82]

Ionizing radiation creates DNA damage sensed by the MRE11/NBS1/RAD50 (MRN) complex, which initiates cell cycle checkpoints, activates apoptosis, and is involved in MRN-mediated DSB repair. MRE11 (meiotic recombination homolog) is a vital member of the MRN complex responsible for detecting DNA DSB. Along with Rad50 and NBS1/XRS2, MRE11 is responsible for activation of checkpoint kinases and induction of cell cycle arrest in response to DNA damage. It is vital for recruiting ATM and other mediators of DSB repair. A group in the United Kingdom has shown that reduced tumor MRE11 protein expression by immunohistochemistry is associated with and appears to be predictive of poorer cause-specific survival (CSS) following radical RT for bladder cancer.[83] High-MRE11 expression was associated with superior CSS in patients treated with radical RT with a 57% improvement in CSS at 3 years ($p = 0.012$). The effect of MRE11 expression on clinical outcomes was only evident in patients treated with RT and not those treated with cystectomy. When compared, similar patients with high-MRE11 expression had improved CSS when treated with RT compared to cystectomy, whereas the opposite was true for those with low-MRE11 expression. MRE11 expression levels may therefore identify a cohort of patients with improved survival when treated with RT compared to cystectomy.

Mechanistically, it was postulated that failure of cell cycle arrest/apoptosis responses may result in radioresistance and reduced local tumor control.

The MRE11 findings were validated by a Danish group, who showed that TIP60 (histone acetyltransferase involved in chromatin remodeling and DNA repair) was a predictive marker for DSS in a cystectomy cohort, and MRE11 in an RT cohort.[84] In that study, *p16* also correlated with DSS, but was not predictive. *Ki67*, *p53*, and *pATM* were not correlated with DSS in any of the cohorts.

Hypoxia

Hypoxia is well recognized to be strongly associated with both radiation and chemotherapy resistance. Indeed, the addition of carbogen and nicotinamide (CON) to RT improves OS in invasive bladder cancer. Hypoxia results in the upregulation of genes that facilitate anaerobic metabolism and promote tumor vascularization. One such hypoxia–inducible factor is carbonic anhydrase IX (CA IX). It appears to be useful as a surrogate marker of hypoxia within bladder tumors. Several studies have shown that the majority of bladder tumors express this marker though it appears, strangely, to be more strongly expressed in superficial than invasive tumors. Evidence on its role as a prognostic marker has been conflicting.[85,86] Necrosis seems to predict benefit from hypoxia modification in patients with high-risk bladder cancer.[87] The hypoxia marker hypoxia-inducible factor-1α (HIF-1α) may be used to predict benefit from CON in patients with bladder cancer but does not improve on use of necrosis.[88]

Future of Molecularly Targeted Therapy

To date, no molecularly targeted agents have been approved for treatment of bladder cancer. Large scale sequencing efforts are likely to change this and provide new insights into the molecular alterations in bladder cancer and targetable mutations.

The addition of rational molecular targeted therapy and personalized treatment selection based on biomarkers (e.g., DNA repair, apoptosis, proliferation, hypoxia, such as high MRE11, normal Her2, low ERCC1, high XRCC1/APE1) of response and outcome, continues to be investigated and needs further validation. Future focused correlative analyses using findings discussed in this section are likely to refine clinically useful biomarkers for patients undergoing selective bladder preservation.

CLINICAL PRESENTATION, PATIENT EVALUATION, AND STAGING

Clinical Presentation

Painless, gross, and episodic hematuria is the most frequent presenting manifestation of bladder cancer (80%), typically present through urination. It also may be associated with irritative symptoms (dysuria, frequency, urgency), which can occur in up to one third of patients and is suggestive of bladder carcinoma in situ (CIS). Ten percent to 20% of patients presenting with gross hematuria are diagnosed with bladder cancer.[89,90] Some asymptomatic patients proven to have bladder cancer are found to have microscopic hematuria or less frequently pyuria. Bladder tumors can cause strangury (pain on straining to urinate), urinary retention, ureteral obstruction, sepsis, and rarely life-threatening hematuria. Regional pelvic disease may cause flank pain because of nerve invasion, edema, and ureteral obstruction. The signs and symptoms of bone, liver, pulmonary, and central nervous system metastases may be present if disease has disseminated.

Workup of Hematuria or Suspected Bladder Tumor

Patient workup should include physical examination (including digital rectal and bimanual), voided urine analysis, urinary cytology, intravenous pyelogram or CT urogram (for upper tract evaluation), and cystoscopy with biopsy of suspicious lesions. If the disease is classified as T1 or greater, the work-up must include abdominopelvic CT scan or MRI and chest radiograph (or chest CT). For those with muscle-invading disease a bone scan is also necessary.

Endoscopy

The endoscopic evaluation forms the mainstay of diagnosis and staging. Initially, an outpatient cystoscopy with biopsy is performed, and urine is obtained for cytology. Cystoscopy provides direct visualization of the bladder and facilitates biopsy of the bladder. Number, size, shape, and location of tumors as well as appearance of the surrounding mucosa, urethra, and urethral orifice are documented. Size (<2 cm, >5 cm), shape (papillary or flat), and associated Tcis lesions are of predictive importance. Using an illustrative bladder map, the location, number, size, and characteristics (papillary versus sessile) of the bladder tumor as well as presence or absence of CIS should be noted. Fluorescence cystoscopy after intravesical instillation of a photoactive substance (a porphyrin such as 5-aminolevulinic acid [5-ALA]) that preferentially accumulates in neoplastic tissue may be more effective than white light cystoscopy. Randomized trials have shown that fluorescence endoscopy detects more tumors (particularly CIS) and this improved tumor identification may result in better patient management and reduced disease recurrence,[91-93] though not all clinical trials have shown a benefit.

If the findings are positive for bladder cancer, a subsequent cystoscopic TURBT, which is generally performed under epidural or general anesthesia, is scheduled.

TURBT and Bladder Biopsy

Cold cup biopsies of all suspicious areas, the mucosa surrounding the area, any exophytic lesions, and the prostatic

The Cancer Genome Atlas project recently reported an integrated analysis of 131 urothelial carcinomas to provide a comprehensive landscape of molecular alterations.[49] There were statistically significant recurrent high frequency mutations/alterations in 32 genes, including multiple genes involved in cell-cycle regulation, chromatin regulation, and kinase signaling pathways, as well as 9 genes not previously reported as significantly mutated in any cancer. RNA sequencing revealed four expression subtypes, two of which (papillary-like and basal/squamous-like) were also evident in microRNA sequencing and protein data. Whole-genome and RNA sequencing identified recurrent in-frame activating FGFR3-TACC3 fusions and expression or integration of several viruses (including HPV16) that are associated with gene inactivation. These analyses identified potential therapeutic targets in 69% of the tumors, including 42% with targets in the phosphatidylinositol-3-OH kinase/AKT/mTOR pathway and 45% with targets (including ERBB2) in the RTK/MAPK pathway. Chromatin regulatory genes were more frequently mutated in TCC than in any other common cancer studied so far, indicating the future possibility of targeted therapy for chromatin abnormalities.

urethra as well as random biopsies of all four quadrants are obtained. All material is collected. When diffuse CIS is present, the prostatic urethra contains neoplastic cells in up to 25% of cases. For evaluation of muscle invasion, sufficient resection to provide adequate staging has to be done. An attempt is usually made to resect the bladder tumor as completely as is safely possible (i.e., a maximal safe resection).

Bimanual Examination

Bimanual examination is performed before and after complete TUR, and the size and mobility of any palpable mass are evaluated. A residual palpable mass suggests muscle invasion. Most invasive bladder cancers are located near the trigone or posterior bladder wall and cannot be reliably palpated. This procedure alone leads to understaging in up to 50% of patients.

Urinary Cytology

Urine cytology should be used to complement the findings of cystoscopy. It is extremely valuable for the diagnosis of high-grade TCC, especially CIS that might be difficult for the endoscopist to visualize, and upper tract malignancies. The presence of high-grade TCC in the cytology specimen in patients with low-grade papillary TCC suggests either unrecognized CIS or less commonly high-grade disease in the upper urinary tracts.[94,95] For the diagnosis of low-grade papillary tumors, cytology is not sensitive because grade 1 TCC appears to be identical to normal urethral cells.[31]

Cytology has been regarded as the gold standard for noninvasive screening of urine for bladder cancer. It has a sensitivity of around 40% to 60% with specificity in excess of 98%.[31] Cytology is illustrative of the problems of noninvasive screening. Poorly differentiated tumors have a 20% false-negative detection rate whereas well-differentiated tumors have up to an 80% false-negative detection rate.

Multiple urine-based biomarkers have been developed because of the low sensitivity of cytology and perhaps benefit from the lack of subjectivity by the person reading the test.[96-101] These tests identify proteins in urine, detect cellular antigens by immunohisto- or cytochemistry, or use FISH microsatellite analysis of free DNA, and telomerase reverse transcriptase determination to identify genetic alterations associated with bladder cancer.

Imaging

Although fewer than 60% of bladder cancers are seen on intravenous urography, this imaging modality provides valuable information about the status of the upper urinary tract.[102] Ureteral obstruction or a nonfunctioning kidney predicts muscle-invasive disease in 90% of cases.[103] Concomitant or subsequent upper urinary tract tumors are found in 2% to 5% of patients. CT urography has replaced IVP as the procedure of choice, though IVP remains an appropriate alternative when CT is not available.

Evaluation of a patient with potential muscle-invading bladder cancer should include CT scan of the abdomen and pelvis (with and without contrast and with delayed images). Although it is not sensitive in reliably describing the depth of invasion or lymph node involvement, it can be helpful in determining extravesical extension and the planning for subsequent treatment. Notably, the detection of lymph node metastases with CT imaging is poor (high false-negative rate). About 20% to 30% of patients with node-negative disease by CT have positive nodes at time of cystectomy with lymphadenectomy.[104,105]

Gadolinium-enhanced MRI imaging may prove useful in distinguishing superficial from invasive disease and in distinguishing intra- from extravesical tumor.[106-110] Lymphangiography using iron nanoparticles and MRI might be particularly useful in detecting early nodal metastases.[110] Positron emission tomography (PET) has limited value. All bladder-specific imaging should be performed before TURBT, because of postsurgical edema.

Patients with Ta or low-grade T1 tumors do not require extensive metastatic workup. However, those with muscle-invading tumors have up to a 50% risk of occult metastatic disease and should have chest imaging and a bone scan.

Staging

Stage is the most important independent prognostic variable for progression-free survival and OS for invasive bladder cancer. The basis for the major staging systems is the classic clinicopathologic study by Jewett and Strong,[111] which correlates the probability of regional lymph node and distant metastases with the depth of invasion of the primary bladder tumor. The tumor, node, and metastasis (TNM) system of 2010 is shown in Table 54-1 and Figure 54-1.[46] Of note, CT and MRI are not used for staging of the primary in the TNM system. If lymphadenectomy is performed, sampling should include excision of an average of 12 or more lymph nodes.

In clinical practice, the correlation between depth of invasion, based on cystoscopic evaluation, and the final cystectomy specimen is only 50% to 60%. Significant rates of clinic-pathologic stage discrepancy and clinical (TURBT) understaging have been described. That is to say that 40% to 50% of patients undergo pathologic upstaging.[113,114] The accuracy of the determination of degree of muscle infiltration is, therefore, modest at best. The clinical staging system as

TABLE 54-1 AJCC 2010 TNM Bladder Cancer Staging

PRIMARY TUMOR(T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary tumor
Tis	Carcinoma in situ
T1	Tumor invades the lamina propria (subepithelial connective tissue), but not beyond
T2	Tumor invades the muscularis propria
pT2a	Tumor invades superficial muscle (inner half)
pT2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate, seminal vesicles, uterus, vagina, pelvic or abdominal wall
T4a	Tumors invade prostatic stroma, uterus, vagina
T4b	Tumor invades pelvic or abdominal wall
REGIONAL LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed
NO	No regional lymph nodes metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Multiple regional lymph node metastases in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Lymph node metastasis to the common iliac region
DISTANT METASTASIS (M)	
MX	Distant metastasis cannot be assessed
MO	No distant metastasis
M1	Distant metastasis

Markers include nuclear matrix proteins (e.g., NMP22), fibrin/fibrinogen degradation products (FDP), cytokeratins,[6,16-18] hyaluronic acid, urinary bladder cancer antigen (BTA), basic fetoprotein, survivin, telomerase, microsatellite DNA, UroVysion, and chromosomal abnormalities (3, 7, 17, 9p21). These approaches have demonstrated a higher sensitivity than urine cytology, but lower specificity. However, none of these markers have sufficient sensitivity (especially for low-grade small tumors) and diagnostic reliability to replace cystoscopy and their clinical use has not been recommended by consensus panels. Additional trials are needed to evaluate these newer techniques and their clinical and cost-effectiveness as they are integrated into patient management.

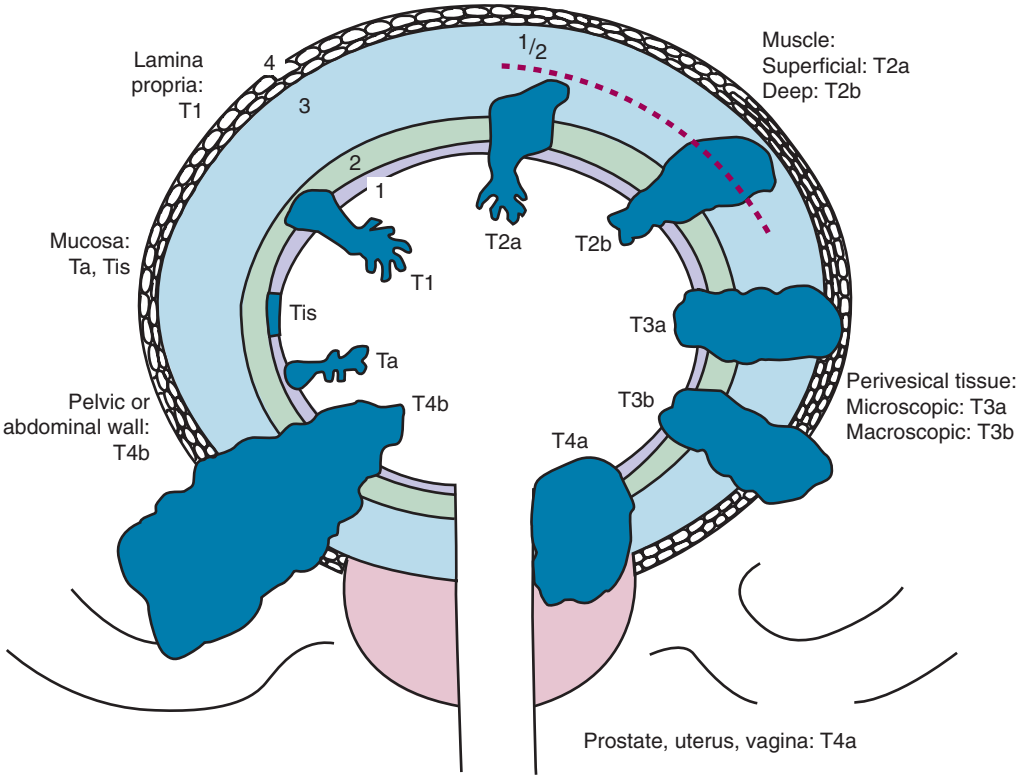

Figure 54-1 Staging of bladder tumors.

proposed by Union Internationale Contre Cancer was often more practical. Cancer without residual induration after TURBT was staged as T2 and cancer with palpable residual induration, T3. The most important determination of treatment outcome seems to be whether the tumor is organ confined (≤T2) or not organ confined (≥T3). When comparing outcome for different treatment modalities, it is important to consider whether the disease was staged clinically or whether a cystectomy specimen was available for a thorough pathologic staging.

PRIMARY THERAPY

The presence or absence of muscle invasion is the key factor in determining the appropriate treatment option for bladder cancer. In the absence of muscle invasion, endoscopic TUR with or without intravesical therapy is the therapy of choice.

The most appropriate treatment algorithm for muscle-invading disease remains controversial. Although radical cystectomy has long been the standard treatment in the United States, organ-preserving regimens using radiation with concurrent chemotherapy have emerged as viable alternatives in select patients (Figure 54-2).[115,116] These two approaches appear to have similar survival rates in uncontrolled comparisons, but strong physician and patient preferences have so far prevented completing a randomized, controlled trial comparing these treatment options.[117]

Noninvasive Bladder Cancer (Ta, T1, Tcis)

Transurethral Resection (TURBT)

Patients with superficial nonmuscle-invasive TCC (including Ta, T1, and Tis) account for approximately 70% of all newly diagnosed bladder cancer cases and are initially treated by TURBT. The appropriate treatment regimen may also include adjuvant intravesical therapy for a selected patient population. Decisions concerning the use of adjuvant therapy are based primarily on the probability of disease progression, not the probability of recurrence.

The majority (40% to 80%) of patients with superficial TCC will eventually experience recurrent disease after TURBT.[118] Progression to invasive disease after TURBT alone occurs in 10% to 25% of patients and is closely associated with tumor type, stage, and grade.[119,120] Other factors include multicentric disease, frequency of recurrence, tumor size, and presence or absence of concomitant CIS.

Although Ta, G1 tumors have recurrence rates higher than 50% at 5 years, they rarely (5% or less) invade or cause death. Consequently, TUR alone may be sufficient treatment for these tumors.

The risk of progression is substantially higher for tumors of higher grade or stage. Ta, G2-3 disease will progress to invasive TCC in 20% of cases at 5 years after treatment with TURBT alone. Nearly all patients (>70%) with T1 disease have high-grade tumors, and approximately 50% experience invasive disease at 5 years. In patients with T1 disease with CIS in the pathologic specimen, the rate of progression rises to 80% at 5 years.[121,122]

Intravesical Therapy

Bacillus Calmette-Guérin

Intravesical therapy involves the instillation of high local concentrations of a therapeutic agent into the bladder, potentially destroying viable tumors cells and preventing implantation. BCG, a live attenuated form of *Mycobacterium bovis*, is currently the most effective and most commonly used intravesical agent for treatment of nonmuscle-invasive TCC of the bladder. BCG is typically instilled into the bladder weekly for 6 weeks. The role of maintenance BCG for longer than 6 weeks remains

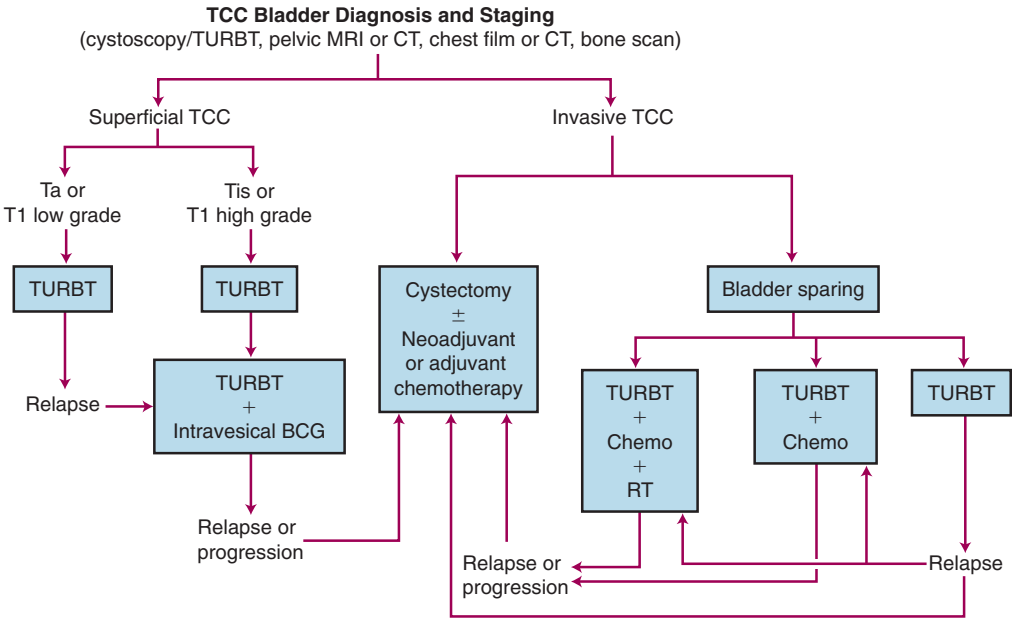

Figure 54-2 Diagnosis and treatment algorithm. *BCG*, Bacillus Calmette-Guérin; *Chemo*, chemotherapy; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *RT*, radiation therapy; *TCC*, transitional cell carcinoma; *TURBT*, transurethral resection of the bladder tumor.

controversial. For a number of patients who respond to induction, maintenance BCG therapy may be used for up to 3 years, although patients frequently discontinue therapy early because of bladder toxicity.

Several randomized, controlled trials compared TURBT alone with TURBT plus BCG.[123-127] Those treated with BCG had significantly fewer recurrences at 12 months. For patients with Ta, G2-3, and T1 disease, adjuvant therapy with BCG reduces the rate of progression to 5% to 15% at 5 years. Nonetheless, 50% of patients with T1/CIS will experience muscle-invading cancer at 10 years. Progression rates to muscle invasion among patients who respond to BCG are 1% at 1 year, 5% at 3 years, and 15% at 5 years.

The positive impact on progression translates into a survival advantage.[128,129] With long-term follow-up, adjuvant intravesical BCG improved survival rates to 88%, compared to 63% with TURBT alone, and reduced the cystectomy rates from 42% to 20%.[128]

Besides reducing progression and improving survival, BCG treatment also delays tumor recurrence in approximately 50% of patients. In the published randomized, controlled trials in which TURBT plus BCG was compared with TURBT alone, recurrence rates ranged from 20% to 42% with intravesical therapy versus 42% to 100% without.

Intravesical therapy is the first-line treatment for diffuse CIS. The average complete response rate of CIS to BCG is greater than 70% for more than 1 year.[130] It prevents subsequent disease in 60% of cases for up to 5 years and in 40% of cases for up to 10 years. Particularly in CIS of the prostatic urethra, BCG has spared many patients cystectomy. TURBT is recommended to stage the disease and to open the bladder neck to allow BCG to bathe the prostatic urethra.

One consequence of controlling the bladder component of disease in a patient with a TCC of the bladder is an increase in the frequency of extravesical relapses,[131] hence careful follow-up is required. Relapses can develop anywhere transitional epithelium is found: renal pelvis, ureters, and urethra. The risk for upper tract tumor is 20% at 5 years, 25% at 10 years, and 33% at 15 years. Prostatic urethra and duct involvement at 5 years is 10% to 15% and at 10 years, 20%. If a complete resection of tumors of the urethra cannot be obtained, patients are managed with cystectomy. Patients with a positive cytology and no obvious bladder tumor need careful monitoring of the upper tracts. Urethroscopic resection and instillation of BCG through the renal pelvis is possible.

Careful follow-up surveillance is required after intravesical therapy. This includes repeat cystoscopy and urine cytology 3 months after therapy, at 3- to 6-month intervals for the first few years and then annually. Surveillance should include imaging of the upper tracts every 1 to 2 years, unless very low risk. For residual or recurrent disease, a repeat TURBT and course of intravesical therapy may be indicated. Cystectomy should be considered for persistent or recurrent tumor after one to two cycles of intravesical therapy.

Role of Irradiation in High-Risk Superficial Bladder Cancer

It is well recognized that TURBT may clinically understage tumors as noninvasive when they have already invaded into the muscle wall (approximately 20% to 30%). Radiation therefore has an advantage in that it can reach tumor deposits too deep for instillation therapy. There have been no randomized trials comparing RT to current intravesical treatment options. The Dutch South Eastern Bladder Cancer Group has presented data in 121 patients with T1G3 cancers.[135] External RT with 50 Gy was one treatment option and 17 patients received this. Though the numbers are limited it appeared to be as effective as intravesical BCG or mitomycin. Good results have also been achieved at the University of Rotterdam with interstitial implants.[136] In this selective but prospective series, patients with single T1-tumors of less than 5 cm in diameter underwent TURBT and subsequent local irradiation of the tumor area in the bladder wall by an interstitial radium implant. The definitive local control rate was 82% and the 10-year survival rate 76%. Another group in the Netherlands has published their results using a combination of transurethral resection, external beam radiotherapy (EBRT; 3.5 Gy × 3 to 4), and interstitial radiotherapy (mean implant dose of 55 Gy) in patients with solitary T1G3 and T2-tumors.[137] The local control rate was 70% in the whole patient population.

BCG triggers a variety of local immune responses and has been shown effective in reducing rates of disease progression, decreasing recurrence and the need for subsequent cystectomy, and improving survival. Toxicities of intravesical therapy include symptoms of bladder irritation (dysuria and frequency).[122a] To minimize risk of systemic infection, intravesical therapy should not be given to patients with traumatic catheterization, active cystitis, or persistent gross hematuria.

Several conditions other than those just outlined call for the use of intravesical therapy with BCG. These include CIS and frequent recurrence of low-grade disease. Urothelial dysplasia or severe atypia can be treated prophylactically with BCG. Persistent positive urine cytology without associated upper tract lesions, and disease involving more than 40% of the bladder surface are also indications for intravesical therapy.

Other Agents

Although BCG is the treatment of choice for intravesical therapy, a variety of other agents have been investigated, such as mitomycin C, doxorubicin, epirubicin, valrubicin, thiotepa, gemcitabine, interferon, and docetaxel. None has proved consistently superior to BCG,[130,132-134] especially in cases of high-risk disease features (high grade, T1, Tis), though they may have a role in BCG failures and as an immediate single postoperative dose for patients at low risk of recurrence following TURBT. Novel approaches to decrease recurrence following initial treatment for nonmuscle-invasive bladder cancer include photodynamic therapy.

The 5-year DSS was 80% for T1 tumors and 60% for T2a. One randomized trial of EBRT alone (60 Gy in 30 fractions) in the management of high-grade T1 TCC of the bladder did not seem to indicate a benefit over observation for patient with unifocal disease or over BCG for those with multifocal disease or CIS.[138]

A large series of 141 patients with high-risk T1 cancers treated with either TURBT plus EBRT with or without platinum-based chemotherapy comes from the University of Erlangen.[139,140] In this series, 88% of patients achieved a CR, about 15% progressed to muscle-invasive disease after 5 years and 30% at 10 years, which compares favorably to most studies of TURBT and instillation therapy. DSS at 5 years and 10 years was 82% and 73%, respectively. More than 80% of survivors preserved their bladder, and 70% were "delighted" or "pleased" with their urinary function. These results suggest that irradiation may have a role to play in patients with high-grade or recurrent T1 lesions and may be attempted ahead of cystectomy on protocol or in place of cystectomy in those who are medically inoperable.

Currently there is an open Phase II protocol in RTOG (protocol 0926) for patients with recurrent BCG refractory T1 bladder cancer evaluating selective organ preserving treatment by irradiation plus concurrent chemotherapy (either cisplatin or 5-fluorouracil [5-FU]/mitomycin C) following a thorough TURBT.

Muscle-Invading Bladder Cancer (T2-4)

Muscle-invading tumors comprise 20% to 25% of all newly diagnosed bladder cancers. The most appropriate treatment algorithm for muscle-invading disease remains controversial. Although radical cystectomy and urinary diversion has been the mainstay for treatment for decades, organ-preserving regimens using predominantly multiple-modality therapy, consisting of TURBT followed by irradiation with concurrent chemotherapy, have emerged as viable proven alternatives in select patients. Refining the treatment choice by maximizing quality of life without compromising survival is the ultimate goal.

Radical Cystectomy

Surgical Methods

Radical cystectomy entails the surgical removal of the bladder, adjacent organs, and regional lymph nodes. Although traditionally performed as an open procedure, laparoscopic and robotic radical cystectomy have been investigated as less-invasive alternatives. In male patients, the bladder, prostate, seminal vesicles, proximal vas deferens, and proximal urethra, with a margin of adipose tissue and peritoneum, are resected en bloc. In females, the procedure involves an anterior pelvic exenteration to remove the bladder, urethra, uterus, fallopian tubes, ovaries, anterior vaginal wall, and surrounding fascia en bloc. The extent of bilateral pelvic lymph node dissection is an important predictor of outcome and many centers have adopted an extended template dissection to include presacral and common iliac lymph nodes to the aortic bifurcation and often more proximal to the origin of the inferior mesenteric artery, in addition to pelvic lymph nodes distal to the common iliac bifurcation.[141] Before cystectomy, grossly abnormal lymph nodes are sampled. In case of metastases, cystectomy is aborted unless urinary diversion is required to relieve symptoms. Urinary diversion is usually accomplished through an ileal conduit opening onto the anterior abdominal wall through a urostoma though continent diversions including a neobladder reconstruction are growing in popularity.

Incontinent Urinary Tract Reconstruction. In the early 1950s, Bricker et al developed what was to become the most common type of diversion after cystectomy, the ileal conduit diversion. Urine drains directly from the ureters through a segment of ileum to the skin surface, where it is collected by an external collection appliance.

Continent Urinary Tract Reconstruction. Techniques for performing continent urinary diversions have been developed over the past 20 years. The two most important approaches are formation of a continent urinary reservoir made of bowel (small bowel alone or plus colon), which drains to a stoma that can be catheterized, and creation of an orthotopic neobladder, in which a newly formed urinary reservoir made out of bowel (ileum, ileo-colon, sigmoid colon) is anastomosed to the urethra.

Morbidity of Cystectomy

Operative mortality from cystectomy in modern series ranges from 1% to 3%, with postoperative complication rates ranging from 15% to 64% and a 26% readmission rate.[147-150] Complications include hemorrhage, rectal injury, deep venous thrombosis, pulmonary embolus, pelvic abscess, sepsis from urine or bowel leak, wound infection/dehiscence, and small-bowel obstruction. The frequency of complications appears to be related to surgeon experience, hospital volume, age, and presence of comorbidities.

The need for urinary diversion and loss of sexual function in patients undergoing radical cystectomy are the most serious side effects and may impair quality of life dramatically. In women, loss of sexual function occurs secondary to subtotal vaginectomy and in men secondary to prostatectomy with loss of vascular supply or nerves serving penile erection. Newer nerve-sparing techniques for men may allow for up to approximately 50% of selected patients to regain their erectile potency.[151]

When feasible, continent urinary diversions achieve 82% continence rates with early complication rates of 15% to 20% and mild hypochloremic acidosis in 50% of the patients. Intestinal obstruction, acute pyelonephritis, ureteral obstruction, hydronephrosis, stomal stenosis, intestinal fistula, and ureteroileal urinary leakage are also reported. Ten percent of patients experience ureteral-intestinal strictures, reservoir dysfunction requiring augmentation of the pouch, and dysfunction of the stoma. Overall, 10% to 15% of patients require reoperation. Decreased renal function is noted in most patients during long-term followup after radical cystectomy.[152] Choice of urinary diversion does not appear to be independently associated with decreased renal function.

Cancer Outcome after Cystectomy

Contemporary large series provide the best data on outcome after radical cystectomy.[153-157] The University of Southern California reported on 633 patients undergoing radical cystectomy with pathologic stages pT2-T4a with an actuarial OS rate at 5 years of 48% and at 10 years of 32%.[153] The series from the Memorial Sloan Kettering Cancer Center (MSKCC) showed that in 184 patients with tumors of pT2-4, the 5-year OS was 36%. The 5-year OS for all 269 patients with pathologic stages ranging from pT0 to pT4 was 45%.[154] Pathologic stage or T category is a significant independent predictor of survival and local control. By clinical stage, 5-year OS was 56% for T1, 50% for T2, and 23% for T3a-b. Five-year local relapse rates by pathologic stage ranged from 6% for pT2 disease to 51% for pT3b.

The presence or absence and extent of lymph node disease, and the lymph node density (ratio of number of positive lymph nodes to the number of lymph nodes removed) are also significant determinants of survival.[158] The estimated

a. Cutaneous Urinary Reservoir. The two main options are reservoirs made from colon and small bowel (Indiana pouch) or entirely from small bowel (Kock pouch).[142,143] The Indiana pouch consists of approximately 25 cm of right colon often including some distal ileum, which is brought to the abdominal wall. It relies on the ileocecal valve for continence. Patients catheterize the pouch on average four to six times per day.

The Kock pouch is a cutaneous continent urinary reservoir constructed from 60 cm of ileum, with an afferent antireflux nipple valve for the ureteral intestinal anastomosis and an efferent nipple valve for the catheterizable stoma. Major complication rates of around 20% are reported. Incontinence, difficulty with catheterization, loss of antireflux features of the nipple valve, and urinary leaks are the major problems with these diversions.

b. Orthotopic Diversion. A neobladder is constructed from ileum, ileo colon, or sigmoid colon and anastomosed to the native urethra as opposed to the abdominal wall. This permits the patient to void in a relatively normal fashion per urethra. The Mainz pouch (neobladder) consists of an ileocecal segment, which is detubularized and anastomosed to the urethra.[144] The Hautmann pouch consists of a W-shaped ileo-neobladder, in which 60 cm ileum is configured into a sphere.[145]

The choice of urinary diversion is based on patient and surgeon preferences and may be influenced by the extent of cancer. Orthotopic bladders are contraindicated when the tumor involves the urethra. Orthotopic neobladders are becoming increasingly common in patients undergoing cystectomy but have been predominantly used in men. They are less common in women because of the technical difficulties in maintaining continence and the risk of urethral recurrence given the shorter length of the female urethra.[146]

It remains true, however, that many patients still do not receive a continent reservoir because of intercurrent disease, impaired renal function, surgery time, dilated ureters, and bowel disease.

probability of 5-year OS of patients with nodal metastases is 29%; with one to five nodes positive 35%, and with six or more nodes positive 17%.[159] The incidence of positive lymph nodes varies according to pathologic tumor stage. In cystectomy series, it ranged from 0% to 6% for superficial disease, 18% to 22% for muscle-invasive disease (pT2, 6% to 20%; pT3a, 30% to 31%), 30% to 64% for disease invading the perivesical fat (pT3b), and 45% to 59% for disease invading adjacent organs (pT4).[160-162]

Other factors that may influence outcome include the quality of surgery, margin status, presence of lymphovascular invasion and marker status (*p53, p21, pRb, p16*). Nomograms that consider multiple prognostic factors such as stage, nodal status, tumor grade and histology, lymphovascular invasion, and age have been developed.[163]

Although the disease is locally controlled, many patients will ultimately develop distant metastases (5-year distant disease rate for T3-4, 40% to 50%; T2, 30%). Median time to diagnosis of distant metastases is approximately 18 months. The most common sites for distant metastases are bone, lung, and liver.

Radiation as an Adjunct to Cystectomy

Preoperative Radiation Therapy

The recognition that moderate-dose radiation (20 Gy to 50 Gy) may reduce the volume of gross disease and eradicate microscopic TCC led to its frequent use before cystectomy in the 1970s.[164,165] In nonrandomized studies, these doses were found to reduce the frequency of metastases in the lymphadenectomy specimens by approximately 50%.[166] By the 1980s, improvements in the technique of radical cystectomy, together with the introduction of more extensive therapeutic lymphadenectomies, made many question the need for radiation.[167] It has been argued that radiation delays the time to definitive surgery, increases its morbidity, and may compromise the surgeon's ability to perform continent urinary diversions. The question was addressed by an intergroup trial reported in 1997[168] in which 140 patients with invasive or recurrent superficial bladder cancers were randomized to receive cystectomy alone or plus preoperative radiation (20 Gy in five fractions). There was no significant survival advantage to either group at 5 years. The trial was small, the doses low, and the predominant pattern of failure distant, all factors that would make it practically impossible to detect any advantage to radiation. Parsons and Million[169] did, however, demonstrate an apparent survival advantage for patients with clinical T3 tumors who received preoperative radiation.

Cole et al reported on 133 patients with T3b disease treated at the M. D. Anderson Cancer Center (MDACC).[170] This retrospective review documented that when pelvic wall recurrence occurs following modern radical cystectomy, it is usually only in patients who had clinical stage T3b or T4 tumors. They report a 28% incidence of pelvic recurrence in patients with stage T3b disease treated by radical cystectomy, with or without multidrug chemotherapy. However, when patients with stage T3b disease were treated with preoperative EBRT (which this institution used extensively before 1980), the pelvic recurrence rate was only 10%. Before 1983, all patients underwent 50-Gy preoperative EBRT (25 to 28 fractions over 5 to 5.5 weeks), followed 4 weeks later by cystectomy. Actuarial 5-year pelvic control was 91%. After 1983, radiation was discontinued, and subsequent pelvic control rates fell to 73% despite improvements in surgical technique, staging, and the addition of systemic chemotherapy. A survival decrement (52% to 42%) was also seen. The extent to which patient-selection factors contributed to this observed difference is unknown. Others have reported lower rates of pelvic recurrence using cystectomy alone for this subset of patients, and it therefore remains uncertain whether these findings are widely applicable.[167]

The morbidity of preoperative RT is small. Whitmore reported comparable rates of wound healing and perioperative mortality for patients who received and those who did not receive irradiation before cystectomy.[166] There is limited experience in the creation of continent urinary diversions after preoperative RT, although Housset et al report that it is possible after the delivery of 44 Gy (24 Gy delivered in 8 fractions over 17 days according to a modified bifractionated split-course schedule [3 Gy fractions twice daily on days 1, 3, 15, 17] followed by a 20 Gy boost [2.5 Gy fractions twice daily on days 64, 66, 78, 80]).[171] TCC of the bladder have a high propensity to autotransplantation. Iatrogenic wound seeding after cystotomy was commonly reported by those who performed partial cystectomies or bladder brachytherapy. Low-dose preoperative radiation (8.5 Gy to 20 Gy) profoundly reduced the incidence of this problem.[172] Low-dose radiation is still occasionally given in the United States before a partial cystectomy. The partial cystectomy is, however, not commonly performed because it is limited to small, unifocal tumors of the dome, an unusual location.

Postoperative Radiation Therapy

When the cystectomy specimen shows extensive extravesical disease or positive surgical margins, the risk for pelvic recurrence is high. Postoperative RT has been evaluated in only one randomized study. The National Cancer Institute of Egypt reported on 236 patients with T3-4 tumors (68% squamous cell) who received either no adjuvant therapy or postoperative radiation (using three daily fractions of 1.25 Gy each, with 3 hours between fractions, up to a total dose of 37.5 Gy in 12 days [75 patients] or conventional fractionation for a total dose of 50 Gy over 5 weeks [78 patients]).[173] The 5-year rates of disease-free survival ([DFS] 44% to 49% versus 25%) and local control (87% to 93% versus 50%) were improved while the incidence of pelvic recurrence was significantly reduced in the groups receiving postoperative radiation. Whether this finding is as applicable to transitional as to squamous cell tumors remains an unanswered question. Today, patients with such extensive disease commonly receive adjuvant chemotherapy, although the ability of this modality to prevent local recurrence has been called into question by Cole et al.[170] RT rarely cures patients with pelvic wall recurrences following radical cystectomy.[174] Perhaps some could be cured if given adjuvant RT.

The morbidity of postoperative irradiation is high because of the large volumes of small bowel that occupy the pelvis after cystectomy if the urologist does not use pelvic reconstruction techniques to displace small bowel loops from the tumor bed (omental pedicle flap, mesh, other). Two series reported a greater than 30% incidence of small-bowel obstruction when 50 Gy was delivered using conventional fractionation.[175] So although adjuvant radiation therapy could reduce local failure it currently has no defined role because of a concern for morbidity. Modern techniques with improved normal tissue sparing have however rekindled interest in RT. Models of risk stratification based on pathologic stage of disease, margin status, and number of nodes removed have been developed that stratify patients into groups with significantly different local-regional failure risks.[176] Patterns of failure studies within the pelvis suggest that RT should target the iliac and obturator nodes and possibly the presacral nodes and cystectomy bed.[177] A cooperative group randomized trial GU001 recently opened in NRG Oncology to further evaluate the role of adjuvant RT in patients at higher risk for pelvic failure after cystectomy.

Salvage Radiation Therapy

Attempts to salvage patients with TCC of the bladder at the time of symptomatic or gross pelvic recurrence after radical cystectomy with RT or with combined chemotherapy and RT are usually unsuccessful. Some palliation can be achieved.[174] In some centers consideration is given to preoperative chemoradiation followed by attempted resection of the pelvic mass and intraoperative radiation. There is no large published experience looking at this approach.

Bladder Preservation

Conservative Surgery

Partial Cystectomy

Surgical resection by partial cystectomy requires careful patient selection, that is, the lesion should be solitary and located in a region of the bladder that allows for complete excision with a 2-cm tumor-free margin (e.g., the bladder dome). The portion of the bladder to be resected should be small enough to allow adequate bladder capacity. Contraindications include association with CIS in other sites of the bladder, prostatic urethral involvement, prior recurrent bladder or upper tract tumors, and bladder neck or trigone tumors in which ureteral reimplantation would be required to achieve an adequate margin. Given these constraints, only 6% to 19% of patients with primary, muscle-invading bladder cancer are potential candidates.[178] Even for this select group of patients, local recurrence rates range from 38% to 78%; one half of the recurrences appear in the first year and two thirds by 2 years.

Transurethral Resection of Bladder Tumor

Clinical complete response rates after TURBT alone (assessed cytoscopically with repeat biopsy 3 weeks after initial TURBT) for T2 and T3 cancers overall are in the 10% to 20% range.[179,180] Five-year OS in 85 patients with grades 1 and 2 T2 cancers was an unacceptable 27%.[181] Some studies have reported 10-year DSS as high as 76%,[182] but these results included only those patients who had no residual disease or no invasive disease on repeat biopsy and urine cytology. Although potentially effective in a small proportion of favorable T2 tumors, TURBT is usually not sufficient as monotherapy in muscle-invading bladder cancer.

Radical External Beam Irradiation

In the past, EBRT was widely used as a single modality for T2-4 bladder cancers, particularly in Europe. In the United States, however, the use of RT was frequently limited to patients whose tumor characteristics or medical comorbidities made them poor candidates for surgical monotherapy.

The total radiation dose used in these series (Table 54-2) varied from 55 Gy to 65 Gy, with 1.8 Gy to 2 Gy per fraction in North America, and from 50 Gy to 55 Gy at 2.5 Gy to 2.75 Gy per fraction in the United Kingdom.[183-196] Most patients were treated with one fraction per day five times a week. Patient response was evaluated by cystoscopic examination and biopsy 3 to 6 months after completion of RT. Patients with residual tumor and no known metastatic disease underwent salvage surgery (range of salvage cystectomy rate, 13% to 24%) if they were suitable surgical candidates. Those unfit received palliative measures.

The 5-year local control ranged from 31% to 50% for the entire patient population and from 49% to 79% for the subgroup of patients with complete response. Factors reported as having a significant favorable effect on local control[196] with RT included:

- Early clinical stage (T2 and T3a)
- Absence of ureteral obstruction

TABLE 54-2 External Beam Radiotherapy Alone for Muscle-Invasive Bladder Cancer

Study	*n*	5-Year Survival By T Category (%)			
		T2	T3 (T3a/T3b)	T4	Overall
Duncan, 1986[183]	963	40	26	12	30
Blandy, 1988[184]	614	27	38	9	—
Jenkins, 1988*[185]	182	46	35	—	40
Gospodarowicz, 1991*[188]	355	50	(38/28)	—	46
Jansson, 1991*[189]	319	31	16	6	28
Davidson, 1990*[194]	709	49	28	2	25
Greven, 1990[186]	116	59	10	0	—
Smaaland, 1991[187]	146	26	10†	—	—
Fossa, 1993[190]	308	38‡	14§	—	24
Pollack, 1994[191]	135	42	20	0	26
Moonen, 1998[192]	379	25	17	—	22
Borgaonkar, 2002*[195]	163	48	26	—	45

**Cause-specific survival.*
†T3/T4.
‡T2/T3a.
§T3b/T4.

- Complete response
- Visibly complete TURBT
- Absence of coexisting CIS
- Small tumor size (<5 cm maximum diameter)
- Solitary tumors
- Tumor configuration (papillary versus sessile)
- Hemoglobin level (>10 mg/dL)

Tumor eradication ranged from as high as 66% for those with solitary T2 tumors to as low as 9% for those with multiple tumors and hydronephrosis. The 5-year OS in these reports ranged from 25% to 46%. Stage-specific 5-year OS ranged from 49% to 71% for T2 to 37% for T3b.

The success of any bladder conserving strategy rests on the ability to rapidly recognize local recurrence and treat promptly with salvage surgery. Salvage cystectomy can be undertaken safely without significantly increased morbidity after a complete course of RT or chemoradiation regimens.[197,198] After radiation, an ileal conduit, rather than a neobladder is the more likely method of urinary diversion. A Kock pouch urinary diversion may also be performed safely in patients who received prior RT to the pelvis.[199]

Interstitial Brachytherapy

This was developed as a technique in the early part of the 20th century but has progressively declined in popularity and is mainly performed in specialist centers in France, Belgium, and the Netherlands. The early technique involved the implantation of permanent radon seeds or temporary radium or cobalt needles.[200,201] Although effective there were substantial problems with radiation safety and significant morbidity from urinary leakage. Hospital stays were protracted. As alternative techniques employing EBRT became available and as the morbidity and mortality of the cystectomy declined, these became preferred approaches. Over the last three decades, however, afterloading techniques and computer planning mean that some centers are again looking at this as an option for selected patients. Brachytherapy has been combined with EBRT to

TABLE 54-3 Treatment Outcome for Brachytherapy in Combination with External Beam Irradiation

Series	Local Control (5 yr)	OS (5 yr)	DSS (5 yr)	Survival with Preserved Bladder (5 yr)
Moonen[202]	84%	86%	—	90%
Wijnmaalen I[203]	88%	48%	69%	—
Van der Steen[137]	70%	—	T1 80% T2 60%	— —
Mazeron[205]	77%	72%	73%	95%
Rozan[206]	—	67%	83%	96.1%
Pernot[207]	73%	71%	77%	—
Pos[208]	73%	62%	73%	90%
Aluwini[209]	80% (5 yrs) 73% (10 yrs)	65% (5 yrs) 46% (10 yrs)	75% (5 yrs) 67% (10 yrs)	93% (5 yrs) 85% (10 yrs)

DFS, *Disease-free survival;* EBRT, *external beam radiation therapy;* OS, *overall survival;* yr, *year.*
All series employed combinations of EBRT and brachytherapy, usually preoperative EBRT does of <15 Gy to reduce the risk of tumor seeding. The series of Moonen and Pos gave 30 Gy in 15 fractions and those of Van der Steen and Wijnmaalen gave 40 Gy in 20 fractions to tumors of stage T2b or higher.

provide a radiation boost to the primary tumor as well. External-beam doses of 30 Gy are used in combination with an implant tumor dose of 40 Gy. Appropriate candidates for brachytherapy are those with a solitary TCC with a diameter of <5 cm, stage T1 (with high grade) to T3a (muscle invasion but no extension through wall).

Early experience made clear that TCC is a tumor that may be surgically seeded either into the wound or to the peritoneal cavity. Van der Werf-Messing demonstrated the value of small doses of preoperative radiation to prevent iatrogenic scar implantation.[172] In those centers using brachytherapy, low doses of EBRT are given preoperatively with fractionation schemes that fit the convenience and ideology of the center. These range from 1×8.5 Gy or 3×3.5 Gy to 15×2 Gy. Historically wound implants occurred in 10% to 20% and are now rarely seen.

Five-year local control rates for selected patients treated with brachytherapy in combination with EBRT do appear excellent varying between 70% and 90% with DSS of approximately 75% and correspondingly high rates of bladder preservation[202-209] (Table 54-3). In selected patients, survival appears similar to cystectomy.[210]

The most serious acute morbidity is fistula with wound leakage. This is most strongly predicted by tumor size, active length of radioactive sources, and use of a partial cystectomy. Serious late toxicity is rarely reported because the treated bladder volumes are relatively small. A study reported by Pos does however raise the possibility that there is more late morbidity using fractionated high-dose rate than continuous low-dose rate.[211]

Combined-Modality Therapy

Chemotherapy as monotherapy achieves a clinical complete response in only 25% to 37% of patients.[212-219] This is more frequently reported in lower stage disease, small tumors (<5 cm), and papillary tumors. Two-year OS with chemotherapy alone is approximately 30% (cT3-4). Even in responders, chemotherapy alone spares the bladder in only 15% to 20% of patients. Chemotherapy is therefore rarely used alone for localized disease and almost invariably in combination with other therapies.

Chemotherapy and Conservative Surgery

Chemotherapy has been used with TURBT in an attempt to spare the bladder. In a highly selected patient population, 5-year local control rates of up to 48% have been reported. CR rates after chemotherapy and TURBT range from 45% to 54%.[219-225] These findings suggest that the addition of TURBT to MVAC confers a considerable local control advantage over either alone. In a highly selected patient population, chemotherapy followed by partial cystectomy in conjunction with pelvic lymphadenectomy has been used in an attempt to spare the bladder.[226] Patients should meet the following criteria to be considered for such treatment:

- complete or major response to chemotherapy,
- solitary lesion in the dome or the anterior wall of the bladder,
- no history of prior invasive bladder cancer,
- no CIS, and
- a good bladder capacity.

Though 5-year survival is high at close to 50%, less than half of these patients preserve their bladders.

Chemotherapy and Radical Local Therapy

In attempts to eradicate micrometastatic disease and improve survival for patients with muscle-invasive bladder cancer, systemic chemotherapy, given either neoadjuvantly or adjuvantly, has been evaluated.

Neoadjuvant Chemotherapy before Definitive Local Therapy

Neoadjuvant chemotherapy offers the potential to assess the response of the primary lesion and for tumor downstaging, though it may lead to a discordance between clinical and pathologic staging and delayed definitive local therapy. Chemotherapy before definitive local therapy has been well tested in invasive bladder cancer. The results of the major randomized controlled trials are shown in Table 54-4.[227-238]

Many of the earlier trials comparing neoadjuvant chemotherapy and definitive local therapy alone used single-drug (cisplatin) chemotherapy regimens. None of these studies detected a survival difference. The survival rates among both treatment arms were almost identical. The Spanish trial using neoadjuvant cisplatin reported a significant prolongation of disease-free interval with chemotherapy (mean time to progression, 13 months versus 30 months, $p = 0.03$).[229] It is important to note that in these trials the definitive treatment of the primary bladder cancer was delayed for 3 months during the administration of chemotherapy, but ultimate survival was not reduced.

A number of more recent trials[228,231-236,238,239] used cisplatin-based multidrug chemotherapy regimens. These studies, unfortunately, do not provide a clear and consistent indication of the efficacy of neoadjuvant cisplatin-based chemotherapy. The Nordic 1 Cooperative Bladder Cancer Study Group

TABLE 54-4 Randomized Phase III Trials of Neoadjuvant Chemotherapy

Study Group	Neoadjuvant Arm	Standard Arm	Patients	Survival
CISPLATIN TRIALS				
Aust/UK[227]	DDP/RT	RT	255	No difference
Canada/NCI[237]	DDP/RT or preop RT+Cyst	RT or preop RT+Cyst	99	No difference
Spain (CUETO)[229]	DDP/Cyst	Cyst	122	No difference
COMBINATION CHEMOTHERAPY				
EORTC/MRC[232]	MCV/RT or Cyst	RT or Cyst	976	5.5% difference in favor of MCV
RTOG[231]	MCV/RT+C	RT+C	126	No benefit
SWOG Intergroup[238]	M-VAC/Cyst	Cyst	317	Benefit with M-VAC
Italy (GUONE)[236]	M-VAC/Cyst	Cyst	206	No difference
Italy (GISTV)[230]	M-VEC/Cyst	Cyst	171	No difference
Genoa	DDP/5FU/RT/Cyst	Cyst	104	No difference
Nordic 1[228]	ADM/DDP/RT/Cyst	RT/Cyst	325	No difference, 15% benefit with ADM+DDP in T3-T4a
Nordic 2[234]	MTX/DDP/Cyst	Cyst	317	No difference
Abol-Enein[235]	CarboMV/Cyst	Cyst	194	Benefit with CarboMV

ADM, *Doxorubicin;* Carbo, *carboplatin;* Cyst, *cystectomy;* DDP or C, *Cisplatin;* E, *epirubicin;* MTX, *methotrexate;* preop, *preoperative;* RT, *radiation therapy;* V, *vinblastine.*

randomized patients with T1G3-T4a bladder cancer to two cycles of neoadjuvant cisplatin and doxorubicin or to no chemotherapy. Patients in both arms received preoperative irradiation (20 Gy in five fractions) and cystectomy as definitive local treatment. A significant survival advantage was seen in the chemotherapy arm for the subgroup of patients with cT3-4a disease (5-year OS 52% versus 37%, $p = 0.03$), but not for the entire patient population.[228] The subsequent Nordic 2 trial evaluated cisplatin plus methotrexate followed by cystectomy versus cystectomy alone in patients with T3 or T4a disease and did not show a statistically significant survival difference.[234]

The RTOG 89-03 trial evaluated two cycles of neoadjuvant MCV (methotrexate, cisplatin, and vinblastine) chemotherapy before concurrent cisplatin and definitive radiation. Neoadjuvant chemotherapy did not confer any detectable survival advantage. Rates of distant metastases, local metastases, and CR rates were similar in the two arms.[231]

The MRC-EORTC trial randomized 976 patients to three cycles of neoadjuvant MCV versus no chemotherapy.[232,239] Definitive local treatment was cystectomy, radical RT, or preoperative RT followed by immediate cystectomy as determined by physician or patient preference. With a median follow-up of 7.4 years, the trial reported a small but significant survival gain for neoadjuvant chemotherapy with the difference in 5-year survival between those who received chemotherapy (49%) and those who did not (43%) just reaching clinical significance ($p = 0.048$). At 8 years the survival for the chemotherapy patients was 43% compared with 37% in the control arm and the risk of bladder cancer death was reduced by 17%.

MVAC, the most aggressive regimen and most extensively evaluated, has been tested in several studies including an intergroup trial led by SWOG.[238] The SWOG trial, after slow accrual and long follow-up, achieved a trend toward significance with a 25% reduction in the risk of death through the addition of MVAC for three cycles (57% versus 43% at 5 years; $p = 0.06$) given before radical cystectomy, but the side effects were appreciable. One third of patients receiving neoadjuvant chemotherapy had a grade 3 or higher hematologic or gastrointestinal adverse effect, though there were no drug-related deaths nor did the chemotherapy adversely affect the performance of surgery. An almost identical study by the Italian GUONE group showed no significant difference.[236]

A meta-analysis that included data from 3005 patients enrolled in 11 randomized trials demonstrated a 5% absolute 5-year OS advantage (50% versus 45%; hazard ration [HR] = 0.86, 95% CI 0.77 to 0.95, $p = 0.003$) for neoadjuvant cisplatin-based combination chemotherapy compared to local therapy alone.[240,241] There was also a significant DSS benefit of 9% absolute improvement at 5 years (HR = 0.78, 95% CI 0.71 to 0.86, $p < 0.0001$).

Debate continues as to the relevance of all these conflicting findings especially when set against the morbidity of chemotherapy. Newer chemotherapeutic combinations that have activity in patients with metastatic disease, such as dose-dense or accelerated MVAC, and more favorable toxicity profiles, such as gemcitabine and cisplatin, are being investigated.

Although neoadjuvant chemotherapy seems to improve survival only marginally, it certainly has a significant impact in terms of tumor down-staging. Major responses (defined as transition from invasive disease to T0, CIS, Ta, or T1) occurs in approximately 40% of patients. Complete clinical response, as evaluated by repeat cystoscopy and biopsy after chemotherapy, ranges from 25% to 57%.

Response to neoadjuvant therapy certainly seems to predict survival. Survival rates at 5 years range from 62% to 75% among responders versus 20% to 26% among nonresponders in several of the trials.

In the 2015 National Comprehensive Cancer Network *Clinical Practice Guidelines in Oncology: Bladder Cancer*, neoadjuvant chemotherapy is a category 1 recommendation for localized stage T2-T4a disease. However, only a minority of patients in the United States undergo any perioperative chemotherapy with most still being given in the adjuvant setting. Gene profiling may in the future identify those most likely to respond to chemotherapy.[80a]

Adjuvant Chemotherapy after Definitive Local Therapy

Adjuvant chemotherapy allows for pathologic staging and avoids delay in potentially curative local therapy. No randomized trials have compared neoadjuvant to adjuvant chemotherapy in patients undergoing definitive local therapy. Although some trials have suggested a survival advantage

for neoadjuvant chemotherapy, there have been no contemporary studies supporting such a benefit with adjuvant chemotherapy.

A study from MDACC attempted to address the optimal timing of perioperative chemotherapy by comparing neoadjuvant plus adjuvant chemotherapy to postoperative chemotherapy alone and did not show any difference.[242] Several randomized, controlled trials provide information on the value of adjuvant chemotherapy after radical primary therapy (Table 54-5).[243-250] All of these studies used three to four cycles of platinum-based multiagent chemotherapy. As with neoadjuvant therapy the results have been conflicting and most of these studies suffered from underpowering and poor accrual.

In three studies, a significant progression-free survival (PFS) benefit at 3 years and 5 years was observed when patients were randomized to adjuvant chemotherapy compared with observation. However, OS was not significantly different. Patients in the observation group were treated with chemotherapy at relapse except in the study reported by Stöckle et al.[244-246] The failure to provide salvage chemotherapy in this study may explain the low survival rates in the observation arm (5-year crude survival, 17%). The PFS benefit does not translate into an OS benefit if patients receive salvage chemotherapy. In other words, observation with salvage chemotherapy might be just as effective as adjuvant chemotherapy in terms of survival. A meta-analysis including 491 patients from six trials suggested a 25% relative reduction in the risk of death (HR 0.75, 95% CI 0.60 to 0.96, $p = 0.019$) for patients receiving cisplatin-based combination adjuvant chemotherapy; however, the power of this meta-analysis was clearly limited and the authors concluded that there was insufficient evidence on which to base reliable treatment decisions.[252]

More recent studies have used different adjuvant chemotherapy regimens or molecular stratification.[61] A randomized Phase III trial from the Spanish Oncology Genitourinary Group (SOGUG 99/01) comparing four cycles of adjuvant paclitaxel/gemcitabine/cisplatin to observation in patients with resected high-risk (pT3-4 or pN+) bladder cancer was prematurely closed because of poor accrual; however, preliminary results suggest improved 5-year OS (60 versus 31%, $p = 0.0009$).[249]

Bladder Preservation with Limited Resection, Chemotherapy, and Irradiation

The rationale for combining chemotherapy with RT is twofold:

1. Certain cytotoxic agents, in particular cisplatin and 5-FU, are capable of sensitizing tumor tissue to radiation, thus increasing cell kill in a synergistic fashion.
2. Patients with muscle-invading TCC harbor occult metastases in approximately 50% of cases, which makes a case for the addition of systemic chemotherapy in an attempt to control occult distant disease.

Trimodality therapy consisting of TURBT with concurrent chemoradiation may, therefore, increase the efficacy of bladder-sparing protocols. The evolution of this approach over the last three decades is shown in Figure 54-3.

Many Phase II trials have combined chemotherapy and RT in different sequences in patients with invasive bladder cancer. Although a variety of different drugs and radiation doses have been used, it is apparent that the highest clinical CR rate (T0) was achieved in patients who received concurrent chemotherapy and RT compared with sequential regimens.[139,171,237,253-256] Table 54-6 shows results from several modern series of multimodality bladder preservation therapy.[139,171,231,256-265]

The recently reported Phase III randomized Bladder Cancer 2001 (BC2001) trial of 360 patients from the United Kingdom demonstrated that concurrent chemoradiation using 5-FU and mitomycin C is well tolerated and significantly improved locoregional DSS compared to radiation alone (67% versus 54% at 2 years; HR 0.68, $p = 0.03$ with median follow-up of 70 months). Survival at 5 years was higher with chemoradiation (48% versus 35%) but did not reach statistical significance (HR 0.82; $p = 0.16$). Bladder function was good, and no increase in late toxicity was found.[256]

Single-Institutional Experiences

One of the clearest indications of the potential of multimodality therapy for bladder preservation can be found in a study from the University of Paris.[171] In this study, TURBT followed by concomitant cisplatin, 5-FU, and accelerated RT was initially used as a precystectomy regimen. The first 18 patients who had no residual tumor on cystoscopy and repeat biopsy (clinical CR) underwent radical cystectomy as planned. None of these patients had any evidence of malignancy in the cystectomy specimens—a 100% pathologic CR rate. Previous studies using TURBT and chemotherapy found residual tumor in as many as 50% of the cystectomy specimens in clinical complete responders.

After this striking evidence of tumor eradication, the University of Paris investigators changed their protocol to one of selective bladder preservation. In 1988, they converted to induction chemoradiation, restaging with cystoscopy, and repeat biopsy of the tumor site 4 to 6 weeks after completion of the chemoradiation. Subsequent consolidation chemoradiation was only selectively given to patients who did not have any evidence of disease at restaging (CR). In cases of persistent

TABLE 54-5 Randomized Controlled Trials of Adjuvant Chemotherapy

Series	Stage	Treatment	5-yr DFS	5-yr OS	Significance
Skinner[243]	pT3-4	Cyst + 4 × CAP	52	49	Sig. for N+
	Nx	Cyst	38	43	
Stöckle[244-246]	pT3b-4	Cyst + 3 × MVAC	63	—	Sig.
	N+	Cyst	13	—	
Studer[247]	pTa-4	Cyst + 3 × Cis	—	57	Neg
	N+	Cyst	—	54	
Freiha[248]	pT3b-4	Cyst + 4 × CMF	50	40	Neg
	Nx	Cyst	22	38	
Paz-Ares[249]	pT3-4	Cyst + 4 × PGC	—	60	Sig.
	N+	Cyst	—	31	
Cognetti[251]	pT2G3-4	Cyst + 4 × AGC	37	43	Neg
	N0-2	Cyst	42	53	

DFS, *Disease-free survival;* Neg, *negative;* OS, *overall survival;* Sig, *significant;* yr, *year.*

A randomized trial performed in Italy randomized patients after cystectomy either to four courses of gemcitabine plus cisplatin or to the same treatment at time of relapse. There was no difference in the 5-year OS across treatment arms. However, because of poor accrual the study was insufficiently powered to detect a survival difference.[251] Ongoing clinical trials will hopefully provide additional insight into the role of adjuvant chemotherapy.

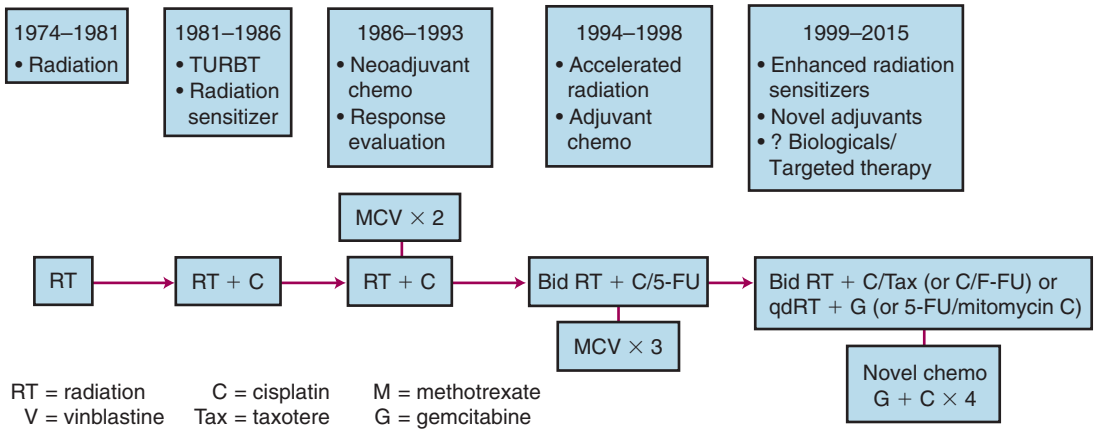

Figure 54-3 Bladder conservation: evolution of multimodality approach. *Bid,* Twice daily; *C,* cisplatin; *chemo,* chemotherapy; *G,* gemcitabine; *M,* methotrexate; *RT,* radiation therapy; *Tax,* Taxotere; *TURBT,* transurethral resection of the bladder tumor; *V,* vinblastine.

TABLE 54-6 Results of Multimodality Treatment for Muscle-Invading Bladder Cancer

Series	Treatment Method	No. Pt.	5-yr OS	5-yr BIS
RTOG 8512 1993[262]	TURBT, external beam radiation + cisplatin	42	52%	42%
RTOG 8802 1996[263]	TURBT, MCV, external beam radiation + cisplatin	91	51%	(4 years)
RTOG 8903 1998[231]	TURBT, ± MCV, external beam radiation + cisplatin	123	49%	38%
RTOG 9906 2009[266]	TURBT, bid external beam radiation + paclitaxel	80	56%	47%
BC 2001 2012[256]	TURBT, QD external beam radiation + 5FU/MMC	182	48%	—
U. Paris 1997[171]	TURBT, 5-FU, external beam radiation + cisplatin	120	63%	NA
Erlangen 2002[259]	TURBT, external beam radiation, cisplatin, carboplatin, or cisplatin and 5-FU	415	51%	42%
MGH 2012[257,258]	TURBT, ± MCV, external beam radiation + cisplatin	348	52%	46%

5-FU, *5-Flourouracil;* BIS, *bladder intact survival;* MCV, *methotrexate, cisplatin, vinblastine;* MGH, *Massachusetts General Hospital;* OS, *overall survival;* TURBT, *transurethral resection of bladder tumor;* U. Paris, *University of Paris.*

disease, patients underwent immediate cystectomy. The 5-year OS for all patients who entered the protocol was 63%.

At the University of Erlangen in Germany, a prospective bladder preservation study was started in 1982. The first 106 consecutive patients, however, were treated only with TURBT followed by EBRT to 50 Gy to 56 Gy at 2 Gy daily. A multimodality approach was initiated in 1985 when chemotherapy (cisplatin or carboplatin) was added concurrently with the radiation regimen in subsequent patients.[139,259] This protocol differed in two aspects from the University of Paris study. All recruited patients underwent the entire course of chemoradiation. Restaging TURBT was performed at 6 to 8 weeks, only after completion of the entire protocol. In addition, only patients with invasive persistent disease or poorly differentiated residual superficial tumors underwent cystectomy. Patients with well-differentiated superficial disease (Ta, CIS) were treated further conservatively with TURBT and intravesical chemo- or immunotherapy. CR was achieved in 72%. Ten-year DSS was 42%, and more than 80% of survivors preserved their bladder. Thirty-five percent developed distant metastases at 10 years. Concomitant chemotherapy was more effective than EBRT alone in terms of CR and survival. The subgroup of patients who either had persistent invasive tumor (nonresponders) at first restaging or needed a cystectomy for early invasive recurrences within 9 months after completion of the treatment had dismal survival rates (5-year OS, 16%) because of early systemic spread. Patients who needed salvage cystectomy later than 9 months after completion of the treatment achieved a 5-year OS comparable to that of the entire group.

In June 1986, investigators from the Massachusetts General Hospital (MGH) implemented a selective bladder preservation protocol for operable patients with muscle-invading bladder cancer. Initially to improve on previous results in terms of both local and distant control, two cycles of neoadjuvant MCV chemotherapy were added before the chemoradiation regimen.[260] MCV was chosen because three- or four-drug (e.g., MVAC) chemotherapy had been shown to be more effective than single-agent cisplatin in metastatic bladder cancer. Five-year OS was 48% (68% for those with T2 disease).

Long-term follow-up of 348 patients with T2-4aNXM0 bladder cancer treated successively at the MGH with combined-modality therapy using concurrent cisplatin-based chemotherapy and RT after maximal TURBT with or without neoadjuvant/adjuvant chemotherapy is available.[258] With a median follow-up for all surviving patients of 7.7 years, the results demonstrate that a visibly complete TURBT was achieved in approximately two thirds of patients and a CR rate to induction chemoradiation (~40 Gy in 1.8-Gy 2-Gy fractions) in 72% (78% in patients with stage T2 disease). Patients with a CR rate and those medically unfit for cystectomy received boost chemoradiation to 64 Gy to 65 Gy. Five- and 10-year OS were 52% and 35%, respectively (61% and 43% for T2 tumors), and 5- and 10-year DSS were 64% and 59% (74% and 67% for T2 tumors). Clinical stage and achieving a CR were significantly associated with both OS and DSS. A nomogram predicting response has been

developed from this data.[261] Ultimately 102 patients (29%) underwent radical cystectomy, 17% for less than a CR and 12% for recurrent invasive tumors. The 10-year DSS for the patients undergoing cystectomy was 44%, illustrating the important contribution of prompt salvage cystectomy. No patient required cystectomy because of treatment-related toxicity. Therefore, combined-modality therapy achieved a CR and preserved the native bladder in ~70% of patients, while offering long-term survival rates comparable to contemporary radical cystectomy series. Use of neoadjuvant chemotherapy did not improve survival or incidence of metastases, though this may warrant further investigation in the modern era.

Cooperative Group Experience: The RTOG

In North America, most cooperative group combined-modality therapy for bladder cancer has occurred within the RTOG. RTOG 85-12 treated 42 patients who were candidates for cystectomy with induction once-daily radiation therapy (40 Gy in 2-Gy daily fractions) and concurrent cisplatin, with prompt cystectomy reserved for patients who responded incompletely.[262] Complete responders received consolidation therapy, with an additional 24 Gy (in 2-Gy daily fractions) delivered with concurrent cisplatin. The approach was feasible and well-tolerated, and yielded a complete response rate of 66%, a 5-year OS of 52%, and a 5-year survival with an intact bladder of 42%.

The subsequent protocol, RTOG 88-02, looked at the role of neoadjuvant MCV given immediately following TURBT. It entered 91 patients and reported a 75% response rate and 51% 5-year OS.[263] This was followed between 1989 through 1994 by RTOG 89-03, which was a Phase III trial that directly tested the contribution of two cycles of neoadjuvant MCV chemotherapy before concurrent cisplatin and once-daily radiation.[231] This study fell short of its accrual goal and was prematurely closed because of an unexpectedly high rate of severe leukopenia in the MCV arm, which resulted in a 67% protocol completion rate (compared to 81% in the non-MCV arm) and three treatment-related deaths. Analysis of 123 patients showed no significant differences between the MCV arm and the non-MCV arm in CR after induction (61% and 55%, respectively), 5-year OS (48% and 49%), 5-year survival with an intact functioning bladder (36% and 40%), or distant metastasis (33% and 39%). Treatment-related morbidity and mortality, however, were significantly higher in the neoadjuvant chemotherapy arm. In summary, this trial suggested that two cycles of neoadjuvant MCV were not a necessary component of a bladder-preservation strategy. Therefore, future studies abandoned neoadjuvant chemotherapy, though they continued to evaluate patient tolerance for newer chemotherapeutic agents and started to explore adjuvant regimens.

In 1995, the RTOG began Phase I-II protocols to evaluate accelerated radiation fractionation schemes in combination with concurrent chemotherapy. RTOG 95-06 evaluated the regimen piloted by the University of Paris, using 5-FU plus cisplatin concurrent with accelerated but hypofractionated radiation therapy delivered over 17 days.[264] Patients with tumor-associated hydronephrosis were excluded, based on findings that these patients had a significantly lower CR rate and a higher cystectomy rate. Among 34 evaluable patients, 67% had a CR on induction and an encouraging 3-year OS of 83%. However, 7 patients (21%) had grade-3 to grade-4 hematologic toxicity on this regimen, though no deaths resulted and no patients required cystectomy for radiation toxicity.

In 1997, the RTOG began to study the role of adjuvant chemotherapy after treatment with either bladder preservation or cystectomy and turned to twice-daily hyperfractionation. In RTOG 97-06, induction and consolidation chemoradiation included twice-daily radiation and outpatient cisplatin (30 mg/m^2) as a radiation sensitizer given on the first 3 days of each week.[265] Radiation doses of 1.8 Gy to the pelvis and 1.6 Gy to the bladder tumor were given daily for 12 days with a 4- to 6-hour interval between fractions during induction treatment. In the consolidation phase, 1.5-Gy fractions were given to both, twice-daily for 8 days (total dose 45.6 Gy to pelvis and bladder, 64.8 Gy to bladder tumor). After consolidation chemoradiation or cystectomy (depending on response), patients received three cycles of adjuvant MCV chemotherapy. The rationale for this protocol was to reduce the duration of the induction treatment to 12 days, thereby decreasing the delay between onset of consolidation chemoradiation or cystectomy for those patients in whom induction therapy failed. The CR rate was 74% and only 11% of patients experienced grade-3 to grade-4 toxicity during induction and consolidation phases. However, only 45% of patients went on to receive a full three cycles of MCV, and of those who did 41% developed grade-3 toxicity. The potential benefit of adjuvant chemotherapy in delaying or preventing metastasis exists because the 2-year actuarial incidence of developing metastasis in this trial was only 18% (compared to about 30% in trials without adjuvant systemic therapy).

RTOG 99-06 added paclitaxel as a radiation-sensitizing agent during the induction and consolidation schedules along with twice-daily radiation.[266] The protocol also used the adjuvant chemotherapy regimen of cisplatin (70 mg/m^2 on day 1) and gemcitabine (1000 mg/m^2 on days 1, 8, and 15). There was a 70% protocol completion rate and an impressive 81% CR rate. Five-year OS and DSS were 56% and 71%, respectively.

More recent RTOG trials have continued to address the question of the optimal concurrent chemotherapy regimen by evaluating different induction regimens in an effort to further enhance the radiation response and improve local control. RTOG 02-33 was a Phase II study that finished accrual of 97 patients in 2008.[267] In this trial, patients were randomized to twice-daily radiation with either concurrent paclitaxel and cisplatin or concurrent 5-FU and cisplatin during the induction and consolidation phases. Adjuvantly, patients received a triplet regimen of gemcitabine (1000 mg/m^2 on days 1 and 8), paclitaxel (50 mg/m^2 on days 1 and 8), and cisplatin (35 mg/m^2 on days 1 and 8). This is similar to the triplet regimen piloted by Bellmunt et al[268] and as tested in a Phase III trial led by the European Organization for Research and Treatment of Cancer (EORTC) and the Southwest Oncology Group (SWOG). RTOG 07-12 is a recently closed Phase II trial randomizing patients to twice-daily irradiation plus concurrent 5-FU and cisplatin or to daily irradiation plus gemcitabine (based on a regimen from the University of Michigan and the United Kingdom) followed by selective bladder preservation and gemcitabine/cisplatin adjuvant chemotherapy. A long-term pooled analysis of a number of RTOG protocols (8802, 8903, 9506, 9706, 9906, 0233) demonstrate an overall CR rate of 69%; 5- and 10-year OS rates of 57% and 36%, respectively; and 5- and 10-year DSS rates of 71% and 65%, respectively. The 5- and 10-year estimates of muscle-invasive LF, nonmuscle-invasive LF, and DM were 13% and 14%, 31% and 36%, and 31% and 35%, respectively.[268a]

Other Experiences

Another original way to combine chemotherapy and radiation has been employed by Eapen et al. This group has combined conventionally fractionated EBRT plus intraarterial cisplatin. Their durable CR rates (83%) are as high as any in the literature. The principal problem they have faced is a high level of sacral neuropathy which, in recent years, they have reduced through reducing the dose of infused cisplatin.[269]

Another novel combination of therapy in locally advanced bladder cancer was undertaken by Hoskin et al who reported a Phase III trial randomizing 333 patients to radiation alone versus radiation plus radiosensitizing carbogen and nicotinamide.[270] A schedule of either 55 Gy in 20 fractions in 4 weeks or 64 Gy in 32 fractions in 6.5 weeks was used. Three-year estimates of OS were 59% and 46% (p = 0.04) and 3-year estimates of relapse-free survival were 54% and 43% (p = .06) for RT + CON compared with RT alone. In multivariate comparison, RT + CON significantly reduced the risk of relapse (p = 0.05) and death (p = 0.03). Risk of death was 14% lower with RT + CON (p = 0.04). There was no indication of an increase in radiation-induced late urinary or gastrointestinal morbidity.

Survival Outcomes Compared to Cystectomy

The primary goal of bladder-preserving therapy, as with any therapy for muscle-invading TCC of the bladder, is optimizing patient survival. Bladder preservation in the interest of quality of life can only be considered a secondary objective. The long-term outcome data presented previously from single-institution and cooperative group experiences suggest that modern combined-modality therapy results in CR rates of 60% to 80%, 5-year OS of 45% to 60%, and 5-year survival rates with an intact bladder of 40% to 45%. Although no completed randomized comparisons of cystectomy with combined-modality therapy exist, these long-term OS rates are encouraging and comparable to those reported in contemporary radical cystectomy series (Table 54-7). Similarly, a retrospective review of a nonrandomized cohort of 458 patients undergoing radical RT or cystectomy in Yorkshire, United Kingdom, showed no significant difference in 10-year OS.[271]

Selection bias makes a nonrandomized comparison difficult. Surgical patients are generally younger with a better performance status. Surgery allows for a more accurate pathologic staging and identification of only surgically identifiable metastatic disease, which leads to a discontinuation of approximately 15% of cystectomies (if node-positive, tumor-unresectable, distant disease), and thus these series do not necessarily report by intention to treat. Furthermore, most cystectomy studies do not provide data on the initial clinical staging and only report outcomes by pathologic stage and rates of clinicopathologic stage discrepancy and clinical understaging are high.[114] The optimum way to compare outcomes of selective bladder-conserving strategies is to compare the outcomes of prospective protocols in which eligibility is based on clinical staging, all patients are cystectomy candidates, and all entered patients are reported for outcome whether or not they completed treatment. Comparison of survival outcomes from contemporary cystectomy and bladder-sparing therapy protocols in patients with muscle-invasive cancer of similar clinical stage, all of whom were potential candidates for cystectomy, are similar, with OS ranging from 45% to 54%.[231,238,256,258,272,273] Martinez-Pineiro et al also reported their cystectomy series by clinical stage.[229] The 5-year OS was 41% (48% for clinical T2); this is similar to that of the bladder-preservation strategy (5-year OS from 45% to 60%), in which all patients who initiated their therapy are reported, not only those whose tumor response was satisfactory to complete the organ-preservation program. It is important to remember that the appropriate strategy for bladder-preservation therapy includes prompt salvage cystectomy for nonresponders. Any comparison of cystectomy protocols with bladder-preservation protocols must include these nonresponders to avoid being biased by patient selection.

Prognostic Factors in Chemoradiation

Complete Response. Clinical CR (or T0 response), evaluated by cystoscopy with tumor site biopsy with or without cytology 2 weeks to 8 weeks after completion of the induction chemoradiation, ranged from 70% to 80%. The CR rate was significantly higher in patients in whom a macroscopically visibly complete TURBT could be achieved compared with patients with residual macroscopic disease after TURBT (80% to 90% versus 60%, $p < 0.001$).[171,257,258] Patients with clinical stage T2-3a achieved significantly more frequent CRs than those with T3b-4 disease (University of Paris, 83% versus 58%, $p < .001$; MGH, T2 vs. T3-4, 81 vs 64%). Patients who presented with *hydronephrosis* achieved a 66% complete response versus 83% in patients who had no hydronephrosis at presentation (University of Paris, $p < 0.05$; MGH, 52% versus 77%). The Erlangen group have shown that those with Tcis disease in the bladder in addition to the invasive tumor are less likely to have a durable response and more likely to require cystectomy.

Chemoradiation added significant improvement to the clinical CR rates compared with the "early" CR after induction chemotherapy alone. After two cycles of MCV, the CR rate for patients with T2 disease was 62% and with T3 or T4 disease, 41%. After adding a course of concurrent chemoradiation, the CR rate increased to 81% and 64%, respectively.[257] Factors predicting for a CR also predict local control and ultimately bladder preservation. For example, among patients who underwent a visibly complete TURBT, only 22% required cystectomy (versus 42% of patients who underwent an incomplete TURBT, $p < 0.001$).[258]

TABLE 54-7 Muscle-Invasive Bladder Cancer: Survival Outcomes Following Curative Therapy in Contemporary Series

		Overall Survival		
Series	**Stages**	**Number**	**5-Year**	**10-Year**
CYSTECTOMY				
USC 2001[153]	pT2-pT4a	633	48%	32%
MSKCC 2001[154]	pT2-pT4a	181	36%	27%
SWOG/ECOG/CALGB*† 2002[238]	cT2-cT4a	317	49%	34%
SELECTIVE BLADDER PRESERVATION				
U. Erlangen* 2002[139,259]	cT2-cT4a	326	45%	29%
MGH* 2012[258]	cT2-cT4a	348	52%	35%
RTOG* 1998[231]	cT2-cT4a	123	49%	—
RTOG 2014 ([268a])	cT2-cT4a	468	57%	36%
BC2001* 2012[256]	cT2-cT4a	*182*	*48%*	—

**These series included all patients by their intention to treat.*

†50% of patients were randomly assigned to receive three cycles of neoadjuvant M-VAC.

Survival. Clinical complete responders generally have significantly higher survival rates than nonresponders. The amount of residual tumor after TURBT is also a prognostic factor for survival as for local control. The same is true for those with T2 clinical category compared with T3-4 and those presenting without hydronephrosis. In multivariate analyses, clinical T category and CR to induction therapy remained significantly associated with improved DSS and OS.[257,258]

The 5-year distant metastasis rate for all patients entered in the protocols ranged from 34% to 40%. In the MGH series, the 5-year distant metastasis rate in the T0 responder group was only 20%.[257,258] Patients who did not respond rapidly (T > 0) and underwent immediate cystectomy had a 50% distant metastasis rate at 5 years. However, it was similar to the 5-year rate of initial T0 responders who subsequently underwent salvage cystectomy for local failure (5-year distant metastasis rate, 54%). Delayed cystectomy for recurrent invasive disease did not confer worse outcomes when compared to immediate cystectomy for a noncomplete response.

Follow-Up after Chemoradiation. All patients with bladder cancer (either superficial or invasive) treated with bladder-preserving therapies must be willing to return for regular, thorough clinical examinations, cystoscopy, biopsy of the tumor site, and urine cytology follow-up so that transurethral surgery, intravesical therapy, or salvage cystectomy can be implemented at the earliest opportunity if necessary. The optimal timing of cystoscopy after RT is unclear but is usually first done at 3 months.[187] At the MGH our protocol mandates cystoscopy and urine cytology every 3 months for the first 2 years, then every 6 months until 5 years and annually thereafter. In patients with a series of negative followup evaluations, the biopsy and examination under anesthesia may be omitted in favor of office cystoscopic evaluation if no worrisome office endoscopic findings are present.

Managing Recurrent Disease in the Bladder. Of patients who have complete response, 84% of patients remained free from invasive recurrence in the bladder at 10 years, and approximately 60% remained free from any noninvasive or invasive occurrence.[257,258] Of patients whose invasive recurrence was cured, 17% to 30% may subsequently experience superficial noninvasive (≤T1) TCC[258,274,275] Eighty-four percent of patients who experienced superficial recurrences (Ta or CIS) at MGH have been maintained in remission by TURBT and intravesical drug therapy.[274] For these individuals the OS and DSS was comparable to those who had no failure. However, significantly fewer patients with a superficial relapse survive with their native bladder and up to one quarter of these patients may ultimately require a salvage cystectomy.

Although superficial tumors may be managed by TURBT and intravesical therapy,[274-276] invasive recurrences are generally managed with salvage cystectomy. In selected series, salvage cystectomy results in a 40% to 50% survival rate at 5 years and good locoregional control rates.[198,258]

Conclusions Regarding Combined Chemoradiation and TURBT. The *ideal* candidate for bladder preservation meets the following criteria:

1. Primary T2-3a tumors that are unifocal
2. TCC (urothelial) histology
3. Tumor size less than 5 cm in maximum diameter
4. Tumor not associated with extensive CIS
5. No presence of ureteral obstruction or tumor-associated hydronephrosis
6. Good capacity of the bladder and good bladder function (i.e., a bladder worth sparing)
7. Visibly complete TURBT
8. Adequate renal function to allow cisplatin concurrent with radiation (though good alternative chemotherapy regimens such as 5-FU/MMC can be considered in patients with lower glomerular filtration rate [GFR][256]).

Notably age is not a contraindication to successful bladder sparing therapy, and indeed results are favorable in patients age 75 or older.[258] This is an important consideration given that the elderly generally appear to be undertreated for invasive bladder cancer in the United States.[277] Bladder-sparing chemoradiation remains a good option for those patients who are not cystectomy candidates and often such patients would be treated with daily radiation and appropriate concurrent chemotherapy without a break.

Quality-of-Life Studies

Radical cystectomy causes changes in many areas of quality of life, including urinary, sexual, and social function; daily living activities; and satisfaction with body image.[278-282] Sexual function has been particularly emphasized because of the high prevalence of erectile dysfunction. Researchers have, over the last decade, concentrated on the relative merits of continent and noncontinent diversions. Available data have been mixed with some groups, surprisingly, reporting few differences between the quality of life of those with an ileal conduit and those with continent diversions.[283] Until recently, little comparative data have been available on those who have neobladders. Hart et al have compared outcome in cystectomy patients who have ileal conduits, cutaneous Koch pouches, or urethral Koch pouches.[282] Of 1074 patients undergoing cystectomy for bladder cancer at the University of Southern California, 368 were eligible for study because they were alive, spoke English, and had no major health issues that would affect global quality of life. Of these, 61% completed self-reporting questionnaires. Regardless of the type of urinary diversion, the majority of patients reported good overall quality of life, little emotional distress, and few problems with social, physical, or functional activities. Problems with their diversions (in approximately 60% of patients) and with sexual function were the most commonly reported. After controlling for age, no significant differences were seen among urinary diversion subgroups in any quality-of-life area. It might be anticipated that those receiving the urethral Koch diversions would be the most satisfied and the explanation why this is not so is unclear. It may be that the subgroups were too small to detect differences, but perhaps it is more likely that each group adapts in time to the specific difficulties presented by that type of diversion.

Zietman et al have performed a study on patients receiving TURBT, chemotherapy, and RT in the treatment of their bladder cancer at the MGH.[284] Of 221 patients with clinical T2-4a cancer of the bladder treated at the MGH from 1986 to 2000, 71 were alive with their native bladders and disease free in 2001. These patients were asked to undergo a urodynamic study (UDS) and to complete a quality-of-life questionnaire. Sixty-nine percent participated in some component of this study with a median time from trimodality therapy of 6.3 years. This long follow-up is sufficient to capture the majority of late radiation effects. Seventy-five percent of patients had normally functioning bladders by UDS. Reduced bladder compliance, a recognized complication of radiation, was seen in 22%, but in only one third of these was it reflected in distressing symptoms. Two of 12 women showed bladder hypersensitivity, involuntary detrusor contractions, and incontinence. The questionnaire showed that bladder symptoms were uncommon, especially among men, with the exception of control problems. These were reported by 19% with 11% wearing pads (all women). Distress from urinary symptoms was half as common as their prevalence. Bowel symptoms (e.g., rectal urgency) occurred in 22% with 14% recording any level of distress. The majority of men retained sexual function.

Global health–related quality of life was high. The great majority of patients treated by trimodality therapy therefore retained good bladder function. It was concluded that there is a small but detectable level of lasting bowel dysfunction and distress and that this might be judged the additional price that these patients have had to pay to retain their bladders.

A prospective Phase II multicenter study from France has recently been reported.[285] It tracked voiding symptoms and quality of life in 53 patients from before their trimodality treatment. Sixty-seven percent retained their bladders and these were interviewed 6, 12, and 24 months later. Levels of urinary symptoms were high but only 5% reported any EORTC grade-3 symptoms. It was also notable that most patients experienced improvement of symptoms over the 2 years after treatment presumably because of the eradication of a symptomatic primary tumor.

Two cross-sectional questionnaire studies, one from Sweden and one from Italy, have compared the outcome following radiation with the outcome following cystectomy.[286,287] The questionnaire results for urinary function following radiation were similar to those recorded in the MGH study. More than 74% of patients reported good urinary function. Both studies compared bowel function in irradiated patients with that seen in patients undergoing cystectomy. In both, the bowel symptoms were greater for those receiving radiation than for those receiving cystectomy (10% versus 3% and 32% versus 24%, respectively) but in neither was this statistically significant.

In the assessment of sexual function, most women in the MGH study preferred not to answer the questions and no data were therefore available for them. Almost all men, however, did. In contrast to patients who have been irradiated for prostate cancer, the majority of male bladder-sparing patients reported adequate erectile function (full or sufficient for intercourse), and only 8% reported dissatisfaction with their sex lives.[284] These are in line with those obtained in the Swedish and Italian series in which 38% and 25% of men retained useful erections as compared with 13% and 8% of cystectomized controls. The MGH series allowed the use of sildenafil probably contributing to the better outcome. Another study reported that 71% of women who underwent bladder-preservation therapy showed no decline in their subsequent satisfaction with sexual intercourse.[288]

An analysis of four prospective RTOG bladder-sparing protocols (89-03, 95-06, 97-06, 99-06) suggested that rates of significant late pelvic toxicity for patients completing combined-modality therapy for invasive bladder cancer and retaining their native bladder is low.[289] Only 7% of patients experienced a late grade-3 pelvic toxicity (5.7% genitourinary and 1.9% gastrointestinal) and in only one patient did the toxicity persist. Notably, there were no late grade-4 toxicities reported and no treatment-related deaths.

LOCALLY ADVANCED DISEASE AND PALLIATION

When bladder cancer has invaded adjacent organs or spread to the pelvic lymph nodes cure is rare, as the primary tumors are typically bulky and distant metastases usually present, even if subclinical. In this situation if the voiding symptoms are not too severe and the renal function allows, it is common to give combination chemotherapy and reassess after several cycles. If the patient has had a good response they may receive consolidation chemoradiation delivered with "curative" intent. If renal function is poor, patients may be given nonplatinum–based regimens such as 5-FU/MMC or taxol either before or with the radiation. If voiding symptoms are severe or there is bilateral hydronephrosis, they may be better served by percutaneous urinary drainage and then cystectomy with urinary diversion. For patients with locally advanced T4 primary tumors or locally recurrent cancer, there is a rationale for combining resection with intraoperative radiation therapy (IORT) but experience is limited. Resection and IORT would preferably be preceded by several cycles of multiagent chemotherapy, then pelvic radiation (45 Gy to 50.4 Gy in 1.8-Gy fractions) plus concurrent weekly cisplatin (see previous section). Trials have been published from our colleagues in Lyon, France, and Pamplona, Spain, demonstrating the potential value of pursuing such approaches in other centers with IORT capabilities.[290-292]

If the patient is unfit for cystectomy then radiation may be given to the bladder for palliation. Duchesne et al reported an MRC trial in the United Kingdom in which 500 patients were randomized to two palliative fractionation schedules: 35 Gy in 10 fractions and 21 Gy in 3 fractions (given weekly). When assessed at 3 months 68% had had some symptomatic improvement but there was no difference between the arms.[293] There was no evidence for a difference in toxicity justifying the use of this ultrahypofractionated regimen for the palliation of patients at the end of their lives.

Metastatic bladder cancer is responsive to platinum-based chemotherapy. MVAC or MCV (often given in dose-dense fashion) have been the usual choices as first-line drugs but gemcitabine and cisplatin (and the addition of taxol) are emerging as reasonable alternatives and may be better tolerated.[294] It is remarkable that, unlike most other solid tumors, CRs are not unusual and durable responses do occur. Recently, immunotherapy with checkpoint inhibitors has shown promise in clinical trials for metastatic bladder cancer.[294a]

Radiation is often used in the palliation of bone and brain metastases. Palliative radiation may also relieve the inferior vena cava or lymphatic obstruction that can occur when there is heavy involvement of the paraaortic nodes.

IRRADIATION TECHNIQUES AND TOLERANCE

External Beam Irradiation

Historically all work on bladder cancer that has been published used RT that was delivered by conventional two-dimensional RT. More recently, three-dimensional (3D) techniques became standard in RTOG protocols employing appropriate margins for an organ as mobile as the bladder. Now, IMRT has emerged as an option given the availability of advanced daily image guidance such as cone-beam CT and even real time tracking of the bladder and the possibility of more conformal treatment to spare central lying low hanging bowel.

At the MGH the following 3D technique has been used on and off-protocol regularly, though IMRT planning has been adopted more consistently in recent years. The standard protocol for radical EBRT as well as combined-modality therapy uses a four-field isocentric technique, which consists of shaped anterior, posterior, right, and left lateral fields for the initial or induction treatment field (Figure 54-4). This is followed by a boost or consolidation field (Figure 54-5).

Simulation

All simulations begin after the patient has voided (i.e., empty bladder). Treatments are also given with the bladder empty as this makes bladder position and tumor localization more reproducible and predictable. The patient is then immobilized in a supine position and a CT simulation is performed.

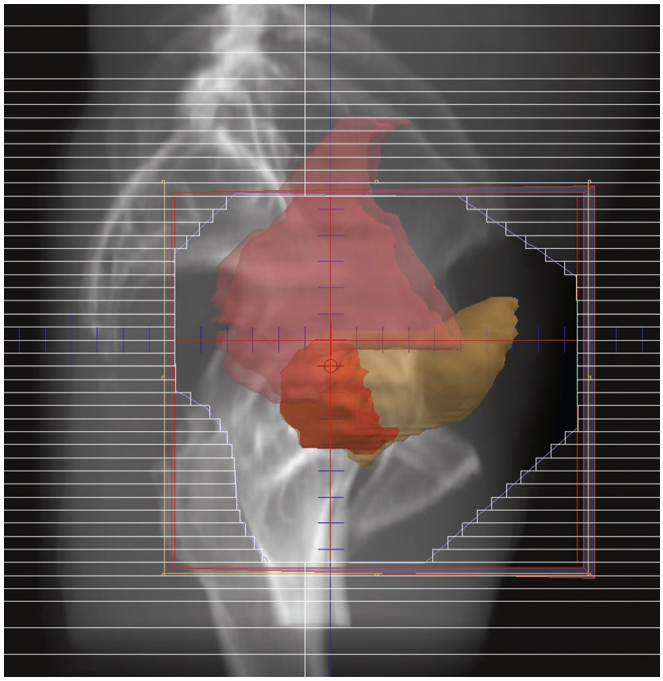

Figure 54-4 Sagittal digitally reconstructed radiograph (DRR) image showing a lateral view of a small pelvis field.

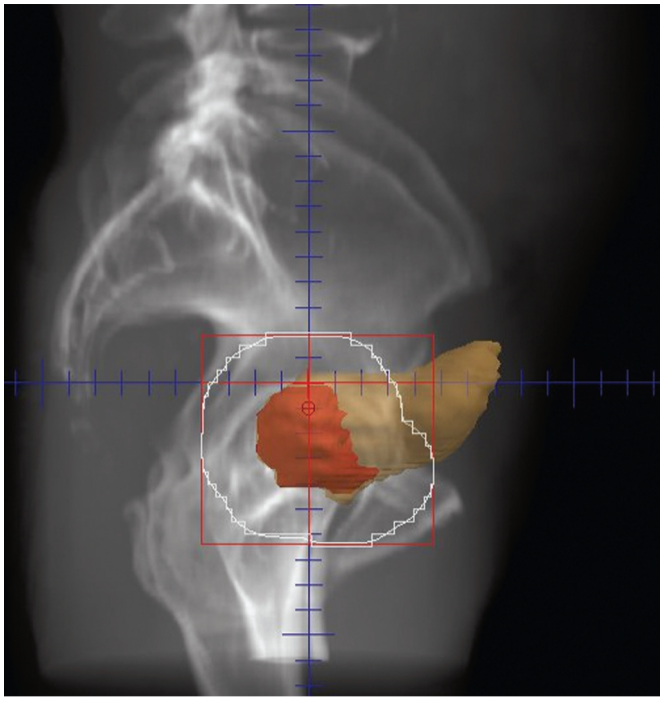

Figure 54-5 Sagittal digitally reconstructed radiograph (DRR) image showing how a lateral boost may be given to a tumor to spare the anterior bladder.

Target Volumes

During the first phase of treatment the bladder is treated along with a margin of 2 cm. In men, the entire prostate is also covered in this first phase because there may be occult stromal invasion or extension into the prostatic urethra. In women, the proximal 2 cm of urethra are also considered target. Care must be taken to avoid the inferior border of the field glancing the vulva because this may limit tolerance. The internal and external iliac lymph nodes of the pelvis are also covered for this phase of therapy. The top border of the field usually lies around the midsacroiliac joint and only at the level of the bifurcation of the common iliac vessels and does not include the entire pelvis. This is because a significant number of irradiated patients may subsequently require salvage cystectomy with urinary diversion. It is therefore prudent to limit the amount of radiation to bowel that may subsequently be needed for this purpose. Another good reason to limit the bowel volume is that quality-of-life studies have shown that the most troublesome consequences of irradiation for bladder cancer relate to the small bowel irradiation rather than the bladder irradiation.[284,287]

During the boost phase of treatment, MGH investigators boost the entire bladder excluding nodes and then further boost the tumor alone with a 2 cm margin (an alternative is to just boost the tumor alone). Defining the tumor may be difficult, but we employ a combination of an operative report and bladder map drawn by the urologist at the time of cystoscopy/TURBT, and CT and MR information from the initial (pre-TURBT) staging work-up. CT scan after TURBT may overestimate the tumor residuum because of edema in the bladder wall. Using these sources of information it is usually possible to exclude at least one third of the bladder from the boost volume (Figures 54-5 and 54-6). Although this may not seem like much, it does mean that less than the entire volume is treated to full dose, a factor that may contribute to the good functional results seen after use of this technique. Fiducial markers may be inserted either cytoscopically or through the anterior abdominal wall into the edges of the resection bed to aid boost visualization (Figure 54-7). Such fiducial markers around the tumor site placed at time of TURBT can help tailor field design and can be used with daily imaging (such as cone-beam CT) for localization to further guide treatment during the tumor boost phase. It is possible that treating with a full bladder during the tumor boost phase could further limit bladder and bowel dose.

Fields

The first phase treats the pelvic lymph nodes, prostate, and bladder (if using a four-field arrangement, roughly mid-SI joint superiorly, bottom of the obturator foramen inferiorly, and 1.5-cm margin on the pelvic brim laterally). The second phase boosts the bladder alone and the third phase the tumor alone. As most tumors are on the bladder trigone or on the postero-lateral walls, it is easiest to boost with opposed lateral fields when not using IMRT. If this is anticipated the 4-field box used in the first phase has to be weighted more heavily toward the antero-posterior (AP) and posterior-anterior (PA) to save femoral head tolerance and allow the lateral boost.

Patients are encouraged to empty their bladders before treatment to achieve a more reproducible target and to minimize volume irradiated. Many patients with bladder cancer have significant postvoid residual volume so artificial emptying of the bladder by catheterization may give a false impression of the shape and size of the target volume at simulation.

IMRT planning has been adopted at the MGH more recently (Figure 54-6). Planning target volume (PTV) expansions of 2 cm around bladder and bladder tumor have been employed, with 0.8-cm margins for prostate (0.5-cm posterior) and pelvic nodes. PTV margins may be decreased a little when targets abut large amounts of low hanging small bowel. A seven-field beam arrangement is typically used for small pelvis, and either a five- or seven-field beam arrangement for bladder only and tumor boost. We start with beams equally spaced and modify the angles as anatomy requires.

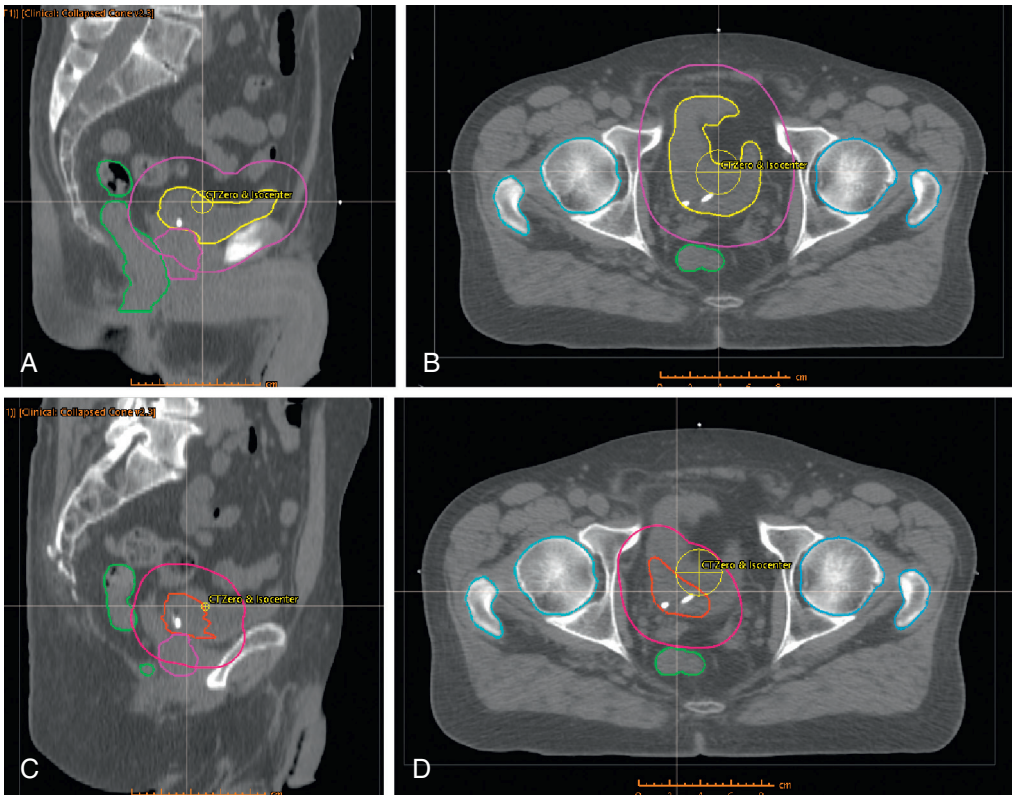

Figure 54-6 **A** and **B,** Planning target volume (PTV) expansions around bladder, tumor, prostate in sagittal and axial CT cuts for small pelvic fields; Panels **C** and **D,** PTV expansions for bladder tumor boost fields.

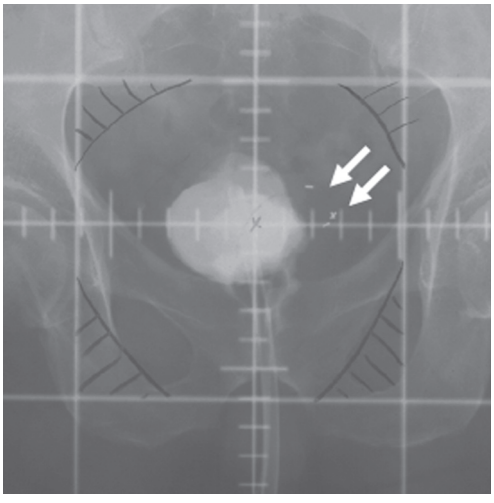

Figure 54-7 Fiducial markers placed adjacent to a bladder tumor at the time of transurethral resection.

Total Dose

At the MGH, investigators have traditionally given total doses on the order of 65 Gy delivered in once daily (1.8-Gy to 2-Gy fractions, 5 days per week) or twice daily (please refer to RTOG 0712) fashion, together with concurrent chemotherapy (cisplatin alone, cis/5-FU or 5-FU/MMC when not on protocol) and a maximal TURBT. Typically, 40 Gy to 45 Gy is delivered in the first phase to the larger small pelvic field covering the entire bladder, prostate, and the low pelvic lymph nodes. The whole bladder receives an additional 10 Gy 14 Gy, and the tumor is boosted to full dose with an additional 10 Gy. If not employing a bladder-alone boost, then the tumor is boosted to the full dose after the small pelvic phase. An invasive local recurrence is limited to only 15% to 18% of all complete responders, implying that this is an adequate dose for durable local control in the vast majority of those who respond to radiation. Investigations into adaptive planning and dose escalation are ongoing.

Treatment Break to Evaluate Response

At the MGH, investigators have routinely built in a 3-week break as an early treatment assessment response following the delivery of 39 Gy to 42 Gy. This is quickly followed by repeat cystoscopy/biopsy of the tumor site (Figure 54-8). Patients are selected to continue and complete radiation (the consolidation phase) on the basis of their response at this point. Those who have had a CR (anticipated to be 80% of patients) or in whom the tumor residuum is less than T1 by stage (Ta or Tis) continue. The others are recommended to undergo an immediate cystectomy. This can thus be performed before the patient has had full-dose radiation, an easier proposition for the surgeon (both in time to cystectomy and in dose to the pelvis). It also means that a patient responding poorly can be identified early and recommended surgery promptly rather than waiting for an entire course of radiation to be completed by which time progression may have occurred that could threaten the efficacy of salvage therapy. Concerns have been expressed on radiobiological grounds that split-course treatment compromises efficacy.[295,296] There is also the worry that those who have not been complete responders after 40 Gy might yet become complete responders after 65 Gy, and thus, some may be recommended an unnecessary

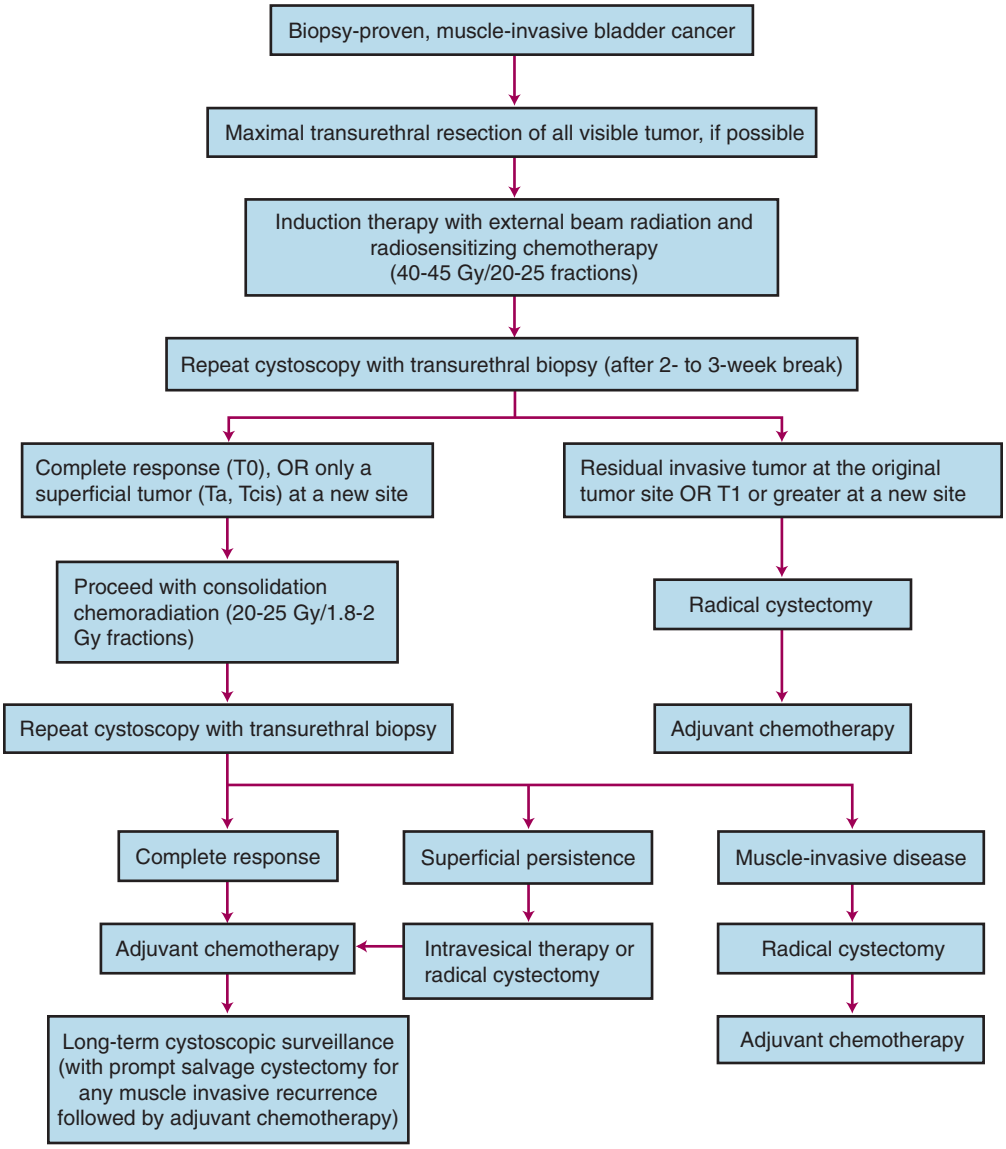

Figure 54-8 **Current algorithm for the trimodality management of invasive bladder cancer.**

cystectomy. This concern, however, probably affects only a minority of patients.

Controversial Issues in EBRT Technique

Nodal Treatment

Lymph node involvement is common in this disease and is seen in approximately 25% of patients coming to a radical cystectomy.[153] The number of lymph nodes involved is well established as a prognostic indicator that surgeons use to determine the extent of their lymph node dissection and the need for adjuvant chemotherapy.[158] This information is, however, unavailable to radiation oncologists. More interesting for them is the knowledge that some patients with positive lymph nodes may be cured by a lymphadenectomy, a situation akin to breast or head and neck cancers. The thoroughness of a lymph node dissection (>10 nodes removed) also correlates with outcome independent of nodal status.[297] Thus, radiation to the pelvis might confer a survival advantage though it comes at the price of additional morbidity. Centers that do irradiate the bladder alone (typical in UK practice) do not report either an increased pelvic failure rate or reduced survival although direct comparisons are difficult and randomized data is not available.[298] It may be that either chemotherapy does the job of the nodal irradiation or that nodal disease extends beyond the confines of the current pelvic template. Surgeons have started to perform extended lymphadenectomies to the level of the inferior mesenteric artery.[141,299]

Partial Bladder Treatment

Estimates of bladder tolerance have been made which suggest that up to 80 Gy could be given if one third of the bladder is spared, whereas 65 Gy is the limit for whole-bladder treatment.[300-302] In addition, the low rate of development of new invasive tumors elsewhere in the bladder after brachytherapy (5% to 7%) suggests that localized partial bladder radiation is a reasonable strategy.[202] Careful selection is, however, necessary with such approaches being limited to smaller tumors (<5 cm), unifocal tumors, and those without extensive Tis tumor elsewhere in the bladder. A randomized trial in the United Kingdom has shown that partial bladder irradiation does allow for the delivery of a higher dose to the

tumor than whole-bladder radiation without an increase in morbidity.[303] It did not, however, show either improvement in local control or survival. One hundred forty-nine patients were randomized to receive whole-bladder conformal RT to 52.5 Gy in 20 fractions or partial bladder conformal radiation to either 57.5 Gy in 20 fractions or 55 Gy in 16 fractions. The 5-year local control rates for these three regimens were 58%, 59%, and 34%, respectively, without any significant differences between arms ($p = 0.18$). The recently reported BC2001 Phase III trial also randomized patients to standard whole-bladder EBRT or reduced high-dose volume EBRT that aimed to deliver full radiation dose to the tumor and 80% of maximum dose to the uninvolved bladder.[304] There were no statistically significant differences between groups in terms of late toxicity and noninferiority of locoregional control could not be concluded formally. Overall low rates of clinically significant toxicity combined with low rates of invasive bladder cancer relapse help to confirm that chemoradiation therapy is a valid option for the treatment of muscle-invasive bladder cancer.

Treatment Margins

At the MGH in expanding the clinical target volume (CTV) to the PTV we have adopted isotropic 2-cm margins around either the bladder (first phase of treatment) or tumor (boost) in all three dimensions. This is to account for set-up errors and organ motion. Several studies employing serial CT scans have shown that margins less than this may be inadequate. Turner et al demonstrated that bladder wall movement of >1.5 cm occurs at least once during a course of treatment in more than 60% of patients.[305] Several others have reported that the gross target volume (GTV) moves outside the PTV on at least one occasion in at least 20%.[306,307] Our own analysis showed that these variations are highly patient dependent and occurred even when strict instructions were given regarding bladder and rectal filling.[308] The greatest degree of bladder wall positional change occurred in the cranial direction with the least variation in the antero-inferior direction, limited by the pubic symphysis. In light of this information it is clear that organ motion is the dominant source of error and that the magnitude of the error depends on the region of the bladder. The solutions are clear though difficult to achieve. Graham et al have recommended anisotropic margin widths of 1.6 cm anterior and posterior, 1.4 cm laterally, 3 cm superior, and 1.4 cm inferior.[309] The problem is that these margins incorporate much normal tissue. Daily image-guided therapy is the only way to reduce these margins significantly. Daily cone-beam CT that can delineate the bladder is one option. There is also interest in the use of fiducial markers that could be placed by the urologist at the time of TURBT in the bladder wall around the tumor crater (Figure 54-6 and Figure 54-7). Roof et al have shown that if the daily treatment is centered on the bladder centroid, rather than referenced to bony anatomy, margins of <1.5 cm could be feasible.[308] None of these studies account for the fact that the bladder not only changes in size but also in shape, it is deformable. This will likely set a limit on our ability to shrink margins significantly anytime soon.

Radiation Dose

There is evidence for a dose-response curve in bladder cancer with most studies showing that doses of <62 Gy (at 1.8 Gy to 2 Gy per fraction) predict poor outcome.[310-312] Most of these studies have, however, employed radiation alone and the curve is likely to be greatly modified by effective debulking of the tumor or by radiation sensitization with concurrent chemotherapy. Increasing dose may result in increased CR rates but may add to the morbidity and may also be limited by the rapid proliferative index and short doubling time of these tumors.[313] Interest recently has therefore concentrated on dose intensification using accelerated regimes rather than an increase in total dose. Acceleration may be achieved through hypofractionation, but this may be better limited to the palliative setting or through the use of conventional 2-Gy fractionation given twice a day.[314] The Royal Marsden Hospital has reported on 85 patients with twice-daily fractions of 1.8 Gy to 2.0 Gy 5 days a week to doses between 57.6 Gy and 64 Gy in 32 fractions over 26 days. Of 70 patients who had cystoscopic reevaluation 3 months to 6 months after RT, 80% were found to be complete responders (i.e., cystoscopy and biopsy negative for tumor 3 months to 6 months later).[315] Plataniotis et al reported a total response rate of 67% when a twice-daily fractionation was used during the last week (fifth week) of RT.[316]

Unfortunately, acceleration with fraction sizes of 2 Gy seems to increase acute toxicity. The RTOG has therefore explored acceleration with hyperfractionation and recent protocols have employed fraction sizes of 1.2 Gy to 1.8 Gy with a concomitant boost technique. No comparative studies have yet been performed but morbidity appears low.[265] The recently closed RTOG protocol 0712 did compare a twice daily to once daily regimen, though results are pending.

Hyperfractionation has also been used to increase the total tumor dose. A randomized trial of 168 patients with T2-4 tumors, unsuited for cystectomy, compared hyperfractionated EBRT (1 Gy three times a day to a total dose of 84 Gy) with conventional fractionation (2.0 Gy every day to 64 Gy).[317,318] Hyperfractionation achieved superior results with respect to 5-year OS (27% versus 18%), local control (12% versus 7%), and clinical CR rates (59% versus 36%) with an increase in late toxicity. Both study arms were treated by a split-course of RT with a 2-week gap after the first 3 weeks, the effect of which is unknown. The benefit of the hyperfractionated schedule persisted over a 10-year follow-up period, both for local control and survival. It should be noted, however, that patients in the conventional fractionation arm did poorly compared with those receiving similar treatment in other studies largely because patients unfit for cystectomy were entered in this study.

Future improvements in the CR rate may also come without any need to escalate radiation dose: better selection of patients, better radiation sensitization (including novel targeted therapy and immunotherapy), and more aggressive TURBT. Others have argued that doses of 65 Gy at 1.8 Gy to 2 Gy per fraction may actually be more than is needed especially for those who have had visibly complete transurethral resections. The Erlangen group has delivered doses tailored to the estimated residuum following resection. These doses are in the range of 50 Gy to 59 Gy (1.8 Gy to 2 Gy per fraction) depending on whether disease to be treated is microscopic or gross in volume.[319]

Brachytherapy

Shortly after completion of the preoperative radiation (<2 weeks), a suprapubic cystotomy is performed to ascertain the true dimensions of the tumor and to confirm that it is indeed unifocal. There are regional differences in the type of surgery performed on the primary tumor. In France, a partial cystectomy is preferred. In the Netherlands, citing concerns about the risk of fistula, this is only performed for lesions on the dome or in a diverticulum. The target area is determined by the surgery and is either the bladder scar after partial cystectomy or the macroscopic tumor plus a 1.5-cm to 2.0-cm margin. It may be marked by fiducials at this point. Narrow afterloading tubes are then inserted into the target area parallel and halfway through the bladder wall. In the case of a partial cystectomy, two tubes one on either side of the scar are sufficient. If a partial cystectomy is not performed, then three to

five tubes in a single plane will encompass most lesions. The tubes are then brought out to the anterior abdominal wall and a suprapubic catheter inserted for drainage. The tubes are removed without anesthesia after the completion of radiation; the urinary catheter is removed 2 weeks later.

Radiation planning may be performed using stereo-shifted radiographs, but it is now preferable to use CT. Doses given vary greatly in the literature according to the additional external beam given and whether or not high- or low-dose rate brachytherapy is planned. If less than 10 Gy to 15 Gy is given preoperatively, then 30 Gy to 60 Gy are given using low-dose rate. The lower doses are given to those who have had partial cystectomies or complete resections. In the Netherlands 30-Gy EBRT is either supplemented with 40 Gy low-dose rate or 10 × 3.2 Gy high-dose rate (two fractions per day with a 6-hour interval).

TREATMENT ALGORITHM, CHALLENGES, AND FUTURE POSSIBILITIES

Selective bladder preservation is based on the response of the tumor to induction combined-modality therapy, which includes a TUR of as much of the primary bladder tumor as is judged safely possible combined with concurrent chemotherapy and EBRT; early salvage cystectomy is recommended for patients whose tumors are not responding to combined-modality therapy or for an invasive recurrence to maximize the possibility of cure (Figure 54-8). In appropriately selected muscle-invasive patients, bladder-preserving treatment with chemo-radiation offers a chance for long-term cure and survival comparable to radical cystectomy, while affording a 70% to 80% chance of maintaining their native bladder (Tables 54-6 and 54-7). Quality-of-life studies have demonstrated that the retained native bladder functions well and long-term toxicity of chemoradiation to pelvic organs is low. These results support the acceptance of modern bladder-sparing trimodality therapy for selected patients as a proven alternative to cystectomy (and for patients who are not good surgical candidates). This approach is not suitable for patients with tumors obstructing a ureter. Twenty percent to 30% of patients cured of muscle-invading bladder cancer will subsequently acquire a new superficial tumor, but these superficial tumors have generally responded well to the usual TURBT and intravesical drug therapy. These patients require close urologic surveillance, as do any patients with superficial bladder cancer treated conservatively. Bladder-preserving treatment usually results in a normally functioning bladder for patients with T2 and T3a disease; however, patients with T3b-4 disease experience local control less frequently using these techniques. No data exist, however, to suggest that patients with more advanced disease are in any way disadvantaged by preoperative chemoradiation as an attempt at bladder conservation. Radiation-based strategies are also being explored in the recurrent T1 BCG refractory and locally advanced postcystectomy settings. Further clinical practice guidelines are available through the updated National Comprehensive Cancer Network[320] and other guidelines.[115]

Although many urologists have found merit in a selective bladder-sparing approach to muscle-invading transitional cell bladder cancer, many more will need to become convinced if there is to be a significant change in treatment practices for bladder cancer across the country. As studies addressing the possibility of organ preservation continue to demonstrate positive results, it is hoped that more patients will become informed about and be offered selective bladder-sparing approaches as an alternative to radical cystectomy. The contribution of selective bladder-sparing therapy to the quality-of-life of patients so treated represents a unique opportunity for urologic surgeons, radiation oncologists, and medical oncologists to work hand in hand in a truly multidisciplinary effort.

The immediate therapeutic challenges for radiation oncologists include:

- More effective radiographic tumor definition and tracking during radiation therapy. This may allow tighter margins, more accurate and higher dose delivery, and higher rates of bladder preservation.
- More effective radiation sensitization. The optimal regimen of combined chemoradiation continues to be investigated. Current standards are cisplatin-based (such as cis/5-FU) or 5-FU/MMC. Gemcitabine has been under evaluation at several centers and by the RTOG.
- More effective evaluation of pelvic lymph nodes using, perhaps, iron nano-particle MR lymphangiography, and more effective treatment of pelvic lymph nodes with either extended lymphadenectomy or radiation delivered using intensity-modulated irradiation (IMRT).
- Further defining a role for radiation-based strategies in the recurrent T1 BCG refractory and locally advanced postcystectomy settings.
- Integrating rational molecularly targeted biologic and immune-based strategies into primary therapy.
- Further defining clinical factors and molecular biomarkers predictive of response and outcome to therapy.

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