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Radical transurethral resection alone, robotic or partial cystectomy, or extended lymphadenectomy: Can we select patients with muscle invasion for less or more surgery?

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Abstract

The contemporary standard of care for patients with muscle-invasive bladder cancer consists of cisplatin-based systemic chemotherapy followed by radical cystectomy and bilateral pelvic lymph node dissection (RC/PLND). For highly selected patients with muscle-invasive disease, surgical bladder preservation approaches including radical transurethral resection (TUR) and partial cystectomy (PC) with or without bilateral PLND may be reasonable alternatives to RC/PLND. In appropriately selected patients, these approaches may offer comparable oncologic outcomes while avoiding the morbidity of radical surgery and urinary diversion. The success of both radical TUR and PC as bladder-sparing alternatives to RC/PLND for muscle-invasive disease requires careful patient and tumor selection, as well as meticulous long-term follow-up. While these approaches have been investigated for patients exhibiting clinical response following neoadjuvant chemotherapy, the results have been mixed. Improvements in the accuracy of clinical staging and refinements in patient selection may allow for improved outcomes of bladder preservation strategies incorporating radical TUR and PC.

The crucial role of lymphadenectomy at the time of RC for staging purposes and its possible therapeutic benefit is generally accepted. Many retrospective studies have reported an association between greater extent of lymphadenectomy and improved clinical outcomes. However, there is no consensus regarding the optimal extent of lymphadenectomy. Currently, there are no reports from prospective, randomized trials to address this issue in regards to cancer-specific and overall survival. Forgoing PLND when managing patients with radical TUR or PC eliminates the opportunity to eradicate occult regional LN involvement. Future advances in our understanding of the appropriate extent of lymphadenectomy will require well-designed prospective clinical trials that directly compare varying extents of surgery with their ability to provide local and distant disease control as well as disease-specific survival.

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Keywords

bladder-sparing; bladder preservation; radical transurethral resection; partial cystectomy; extended lymphadenectomy

Introduction

Radical cystectomy and pelvic lymph node dissection (RC/PLND) remains the gold standard for local and regional therapy for muscle-invasive bladder cancer (MIBC) [1, 2], with more contemporary standards including perioperative cisplatin-based chemotherapy [3, 4]. For highly selected patients, surgical bladder preservation approaches including radical transurethral resection (TUR) and partial cystectomy (PC) with or without bilateral PLND may be reasonable alternatives to RC/PLND. A limited number of series have suggested that in appropriately selected patients, who represent a small fraction of all patients with MIBC, these approaches may offer reasonable oncologic outcomes while avoiding the morbidity associated with radical surgery [5] and body image issues associated with urinary diversion while simultaneously preserving both baseline urinary and sexual function. Furthermore, in the era of increasing perioperative systemic chemotherapy for MIBC, bladder-sparing approaches including radical TUR and PC have been investigated in patients demonstrating clinical response to neoadjuvant chemotherapy.

The multifocal nature of bladder cancer precludes many patients with MIBC from bladder-sparing surgical approaches. Two concepts have been proposed to account for bladder tumor multifocality [6, 7]. The first, known as the “field defect” hypothesis, is that the entire urothelium is exposed to a variety of carcinogenic insults that result in independent tumors. The second is that multiple tumors arise from the spread of a single clone through intraepithelial migration or implantation [8]. Regardless of the etiology, the multifocal nature of bladder tumors and recurrences needs to be taken into account when evaluating and considering bladder-sparing approaches to MIBC.

On the other hand, pathologic findings of no residual tumor at radical cystectomy (pT0) suggest that there is a subset of patients who would be well-suited for bladder-sparing surgical approaches. The reported proportion of patients with a history of MIBC who achieve a pT0 response through TUR alone (without systemic neoadjuvant chemotherapy) ranges from 5% to 20% in the literature [1, 3, 9]. While this identifies a subset of patients who might do well with surgical bladder-sparing therapies, approximately 7.5% of patients who achieve pT0 through TUR alone have lymph node-positive disease detected at time of RC/PLND, and a larger proportion of pT0 patients will experience disease recurrence and ultimately, death from bladder cancer [3, 9]. In sum, while pT0 rates achieved through TUR alone suggest that there may be a subset of patients appropriate for surgical bladder-sparing approaches, the subset does not necessarily include all pT0 patients, nor can we reliably identify such patients. Clinical understaging remains a crucial obstacle to the successful implementation of bladder-sparing surgery for MIBC.

Regardless of the surgical technique used to manage invasive bladder cancer, regional pelvic lymph node (LN) spread is a known pathway of progression. Patients with non-muscle-

invasive and pT2 disease at time of RC/PLND have a risk of LN involvement ranging from 5% to approximately 20% [1, 10]. While LN involvement represents a very strong negative prognostic finding, some patients with low-volume regional LN disease at time of RC/PLND experience long-term disease-free survival without further therapy. Strategies for the management of regional LN management for patients selected for bladder-sparing approaches have not been clearly established; most series of radical TUR or PC as definitive therapy for MIBC have eliminated or limited the extent of PLND. On the other end of the surgical spectrum, another arena for risk-adapted treatment of MIBC is the identification of patients for whom expanding the extent of surgery may be beneficial. The extent of lymphadenectomy in patients with MIBC being treated with RC/PLND improves the accuracy of staging and has a potential therapeutic benefit. Studies are ongoing to define the relationship between the extent of lymphadenectomy and disease progression, disease-specific survival, and overall survival.

Bladder-Sparing Approaches for Muscle-Invasive Bladder Cancer - Radical Transurethral Resection

Transurethral resection (TUR), a diagnostic and therapeutic procedure in patients with non-muscle-invasive bladder cancer, has been studied as a single modality approach in patients with MIBC. Although the recurrence-free and long-term survival of unselected patients with muscle-invasive disease are inferior to those achieved by RC/PLND, in carefully selected patients, bladder-sparing approaches utilizing radical TUR may be appropriate.

Historical series have reported relatively poor survival of patients with MIBC treated with TUR alone [11–13]. For example, in 1977, Barnes et al. reported a 5-year survival rate of 31% for 75 patients exclusively undergoing TUR for the treatment of stage T2 bladder cancer [14]. In contrast, Herr reported that patients with muscle-invasive disease treated with radical TUR achieved a 5-year survival rate of 68% [15]. However, only 45 of 217 patients were eligible for bladder-sparing treatment with radical TUR and 15 of these 45 patients (33%) were subsequently treated with RC or developed metastatic disease.

Henry et al. reported a retrospective series comparing the outcomes of patients with stage B bladder cancer treated from 1974 to 1983 with TUR alone (n=43), preoperative radiation and radical cystectomy (n=40), radical cystectomy alone (n=15), and definitive radiation therapy alone (n=16) [16]. The 5-year survival rates for 43 patients with stages B1 and B2 disease treated with TUR were 63 and 38%, respectively; however, this was reported as comparable to survival rates in patients treated with radical surgery. While the distribution of stage, grade, and number of tumors was not significantly different among the treatment groups, the sample size for each group was small and the groups were not randomized. For example, patients in the TUR groups were older and had more comorbidities than the other patients while having smaller tumors.

Selection of patients for bladder preservation with radical TUR is critical. A second, or restaging, transurethral resection (reTUR) provides an opportunity for more accurate staging in patients initially diagnosed with non-muscle-invasive bladder cancer, allows for assessment of the completeness of the initial resection in patients with muscle-invasive

disease, and provides important information regarding patient selection. A study by Herr revealed that reTUR in 96 patients with non-muscle-invasive tumors revealed residual non-muscle-invasive disease in 55% and upstaging to T2 disease in 20% [17]. Furthermore, in 54 patients with muscle-invasive disease at first TUR, 12 (22%) had no residual tumor and 30 (56%) had residual T2 disease.

Herr further reported on the 10-year outcomes of 151 consecutive patients with MIBC who were offered bladder preservation with radical TUR after reTUR demonstrated no tumor (T0), residual carcinoma in situ (Tis), or non-muscle-invasive (T1) tumor and followed for at least 10 years [18]. Of these 151 patients, 52 elected for immediate radical cystectomy and 99 elected for bladder preservation. Of the 52 patients who elected immediate RC (all of whom had either T0, Tis or T1 disease on reTUR), 35% were upstaged to either pT2, pT3, or pN+ on final pathology, highlighting the problem of clinical understaging. Of the 99 patients treated with TUR alone, 75 (76%) were alive at last follow-up and 24 (24%) died of disease, rates comparable to those treated with radical cystectomy (71% alive and 29% dead of disease). Analysis revealed that 18% of patients who had T0 on reTUR died of bladder cancer compared with 42% of those who had T1 on reTUR ($p = 0.003$). The author concluded that the finding of residual T1 disease on reTUR be used to exclude patients from consideration of a radical TUR approach.

Solsona et al. have reported results from a prospective study of 133 patients with MIBC treated with a macroscopically complete radical TUR who had negative biopsies of the tumor bed [19, 20]. They excluded patients with macroscopically residual tumor after TUR, hydronephrosis, clinical evidence of lymph node involvement, and distant metastatic disease. Additionally, tumors with a sessile appearance or larger than 3cm were excluded from the study. Long-term results from their study included cancer-specific survival rates of 81.9%, 79.5% and 76.7% and progression-free survival of 75.5%, 64.9% and 57.8% at 5, 10 and 15 years, respectively [20]. Approximately 30% of the patients in their study experienced disease progression, 22.5% as local bladder progression alone, 2.2% as local bladder progression associated with metastasis, and 5.5% as distant metastasis alone. Disease progression was associated with a high death rate of 67.5%, as only 12 patients were treated with salvage radical cystectomy. While 10 of the 12 patients treated with salvage RC (83.3%) were rendered free of disease, 89% of the remaining patients with disease progression who either refused or were not fit for salvage RC died of disease.

As demonstrated by the aforementioned reports [18, 20], radical TUR may be an option for highly select patients (excluding those with residual T1 disease on reTUR, sessile lesions or tumors greater than 3 cm) with MIBC desiring bladder preservation (Table 1). Paramount to the success of radical TUR is the quality of initial TUR and reTUR. Furthermore, both the patient and the physician must be dedicated to an intense and life-long regimen of endoscopic and radiographic surveillance. A major obstacle to the success of these approaches remains the inaccuracy of clinical staging, including the limitations of axial and molecular imaging [21]. Given the limited information reported on pelvic progression in these series, it is difficult to assess the need for PLND in these select cohorts. Molecular imaging techniques have not yet matured to allow for accurate detection of primary or recurrent disease. The utility of PET-CT has been limited by urinary excretion, which limits

the ability to detect tumors within the bladder; however, newer tracer agents with minimal urinary excretion, such as ^{11}C -choline, are being tested [22]. Currently, PET-CT has been most effective in staging and the detection of metastatic disease. Kibel et al. performed a prospective study using ^{18}F -FDG PET-CT in 43 patients undergoing radical cystectomy and reported a positive predictive value of 78%, negative predictive value of 91%, sensitivity of 70%, and a specificity of 94%, leading the authors to conclude PET-CT may play an important role in planning treatment prior to cystectomy [23]. MRI is increasingly utilized in the staging and longitudinal follow-up of patients with bladder cancer; however, the added utility of newer functional MRI techniques has yet to be definitively determined. As axial and molecular imaging techniques continue to evolve, additional refinements in the selection of patients suitable for surgical bladder preservation strategies will improve outcomes as those with locally advanced or occult regional disease can be identified and excluded. Long-term follow-up of additional prospective studies with clear patient selection criteria is needed for the critical evaluation of radical TUR as an option for select patients with MIBC.

Bladder-Sparing Approaches for Muscle-Invasive Bladder Cancer - Partial Cystectomy

Partial cystectomy (PC) represents an alternative surgical approach to bladder preservation with the advantages of allowing for accurate staging through full-thickness examination of the primary tumor and the ability to perform a concurrent bilateral pelvic lymphadenectomy. As with radical TUR, patient and tumor selection are critical to the success of PC for the treatment of muscle-invasive disease.

Early experience with PC prior to the 1990s was marked by high recurrence rates, cancer recurrence within surgical wounds, and poor overall cancer control and survival. Historical series described local recurrence rates between 29%–78% [24, 25], with 35% being non-invasive recurrences, 50% muscle-invasive recurrences, and 14% presenting with distant metastases [26]. Tumor recurrences within surgical incisions occurred in up to 40% of all patients and up to 54% in those with high-grade tumors [24, 27, 28]. Up to 20% of patients required salvage RC with 5-year overall survival rates of 50% [29].

During the 1990s additional series from centers using strict selection criteria to identify appropriate candidates were reported [30, 31]. These criteria include a solitary tumor in a location suitable for resection with a 2 cm margin of normal bladder, no associated carcinoma in situ, and no history of prior bladder tumors. Adequate bladder capacity and function should be maintained with the 2 cm margin of resection depending on initial bladder characteristics. Ureteral re-implantation, if necessary, is feasible. However, tumors located at the bladder neck or trigone may not be suitable for PC as achieving a suitable margin may be difficult. Utilizing these more restrictive criteria, only 3%–10% of patients presenting with muscle-invasive tumors remain candidates for PC [30, 31].

Retrospective analysis of 58 patients from Memorial Sloan Kettering Cancer Center (MSKCC) treated with PC (41 with muscle-invasive disease) identified that tumor multifocality ($p<0.001$) and the presence of carcinoma in situ ($p=0.027$) were associated with an increased risk of local recurrence following PC (Table 1) [30]. Pathologic

confirmation of positive lymph nodes and positive surgical margins were associated with advanced recurrences, defined as the development of recurrent muscle-invasive disease or distant metastases ($p=0.012$ and $p=0.022$, respectively). A study from MD Anderson reviewed 37 patients with muscle-invasive urothelial bladder cancer and demonstrated that history of prior bladder tumor ($p<0.003$) was associated with disease recurrence [31]. Adjuvant chemotherapy may be considered for patients with pathologic evidence of extravesical disease or positive LNs after PC. In the series from MD Anderson, high-risk patients with locally advanced disease and positive LNs treated with adjuvant chemotherapy ($n=9$) had significantly longer progression-free survival, but overall and cancer-specific survival were not affected [31]. The ability to achieve an adequate negative surgical margin and adherence to these selection criteria cannot be over-emphasized when evaluating a potential candidate for PC.

With refinements in patient selection, recurrence rates and overall survival in patients treated with PC have improved. Recurrence rates range from 28%–48%; with non-muscle-invasive recurrence in 12%–50%, muscle-invasive recurrence in 17%–57%, and metastatic recurrence in 14%–52% [30–32]. Positive surgical margins are described in 9%–14% of patients undergoing PC; of the 5 patients with a positive surgical margin in the MSKCC series, 3 had muscle-invasive recurrence and one presented with distant metastases [30]. Salvage RC was required in 21%–28% of patients [30–32], with one series describing 75% of patients with muscle-invasive recurrences rendered disease-free after salvage RC [31]. The lack of wound recurrences and tumor implantation in these series is notable and likely reflective of appropriate patient selection and improvements in surgical technique.

These contemporary series report 5-year overall survival rates of 67%–70%, recurrence-free survival rates of 39%–62%, and cancer-specific survival rates of 84%–87% [30–32]. Between 65%–74% of patients maintained an intact bladder and 49%–67% were free of disease with an intact bladder at last follow up [30, 31]. While 86% of recurrences were described in the first 2 years after PC, late muscle-invasive recurrences have been reported indicating the need for life-long surveillance in these patients [31, 32]. Furthermore, these series have relatively short follow-up in comparison to mature RC series. As learned from the long-term follow-up from the Solsona series of radical TUR, longer follow-up is crucial to the evaluation of these results as patients remain at risk of recurrence and progression.

Contralateral nodal involvement in bladder cancer is not uncommon and is important when considering PLND for patients undergoing PC. Leissner reported on 119 patients whose bladder tumors could be strictly localized to one side of the bladder and found a significant rate of contralateral LN involvement with the risk of contralateral lymph node metastases only slightly lower than for the ipsilateral side [33]. Furthermore, of 13 patients with unilateral tumors and a solitary LN metastasis, 3/13 (23%) of the solitary positive LNs were located on the contralateral side. The aforementioned series of PC did not explicitly describe the extent and laterality of the PLNDs performed [30, 31]. Nevertheless, 9% and 14% of the patients in the MSKCC and MD Anderson series had positive LNs, respectively; this proportion might be higher if all patients were treated with bilateral PLND. Currently, the accuracy of both axial and molecular imaging and our ability to predict which patients have occult LN metastases are limited [23, 34]. Patients undergoing a PLND at the time of PC

should have a bilateral node dissection performed for accuracy of staging and added potential therapeutic advantage in the setting of limited pelvic nodal involvement.

Minimally-invasive approaches are being investigated and adopted for a variety of urological oncologic surgeries, including radical cystectomy for bladder cancer [35–37]. Similarly, robot-assisted partial cystectomy might represent an alternative to open partial cystectomy [38]. Surgeons must maintain strict adherence to oncologic principles as the techniques of minimally-invasive partial cystectomy are refined and outcomes should be critically analyzed before widespread adoption of the procedure.

Bladder-Sparing Approaches for Muscle-Invasive Bladder Cancer Following Neoadjuvant Chemotherapy

With the demonstration of benefit and subsequent increased utilization of neoadjuvant chemotherapy for MIBC [3], various investigators have explored the option for bladder-sparing techniques in patients demonstrating clinical responses to chemotherapy.

Herr et al. reported results of 111 consecutive patients with MIBC treated with methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) chemotherapy [39]. Of the 111 patients, 50 (54%) had a complete clinical response (tumor site biopsy negative and urine cytology negative) as evaluated by post-chemotherapy TUR. While all of these patients were advised to undergo radical cystectomy or partial cystectomy, 28 refused surgery and were managed with TUR alone, 15 were treated with partial cystectomy, and 17 elected treatment with radical cystectomy. Although the number of patients in each treatment arm was small and treatment assignment was not randomized, the authors reported no difference in metastasis-free survival at 10 years between the treatment groups (74% with TUR or partial cystectomy, 65% with radical cystectomy), although patients who elected radical cystectomy had more advanced clinical stage pre-chemotherapy. Of the 43 patients who were treated either with TUR alone or partial cystectomy, 25 (58%) retained their bladder beyond 10 years.

In a prospective trial conducted by Sternberg, 104 patients with MIBC underwent TURBT after 3 cycles of MVAC and 49% of the cohort achieved cT0 on restaging (TUR pathology and CT scan) [40]. Thirty-seven patients who achieved cT0 after chemotherapy were treated with TUR alone; 11 were treated for non-muscle-invasive recurrences and 4 underwent salvage RC. Nineteen patients (51%) who had a cT0 response remained alive at a median follow-up of 56 months. Thirteen patients with solitary tumors who responded to MVAC chemotherapy were treated with PC. Two patients (15%) developed non-muscle-invasive recurrences, and 3 patients (23%) developed locally invasive disease. The 5-year overall survival rate for patients treated with PC after MVAC was 69%.

These promising results led to a phase II trial (SWOG 0219) incorporating an option for cystoscopic surveillance following cT0 response to chemotherapy. In this trial, 77 patients were treated with paclitaxel, carboplatin, and gemcitabine (PCG); patients who achieved cT0 status following PCG chemotherapy could elect immediate RC or cystoscopic surveillance [41]. Thirty-four of 74 evaluable patients (46%) achieved cT0 status. Of the 10 patients with cT0 who elected for immediate RC, 6 had persistent muscle-invasive disease. These poor

results highlight the potential inaccuracy of clinical staging that hinders any approach to bladder-sparing therapy for MIBC.

While bladder-sparing surgical therapy may remain an option for patients who exhibit a clinical complete response to neoadjuvant chemotherapy, the success of such an approach relies heavily on the accuracy of clinical staging. Clinical staging, consisting of bimanual examination under anesthesia, TUR of prior tumor sites, and axial imaging, has significant room for improvement. The safety and efficacy of either cystoscopic surveillance or partial cystectomy for patients who achieve cT0 following neoadjuvant chemotherapy for MIBC should be further studied in additional prospective trials, particularly as the accuracy of molecular imaging improves.

Extended Lymphadenectomy for Muscle-Invasive Bladder Cancer

Pathologic tumor (pT) stage and lymph node (LN) status have been shown to be the strongest prognostic factors in patients undergoing RC/PLND for bladder cancer [1, 2, 42, 43]. While the importance of the staging information provided by PLND is well accepted, the anatomic boundaries of the dissections required for adequate and optimal staging remain to be clarified. A lack of prospectively validated studies has led to ongoing controversy regarding the necessary extent of dissection and magnitude of therapeutic benefit conferred [44].

Distribution of Lymph Node Metastases

The primary lymphatic drainage for the urinary bladder includes the internal iliac, external iliac, obturator, and presacral LNs. Secondary drainage progresses to the common iliac LNs and then into the paraaortic, interaortocaval, and paracaval nodes [33, 45, 46]. A number of studies have examined the location of lymph node metastases based upon different anatomic templates of dissection.

Wishnow et al. studied the rate of involvement of the pelvic LNs within the common iliac, obturator, internal iliac and external iliac LNs in bladder cancer patients undergoing RC [47]. In a series of 130 patients with clinically negative LNs at the time of RC, 88% of whom had common iliac LNs resected, 14% were identified to have nodal metastasis. Seventeen of the 18 lymph node-positive patients had only one or two positive LNs. None of the 17 patients with one or two microscopically involved LNs had involvement of the common iliac or lateral external iliac LNs. Based on these findings, the authors advocated limiting the proximal limit of the PLND to the bifurcation of the common iliac vessels for patients with no gross evidence of nodal involvement at the time of surgery [47].

A multi-center, prospective trial in which all patients underwent an extended lymphadenectomy (proximal limit of dissection at or above the bifurcation of the aorta) provided additional information on the distribution of positive pelvic LNs [33]. Of the 290 patients in this study, 81 (28%) had tumor involvement in 599 pelvic LNs. 35% of all positive LNs were proximal to the bifurcation of the common iliac vessels. Twenty patients (6.9%) had common iliac LN involvement without evidence of disease in the more distal nodal regions (obturator, internal iliac, or external iliac). Furthermore, in the 29 patients with

only a single nodal metastasis, 10% had the solitary positive LNs proximal to the bifurcation of the common iliac vessels, providing support for extending the dissection to at least include the common iliac chain [33].

More recently at our institution, a series of 591 patients undergoing RC with extended mapping PLND identified 114 patients (19%) with LN involvement [10]. In the node-positive group, 42 patients (37%) had involvement of the common iliac LNs (pN3), so these patients would have been under-staged had a standard PLND been performed. Even more dramatically, seven of these patients (17% of pN3 patients, 6% of node-positive group) had no positive LNs within the true pelvis, so they would have been classified as node-negative had they undergone a standard PLND. These data provide strong support for the need to extend the PLND to include the common iliac LNs in order to maximize the accuracy of nodal staging [10].

Outcomes Based on Extent of Lymphadenectomy – Number of Lymph Nodes Removed

The number of LNs removed has been widely used as a surrogate for extent of lymphadenectomy and has been demonstrated to be an important prognostic factor in bladder cancer patients undergoing RC/PLND [10, 33, 48, 49]. However, the number of LNs reported depends not only on the quality, extent, and thoroughness of PLND, but also the packaging of specimens and pathologic processing [50]. While the benefit of PLND in terms of oncologic outcomes was initially reported in LN-positive patients [51], its value in LN-negative patients has also been suggested [52].

Leissner et al. studied 447 patients who underwent RC/PLND and reported an association between the number of LNs removed and clinical outcomes. A threshold value of 16 LNs removed was used because the correlation between the total number of LNs removed and the percentage of patients with positive LNs was strongest at this cutoff. The authors found significant differences in recurrence-free survival and cancer-specific survival between patients with ≥ 16 LNs removed and patients with <16 LNs removed [53].

Herr analyzed data on 322 patients with MIBC who underwent RC/PLND. The authors evaluated the associations between the number of LNs removed with local recurrence-free and overall survival. In both LN-negative and LN-positive cases, improved overall survival was associated with a greater number of LNs removed. Herr and colleagues concluded that at least 9 LNs should be removed to accurately define LN status [48].

May et al. reported on 1291 LN-negative patients who underwent RC and PLND and found that a higher number of LNs removed was associated with improved cancer-specific survival [52]. Similarly to Leissner and colleagues, the authors defined a LN threshold of 16 and showed that patients with <16 and ≥ 16 LNs removed had 5-year cancer-specific survival estimates of 72% and 83%, respectively ($p = 0.01$).

The concern that patient selection may bias who receives a more extended PLND at RC led Koppie et al. to control for a variety of factors in their analyses to minimize the effects of surgical selection [54]. The authors found that older patients with a greater degree of comorbidities were less likely to undergo more extensive PLNDs. However, when correcting

for age and comorbidity, reported LN number was still associated with cancer-specific outcomes. The authors demonstrated that the probability of overall survival continued to increase with a greater number of LNs removed.

Outcomes Based on Extent of Lymphadenectomy – Anatomic Limits of Dissection

Given the limitations and biases of studies examining the number of LNs removed, investigators have analyzed data regarding the impact of anatomically defined extended PLND on outcome in bladder cancer patients. Poulsen et al. compared two consecutive series of patients who underwent extended PLND up the aortic bifurcation with those who underwent standard PLND [55]. The authors found that extended PLND was associated with improved 5-year probabilities for pelvic and distant recurrence-free survival in patients with pT3a disease.

A prospective, single-center non-randomized study was performed by Abol-Enein et al. to evaluate the effect of a defined extended lymphadenectomy on recurrence-free survival [56]. Specimens from individual anatomic regions were packaged separately. An intraoperative decision to perform an extended PLND was based upon on the status of the liver, body mass index, and performance status. The authors found that an anatomically defined extended lymphadenectomy up to the level of the inferior mesenteric artery (IMA), compared with a standard PLND (endopelvic region composed of obturator, internal iliac, and external iliac LNs), was associated with an improved recurrence-free survival for LN-positive patients independent of other clinicopathologic factors.

While no prospective randomized data are currently available comparing a standard PLND (bilateral external and internal iliac and obturator nodes) to a more extended PLND, studies have compared outcomes from institutions performing varying extents of PLND. Dhar et al. reported a comparative study evaluating disease-specific outcomes in 336 patients from one institution who underwent RC with a more limited PLND (boundaries included the pelvic sidewall between the genitofemoral and obturator nerves, and bifurcation of the iliac vessels to the circumflex iliac vein) to 322 patients from another institution who underwent a more extensive PLND (cephalad extent extended to the crossing of the ureters with the common iliac vessels and removal of all tissue along the lateral and medial portion of the internal iliac vessels) at RC [57]. Patients who underwent a more extensive PLND were more likely to be lymph node-positive (improved staging) and demonstrated improved recurrence-free survival. Five-year disease-free survival for node-positive patients undergoing an extended PLND was 35% versus only 7% in patients that received a limited PLND. Furthermore, patients treated with a more extensive PLND were less likely to experience isolated local recurrence (4% extended vs. 38% limited); this difference persisted when analyzing by pathologic subgroups (1% extended vs. 19% limited in pT2N0 cases and 7% extended vs. 60% limited in pT3N0 cases).

A study by Zehnder et al. compared outcomes at two separate institutions based upon different templates of PLND; 405 patients underwent extended PLND (mid-upper third of common iliac) and 554 patients underwent super-extended lymphadenectomy (up to the IMA) [58]. Patients who underwent super-extended lymphadenectomy had a higher number of LNs removed, a higher number of positive LNs, and a higher rate of LN metastasis (35%

vs. 28%, $p=0.02$) compared to those who underwent extended PLND. Despite these differences, the two groups had equal recurrence rates and similar 5-year recurrence-free survival when stratified by pathological tumor stage or LN status.

Ongoing Randomized Studies Evaluating Extent of Lymphadenectomy

The aforementioned studies have provided some insights into how the extent of PLND affects the accuracy of staging and may have an effect on clinical outcomes. However, there exists no high-level evidence to define the relationship between the extent of lymphadenectomy and disease progression, disease-specific survival, and overall survival. To that end, there are two ongoing clinical trials designed to address this question (Table 2).

The Association of Urogenital Oncology and the German Cancer Association have completed accrual to a phase 3 trial comparing extended PLND (up to the IMA) with conventional PLND (obturator, internal iliac, and external iliac LNs). The primary endpoint is progression-free survival; the study has 90% power to detect a 15% difference at 5 years. The results are yet to be reported.

The trial being performed by the Southwest Oncology Group (SWOG) 1011 is similarly designed but utilizes different assumptions and power calculations. The SWOG study has 85% power to detect a 28% reduction in the hazard rate of progression or death with extended PLND compared with conventional PLND. The trial is currently accruing patients, with a target of 620 patients.

These two important clinical trials should help to characterize the magnitude of clinical benefit that may be conferred by an extended PLND at RC and will provide additional data to help define appropriate standards of care. Given the previously reported rates of N3 involvement in the overall group of MIBC patients, careful evaluation of the frequency of common iliac LN involvement in these studies will determine if they were adequately statistically powered to reach their primary endpoints.

Conclusions

Anatomic and clinical studies of patients with bladder cancer have provided insights into the natural pathways of disease progression. Decades of experience with surgery for the management of MIBC clearly illustrates the role that surgical quality plays in patient outcomes. Improvements in the accuracy of clinical staging and further refinements in patient selection may allow for improved outcomes of bladder preservation strategies incorporating radical TUR and PC with PLND. Well-designed and properly powered prospective clinical trials will provide the information necessary to establish whether disease-specific survival can be maintained with bladder preservation and improved with use of more extensive PLND at time of RC.

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Key points

- Bladder-sparing approaches may be appropriate for select patients with muscle-invasive bladder cancer.
- In appropriately selected patients, outcomes for radical TUR and partial cystectomy may approach those achieved with radical cystectomy, but will require ongoing, long-term follow-up.
- Bladder-sparing approaches following neoadjuvant chemotherapy are currently limited by the inaccuracy of clinical staging and need further study.
- Some retrospective studies have reported associations between extended lymphadenectomy and improved clinical outcomes in patients treated with radical cystectomy and should be considered when surgically managing invasive bladder cancer.

Table 1

Contemporary series of surgical bladder-sparing approaches for patients with muscle-invasive bladder cancer.

Radical TUR	Eligibility criteria	Cohort size	Follow-up	Outcomes	Notes
Herr et al. [18]	<ul style="list-style-type: none"> Muscle-invasive bladder cancer Non-invasive disease on reTUR 	Radical TUR: n=99 Immediate RC: n=52	Range: 10–20 years	Alive at last follow-up: 75 (76%) Died of disease: 24 (24%)	<ul style="list-style-type: none"> Pts with T0 on reTUR had better outcomes than those with T1 (CSS 82% vs. 58%, respectively) 35% of pts electing immediate RC upstaged to pT2, pT3, pN+
Solsona et al. [19, 20]	<ul style="list-style-type: none"> Muscle-invasive bladder cancer Macroscopically complete radical TUR Negative biopsy of tumor bed Non-sessile appearance Tumor size ≤ 3 cm 	n=133	Mean: 112.1 mos. Median: 99 mos. Range: 11–305 mos.	Recurrence: 40 (30%) Progression: 40 (30%) Died of disease: 27 (20%) Alive without tumor: 14 (11%) OS @ 5, 10 yr: 74%, 40% CSS @ 5, 10 yr: 82%, 80%	<ul style="list-style-type: none"> Progression associated with high death rate (67.5%) Highly select group (T0 byTUR alone)
Partial Cystectomy	Eligibility criteria	Cohort size	Follow-up	Outcomes	Notes
Holzbeierlein et al. [30]	<ul style="list-style-type: none"> Partial cystectomy for primary bladder tumor of nonurachal origin 	n=58	Mean: 33.4 mos. Median: 31.3 mos. Range: 1–82 mos.	Died of disease: 12 (21%) OS @ 5 yr: 69%	<ul style="list-style-type: none"> Only 34 (59%) had cT2N0M0 disease CIS and multifocality associated with superficial recurrence LNI and positive surgical margin associated with advanced recurrence
Kassouf et al. [31]	<ul style="list-style-type: none"> Muscle-invasive bladder cancer Solitary tumor No concomitant CIS No need for ureteral reimplantation 	n=37	Mean: 72.6 mos. Median: 51 mos. Range: 40–82 mos.	Died of disease: 6 (16%) Died of other causes: 8 (22%) OS @ 5 yr: 67% CSS @ 5 yr: 87% RFS @ 5 yr: 39%	<ul style="list-style-type: none"> Adjuvant chemotherapy administered to 9 (24%) pts

Data from Refs 18–20,30,31.

Table 2
Ongoing randomized clinical trials exploring benefit of extended lymphadenectomy at time of RC.

	Accrual goal	Extent of LND	Primary Endpoint/Power	Secondary Endpoints
Association of Urogenital Oncology and German Cancer Association	n=450	Standard: external iliac, obturator, internal iliac LNs Extended: up to IMA	Progression-free survival @ 5 years 90% power to detect a 15% difference	Local recurrence Distant metastases Disease-specific survival Complications
SWOG 1011	n=620	Standard: external iliac, obturator, internal iliac LNs Extended: includes common iliac LNs and presacral LNs; can be extended up to IMA per surgeon preference	Disease-free survival 85% power to detect a 28% reduction in HR of progression or death	Overall survival Operative time Morbidity and mortality Length of hospital stay Lymph node counts Local and retroperitoneal soft tissue recurrence