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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

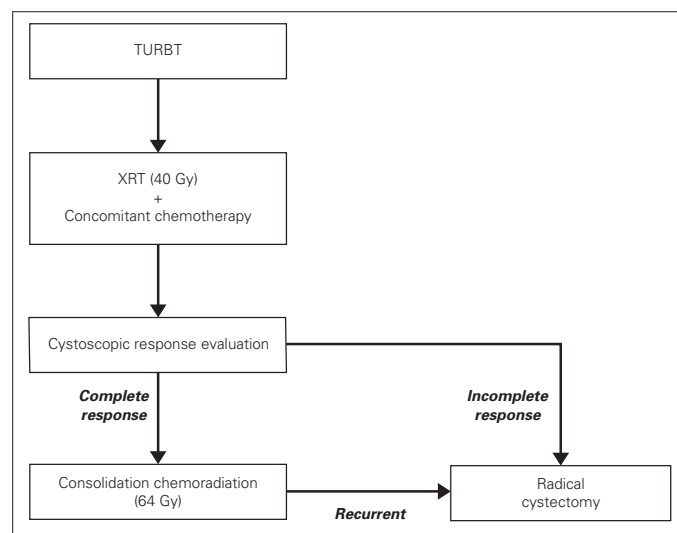
Two large recent radical cystectomy series provide the best data outcomes (Table 1). The University of Southern California (USC) series of 633 patients with pT2–T4a reported 5 and 10 years overall survival of 48% and 32%.<sup>1</sup> The Memorial Sloan Kettering Cancer Center (MSKCC) series of 184 patients 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

of Canada randomized study.<sup>5</sup> One of the clearest indications of the potential for chemoradiotherapy came from the University of Paris, where the concurrent chemoradiotherapy approach (as a planned preoperative approach) did not identify any residual disease at cystectomy in the first 18 patients.<sup>6</sup> These results led to a prospective study of selective bladder presentation using a trimodality strategy.<sup>7</sup> The University of Erlangen reported the results of its trimodality treatment in 2002.<sup>8</sup> In this protocol, patients completed the full course of chemoradiotherapy and underwent transurethral resection of bladder cancer (TURBT) restaging at 6 weeks to 8 weeks and salvage cystectomy for recurrence. The overall survival of the 245 patients at the 5-year point and the 10-year point was 47% and 26%, respectively. The Paris, MGH and Radiation Therapy Oncology Group (RTOG) approaches are a variation of this trimodality approach (Fig. 1). Patients commence chemoradiotherapy and undergo cystoscopy after 6 weeks. Patients found to have a complete response (CR) go on to complete their chemoradiotherapy while patients with residual disease proceed to cystectomy. The advantage with this approach is that it selects patients with CRs as candidates for bladder preservation while the remaining patients undergo early salvage cystectomy. The



**Fig. 1.** Schema for bladder-preserving therapy. TURBT = transurethral resection of the bladder; XRT = radiotherapy.

overall survival of the modern bladder preserving series at 5 years ranges from 45% to 52% (Table 1) and 54% to 67% of surviving patients have a tumour-free normally functioning bladder.<sup>7,9-12</sup>

Unfortunately, in the absence of a randomized study directly comparing radical cystectomy (with or without chemotherapy) with trimodality treatment, it is not possible to have a definite answer that would guide patient care and inform patients. Differences in patient selection and reporting based on pathologic staging (surgical series) versus clinical staging (bladder-preserving trimodality treatment) makes comparability of results from these treatment approaches difficult.

The MGH and RTOG studies show that 70% to 80% of patients achieve CR with chemoradiotherapy and 80% to 89% of these patients remain free from recurrent invasive disease at 5 years. In addition, 60% of patients remained free of any noninvasive or invasive recurrence and 84% of patients with recurrent noninvasive recurrences are maintained in remission with transurethral resection and intravesical therapy.<sup>13,14</sup> Invasive recurrences generally require salvage cystectomy. Salvage cystectomy results in 40% to 50% survival rates at 5 years and local regional control rates of 60%.<sup>12</sup> Interestingly, the 5-year metastatic rate in the early cystectomy patients (who did not complete the full course of chemoradiotherapy) and the later salvage cystectomy patient were similar, at 50%.<sup>12</sup>

A criticism of the chemoradiotherapy approach is that the treated bladder becomes poorly functioning. The MGH group has performed QOL and urodynamic studies (UDS) in 71 patients who are alive with a functioning bladder.<sup>15</sup> The median time from trimodality treatment was 6.3 years, long enough for late effects to arise. Of interest, 75% of

**Table 1. Muscle-invasive bladder cancer: survival outcomes in contemporary series**

			Overall survival	
Series	Stages	No.	5 yrs, %	10 yrs, %
Cystectomy				
USC, Stein, 2001 <sup>1</sup>	pT2-pT4a	633	48%	32%
MSKCC, Dalbagni, 2001 <sup>2</sup>	pT2-pT4a	181	36%	27%
SWOG/ECOG/CALGB, Grossman, 2003 <sup>20</sup>	cT2-cT4a	307	50%	34%
Selective bladder preservation				
University of Erlangen, Rodel, 2002 <sup>7</sup>	cT2-cT4a	326	45%	39%
MGH, Shipley, 2002 <sup>11</sup>	cT2-cT4a	190	54%	36%
RTOG, Shipley, 1998 <sup>9</sup>	cT2-cT4a	123	49%	n/a

USC = University of Southern California; MSKCC = Memorial Sloan-Kettering Cancer Center; SWOG = South West Oncology Group; ECOG = Eastern Cooperative Oncology Group; CALGB = Cancer and Leukemia Group B; MGH = Massachusetts General Hospital; RTOG = Radiation Therapy Oncology Group.

patients had normally functioning bladders by UDS. Reduced bladder capacity was identified in 22% of patients, and only in a third of these patients did distressing symptoms arise. Bowel symptoms occurred in 22% of patients with 14% recording any level of distress. Only 8% of patients reported dissatisfaction with their sex lives. In contrast, in the Swedish and Italian series, 13% and 8%, respectively, of cystectomised controls retained useful erection.<sup>16,17</sup>

Overall, most men treated with trimodality treatment retain good bladder function and maintain sexual functioning. A proportion of patients may experience bowel symptoms that may affect their QOL; however, this should be weighed against the benefits of bladder preservation. A small proportion of patients (2%) will experience unacceptable bladder toxicity requiring a cystectomy.<sup>8</sup> Modern radiotherapy approaches with meticulous attention to planning, shielding of normal structures, intensity-modulated radiation therapy and image guided radiotherapy has the potential to further reduce doses to the bowel and reduce toxicity.

A further criticism of this strategy is that it delays definite surgical treatment. For patients who have an inadequate response, early cystectomy enables this delay to be minimized. In these early salvage patients, the treatment can be considered to be a preoperative chemoradiotherapy approach and randomized studies have failed to show that preoperative radiotherapy is detrimental for important outcomes.

Organ-preserving approaches to manage cancer are well-established and are recognized standards of care in other cancer, such as breast, anal and laryngeal cancers. In contrast, this is less well-established in the management of bladder cancer in North America. Patients have the right to be made aware of all available options in the management of their cancers and should be informed of the pros and cons of the various treatment strategies in a shared decision-making model. Given the complexity of the issues, this discussion is best done in a multidisciplinary setting. Tumour characteristics associated with favourable response to trimodality treatment include primary T2-3a tumours that are unifocal, tumours less than 5 cm in maximum diameter, no ureteric obstruction, good capacity bladder and visibly complete TURBT.<sup>12</sup>

The reported neoadjuvant series and the meta-analysis have shown a 5% survival benefit regardless of the local modality employed (surgery or concurrent chemoradiotherapy).<sup>18-27</sup> Thus neoadjuvant chemotherapy needs to be seriously considered in addition to local treatment strategies. The treatment options boil down to radical cystectomy (with neoadjuvant chemotherapy or adjuvant chemotherapy for selected patients) or TURBT and neoadjuvant chemotherapy followed by concurrent chemoradiotherapy and sal-

vage cystectomy.

In conclusion, patients have the right to be informed of all treatment options in the management of their bladder cancer. Organ preservation is a well-recognized treatment strategy in some cancers. While radical cystectomy is considered the standard of care in North America, results of trimodality treatment (involving TURBT, neoadjuvant chemotherapy, concurrent chemoradiotherapy and salvage cystectomy) have demonstrated comparable results (though the series are not directly comparable) and 54% to 67% of surviving patients have a tumour-free, normally functioning bladder. Patients with residual or recurrent disease are candidates for either early cystectomy (before completion of their full course of chemoradiotherapy) or later salvage treatment. This maintains the surgical option for recurrent patients while providing patients who achieve a CR the opportunity for bladder preservation. Urodynamic studies and QOL studies have shown that these patients have well-functioning bladders and have mild bowel symptoms following radiotherapy. Besides the obvious benefits of organ preservation, the reported sexual functioning of the trimodality approach is good in contrast to the surgical approach. Patients should be evaluated both for cystectomy and bladder preservation based on patient and tumour characteristics to optimize survival and QOL and minimize toxicity.

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