

## Radical cystectomy is the treatment of choice for invasive bladder cancer

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**B**ladder cancer is the second most common urologic cancer and the sixth most common overall cancer in Canada, accounting for 6700 new cases per year. It has the fourth highest incidence among cancers in men and the twelfth in females. It represents up to 5.8% of new cancer cases and 3.3% of deaths in Canadian men.<sup>1</sup> Tobacco smoking is the most established risk factor, leading to 50% to 65% and 20% to 30% of male and female cases, respectively.<sup>2</sup> Other risk factors include occupational exposure to benzene derivatives and aryl amines, phenacetin abuse, external beam radiation therapy, dietary factors, cyclophosphamide and chronic urinary tract infections (especially with schistosomiasis in endemic areas).<sup>3-8</sup>

### Radical cystectomy for muscle-invasive bladder cancer

For muscle-invasive tumours, radical cystectomy with pelvic lymphadenectomy has been the gold standard for the past several decades. New advancements in neoadjuvant and adjuvant chemotherapy, radiation therapy and bladder-preservation protocols have been introduced for a subset of patients. In the past, radical cystectomy was not universally accepted because of high recurrence, complication rates and poor subsequent quality of life. However, many improvements have been made in the surgical approach and techniques. Complication and perioperative mortality rates have been declining, with reported rates as low as 17% to 32% and 2% to 3%, respectively.<sup>9-11</sup> Other voiced concerns with surgery were incontinence and impotence. With an orthotopic ileal neobladder, daytime and nocturnal continence rates as high as 85% to 90% and 50% to 90%, respectively, can be achieved.<sup>12</sup> Also, with unilateral and bilateral nerve-sparing cystectomy, potency rates of 33% and 60% can be achieved.<sup>13</sup> These results are comparable to radiation therapy, with 54% of these patients having adequate erections.<sup>14</sup>

There is also recent interest on the importance of lymphadenectomy and its therapeutic and prognostic value. About 25% of patients present with lymph node involvement at the time of surgery. Skinner was among the first physicians to advocate radical cystectomy with wider resection of perivesical soft tissue and extended lymph node den-

sity (LND) in an effort to decrease local recurrence of disease and improve cure rates for invasive bladder cancer.<sup>15</sup> A combined effort between the Cleveland Clinic and the University of Bern compared 2 groups of patients who underwent a radical cystectomy with a limited LND in the prior and an extended LND in the latter and showed improved survival in the second group.<sup>16</sup> Multiple studies show that an extended lymphadenectomy up to the aortic bifurcation offers improved patient survival with low associated morbidity and mortality.<sup>9-11</sup> Several studies demonstrate that the number of nodes resected was associated with improved survival in patients with invasive bladder cancer.<sup>17-19</sup> Furthermore, in the widely quoted South West Oncology Group (SWOG) trial evaluating the role of neoadjuvant chemotherapy, Herr and colleagues examined surgical factors as surrogates for outcome.<sup>20</sup> The number of nodes removed (>10) in both node-negative and node-positive patients was associated with prolonged survival and remained an independent prognostic factor even after adjusting for the use of neoadjuvant chemotherapy, surgical margin status, pT stage and nodal status. With radiation therapy, however, disease control in the pelvis may be suboptimal, as areas covered may include the internal and external iliac lymph nodes but not the aortic bifurcation where the associated toxicity can be much higher.<sup>21</sup>

More importantly, patients who are found to have occult nodal metastasis or extravesical disease at cystectomy are at high risk of recurrence and are commonly offered adjuvant chemotherapy. The benefit of adjuvant chemotherapy for pT3 or pN+ disease has been shown in 3 randomized trials, which demonstrated significantly improved 5-year recurrence-free survival of 22% to 51% and confirmed by a meta-analysis that showed a 25% relative reduction in

*The purpose of the Point/Counterpoint section is to encourage vigorous and informed discussion on controversial issues in urology through the presentation of diverse opinions. We aim for a dispassionate discussion of controversies, recognizing that strong passions may exist in support of some positions.*

## Point/Counterpoint

the risk of death.<sup>22-25</sup> Concomitant pelvic lymphadenectomy with radical cystectomy offers more accurate staging that increases detection of micrometastasis allowing adjuvant chemotherapy to be offered early where the tumour burden is lowest. Patients treated with bladder preservation strategies, however, are offered radiosensitizing chemotherapy, then are treated with salvage chemotherapy upon recurrence; these patients rarely receive adjuvant chemotherapy when the tumour burden is low and the chance of cure is highest. Furthermore, at our institution, many patients with muscle-invasive bladder cancer who are treated with bladder-preservation strategies often have compromised renal function, which precludes the use of sensitizing platinum-based chemotherapy in combination with radiation; these patients commonly receive gemcitabine or carboplatin, which are inferior to cisplatin for bladder cancer therapy. As such, this particular group of patients would also benefit from surgery.

In the absence of any randomized clinical phase III trials comparing radical cystectomy and bladder-preservation therapies, it is difficult to clearly delineate the optimal management option. Contemporary series show impressive 5-year pelvic control rates of 80% to 90% and 5-year overall and disease-specific survival (DSS) rates of 59% to 60% and 55% to 65%, respectively, for radical cystectomy.<sup>9-11,26</sup> Radiotherapy, as a single modality, is certainly suboptimal to surgery, with 5-year overall survival (OS) of only 25% to 30%.<sup>27</sup> While the reported 5-year OS rates of 48% to 63% for bladder preservation therapies consisting of transurethral resection of bladder cancer (TURBT) followed by chemoradiation may be comparable to the cystectomy group, it is noteworthy that with longer follow-up, 35% to 45% of these patients end up requiring salvage cystectomy (due to suboptimal local disease control), which is certainly technically more challenging, with reported complications as high as 58.5% within 90 days of surgery.<sup>9,28-33</sup> A study comparing immediate versus delayed salvage cystectomy has shown that the latter is associated with significantly higher regional lymph node metastasis (26% vs. 12%) and shorter 5-year DSS in patients with advanced bladder cancer (56% vs. 80%).<sup>34</sup> Furthermore, in those who have their bladders preserved and choose not to undergo salvage cystectomy, the 5-year survival drops to 36%.<sup>28-32</sup> Ileal neobladders also become much more challenging following pelvic irradiation, with complication rates as high as 33% including prolonged urinary leakage, ureteral stenosis, fistulas, and urinary retention with a re-operation rate of 17% at 28 months and significant day and night incontinence rates of 33% and 44%, respectively.<sup>35,36</sup>

One should also not overlook the long-term risk of secondary malignancies following radiotherapy as irradiating

the pelvis (e.g., in patients with prostate cancer) has been shown to increase the rate of cancer with relative risks of bladder and rectal cancers of 1.88 and 1.26 for external beam radiotherapy, 1.52 and 1.08 for brachytherapy and 1.85 and 1.21 for external beam radiotherapy-brachytherapy compared to prostatectomy alone.<sup>37</sup> Lastly, although comparable results may be achieved in only select patients, patients with compromised renal function, hydronephrosis, concomitant carcinoma in situ (CIS) or large tumour burden will respond poorly to bladder preservation strategies with radiation. Wolf and colleagues reported that when there was CIS on initial presentation, new bladder tumour recurrences were noted in 58% of patients following radiotherapy.<sup>38</sup> Hydronephrosis, for its part, is associated with worse complete response rate (37% vs. 68%), overall (48% vs. 53%) and DSS (55% vs. 64%) with combined chemoradiation and as such these patients should preferentially be candidates for surgical intervention.<sup>14</sup> Finally, one must also take into consideration that following bladder preservation, strict follow-up with frequent and lifelong cystoscopies is required, which can be uncomfortable for patients and associated with a higher risk of bleeding and infections.

After taking into account all the above-mentioned points, chemoradiation is a good option only for select patients, such as the elderly, those with significant comorbidity or those who refuse surgery and are strongly motivated to keep their bladder while adhering to a strict surveillance regimen.

### Radical cystectomy for non-muscle-invasive bladder cancer

For non-muscle-invasive tumours (NMIBC), a complete TURBT is the treatment of choice followed by intravesical therapy or close surveillance.<sup>39</sup> These tumours should be further stratified by risk. Immediate cystectomy is advocated when there are multiple recurrent high-grade tumours, high-grade T1 tumours and high-grade tumours with concomitant CIS as well as in the context of Bacillus Calmette-Guerin (BCG) failure.<sup>39</sup> At radical cystectomy, up to 43% of patients with these features have muscle-invasive disease despite treatment with intravesical therapy, lending further support to the role of early surgical intervention in this group.<sup>40</sup> Interestingly, a delay in surgery has been shown to decrease DSS in these patients. Herr and colleagues have demonstrated that DSS is significantly longer in patients with NMIBC who recur and are subsequently treated with radical cystectomy within 2 years of BCG therapy compared to those treated after more than 2 years from BCG therapy (92% vs. 56% 15-year disease-specific survival);<sup>41</sup> improved survival with early cystectomy was demonstrated regardless if patients with NMIBC recurred with NMIBC or with muscle inva-

sion. In patients with high-risk NMIBC, the impact of radiation therapy has been studied in a randomized clinical trial of 210 patients with T1G3 bladder tumours comparing conservative measures and intravesical therapy to radiation therapy. No benefit was found with radiotherapy in terms of progression-free interval (hazard ratio [HR] 1.07,  $p = 0.785$ ), progression-free survival (HR 1.35,  $p = 0.133$ ) or OS (HR 1.32,  $p = 0.193$ ).<sup>42</sup> As such, radical cystectomy remains the primary choice in patients with high-risk NMIBC who fail BCG.

## Summary

Radical cystectomy with lymphadenectomy continues to be the standard of care and primary choice for patients with muscle-invasive and recurrent or refractory NMIBC. Bladder-preservation strategies, such as chemoradiation, are good options for select patients, such as the elderly, those with significant comorbidity or those who refuse surgery and are strongly motivated to keep their bladder while adhering to a strict surveillance regimen including lifelong cystoscopy.

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## In favour of bladder preservation using combined modality treatment

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All health care professionals would agree that the primary goal of bladder cancer treatment should be to maximize patient survival while minimizing toxicity and negative impact on a patient's quality of life (QOL). Bladder preservation (and its impact on QOL) can only be considered an important secondary objective. Bladder cancer management has seen a significant change with the increasing use of multimodality treatment (e.g., surgery, radiotherapy and/or chemotherapy) as opposed to unimodality treatment.

To enable all treatment options to be discussed and to avoid unnecessary delays in treatment, ideally patients should be seen by urologists, radiation oncologists and medical oncologists in a multidisciplinary setting. Urologists would be strongly encouraged to refer their patients with invasive bladder cancer for a multidisciplinary opinion with the understanding that patients requiring a cystectomy would be referred back to the referring urologists.

### Cystectomy as a treatment option

Radical cystectomy remains the primary treatment in the local management of bladder cancer in North America. In contrast, bladder preservation with salvage cystectomy in Europe has had a longer history—in some centres, it is the recommended approach. In North America, the centre with the largest experience with bladder preservation using a trimodality treatment is Massachusetts General Hospital (MGH) in Boston. While continent urinary tract reconstruction using cutaneous urinary reservoirs or orthotopic diversion is a step up from urinary diversion with an ileal conduit and urostoma, limited number of patients, in practice, have continent urinary tract reconstruction.

### Results of cystectomy

Two large recent radical cystectomy series provide the best data outcomes (Table 1). The University of Southern California (USC) series of 633 patients with pT2–T4a reported 5 and 10 years overall survival of 48% and 32%.<sup>1</sup> The Memorial Sloan Kettering Cancer Center (MSKCC) series of 184 patients with pT2–4 reported overall 5-year survival rates of 36%.<sup>2</sup> While the operative and perioperative care has improved, operative mortality in modern series ranges from 1% to 2% and postoperative complications range from 15% to 32%.<sup>3,4</sup> Studies confirm that the most serious side effects are urinary diversion and loss of sexual function in men and women; these effects also have a significant impact on QOL. Continent urinary procedures achieve 82% continence rates, yet complications require reoperation in 10% to 15% of these patients.

### Bladder preservation

Radiotherapy in the local management of bladder cancer has seen a significant change over the last couple of decades, evolving from the use of radiotherapy alone to preoperative radiotherapy, and more recently the use of trimodality treatment. The modern approach to bladder preservation involves careful cystoscopic evaluation, transurethral resection of the bladder to minimize the extent of residual disease, concurrent chemoradiotherapy followed by regular cystoscopic evaluation, and salvage cystectomy for recurrence. These strategies require the active participation of the urologist in the preradiotherapy assessment, decision-making, postradiotherapy monitoring and surgical intervention for salvage radiotherapy.

Concurrent cisplatin with radiotherapy is recommended to improve local control based on the National Cancer Institute