Contemporary Management of Locally Invasive Bladder Cancer

By Rian J. Dickstein, MD [2] and Ashish M. Kamat, MD [3]

Muscle-invasive bladder cancer is an aggressive and potentially lethal disease. Integration of multimodal therapies, improved surgical techniques, and utilization of targeted agents has tremendously improved outcomes.

Introduction

Bladder cancer remains the fourth most common cancer in men and consistently falls within the top 10 most common cancers in women.[1] Additionally, in the United States, it is one of the most expensive cancers to treat, costing the government an estimated $3.7 billion per year, mainly because of the rigorous follow-up needed to detect recurrent disease.[2] Initially, the majority of patients are diagnosed with localized disease (20% of which is muscle-invasive), with only 8% and 4% of patients having locally advanced and metastatic disease, respectively.[1] Radical surgery is the predominant treatment for those who present with de novo muscle-invasive bladder cancer (MIBC) and those with non–muscle-invasive disease that progresses after intravesical therapy. However, because bladder cancer typically affects an elderly population (with a median age of 73 years at diagnosis[3]), there is a need for less invasive and bladder-conserving therapies.

Radical Surgery

Radical cystectomy (RC) involves removal of the bladder and seminal vesicles en bloc in males, and removal of the bladder, uterus, fallopian tubes, ovaries, and a segment of the anterior vaginal wall in females. Bowel is commonly utilized for reconstructive purposes to store and empty the urine. RC typically involves an operation lasting between 4 and 10 hours and a hospital stay ranging between 5 and 10 days. Postoperative complications are common and include atelectasis, wound infection, and ileus, plus the complications of prolonged anesthesia that occur in an elderly population, most of whom have pre-existing coronary and pulmonary disease.

Current surgical techniques have been in evolution for the last 40 years. Early results indicated that only about 50% of patients were cured with surgery, and most patients died of metastatic disease within 3 years of diagnosis. During the 1970s, various preoperative radiation regimens were employed, but these failed to show convincing evidence of benefit. The main limitation of RC was the considerable associated morbidity. However, surgical techniques have significantly improved over time, and the procedure has become much more accepted, particularly since the implementation of orthotopic urinary diversions (ie, neobladders).

Now RC with pelvic lymph node dissection is considered the gold standard of treatment for MIBC and offers the best chance of long-term disease control. However, survival is closely associated with pathologic stage, and unfortunately, clinical staging diverges from pathologic staging in around 50% of cases.[4] Consequently, there is obviously a great need for better determinants of stage. Molecular markers are in the forefront of research in this area, with many groups trying to identify gene signatures for each pathologic feature.[5]

Lymph node dissection

A well-performed lymphadenectomy is an essential component of RC. Not only is the removal of lymph nodes prognostic, as in most other cancers, but the extent of dissection has an impact on outcome.[6,7] A “standard” lymph node dissection involves removal of all tissue within the boundaries of the genitofemoral nerve laterally, the bladder medially, the circumflex iliac vein inferiorly (lymph node of Cloquet), the bifurcation of the common iliac artery superiorly, and hypogastric vessels posteriorly. Lymph node packets are typically removed from regions around the external iliac, internal iliac, and obturator vessels, but recent mapping studies have more accurately described the common landing zones for nodal metastases.[8] An “extended” lymph node dissection
is carried up to the aortic bifurcation and includes presacral nodes. There is no exact consensus on the minimum number of lymph nodes that must be removed for success, but early reports suggested that at least nine would ensure adequate information for proper staging.[9] Most urologists would agree that the removal of more nodal tissue results in more accurate staging and removal of undetected micrometastases. Thus, there is growing evidence that an extended dissection may provide a clinically meaningful benefit by conferring a survival advantage in both node-positive and node-negative patients.[10,11] A randomized trial of “standard” vs “extended” lymph node dissection is currently enrolling patients, and its results will be crucial in expanding our understanding of this key question.

The concept of lymph node density (ie, the number of positive nodes as a percentage of total nodes removed) reflects the quality of the nodal dissection and tumor burden.[12] Lymph node density has been confirmed as a useful tool in predicting survival,[13,14] and data suggest that lymph node density performs better than the N status of TNM staging in risk stratification. Recently, the relevance of lymph node metastases and the benefits of lymphadenectomy have been nicely summarized in a collaborative review concluding that an “extended” lymph node dissection can be curative in patients with metastases or micrometastases and thus should be offered to all patients undergoing curative radical surgery.[8]

**Urinary diversion**

Diversion of urine after removal of the bladder is a permanent quality-of-life issue after surgery. Today, there are three main categories of urinary diversion: a noncontinent cutaneous diversion (most commonly the ileal conduit), continent cutaneous diversions, and orthotopic reservoirs attached to native urethra (ie, neobladders). An ileal conduit represents the simplest type of diversion and is associated with the fewest intraoperative and immediate postoperative complications. However, there are several prevalent associated long-term complications, including stomal stenosis, chronic or recurrent pyelonephritis, calculus disease, ureteroenteric anastomotic strictures, and renal deterioration. With regard to continent cutaneous diversions, the major long-term problem remains the provision of a durable continence mechanism. Orthotopic neobladders have become more popular because they offer a number of theoretical advantages, including the ability to most nearly recreate normal voiding function, the ability to achieve continence with use of the native rhabdosphincter, avoidance of an abdominal stoma, easier urethral surveillance, a potentially lower urethral recurrence rate, and a superior body image.[15,16] However, there are risks of urinary incontinence, particularly nocturnal enuresis, of hypercontinence, and potentially of the need to catheterize and irrigate a pouch to drain excess mucus. Various factors are important in the selection of patients for each type of diversion. To minimize the risk of urethral recurrence, investigators have found that patients undergoing orthotopic neobladder should not have bladder neck involvement, prostatic stromal invasion, or positive surgical margins on frozen section analysis.[17] Additional considerations include patient preference and ability, mobility, manual dexterity, renal dysfunction, mentation, bowel availability, comorbidities, and life expectancy.

Disease recurrence rates are independent of urinary diversion type. Approximately 5% to 7% of men and 1% to 4% of women develop a urethral recurrence after the creation of an orthotopic neobladder.[18-20] Daytime continence rates remain greater than 95% for men and 90% for women, with nocturnal continence rates as high as 75% in men and 57% in women.[21,22] Some believe that an orthotopic neobladder improves quality of life compared with an ileal conduit, but most retrospective studies report no significant measurable difference.[23] Recently, investigators evaluated the utilization of ileal conduits and orthotopic neobladders in a large series of patients. They found a significant trend toward the use of ileal conduit urinary diversion in female patients, patients of advanced age, those with significant medical comorbidities, and those with locally advanced disease. However, orthotopic neobladders continue to be the most common urinary diversion in patients younger than 65 years.[24]

**Complications**

RC remains one of the most challenging and complex surgeries in the urologic arsenal, for both the surgeon and the patient. Although operative mortality is low at 1%, overall complications are common, with an incidence near 40%.[25] Early complications include pulmonary (atelectasis, pneumonia, pulmonary embolus, etc), gastrointestinal (ileus, small bowel obstruction, enterocutaneous fistula, etc), anastomotic (urea leak or obstruction), hemorrhagic, and
wound-related effects (infection, dehiscence, and evisceration). Late complications include anastomotic site-related effects (strictures, stones, reflux), ostomy-related effects (hernias, prolapse), infections (pyelonephritis), and metabolic effects (acid/base disturbances, electrolyte disturbances, vitamin B<sub>12</sub> deficiency).[26] Quality of care and the ability to control and improve outcomes continue to be important issues. We know that postoperative mortality after RC is inversely associated with the number of procedures performed. Many studies have suggested that high-volume providers have better infrastructure and more experience, which can lead to better outcomes. Volume is seen as a proxy for high quality of care; thus, centralization is believed to improve outcomes for patients undergoing RC. A recent meta-analysis confirmed this volume-outcome relationship. In particular, positive associations are seen between high-volume hospitals (and high-volume surgeons) and both mortality and survival.[27] Furthermore, application of a fast-track clinical care pathway for patients undergoing RC reduces morbidity and improves recovery.[28]

**Minimally Invasive Surgery (Laparoscopic and Robotic Cystectomy)**

Open surgery remains the mainstay of treatment for MIBC; however, some practitioners have attempted to minimize surgical morbidity by pursuing minimally invasive techniques. Laparoscopic RC offers the potential for quicker convalescence. Preliminary studies suggest that this technique results in reduced blood loss and transfusion requirements, with comparable complication rates. Unfortunately, laparoscopic RC remains technically challenging and difficult to learn. Currently, it is only performed by surgeons with extensive experience in laparoscopic pelvic surgery.[29] With the introduction of the da Vinci robot into the realm of urology, laparoscopic RC has largely been supplanted by robotic surgery. The first reports of RC with robotic assistance were published in 2003. With careful attention to detail, removal of the bladder with adequate margins is certainly feasible with this approach; however, it is dependent on the oncologic training of the individual surgeon. Margin-positive rates of up to 10% have been reported in the literature, and this must be recognized as a major determinant of outcome because there is no truly effective salvage for a surgical misadventure in bladder cancer.[30] Notably, there have been over 100 publications on robotic RC. Most of these have focused on the decrease in blood loss (from a median of 750 mL to 400 mL) and shorter hospital stay; however, these benefits are offset by an increase in operative time.[31]

Lymph node yield following robotic surgery has been reported by some authors as a surrogate for oncologic efficacy, to enable a comparison of the minimally invasive technique and the standard open procedure. It is well known that one of the more difficult parts of the robotic operation is the lymph node dissection.[32] However, all series to date have reported acceptable lymph node yields that indicate an adequate lymphadenectomy with the robot-assisted technique; the average yield has ranged between 17 and 19 nodes removed.[33-36] We performed a prospective study at MD Anderson Cancer Center in which we evaluated lymph node yield through a second-look open pelvic lymph node dissection and found a 93% yield. Specifically, 67% of patients were clear of residual tissue, 13% had residual tissue without lymph nodes, and 20% had residual lymph node tissue.[37] A cost analysis of robotic and open RC found that overall, the robotic approach is associated with a cost increase of $1,640 ($16,248 [robotic] vs $14,608 [open]).[38] Operative time and length of hospital stay have the greatest impact on costs. When comparing direct operative costs, robotic RC is about 16% more expensive; however, actual patient costs are less for the robotic approach due to the higher complication rate and increased hospitalization costs associated with the open procedure.[39] Clearly, these are important factors to consider in the current healthcare environment.

Although early reports described an extracorporeal urinary diversion following robot-assisted RC and lymph node dissection, more recently, intracorporeal diversions have been reported in small series of patients.[40] With improved instrumentation, intracorporeal diversion might be more widely adopted; it potentially offers less incisional pain, decreased bowel dysfunction with less exposure and desiccation, and decreased fluid imbalances. However, despite the surge in institutions adopting a robotic approach to RC, the long-term effectiveness of these techniques must be monitored and considered. Ongoing head-to-head randomized comparisons between robotic and open procedures will provide the most useful data.

**Prostate-Sparing Surgery**

Some surgeons have proposed a prostate-sparing approach to RC in select patients, with
hypothesized benefits in urinary continence, sexual potency, and fertility preservation. This modified surgical approach generally includes sparing the prostate capsule, vasa deferentia, and seminal vesicles while resecting a prostatic adenoma (in some cases). However, there is concern about the oncologic efficacy of this procedure. In particular, local recurrence rates range between 5% and 20%, and the distant recurrence rate is twice as high as with standard RC.[41,42] In fact, prostate involvement by urothelial carcinoma in patients undergoing cystoprostatectomy for bladder cancer has been reported in 5% to 40% of patients.[43] Moreover, the reported incidence of prostate cancer in cystoprostatectomy specimens is approximately 40%, with about 20% of these tumors considered potentially clinically significant.[44-46] In addition, it is now apparent that the hypothetical benefits of prostate-sparing surgery are also not as relevant as previously thought. The approach does not seem to result in any significant improvement in daytime continence rates, although nighttime continence may be slightly better. However, the issue of urinary retention and the need for intermittent catheterization appears to be more problematic. Also, most men are not concerned with fertility at the time of surgery (median age, 67 years). Erectile function preservation represents the single greatest advantage of prostate-sparing cystectomy.[47] Consequently, prostate-sparing cystectomy should not be considered part of standard therapy.

**Systemic Therapies**

Clinical data suggest that RC provides insufficient treatment for certain patients at high risk for tumor recurrence, namely those with advanced stage disease or lymph node involvement. Multimodal therapy (chemotherapy and surgery) provides an improved cure rate in high-risk patients with bladder cancer, whether chemotherapy is given before or after surgery.[48] However, this increased probability of improved outcome with multimodal therapy is accompanied by an almost certain risk of increased toxicity. Thus, the most critical issue in multimodal therapy is patient selection.

**Neoadjuvant chemotherapy (NAC)**

Locally advanced bladder cancer is associated with a high risk of distant occult disease, as exemplified by a high rate of upstaging and death from metastases after local surgical treatment. One of the aims of NAC is to lower cancer mortality caused by occult metastatic disease that is present at the time of local radical treatment. NAC results in de-bulking of patients’ tumor burden and potential eradication of micrometastases. Additional benefits of NAC include the ability to serve as a barometer of disease aggressiveness, improved compliance with planned treatment, and better tolerability than is seen with adjuvant chemotherapy. Currently, there is a push to utilize the neoadjuvant platform to explore molecular profiling of tumor chemosensitivity and as a venue for testing novel targeted agents.

Pathologic T0 status at the time of RC confers a survival advantage, since this is based on tumor biology and not treatment effect.[49] Unfortunately, clinical upstaging at the time of RC is seen in about 50% of patients; these patients have a worse prognosis, with an increased risk of disease recurrence and lower survival rates.[50-52] Thus, the basic premise for NAC in urothelial cancer is to minimize tumor burden, especially in patients with locally advanced disease for whom transurethral resection may be insufficient or incomplete.

The largest study to date supporting NAC was an international collaboration that demonstrated a 5.5% difference in 3-year survival for all patients with MIBC receiving NAC with RC compared with RC alone.[53] A recent update on this study showed a significant 16% reduction in the risk of death and increased median survival (37 to 44 months) with NAC.[54] A landmark study was published in 2003 that demonstrated the benefits of NAC preceding RC vs RC alone. There was a statistically significant benefit in all patients with MIBC, but the greatest benefit was seen in patients with extravesical disease.[55]

Thus, there is level 1 evidence to support the use of NAC in patients with MIBC. However, despite the evidence, perioperative chemotherapy is highly underutilized in appropriate patients. In fact, only 12% of patients actually receive NAC.[56] Recently, there has been a large effort to educate the public about the benefits of combined modality treatment, and investigators are working hard to refine the selection criteria for patients who stand to benefit the most and those who should avoid this treatment regimen.[57,58]

**Adjuvant chemotherapy**

Proponents of adjuvant therapy argue that this treatment approach permits appropriate patient
selection for chemotherapy based on pathologic findings and may minimize the number of patients who receive unnecessary toxic therapy. There have been many trials investigating the benefit of adjuvant chemotherapy, but most have failed to show a clear benefit, arguably because of poor accrual and low power. In 2005, a collaborative meta-analysis reported a 9% absolute survival benefit in patients who received adjuvant chemotherapy compared with those who received local treatment only; however, the data were very limited.[59] Most recently, a retrospective cohort analysis from multiple institutions of excellence confirmed the survival benefit in patients treated with adjuvant chemotherapy; in particular, those with the highest risk for progression, including those with advanced pathologic stage and nodal involvement, may be the patients who benefit the most from this therapy.[60]

One of the major concerns with adjuvant chemotherapy is the patient’s ability to tolerate treatment and thus comply with the prescribed regimen. RC is a major surgical undertaking, with a variable recovery period averaging 6 to 8 weeks. Moreover, chemotherapy may induce pancytopenia, nausea and vomiting, stomatitis, diarrhea, constipation, renal toxicity, neuropathy, fatigue, lethargy, and malaise. Thus, patients should be carefully selected for this therapy.

Our group from MD Anderson Cancer Center uses a risk-adapted approach to potentially better select patients for multimodal therapy. Those at high risk for death from disease are offered NAC, whereas those at lower risk (defined as clinical stage no higher than T2 and an absence of lymphovascular invasion, variant histologies, or hydroureteronephrosis) are offered RC initially. Patients who are upstaged at RC are subsequently offered adjuvant chemotherapy. Future endeavors will be focused on refining selection criteria for each treatment modality, with encouraging molecular methodologies on the way.

Newer agents

Cisplatin-based chemotherapy regimens—such as methotrexate, vinblastine, doxorubicin, and cisplatin (ie, MVAC), and cisplatin, methotrexate, and vinblantase (ie, MCV)—have been standard treatment in patients with urothelial cancer since the 1980s.[61] MVAC continued to be the most common chemotherapy treatment for advanced urothelial cancers until the combination of gemcitabine [Gemzar] and cisplatin was shown to be noninferior and better tolerated in a randomized trial.[62] The most common concern with administering chemotherapy, particularly in older patients, is the associated nephrotoxicity. Renal insufficiency is a common finding in patients with bladder cancer and thus precludes some patients from receiving this beneficial therapy. Thus, there is impetus to develop newer therapies that are less dependent on renal clearance.

Recently, a number of new systemic therapeutic agents have been tested. The list of agents studied includes chemotherapies (ifosfamide, oxaliplatin [Eloxatin], irinotecan, epothilones, vinflunine ditartrate [Javidor]); metal agents (gallium nitrate [Ganite]); antimitabolites (pemetrexed); monoclonal antibodies (trastuzumab [Herceptin; targeting HER2/neu], bevacizumab [Avastin; targeting the vascular endothelial growth factor, or VEGF], cetuximab [Erbitux; targeting the epidermal growth factor receptor, or EGFR], ipilimumab [Yervoy; targeting CTLA-4]); tyrosine kinase inhibitors (sorafenib [Nexavar; targeting the VEGF receptor, or VEGFR], sunitinib [Sutent; targeting VEGFR], pazopanib [Votrient; targeting VEGFR and the platelet-derived growth factor, or PDGF], lapatinib [Tykerb; targeting EGFR and HER2/neu], erlotinib [Tarceva; targeting EGFR], gefitinib [Iressa; targeting EGFR], dasatinib [Sprycel; targeting BCR-ABL]); histone deacetylase inhibitors (bortezomib [Velcade]); and other targeted therapies (farnesyltransferase inhibitors, angiozyme [a ribozyme targeting VEGF-R1]).[63,64]

Bladder Preservation Strategies (ie, Trimodality Therapy)

Selective bladder preservation strategies for MIBC have been promoted since the early 1990s and were primarily adopted from practices in the United Kingdom. Trimodality therapy has typically incorporated a complete transurethral resection, external beam radiation, and concurrent radiosensitizing chemotherapy. Patients are restaged at established intervals for evidence of response; those without complete response are encouraged to undergo RC, and the remaining patients continue on to receive consolidative radiotherapy. Radiation to the bladder and regional nodes is generally administered in 5 weekly fractions of 1.8–2.0 Gy up to a total dose of 50–55 Gy, followed by a small-volume boost to a total of 64 Gy. The most widely used cisplatin regimen is 70 mg/m² every 3 weeks for a total of 3 courses, or 25 mg/m² cisplatin on days 1–5 and 29–33 of radiotherapy.[65] The approach taken in the United States has been to preselect patients likely to do well with
trimodality therapy and then further select according to these patients' response to induction chemoradiation. One of the key factors in the success of this approach is complete tumor removal by transurethral resection with the intent to remove all evidence of macroscopic disease and optimize the relationship between tumor volume and radiation dose required for sterilization.[66] Evidence suggests that patients who are ideal candidates for trimodality therapy are those with a small (< 5 cm), solitary tumor, no associated carcinoma in situ, and a normally functioning bladder. The patient must be highly motivated to preserve a normal bladder and committed to lifelong surveillance and prompt treatment of new disease. Advanced stage, extravesical disease, large tumor size, and hydroureteronephrosis have been associated with reduced local control and survival.[67,68] Other inclusion criteria have typically included adequate renal function, a normal hemogram, and medical fitness for surgery.

The primary goal has been to maximize survival, with bladder preservation a secondary goal. In terms of the latter, quality of life is satisfactory in about 67% of patients.[69] A third objective has been to study the tolerability of giving newer systemic chemotherapeutic regimens concurrently vs sequentially during treatment.[70]

Outcomes with trimodality therapy

Early reports described a complete remission rate of 64% to 77%, with a little less than half of the patients able to retain a functional bladder and about one third of patients needing to undergo salvage cystectomy. Long-term outcomes typically involve 10-year disease-specific survival (DSS) rates of 40% to 60% and recurrence-free survival rates of about 65%, with almost 80% of survivors preserving their bladders.[71-74] Most recently, a phase II nonrandomized trial was reported that compared trimodality therapy to RC; the 5- and 10-year DSS rates did not significantly differ.[75]

Toxicities of trimodality therapy

Toxicity with trimodality therapy is moderate; symptoms primarily involve the bladder (cystitis) and bowel (enteritis). Mild to moderate acute radiation cystitis with dysuria and urinary frequency (grades 1 and 2) is present in about half of patients, but the symptoms are usually self-limited. Acute bowel toxicity is present in less than 15% of patients.[73] Neutropenia is nearly universal, and one third of patients may develop grade IV complications (mainly hematologic). Other complications include alopecia, vomiting, mucositis, and diarrhea; however, these are not typically a serious problem in those patients with good performance status.[75] Potential long-term toxicities of trimodality therapy include hemorrhagic cystitis, lower urinary tract symptoms (including urgency and frequency), and loss of bladder function with diminished capacity and compliance. For some patients, these can be crippling and cause serious morbidity, potentially requiring surgical intervention.

Radiation Therapy Oncology Group (RTOG) trials

The first of many RTOG trials evaluating trimodality therapy for bladder cancer was completed in the early 1990s. Initially, patients were treated with induction radiotherapy (40 Gy) and concurrent cisplatin. Complete responders received consolidation radiation with an additional 24 Gy.[65] Follow-up protocols have consecutively added combinations of chemotherapy, including MCV, cisplatin and fluorouracil (5-FU), paclitaxel, and gemcitabine with cisplatin.[76-79] Other protocols have further evaluated alterations in dose and fractionation of radiation delivered.[80] Recently, the RTOG finished accruing for a randomized trial that is evaluating different protocols for both induction chemotherapy and adjuvant chemotherapy; results are pending.

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Lapatinib (Tykerb)

MCA (methotrexate, cisplatin, vinblastine)

Methotrexate

MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)

Oxaliplatin (Eloxatin)

Paclitaxel

Pazopanib (Votrient)

Pemetrexed

Sorafenib (Nexavar)

Sunitinib (Sutent)

Trastuzumab (Herceptin)

Vinblastine

Vinflunine ditartrate (Javlor)

Proton therapy
Radiation therapy with protons, as opposed to photons, has been increasingly studied in multiple disease settings in recent years. Because of its unique properties, proton therapy can deliver highly conformal radiation, minimizing exposure of the surrounding structures. In particular, proton irradiation to the bladder potentially reduces the dose delivered to the small/large intestine and the normal bladder wall, with an increased dose delivered to the tumor. Unfortunately, there is limited literature evaluating the efficacy and toxicity of proton irradiation in this setting.

**Brachytherapy**

Interstitial radiation, as opposed to external-beam radiation, allows a higher dose of radiation to be delivered focally to a small area of the bladder, with relative sparing of surrounding normal tissues. For bladder cancer, it has been used to treat select patients with small, solitary, confined tumors. Survival rates have been reasonably comparable to the rates in surgical series, although inferior; recurrence rates have been as high as 17%.[81-83] There are regional differences in the way brachytherapy is administered. The Dutch irradiate the regional lymph nodes (approximately 28 Gy) and implant the tumor area with iridium after loading brachytherapy (40 Gy), whereas the French perform lymph node dissection and partial cystectomy, followed by source implantation into the post-cystectomy scar. Ultimately, brachytherapy fails to address the fact that urothelial cancer is a field defect malignancy with multifocal recurrences.

**Hyperthermia**

Investigators have studied the use of regional deep hyperthermia in bladder-sparing techniques and initially found a decrease in local recurrence and an increase in complete response rate.[84, 85] More recent investigations with quadrimodal therapy in a small cohort of 45 patients with either cT1 or cT2 disease found an 88% DSS rate and an 85% recurrence-free survival rate. Ninety-six percent of patients were able to retain their bladder at 3 years. Twenty-four percent of patients sustained chronic sequelae after treatment, and 80% were satisfied.[86] Hyperthermia is believed to enhance radiation-induced DNA damage and drug cytotoxicity and may even lead to direct cell killing. Secondary effects include vascular damage and stimulation of the immune response.

**Translational approach**

More recently, proponents of bladder-sparing approaches have sought to identify markers of response to therapy. EGFR positivity seems to be a favorable prognostic factor and correlates with improved DSS and survival with an intact bladder. Conversely, HER2 overexpression correlates with reduced rates of complete response to chemoradiation.[87] Immunohistochemical studies have shown that retinoblastoma (Rb) and bcl-2 expression are the strongest independent correlates of radiation response in MIBC.[88,89] The prognostic value of p53 expression has been well established,[90,91] and the level of apoptotic index has correlated to treatment response.[92] However, another group found that cell cycle checkpoint proteins, such as p53 and p16, have no prognostic significance in patients with invasive bladder cancer.[93] Lastly, the excision repair cross-complementing group 1 gene (ERCC1) is associated with resistance to cisplatin and radiation therapy. Therefore, it is a good predictor of efficacy in patients receiving chemoradiation. Furthermore, lack of ERCC1 expression may help select patients in whom trimodality therapy is more likely to result in a meaningful response.[94]

**Future endeavors**

There are many investigators searching to improve the trimodality approach to bladder cancer. The use of nanoparticles continues to be an avenue of avid investigation. For example, carbon and nicotinamide, sensitizers used to overcome tumor hypoxic radioresistance and tumor cell proliferation, have been examined in patients being treated with radiation for locally invasive bladder cancer.[95] Others have sought to improve targeting accuracy by utilizing fiducial markers, real-time imaging guidance of radiation delivery, and newer intensity-modulated techniques. Finally, there is ongoing evaluation of chemotherapy administration, including regimen, dose, and schedule.

**Conclusion**

Trimodality therapy with selective bladder preservation for MIBC should be considered in appropriate patients. It is not necessarily designed to replace RC, but is rather a consolidative therapy for those who appear to have a favorable clinical course (good response to initial selection) and one that may be offered as a reasonable alternative to patients who are averse to undergoing RC and urinary
diversion.

**Novel Imaging**

Contemporary staging and tumor evaluation for bladder cancer relies on cross-sectional images obtained by computed tomography (CT) and magnetic resonance imaging (MRI). Unfortunately, these modalities are limited in their ability to detect microscopic or small-volume extravesical tumor extension and lymph node metastases, leading to an unacceptably high rate of understaging.[96] A major improvement in the detection of bladder cancer came with the introduction of 64-slice multidetector CT, which provides higher spatial resolution. The sensitivity, specificity, and accuracy of multidetector CT are 85%, 94%, and 90%, respectively.[97] However, despite the fact that multidetector CT provides greater diagnostic accuracy than a conventional CT urogram, it is still limited in its ability to detect lesions < 1 cm.[98] Newer MRI analyses developed for other cancer models have been incorporated into the care of patients with bladder cancer. In particular, diffusion-weighted imaging provides greater accuracy of T stage for bladder tumors compared with T2 imaging alone.[99,100] Diffusion-weighted imaging and contrast-enhanced MRI with ultra-small superparamagnetic particles of iron oxide also improve the detection of nodal metastases in patients with urothelial carcinoma.[101]

Positron-emission tomography (PET) is a nuclear medicine imaging technique that can be used to measure areas of increased metabolic activity, which is common in many types of malignant tissue. Radiolabeled fluorodeoxyglucose (FDG), an analog of glucose, is an imaging agent commonly used to measure regional glucose uptake. The utility of $^{18}$F-FDG-PET in bladder cancer is limited by urinary excretion of the radiotracer, causing increased background noise and making it difficult to distinguish areas of increased uptake. In MIBC, it has better sensitivity but worse specificity for the detection of primary tumors compared with conventional CT.[102] A large prospective trial showed that PET findings not only improve diagnostic accuracy but also strongly correlate with survival outcomes.[103] However, whether PET has the added benefit of detecting nodal metastases (compared with conventional CT alone) remains in question.[104] $^{11}$C-acetate, which is not excreted in the urine, has been studied as an alternative agent for PET imaging, but there is a high false-positive rate in patients previously treated with intravesical bacille Calmette-Gurin because of inflammation or granulomatous infection.[105] Finally, $^{11}$C-choline PET appears to have no advantage compared with $^{18}$F-FDG PET in the detection of metastatic bladder cancer.[106]

**Summary**

Muscle-invasive bladder cancer is an aggressive and potentially lethal disease. Integration of multimodal therapies, improved surgical techniques, and utilization of targeted agents has tremendously improved outcomes. We expect even better results with further refinements in patient selection, based on detailed clinical and molecular assessments. The future lies in effective multidisciplinary collaboration and further investigation into the biology of urothelial tumors and host responses.

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