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Contemporary Management of Muscle Invasive Bladder Cancer

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to discuss the contemporary medical and surgical management of muscle invasive bladder cancer.

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INTRODUCTION

Muscle invasive bladder cancer continues to be an important health issue with substantial patient burden from the disease and its associated treatment. Radical cystectomy has long been the standard treatment for muscle invasive cancer but it has been associated with significant morbidity and postoperative recovery. Although excellent local control can be achieved with radical surgery, it is clear that cystectomy as monotherapy is less effective in extravesical or locally advanced disease settings. Consequently, advances in the management of this disease have had to address treatment of locally advanced tumors, the need for improvements in immediate recovery after cystectomy, and methods to measure and enhance posttreatment quality of life. We review the recent medical and surgical advances in the management of MIBC.

INCIDENCE AND TIME TRENDS

In 2009 bladder cancer was the 4th most common malignancy among men and 12th most common among women, accounting for an estimated 70,980 incident cases and 14,330 deaths in the United States.[1] Bladder cancer disproportionately affects the elderly with the incidence directly increasing with age. **While most newly diagnosed bladder cancers are non-invasive, approximately 20% to 25% of patients harbor muscle invasion at presentation and nodal or distant metastases, or invasion of the pelvic sidewall is identified in 5% to 7% of patients.**[2, 3] **This pattern of presentation has not changed appreciably in 4 decades,**[2, 4] standing in stark contrast to other genitourinary malignancies such as prostate and kidney cancer, which have seen a dramatic stage migration towards early stage tumors in recent years, likely related to widespread screening or incidental detection. However, **the 5-year overall survival for bladder cancer improved from 74% to 81% between 1975 and 2003**.[1] Although the exact cause of improved survival is unknown, a trend towards early surgical treatment and multimodal therapeutic strategies likely played some role.

The incidence and survival rates for bladder cancer are strongly influenced by race and gender. **During the first year following diagnosis women have an 80% increased hazard of death from bladder cancer and do not reach an equivalent annual mortality rate until 4 years following diagnosis.**[5] Similarly, **the 5-year actuarial survival from bladder cancer is significantly higher among white (81%) vs black (65%) patients**.[1] The reason for these gender and racial discrepancies is multifactorial. **Women are more likely to present with muscle invasive disease compared to men. Similarly, black patients have a higher rate of muscle invasion at diagnosis than white patients.** Even after adjusting for grade and stage at presentation, both groups have increased cancer specific mortality compared to their white male counterparts.[4, 5] Whether these poorer outcomes are due to fundamental differences in disease biology, access to health care or treatment decision making is not entirely clear, although each is a likely contributing factor.

RISK FACTORS

There is strong epidemiological evidence implicating tobacco smoke in the promotion of bladder carcinogenesis.[6] **A meta-analysis revealed that current and former smokers have a 3-fold increased risk of bladder cancer compared to those who never smoked.**[7] **Accordingly, the risk is even greater with increased duration and intensity of smoking. Overall, cigarette smoking may account for bladder cancer in 35% of females and in up to 50% of males.** A direct association with secondhand smoke is less clear. In a recent meta-analysis subjects exposed to secondhand smoke had significantly higher serum and urine concentrations of 4-aminobiphenyl (a constituent of tobacco smoke and well documented urothelial carcinogen) than unexposed subjects but there was no difference in bladder cancer rates between the 2 populations.[8]

Radiation therapy and chemotherapy have long been implicated in the development of secondary malignancies in the bladder. Women treated with pelvic irradiation for ovarian cancer have a 4-fold increased risk of bladder cancer compared to those who underwent surgery only.[9] This risk may be augmented by coadministration of systemic chemotherapy. **The chemotherapeutic agent cyclophosphamide has been causally implicated in the development of hemorrhagic cystitis and bladder cancer via its urinary metabolite acrolein. Patients treated with cyclophosphamide have up to a 9-fold increased risk of bladder cancer, although this risk can be reduced with the uroprotectant mesna.** Bladder tumors associated with pelvic irradiation and chemotherapy tend to be aggressive, and early definitive therapy is warranted. It is unclear whether smaller radiation fields (ie intensity modulated radiation therapy) delivered in association with chemotherapy will help mitigate this increased risk as the latency period for bladder cancer tends to be protracted, necessitating large, long-term studies.[10]

There continues to be strong evidence implicating environmental toxins in bladder carcinogenesis with up to 20% of all cases of bladder cancer directly linked to occupational exposure.[11] **Most chemicals thought to initiate bladder cancer are aromatic amines.** While many of these compounds (such as aniline dyes) have been banned from the workplace in most nations, several are still used in the manufacture of pesticides, paint, rubber, diesel fuel and dyes.[12] The industries with the highest bladder cancer risk include printing companies, and manufacturers or heavy users of paint products, textiles, rubber and leather. Other factors may also increase the risk of bladder carcinogenesis including arsenic in drinking water and chronic inflammation from foreign bodies or urinary tract infection.

NATURAL HISTORY

Muscle invasive bladder cancer has an aggressive natural history. Data are lacking in untreated patients but significant progression and death occur even in those who undergo radical therapy. **Approximately 50% of patients with clinical muscle invasion will die of progressive disease within 5 years after cystectomy.**[13-15] **Similarly, more than 50% to 60% of patients treated with radical radiation will die within 5 years of therapy.**[16] Without treatment, muscle invasive tumors will progress within 3 months, as evidenced by lower rates of disease specific survival observed in patients treated with delayed

ABBREVIATIONS: CR (complete response), CT (computerized tomography), DSS (disease specific survival), 18-FDG (2-deoxy-2-[^{18}F] fluoro-D-glucose), GC (gemcitabine plus cisplatin), LND (lymph node dissection), LRC (laparoscopic radical cystectomy), LVI (lymphovascular invasion), MCV (methotrexate, cisplatin and vinblastine), MIBC (muscle invasive bladder cancer), MRI (magnetic resonance imaging), MVAC (methotrexate, vinblastine, doxorubicin and cisplatin), NAC (neoadjuvant chemotherapy), PET (positron emission tomography), QOL (quality of life), RARC (robotic assisted laparoscopic radical cystectomy), RC (radical cystectomy), RT (radiation therapy), TUR (transurethral resection)

cystectomy.[17, 18] Expected progression is greatly dependent on tumor characteristics with more rapid recurrence and diminished survival in patients with extravesical tumors, nodal invasion, lymphovascular invasion and aggressive histological variants.[19, 20]

STAGING

Accurate staging of MIBC has been difficult. Clinical under staging remains a significant problem in determining appropriate treatment. Lee et al reported that clinical T2 disease was under staged in up to 60% of patients.[15] Traditional imaging with CT does not permit a clear distinction between organ confined and extravesical tumors, but MRI may have some advantage as it has good soft tissue resolution and multiplanar capabilities. When combined with recent advances in MRI, more accurate staging has been demonstrated.[21] Tekes et al noted an accuracy of 85% in distinguishing non-invasive from invasive disease using gadolinium enhanced MRI, and 82% accuracy in differentiating organ confined and extravesical tumors.[22] However, over staging with MRI can occur due to acute edema and hyperemia after recent resection, giving the appearance of tumor extension.[21] **Another important application of MRI has been its use in patients with renal insufficiency to avoid nephrotoxic contrast agents used with CT. However, nephrogenic systemic fibrosis from administration of gadolinium has limited its current role in this population.**[23]

Conventional CT and MRI lack the sensitivity to detect early metastatic disease, particularly in normal sized lymph nodes.[21] **The specificity of both techniques can also be hampered by reactive nodes that mimic metastatic disease, resulting in over staging and potential overtreatment.** More accurate assessment of regional and distant lymph nodes is needed. PET with the glucose analogue 18-FDG is a non-invasive imaging modality used for a variety of malignancies including lymphoma and lung cancer. The 18-FDG detects increased glycolytic activity in neoplastic cells with a high metabolic rate and has increased uptake on PET imaging.[21] **The whole body imaging obtained with PET scans aids in identification of distant metastatic sites but the accumulation of 18-FDG in urine and the inability of PET to detect metastatic lymph nodes smaller than 10 mm can limit its use in equivocal cases of distant metastatic disease.**[21, 24, 25] **Newer agents such as ^{11}C methionine and choline are not excreted in urine and may have a more pronounced role in bladder cancer staging.**[21]

Lymphotropic nanoparticle enhanced MRI, which provides intranodal macrophage function to detect metastases, is another technique with potential promise for nodal staging of bladder cancer.[26-30] Although the technology is not widely available at all hospitals, it may improve the sensitivity and negative predictive value of MRI in the detection of nodal metastases.[31] Furthermore, lymphotropic nanoparticle enhanced MRI may detect tumor metastases in normal sized lymph nodes and identify suspicious nodal packets as resection targets before cystectomy. Although its role has not been fully defined in bladder cancer and additional studies are needed to better understand its potential application, the technology is interesting and it could have a positive impact on staging.

DEFINITIVE TREATMENT OPTIONS

Radical cystectomy. Indications: Radical cystectomy remains the standard of care for MIBC in the absence of known metastatic disease. The standard surgical procedure includes en bloc resection of the bladder with perivesical fat, prostate and seminal vesicles in the male, and uterus, fallopian tubes and ovaries in the female followed by urinary diversion. Additionally, lymph node dissection should be performed as it is diagnostic and, in certain circumstances, therapeutic. Efforts to maintain sexual and reproductive function have led to the preservation of the neurovascular bundles, vagina, female reproductive organs, prostate capsule and seminal vesicles in select patients. Organ preservation has been accomplished without an increase in the risk of tumor recurrence.[32, 33]

Radical cystectomy is indicated in patients with high risk bladder cancer, including those with early stage disease refractory to conservative therapy. For patients with muscle invasion, radical cystectomy is considered definitive therapy and may be delivered as monotherapy or in conjunction with perioperative systemic chemotherapy. **Optimal candidates for cystectomy as primary therapy are those with low volume resectable tumors without evidence of extravesical extension, or nodal or distant metastases. Patients with clinically organ confined tumors with aggressive chemosensitive histological variants or LVI are best served with neoadjuvant chemotherapy before cystectomy (see Appendix)**. Patients must be medically optimized since RC remains a challenging procedure typically performed in an older population with existing comorbidities.

Advanced age is not a contraindication to cystectomy. Several studies have shown that RC can be performed safely in well selected older patients. Figueroa et al evaluated 404 patients older than 70 years and found their overall mortality rate to be comparable to that of historical controls of younger patients (2.8% vs 2.0%).[34] Similarly, Clark et al reported no significant mortality difference in a direct comparison of young and old patients.[35] Also the older group was more likely to suffer early complications, whereas young patients were more likely to have late complications. Weizer et al confirmed that Karnofsky performance status is a clinical predictor of overall survival in elderly patients undergoing RC, reinforcing the importance of global assessment of functional status in a high risk group.[36]

Outcomes: Improvements in surgical technique, anesthesia and critical care management have dramatically decreased perioperative morbidity and mortality of RC. **However, contemporary series indicate an early overall complication rate of ~30% and in-hospital mortality rate of 2% to 3%**[37, 38] with the majority of deaths in the perioperative period due to cardiovascular or septic complications.[39] In a population based cohort study of 6577 patients younger age and large urban teaching hospitals were independently associated with decreased risk of complications.[38] **Digestive system complications occurred most commonly (16.1%), while wound, cardiac and urological complications occurred in 4.27%, 4.12% and 2.92% of patients, respectively.**

Mortality rate after cystectomy is likely to be lower when performed at high volume centers and by high volume surgeons. Based on national Medicare data, patients undergoing RC at low volume hospitals (ie <2 procedures a year) had a 2.1-fold increased risk of death compared to those treated at high volume centers (>11 procedures a year).[40] This finding may reflect differences in hospital structure with respect to consultation, diagnostic and ancillary services.[39] **Similarly, patients treated by low volume surgeons had a 1.8-fold increased risk of death compared to high volume surgeons.**[41] While there has not been an organized effort by payers to concentrate RC to high volume surgeons and medical centers, data show that RC has undergone a spontaneous regionalization of care towards high capacity, urban teaching hospitals.[42] The exact reasons for this are not clear but likely involve increased complexity of care, changes in reimbursement and patient preference.

Cystectomy is most effective when performed expeditiously. The time from diagnosis to RC can influence survival of invasive disease. Using SEER (Surveillance, Epidemiology and End Results)-Medicare data, a 2-fold increased risk of cancer specific mortality was noted when RC was delayed for 12 to 24 weeks compared to when it was

performed within 12 weeks of initial diagnosis.[17] Similarly, a 3-month delay in cystectomy resulted in decreased cancer specific and overall survival (p=0.05 and 0.02, respectively) without significant difference in pathological stage.[18] The most common causes of delayed therapy were scheduling conflicts (46%), whereas multiple opinions, patient social issues and misdiagnosis (4% each) were infrequent causes of delay.

Survival after cystectomy is largely dependent on tumor stage. For patients with pathological stage T2 disease, 5-year overall survival following RC is approximately 60% to 72%. Survival outcomes are worse when the tumor has spread beyond the bladder with 5-year disease-free survival rates of 43% to 52% for pT3 tumors, 28% to 44% for pT4 tumors and 20% to 35% for N+ disease.[19, 20, 37, 43] While pathological stage is the most commonly used variable to predict survival outcomes following RC, several recent reports have shown improved accuracy with the use of multivariable nomograms incorporating pathological and clinical variables. The largest such nomogram included a total of 9000 patients from 12 institutions. Gender, age, pathological stage, histological type, node status, time from diagnosis to cystectomy and grade were used to predict 5-year progression-free probability after cystectomy.[43] In this context the model outperformed the TNM classification (p <0.001).

Shariat et al developed a nomogram that incorporated pathological factors (stage, LVI and carcinoma in situ), treatment variables (ie chemotherapy and radiation therapy) and demographic variables (gender and age).[44] This model outperformed pathological stage when predicting overall (73% vs 62% accuracy, respectively, p=0.001) and cancer specific (79% vs 66% accuracy, respectively, p=0.001) survival.[44] The inclusion of 5 molecular biomarkers (p53, pRB, p21, p27 and cyclin E1) further improved the prognostic power of the postoperative nomogram.[45] In this model incorporation of biomarker status along with pathological stage and presence of LVI into a prognostic nomogram significantly improved the accuracy of predicting disease recurrence (83.4%) and cancer specific survival (86.9%). Such nomograms may help direct patients towards adjuvant treatment and participation in clinical trials.

Robotic assisted radical cystectomy. The first reported LRC for cancer was performed in 1993[46] followed in 2003 by the first robotic assisted laparoscopic radical cystectomy.[47] Wide acceptance of LRC was limited due to the extreme complexity of the procedure, technical challenges of standard laparoscopy and oncologic concerns. However, the incorporation of robotic assistance in laparoscopy has renewed enthusiasm in minimally invasive radical cystectomy. Because RARC has largely supplanted LRC as the minimally invasive procedure of choice at most centers, we will focus on the perioperative and oncologic outcomes of RARC.

To date there have been no prospective randomized trials comparing the outcomes of RARC and open RC, although there are several case series that attempt to make comparisons between these 2 approaches. The perioperative results of these studies are summarized in table 1. **Compared to open RC, RARC has been associated with longer operative time but less blood loss and shorter hospital stays.**[48-50] After an expected learning curve, Wang et al noted a shorter operative time in their most recent 17 cases compared to their initial 16 cases (338 vs 450 minutes, respectively, p=0.007).[49] **The application of robotic technologies to RC has been increasingly adopted with the hope that it would reduce morbidity from the procedure but currently RARC does not have an advantage over open surgery in this regard, as a clear reduction in the incidence of perioperative complications has not been demonstrated**.[47, 50-52]

While RARC may provide short-term benefits in the perioperative period, it cannot compromise oncologic outcomes. The short-term oncologic outcomes reported in several single institution studies are summarized in table 2.[49, 52-54] However, these series are greatly limited by small patient samples and short duration of follow-up (mean <18 months). Disease specific survival at this early assessment is reportedly 94% to 96%.[53, 54] **Since open RC provides excellent local control with positive surgical margin rates typically <10%,[55] an equally low margin rate is expected with RARC.[49, 53] As local or distant recurrence typically results in a bladder cancer specific death, the importance of negative surgical margins cannot be understated.**

Adequate lymphadenectomy during RARC has been another concern of the oncology community since the extent of lymphadenectomy and number of lymph nodes removed have been directly associated with survival outcomes. Most RARC series report an average of 13 to 19 nodes resected. In a retrospective comparison lymph node counts were comparable between RARC and open RC.[49] **Those performing RARC have been held to a higher standard than many performing open RC, since historically the majority of patients have fewer than 10 nodes resected.**[56]

Urinary diversion, whether continent or incontinent, remains a technical challenge during RARC. Consequently, diversion is generally performed extracorporeally through a mini-laparotomy incision, although some have investigated the feasibility of intracorporeal urinary reconstruction. In a comparison study the open assisted laparoscopic approach for urinary diversion was 3.1 hours shorter (p <0.0001) and had fewer overall complications (22%) than the pure laparoscopic approach (70%) (p=0.0005).[57] Balaji et al performed total intracorporeal RARC with urinary diversion in 3 cases, each of which took more than 600 minutes with the longest requiring 828 minutes.[58] Most now perform urinary diversion through an extracorporeal approach because of the technical difficulty and marginal advantage (if any) of a pure laparoscopic approach.

In general, RARC appears to be a safe and effective alternative to standard open RC at experienced centers but data regarding long-term oncologic outcomes are still premature and require further study. While there may be some short-term advantages (ie less blood loss, shorter hospitalization) to RARC, one must question its broad application to the cystectomy population given the learning curve and risk of increased positive margins, without a substantial reduction in perioperative morbidity. Unlike prostatectomy, few urologists perform enough cases to get beyond the learning curve. Certainly, the outcomes experienced with RARC have inspired open surgeons to explore more aggressive approaches to reduce blood loss and hospital stay for patients undergoing open RC.

Extent of lymphadenectomy. **Lymph node dissection is a critical component of RC offering staging and therapeutic benefit. Approximately a quarter of patients treated with RC have lymph node metastases discovered at surgery,[19, 20] and they are known to have inferior recurrence-free, overall and disease specific survival.**[19, 20, 59, 60] Shariat et al reported a 3-year DSS of 80% in patients without nodal invasion of tumor, whereas survival was only 38% among patients with lymphatic metastasis.[19] **Lymph node density (ie the ratio of positive lymph nodes to the total number of nodes removed) may also have important prognostic implications, further refining risk stratification.** The 5-year overall survival among patients with positive nodes and lymph node density ≥20% was 8% compared to 43% for those with lymph node density <20%.[61] Likewise, Kassouf et al reported 5-year DSS of 55% for patients with lymph node density <20% compared to 15.3% for those with lymph node density ≥20%, and lymph node density outperformed the TNM node classification in a prognostic model.[62] Lastly, preliminary evidence suggests that LND improves survival among patients with positive and negative nodes.[63]

TABLE 1. *Surgical outcomes of robotic assisted radical cystectomy*

References	No. Pts	Estimated Ml Blood Loss	Operative Time	No. Major Complications	Days of Stay
Wang et al[49]	Robotic 33, open 21	Mean 750 vs 400 (p=0.002)	Mean 390 vs 300 mins (p=0.03)	Open 4 (abscess, dehiscence, respiratory failure, myocardial infarct), robotic 3 (conversion to open, abscess, enterocutaneous fistula)	Mean 5 vs 8 (p=0.007)
Guru et al[52]	Robotic 20	Mean 555	Mean 197 mins (RARC), 44 mins (LND), 133 mins (diversion)	Death from internal hernia 1, bowel obstruction 1	Mean 10 (range 4-37)
Dasgupta et al[51]	Robotic 30	Median 150 (range 100-1150)	Median 330 mins (range 295-510)	Hemorrhage 1, rectal injury 1	Median 10 (range 7-22)
Menon et al[47]	Robotic 17	Mean <150	Mean 140 mins (RARC), 120 mins (ileal conduit), 168 mins (ileal neobladder)	Hemorrhage 1	Not recorded
Pruthi and Wallen[50]	Robotic 20, open 24	Mean 313 vs 588 (p <0.001)	Mean 6.1 vs 3.7 hrs (p <0.001)	Open or robotic 4 (hemorrhage, deep venous thrombosis, peristomal hernia, rectal injury)	Mean 4.4 vs 5.3 (p=0.007)
Galich et al[48]	Robotic 13, open 24	Mean 500 vs 1250 (p=0.0002)	Mean 697 vs 395 mins (p=0.0002)	Open 4 (dehiscence, 2 myocardial infarctions, pneumonia), robotic 3 (enterovesical fistula, small bowel obstruction, abscess)	Median 8 vs 10 (p=0.044)

TABLE 2. *Oncologic outcomes of robotic assisted radical cystectomy*

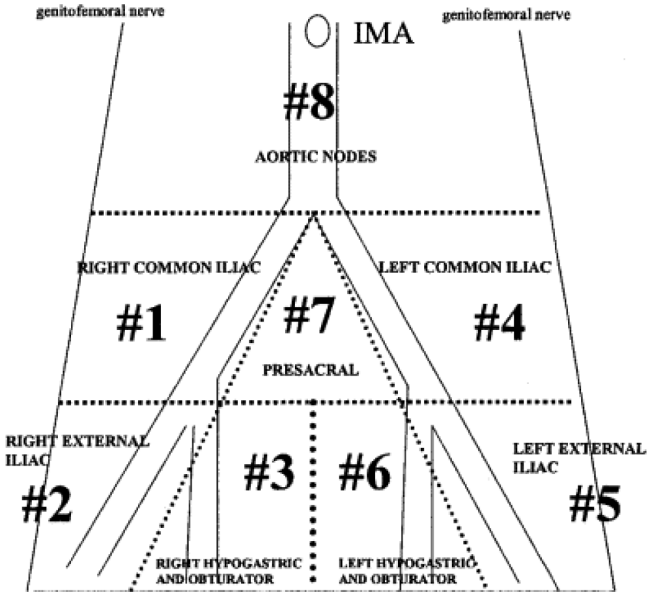
References	No. Pts	No. Nodes	No. Pos Margins/ Total No. (%)	% Survival	No. Recurrence/ Total No. (%)	Mos Follow-Up
Pruthi and Wallen[53]	Robotic 50	Mean 19 (range 8-37)	0	Overall 90, DSS 94	7/50 (14)	Mean 13.2 (range 2-24)
Murphy et al[54]	Robotic 23	Median ± SD 16 ± 8.9	0	DSS 96	2/23 (8.7)	Mean ± SD 17 ± 13
Guru et al[52]	Robotic 20	Mean 13 (range 6-16)	3/20	Not recorded	Not recorded	Not recorded
Wang et al[49]	Robotic 33, open 21	Median 17 (range 6-32), 20 (8-36)	2/33 (6), 3/21 (14)	Not recorded	Not recorded	Not recorded

The optimal extent of LND is controversial. The contemporary **total pelvic lymphadenectomy for invasive bladder cancer includes resection of nodal tissue bordered by bifurcation of the common iliac artery (superior extent), genitofemoral nerve (lateral extent), circumflex iliac vein and node of Cloquet (inferior extent), and hypogastric artery (posterior extent).**[64] **In the extended LND presacral nodes are removed and the superior border of the dissection is broadened to include tissue up to the aortic bifurcation.**[65] Bochner et al reported a significant increase in lymph node yield using the extended template (see figure) compared to standard LND (mean 36.5 vs 8.5 nodes removed, respectively).[66, 67] While the obturator and external iliac lymph nodes are most commonly involved in bladder cancer, a prospective study mapping the nodal metastases in an extended LND showed that 16% of lymph node metastases were located above the aortic bifurcation and 8% were located in the presacral region.[68]

In addition to improved staging, LND may also have a therapeutic role as the extent of dissection has been shown to correlate with survival outcomes. Poulsen et al reported improved survival among patients with ≤pT3a tumors and negative nodes who underwent extended lymph node dissection compared to those treated with standard dissection (90% vs 71%, respectively).[69] Interestingly, Herr reported improved survival for patients with negative and positive nodes when a greater number of nodes were examined.[63] In patients with node negative disease this improved survival may be due to 1) removal of undetected micrometastatic disease or 2) improved segregation of node status, the so-called Will Rogers effect. Extended LND is more likely to detect those patients with micrometastatic disease enriching the negative cohort with patients with truly negative nodes.

Ultimately there is a likely benefit to increasing lymph node counts, which can be accomplished by extending the limits of LND but also can occur with submission of individual node packets by the surgeon at the time of dissection, highlighting extraneous factors that may impact the node count.[67] Identification of lymph nodes is somewhat dependent on the diligence of the pathologist or pathology technician quantifying the number of malignant and total number of lymph nodes recovered. Several groups have attempted to define a minimum number of lymph nodes that should be resected at LND.

Kassouf et al examined 248 patients with positive nodes and reported significant improvement in median disease specific survival when >12 nodes vs 1 to 12 nodes were examined (72 vs 24 months, respectively).[62]



Individual lymph node packets comprising extended lymphadenectomy during radical cystectomy. Limits of extended dissection include internal mesenteric artery proximally, genitofemoral nerves laterally, and node of Cloquet and takeoff of circumflex iliac vein distally. Reprinted with permission from Bochner et al.[66]

Leissner et al reported improved 5-year cancer specific survival among patients who had at least 16 nodes vs 15 or fewer nodes removed (65% vs 51%, respectively).[70] Capitanio et al examined 731 patients undergoing RC for all stages of disease and found that removing greater than 25 lymph nodes provided a 75% chance of detecting 1 or more lymphatic metastasis, suggesting this as a threshold.[71]

The SEER cancer registry was used to examine the extent of LND on survival in 2 studies. Konety et al found that in all patients with >3 lymph nodes examined survival improved and the best outcomes occurred in those with 10 to 14 nodes examined, leading them to suggest 10 nodes as an appropriate goal.[56] Wright et al examined 1260 patients with nodal metastases and also noted a threshold of 10 nodes associated with improved survival.[72] The differences in these cut points likely reflect methodological variation between studies and should be interpreted carefully. **In general, while it is useful to have a benchmark goal for the number of lymph nodes removed, the aim of LND should be to carefully remove all nodal tissue from specific nodal regions rather than achieve a certain number of nodes.**

Urinary diversion. Urinary tract reconstruction attempts to provide an acceptable alternative to the native bladder by creating adequate storage and continence or a reasonable conduit. Two decades ago nearly all patients were treated with incontinent cutaneous diversion. **Today, expert surgeons perform continent orthotopic diversion in nearly 50% of patients undergoing RC worldwide, and it is considered an ideal method of diversion for most patients.**[73] There are few absolute contraindications regarding ileal neobladder reconstruction. **From an oncologic perspective, it is imperative to ensure that the urethral margin is free of tumor involvement before proceeding with neobladder construction to minimize the risk of future urethral recurrence.** This margin is best assessed through intraoperative frozen section. It is important for the patient to understand that while an attempt will be made to perform a continent reservoir, an incontinent conduit may be necessary for cancer control or other technical factors. In a retrospective review of more than 400 patients undergoing RC there was no difference in cancer specific survival among patients undergoing neobladder diversion compared to those diverted with an ileal conduit.[74] The only patient who had a urethral anastomotic recurrence did in fact have a positive urethral margin, underscoring the importance of intraoperative frozen section analysis.

Presently, there is no consensus regarding the optimal diversion type as individual preferences vary between patients and providers. Although a variety of validated questionnaires have been developed to measure health related quality of life for patients undergoing urinary diversion, comparisons between continent and incontinent urinary diversion populations have generally failed to demonstrate superiority of any diversion type.[73, 75-77] Whether this reflects a selection bias (ie patients choose the diversion method that best suits them) or a true lack of superiority of a diversion type is not known. Further refinements of surgical technique such as prostate capsule sparing and vaginal sparing RC may improve sexual and urinary function,[78] tilting the QOL equation in favor of orthotopic diversion, but this is purely speculative.

Some evidence suggests that patients undergoing orthotopic diversion may, in fact, have poorer urinary QOL than expected. In a cross-sectional study the Bladder Cancer Index showed inferior urinary domain scores for patients undergoing orthotopic diversion compared to those treated with ileal conduit diversion.[79] Despite these lower functional outcomes, patients with the neobladder had similar bother scores regarding compromise of urinary function. An explanation for this lack of bother might be the benefit of an enhanced body image provided by the orthotopic diversion compared to the incontinent cutaneous approach. When comparing neobladder and ileal conduit groups using the EORTC (European Organisation for Research and Treatment of Cancer) Body Image Scale, there was no significant difference in mean body image scores at baseline or any point after treatment in 336 patients with bladder cancer.[80, 81] Given these data, it is likely that factors other than body image are involved in the tolerance of less urinary function experienced by patients with neobladder.[82]

In general, patients should be counseled about continent and incontinent options for diversion. It is imperative that they be informed not only about the perioperative risks and anatomic limitations of each type of urinary diversion, but also about short and long-term outcomes so an adequate diversion choice can be made.

CHEMOTHERAPY FOR UROTHELIAL CARCINOMA

Urothelial carcinoma of the bladder is known to be chemosensitive, responding optimally to platinum based regimens. Initial results with the combination of methotrexate, vinblastine, doxorubicin and cisplatin showed tumor regression in 78% and complete response in 36% of patients with surgically unresectable and metastatic urothelial tumors (although 68% of these patients eventually had relapse).[82] **Median survival of the entire cohort was 13.3 months but only 8 months for those with progression, 11 months for partial responders and greater than 38 months for complete responders. Unfortunately, toxicity associated with MVAC was significant with 3% associated mortality and 25% likelihood of nadir sepsis.**

Despite serious toxicities, MVAC remained a standard as it proved to be superior to single agent cisplatin or cyclophosphamide, doxorubicin and cisplatin.[82, 83] More recently, a prospective randomized trial of 405 patients with locally advanced or metastatic bladder cancer were treated with either gemcitabine plus cisplatin or MVAC.[84] While median overall survival and response rates were similar between the 2 regimens, GC had significantly lower neutropenic sepsis and drug related death rates compared to MVAC (1% vs 12% and 1% vs 3%, respectively) and was generally better tolerated. Currently, GC has essentially replaced MVAC as the standard regimen for urothelial malignancies. While these initial trials were conducted in the metastatic setting, conversion of unresectable cases to surgically operable cases

suggested a role for neoadjuvant systemic therapy before local therapy. Moreover, because of the promising response rates, a potential benefit to an adjuvant approach was suspected in patients with high risk disease.

Neoadjuvant chemotherapy. There are numerous theoretical advantages to the administration of chemotherapy before performing radical cystectomy including tumor down staging, early treatment of chemosensitive micrometastatic disease and improved chemotherapy compliance due to optimal patient performance status in the preoperative setting. Disadvantages include overtreatment of patients with chemoinsensitive disease and the surgical delay for those in whom RC alone would be curative.

Several randomized trials have compared the use of NAC and cystectomy to cystectomy alone in patients with invasive bladder cancer. In the largest study, led by the Medical Research Council and EORTC, 976 patients were randomly assigned to 3 cycles of neoadjuvant MCV or immediate local management (ie RC or radiation therapy alone).[13] The initial results revealed no significant survival differences between the groups. However, the study was updated in 2002 with a median follow-up of 7.4 years and a significant survival advantage was noted for those patients receiving NAC (HR 0.85, p=0.048).[85]

In the SWOG (Southwest Oncology Group) 8710 trial 307 patients with stage T2-T4a bladder cancer were randomized to receive 3 cycles of neoadjuvant MVAC and RC or RC alone.[14] There was significant improvement in median survival for the neoadjuvant group compared to the RC alone group (77 months vs 46 months, respectively). Interestingly, while there was no difference in 5-year survival among the patients who were pathologically tumor-free (ie pT0), a higher proportion of those treated with NAC had no residual disease (38%) vs those treated with RC alone (15%). **The benefits of NAC were further suggested by a large meta-analysis of 2688 individual patients from 10 randomized trials which indicated that the addition of platinum based combination NAC conferred a 13% reduction in risk of death and 5% absolute survival benefit at 5 years.[86] However, single agent chemotherapy did not show a survival benefit.**

Extrapolating the data from comparison of GC and MVAC, Dash et al performed a retrospective review of the experience at a single center with neoadjuvant GC before RC.[87] Of patients treated with neoadjuvant GC disease was down staged to pT0 in 26% compared to 28% of those receiving MVAC. To our knowledge, there have been no prospective trials evaluating GC in the neoadjuvant setting, although many centers now use GC as standard therapy before RC for MIBC based on a presumed equivalency.

Based on the favorable outcome of a CR following NAC, a phase III SWOG trial investigated immediate cystectomy vs cystoscopic surveillance of patients who received NAC.[88] Although the planned accrual was not achieved, 34 (46%) of 77 enrolled patients had stage cT0 disease based on post-chemotherapy transurethral resection. Of those patients 10 underwent immediate cystectomy and 6 had pathological evidence of residual disease. The 2-year survival was similar between patients who underwent immediate cystectomy and those who underwent cystoscopic surveillance (70% and 75%, respectively). **While this study confirms the favorable survival for NAC responders, interval cystoscopic evaluation to assess CR is inherently inaccurate and should not be used in isolation to guide definitive treatment.**

Despite evidence that administration of platinum based NAC improves survival, widespread use has been poor. Of patients with stage III bladder cancer treated between 1998 and 2003 merely 11.6% received any perioperative chemotherapy with only 1.2% receiving NAC.[89] Similar results were seen in a Medicare population between 1992 and 2002 in which chemotherapy was administered to 11% of patients with stage IV disease and NAC was only administered to 1.4% of those with stage II disease.[90] The low rate of use of NAC in these studies may, in part, be due to treatment periods that antedate recent reports of large randomized trials demonstrating a survival benefit with this treatment approach. However, the efficacy of MVAC for advanced bladder cancer was demonstrated several years before these treatment periods, and yet use of systemic therapy was still low in patients with advanced disease. **Although several factors may influence the decision to use NAC (see Appendix), all patients with muscle invasion should be considered for this treatment strategy.**

Adjuvant chemotherapy. The primary benefit of adjuvant chemotherapy is its delivery to a high risk population defined by pathological staging. In addition, surgical delay is avoided in patients with chemoresistant tumors. Unfortunately, few randomized trials have evaluated the role of adjuvant chemotherapy after cystectomy. **In a recent meta-analysis the records of 491 patients with pathologically proven high risk disease from 6 randomized trials were evaluated to compare cystectomy with adjuvant chemotherapy to cystectomy alone.**[86] Despite serious methodological flaws evident in each of the evaluable studies (small sample size, heterogeneous therapies, early study cessation, inappropriate statistical methods and non-reporting of overall survival results), many of the limitations were addressed by individual patient review. **A 9% absolute improvement in overall survival at 3 years was observed for the adjuvant chemotherapy arm compared to controls (HR 0.75, p=0.019). The absolute survival benefit increased to 11% when only trials using cisplatin based combination chemotherapy were used.**

Large adjuvant trials have been subject to poor accrual as evidenced by closure of a prospective, randomized trial of 4 cycles of immediate adjuvant therapy vs salvage therapy in patients with pT3/4 or N+ disease led by the EORTC.[91] Acceptable chemotherapy regimens in this study were high dose MVAC, low dose MVAC and GC. To our knowledge, there are no trials directly comparing NAC to adjuvant chemotherapy in patients undergoing RC. Previously Millikan et al evaluated the optimal timing of chemotherapy administration by randomly assigning 140 patients with locally advanced bladder cancer to 2 neoadjuvant plus 3 adjuvant cycles of MVAC vs 5 cycles of adjuvant MVAC.[92] There was no significant difference in overall survival between the groups (p=0.54) at a median follow-up of 6.8 years. However, those treated with preoperative chemotherapy had a lower incidence of positive surgical margins compared to those receiving immediate RC (2% vs 11%, respectively). A total of 9% of the patients in each arm died of therapy related toxicity, illustrating the associated risk of aggressive treatment of this nature.

Without specific randomized trials comparing these 2 strategies, definitive recommendations regarding the optimal timing of chemotherapy can be difficult. **However, it is clear that patients with advanced stage bladder cancer benefit from perioperative chemotherapy and the current evidence preferentially supports a neoadjuvant approach when feasible.**

BLADDER PRESERVATION PROTOCOLS

Bladder preservation broadly includes radiation therapy, chemotherapy or surgical therapy (partial cystectomy or TUR) alone or in combination. The obvious advantage of these treatment strategies is avoidance of radical extirpative surgery, and its associated recovery and complications. However, when bladder sparing treatment is considered, patient selection and education are critical to optimize oncologic outcomes while considering quality of life.

Bladder cancer is highly sensitive to radiation therapy, thereby providing a strong rationale to investigate RT based treatment strategies.

Although to our knowledge no randomized trial has specifically compared survival between RT and RC, non-randomized cohort studies show the 5-year overall survival of invasive bladder cancer treated with RT alone to be 24% to 46%.[16] Whether this rate represents inferiority of therapy or population heterogeneity is not known but **RT as monotherapy has essentially been abandoned as definitive therapy since survival is substantially enhanced by the addition of radical transurethral resection of the bladder tumor and systemic chemotherapy.**

In a multimodal protocol developed at the Massachusetts General Hospital patients undergo debulking TUR followed by an induction course of RT to 40 Gy with concurrent cisplatin based chemotherapy.[93] Those patients with complete clinical response (based on negative cystoscopy with biopsy, urine cytology and bimanual examination every 3 months for 2 years) received an additional 25 Gy with chemotherapy, whereas those with disease progression underwent salvage RC. Of the 162 patients who completed the protocol 41 had an incomplete response and were treated with RC, and 27 underwent RC after an initial CR. At 5 years 54% of the participants were alive and 45% had an intact bladder. At a median follow-up of 6.3 years after therapy 75% of patients had normal bladder function on urodynamic evaluation.[94] These results are comparable to a large bladder sparing series of 415 patients (79% with T2-T4 disease) treated with either RT alone (126) or RT combined with various chemotherapy regimens (289).[95] The overall 5-year survival was 51% and 42% survived with an intact bladder, although the results were not stratified by treatment modality.

Several questions remain regarding the optimal radiation and chemotherapy regimens. The RTOG (Radiation Therapy Oncology Group) 89-03 trial was a phase III trial comparing neoadjuvant MCV followed by concurrent cisplatin plus RT to concurrent cisplatin plus RT alone. There was no difference in response rate or survival with the addition of neoadjuvant chemotherapy, although the study was underpowered to assess such a difference.[96] Phase I trials with RT sensitizing agents such as paclitaxel[97] and gemcitabine[98] have shown promise but need to be confirmed in larger randomized trials. A phase I-II study of hypofractionated (ie twice daily) RT with concurrent MCV with adjuvant chemotherapy revealed 74% CR after induction.[99] However, the adjuvant chemotherapy was poorly tolerated with only 45% of patients completing 3 cycles of adjuvant chemotherapy.

While these studies suggest that trimodal therapy consisting of aggressive TUR, chemotherapy and RT may be comparable to RC for the treatment of invasive bladder cancer, several aspects need further study. For this reason, bladder preservation protocols are best considered for highly motivated patients willing to adhere to strict follow-up and comply with salvage cystectomy in the context of recurrent disease.

FOLLOW-UP

An optimal surveillance program evaluates the patient at intervals of tumor recurrence that permit an opportunity for cure or palliation by a salvage option for the patient. Thus a clear knowledge of the local, distant and urothelial recurrence patterns is essential as these dictate intervals of surveillance. Tumor characteristics are critical since the risk of recurrence increases as the tumor stage increases, with the highest rates demonstrated in patients with extravesical tumor and nodal involvement.[37] Other factors including LVI, surgical margin status and extent of lymphadenectomy are important predictors of recurrence and should be considered along with the risk of radiation exposure, when outlining a surveillance plan for patients.[63, 86, 100]

After RC with LND, approximately 30% to 40% of patients will have disease recurrence within 5 years.[19, 20, 37, 59] Although the majority of recurrences present within the first 2 years following surgery,[20, 59, 100] disease can recur several years later, illustrating the need for aggressive early follow-up with lifelong surveillance. **Local tumor recurrence in the surgical bed or regional lymph nodes is often seen in patients with early relapse (ie within 1 year of RC). After 1 year visceral organs become the most common site of disease recurrence.[100] The most common sites of distant recurrence are the viscera (27%), bone (16%) and retroperitoneum (16%). Distant, local or urothelial recurrence 10 years after cystectomy is uncommon, and a relaxed tumor surveillance plan is reasonable at this point.[20]**

The risk of upper tract recurrence following RC is relatively low at 0% to 4%[74, 100] but these recurrences develop late with a median time

TABLE 3. *Recommended bladder cancer follow-up after cystectomy and urinary diversion*[104]

	3 Mos	6 Mos	12 Mos	18 Mos	Yr 2	Yrs 3 + 4	Yr 5 Then Every 2 Yrs
Abdominal + pelvic CT or abdominal + pelvic MRI	X	X*	X	X*	X	X*	X*
Chest x-ray or chest CT	X	X	X	X	X	X	X
CT urography† or excretory urography	X		X		X	X	X
Vitamin A, B12, D25-OH, D 25-Di-OH, folate					X	X	X
Physical examination	X	X	X	X	X	X	X
Electrolytes, magnesium, blood urea nitrogen, creatinine, albumin, liver function tests, thyroglobulin, cholesterol, alkaline phosphatase	X	X	X	X	X	X	X
Urethral wash or voided cytology‡ + upper tract urine cytology	X	X	X	X	X	X	X

* May be omitted in patients with pathological stage $<T_2N_0M_0$ disease.

†Should be omitted if an abdominal and pelvic CT or MRI is performed.

‡Urethral wash cytology is best performed in patients with non-orthotopic diversion with retained urethra and voided cytology is an accepted urethral screen in patients with orthotopic diversion.

to relapse of up to 37 months.[101] When identified early, urothelial recurrence is curable. As a result, upper tract surveillance with imaging and urinary markers is suggested for early detection of these tumors, although it is widely recognized that a majority of these recurrences will be detected by signs and symptoms. Urethral recurrence is seen more frequently with an incidence of up to 17% following RC.[102, 103] In men the most significant risk factor for urethral recurrence is tumor involvement of the prostatic urethra, while tumor at the bladder neck is a primary risk factor for women.[104]

The potential for metabolic disturbance and failure of the urinary diversion or reconstruction also necessitates early and late metabolic surveillance with serum electrolytes and liver function.[104] **Vitamin B12 levels should be assessed beginning at year 3 when depletion can become evident. Monitoring the urinary diversion is a long-term commitment that must be continued even when the likelihood of tumor recurrence is low.** Taken together, these data support the use of frequent surveillance in the first 2 years after RC. The surveillance schedule should identify recurrent disease early in its course based on known patterns of recurrence in conjunction with the individual risk of recurrence. A reasonable follow-up plan is outlined in table 3.[104]

SURVIVORSHIP

Cancer survivorship covers a broad range of issues that accompany a cancer diagnosis and treatment. These issues may be physical or psychosocial encompassing health care, cancer surveillance, late effects of treatment, secondary malignancies and quality of life. The importance of cancer survivorship has been increasingly appreciated by the oncology community. Survivorship clinics have been established at some centers to facilitate physical and psychosocial rehabilitation. When treating patients with urological malignancies, multidisciplinary teams consisting of nursing professionals, sex therapists, social workers, psychologists and urologists collaborate on methods to reduce patient stress, diminish fear, improve sexual and urinary function, and regain a sense of well-being. Such clinics are models for potential psychosocial interventions that can assist in the global recovery of patients undergoing radical cystectomy and urinary diversion.

In addition to the physical and psychosocial sequelae of bladder cancer, patients must understand their ongoing needs for follow-up care. Survivorship care plans represent an approach to documenting previous cancer treatments and needs for future care.[105] Although such care plans are not yet in wide use, they hold promise as a way of assembling previous cancer related treatments, history of comorbid conditions and other relevant medical information so that it can be accessible to the patient and future health care providers. The plan may document the need for late toxicity monitoring, as well as the surveillance needed for cancer recurrence. The traditional patient care plan was designed for patients treated with chemotherapy. As a greater number of patients with cancer have access to survivorship programs, it is likely that the traditional plan will evolve with a notable expansion for patients treated with radical surgery. Patients treated for MIBC are likely to benefit from this approach given long-term sequelae of the treatment and need for extended surveillance.

CONCLUSIONS

During the last 2 decades great efforts have been made to advance the treatment of muscle invasive bladder cancer. While radical cystectomy remains the definitive treatment for this disease, its associated morbidity and limitations in certain disease settings are well recognized. Thus, survival outcomes associated with radical cystectomy have been enhanced with the use of neoadjuvant chemotherapy and extended lymphadenectomy. A heightened awareness of posttreatment quality of life has led to the development of several important tools to measure changes in urinary, bowel and sexual function after radical surgery. Organ preserving surgical techniques, greater use of continent diversion and optimized bladder preservation strategies have all been aimed at improving functional QOL while maintaining cancer outcomes. Moreover, in some series a reduction in operative blood loss and hospital stay has already been realized with the use of robotic assisted technologies during radical cystectomy.

Taken together, these approaches have led to better survival outcomes while maintaining and, in some cases, surpassing traditional QOL outcomes. Still, many of these strategies including radical cystectomy are greatly underused. The challenge will be to increase the use of effective treatments while continuing to develop and infuse novel approaches to the treatment and management of the disease. At the same time we must help patients adjust to physical and psychosocial impairments related to therapy by providing continuity of care, educating them about expected surveillance and enlightening families about long-term effects of treatment. Bladder cancer survivorship planning will be a step in the right direction.

APPENDIX: FACTORS FAVORING ADMINISTRATION OF NEOADJUVANT CHEMOTHERAPY

Pathological:
- Muscle invasion
- Lymphovascular invasion
- Bulky tumor
- Urothelial histology
- Histological variants (ie micropapillary, inverted growth pattern)
- Aggressive histology (ie small cell carcinoma)

Radiographic:
- Perivesical stranding
- Hydronephrosis
- Suspicious nodes

Clinical:
- Palpable pelvic mass on physical examination (pelvic, digital rectal examination, examination under anesthesia)
- Favorable performance status

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1. The clinical variable that is not included in nomogram models designed to predict aggressive bladder cancer is
   a. Lymphovascular invasion
   b. Carcinoma in situ
   c. p53 status in the tumor
   d. Histological subtype
   e. Race/ethnicity
2. Radical cystectomy is associated with an operative mortality rate of
   a. <5%
   b. 10%
   c. 15%
   d. 20%
   e. 25%
3. Compared to open radical cystectomy, robotic assisted radical cystectomy is associated with
   a. Decreased operative blood loss
   b. Prolonged hospitalization
   c. Decreased operative time
   d. Increased lymph node yield
   e. Improved surgical margin rate
4. Neoadjuvant chemotherapy before radical cystectomy
   a. Is associated with an increased risk of perioperative complications
   b. Has a similar survival advantage to adjuvant chemotherapy
   c. Increases the rate of pathological complete response (pT0)
   d. Has a demonstrated survival advantage using the gemcitabine/cisplatin regimen
   e. Is used nationally in 28% of patients with locally advanced disease
5. When performing pelvic lymphadenectomy
   a. Resection of the obturator and external iliac node packets is sufficient in patients with organ confined disease
   b. Total node counts are increased by submitting individual lymph node packets
   c. A yield of 5 or more lymph nodes has been shown to improve survival
   d. An extended node dissection is only indicated in patients with clinically positive nodes
   e. The superior limit of an extended dissection is the inferior mesenteric vein