Primary Bladder Preservation Treatment for Urothelial Bladder Cancer

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Background: Significant advancements have occurred in surgical procedures and chemoradiation therapy for bladder preservation.

Methods: This review addresses primary treatment options for bladder cancer, including an overview of bladder-sparing strategies.

Results: Surgical series demonstrate that highly selected patients with cT2N0M0 urothelial bladder cancers can be managed with partial cystectomy and bilateral pelvic lymphadenectomy. For patients with cT2N0M0 to cT4aN0M0 urothelial bladder cancers, neoadjuvant chemotherapy followed by radical cystectomy or maximal transurethral resection of the bladder tumor (TURBT) followed by chemoradiation therapy results in equivalent survival rates. However, each treatment option has a different impact on quality of life. Current chemoradiation therapy trials are evaluating novel approaches to improve outcomes.

Conclusions: Maximal TURBT followed by chemoradiation therapy demonstrated equivalent survival with radical cystectomy while preserving bladder function in the majority of patients. Future efforts will be directed toward improving survival and quality of life.

Introduction

Radical cystectomy remains the mainstay of treatment in patients with muscle-invasive urothelial bladder cancer, with the primary goal of maximizing survival. However, important secondary goals include minimizing toxicity and maximizing quality of life (QOL). This review article describes modern approaches to bladder cancer, particularly bladder preservation strategies.

Epidemiology and Histology

Based on the 2012 estimates from the American Cancer Society, bladder cancer represents the fourth most common cancer in men and the twelfth most common cancer in women in the United States. The estimated overall incidence of bladder cancer in the United States for 2012 was 73,510 new cases involving 55,600 men and 17,910 women. The median age at diagnosis is 65 years. There are 14,880 deaths per year in the United States, of which 10,510 are men and 4,370 are women. The incidence and mortality rates per 100,000 persons...
are 31.1/12.1 among men and 9.5/4.5 among women. The incidence among white men is twice that of African American men. Although bladder cancer incidence rates are stable among men, they are increasing among women by 0.2% per year. Alternatively, mortality rates are stable in men, yet they have been declining in women by 0.4% each year since 1986. The increasing incidence and decreasing mortality in women are most likely due to greater early detection. However, no major cancer group recommends screening the general population for bladder cancer.

The majority of bladder cancer cases are urothelial (transitional cell) carcinomas, representing 90% to 95% of all cases. Other histologies include squamous cell carcinoma (1.5%), adenocarcinoma (1.2%), and small cell carcinoma (< 1%). The vast majority of nonsurgical trials have excluded patients with nonurothelial carcinoma.

Staging
The seventh edition of the American Joint Committee on Cancer (AJCC) staging of bladder cancer uses the tumor/node/mетastasis (TNM) system. A total of 75% to 85% of bladder cancers are superficial (stages pT1a, pTis, and pT1), while 7% of patients present with lymph node involvement, and another 4% present with distant metastases. Patients with papillary carcinoma or in situ disease have a 5-year overall survival (OS) rate higher than 85% compared with 14% for patients with node-positive disease.

Transurethral Resection of Bladder Tumor
Limited research evaluates transurethral resection of bladder tumor (TURBT) alone as curative treatment. However, in select patients with small, solitary tumors with focal invasion into the muscularis propria, long-term, bladder-intact survival rates of 60% to 70% have been reported. A large retrospective series of 432 patients referred for definitive management of muscle-invasive disease evaluated 151 patients who, after maximal TURBT, had either no residual or T1 stage disease. Ninety-nine patients were managed with active surveillance and 52 underwent radical cystectomy. The 10-year disease-free survival (DFS) rate was equivalent between the two groups, and 57% of those managed with surveillance retained their bladders. A subsequent phase II prospective trial of 133 patients treated with radical TURBT alone was performed. The inclusion criteria required no residual tumor after TURBT (T0), negative repeat biopsies of the tumor bed, and absence of hydronephrosis. In addition, the majority of patients had unifocal disease and no evidence of carcinoma in situ. The researchers found 10-year OS and bladder-intact survival rates of 79% and 65%, respectively.

Despite these encouraging results, a separate retrospective review of 327 patients found that 35 patients (11%) were candidates for surveillance following TURBT. Of the 27 patients who opted for surveillance, 15 developed subsequent recurrence, with 8 undergoing radical cystectomy. Consequently, TURBT alone is best suited to patients with noninvasive (cTa or cTis) disease. If there is an incomplete resection or no muscle in the specimen, then a repeat TURBT should be performed.

Partial Cystectomy
Compared with radical cystectomy, removal of a portion of the bladder may result in better retention of sexual function. Optimal candidates for partial (segmental) cystectomy are those who have solitary lesions with focal muscularis propria involvement located either anteriorly or on the bladder dome where a 1- to 2-cm resection margin is possible. Patients should also have an absence of carcinoma in situ secondary to an increased risk of recurrence. In addition, Smaldone et al demonstrated that, in 25 highly selected patients who underwent partial cystectomy for solitary tumors, tumor size was significantly associated with local recurrence. In appropriately selected patients, partial cystectomy can result in long-term, bladder-intact survival rates ranging from 50% to 75%. However, only 5% to 10% of patients with cT1N0 to cT2N0 disease are candidates for this treatment. Bilateral pelvic lymphadenectomy should be performed and minimally include common, internal, and external iliac, and obturator nodes.

Neoadjuvant Chemotherapy Followed by Partial Cystectomy or Transurethral Resection of Bladder Tumor
The Medical Research Council (MRC) and Southwest Oncology Group (SWOG) trials evaluating neoadjuvant cisplatin-based chemotherapy prior to cystectomy demonstrated a survival advantage in patients with pT2N0 to pT4aN0 urothelial bladder cancers. Some of the patients who received neoadjuvant treatment had complete responses at the time of cystectomy. Consequently, it may be possible to perform partial cystectomy on these patients with similar oncological results as radical cystectomy but with less functional morbidity. In a prospective trial, Sternberg et al evaluated 104 patients with muscle-invasive disease who underwent 3 cycles of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy followed by TURBT alone (n = 52), partial cystectomy (n = 3), or radical cystectomy (n = 39) based on the response to neoadjuvant chemotherapy. Of the 52 patients who underwent TURBT alone, 29 had either a pathological complete response (pT0) or superficial disease after chemotherapy. In addition, 44% maintained an intact bladder, with a 5-year OS rate of 67%.

In a separate study of 111 candidates for cystectomy...
with cT2 to cT3 disease who had undergone neoadjuvant MVAC chemotherapy, 60 were found to have a complete response (pT0) on restaging TURBT.17 Of these 60 patients, 43 had bladder-sparing surgery and 17 underwent radical cystectomy. The 10-year OS rate for the 45 patients who underwent partial cystectomy was 74% compared with 65% in the radical cystectomy group. In the bladder-sparing group, 40% of patients ultimately underwent cystectomy, due in part to the limitations of restaging TURBT in determining the full extent of disease in the bladder.

In the SWOG S0219 trial, 46% of the 74 evaluable patients who received 3 cycles of neoadjuvant paclitaxel, carboplatin, and gemcitabine chemotherapy for cT2 to cT4a bladder cancer had a pathological complete response on restaging TURBT.18 Of these 34 patients, 10 underwent immediate cystectomy. Six of the 10 patients who underwent cystectomy had persistent muscle-invasive disease despite a negative restaging TURBT. Although this study did not include cisplatin chemotherapy, neoadjuvant chemotherapy and TURBT are typically reserved for patients with extensive comorbid disease or a poor performance status.

Radiation Therapy
Predating the use of concomitant chemoradiation therapy, patients with muscle-invasive bladder cancers deemed inoperable or those who were nonsurgical candidates secondary to comorbidities were treated with radiation therapy alone. Currently, radiation therapy is rarely used by itself in the definitive management of bladder cancer in the United States except in rare cases of inoperable patients with cT2N0 to cT3N0 disease and extensive comorbid disease or a poor performance status in which chemotherapy is not possible. More commonly, radiation therapy alone is used to palliate metastatic disease in cases where chemotherapy is not possible.

Few contemporary, large prospective trials have been conducted involving radiation therapy alone for bladder cancer. Rather, most studies of external beam radiation therapy are retrospective analyses from single institutions, and they describe varying techniques. Outcomes with radiation therapy alone are inferior to those with surgery. Radiotherapy alone results in 5-year OS rates of 20% to 50% and local control rates of approximately 50% to 60%.19-22 In the 1970s, preoperative radiation therapy appeared to provide a benefit as demonstrated by pathological downstaging in a subset of patients with muscle-invasive bladder cancer.23,24 However, subsequent randomized trials demonstrated no benefit in OS rates when compared with radical surgery alone; moreover, the use of preoperative radiation complicated the urinary diversion reconstruction.25,26 Randomized trials have demonstrated the inferiority of radiation therapy alone compared with chemoradiation therapy both in tumor response and in OS rates (Table 1).27-29 In a phase III randomized trial performed by James et al29,30 the 2-year locoregional DFS rate for those receiving radiation therapy alone was 54% compared with 67% for those receiving chemoradiation therapy (P = .02). The chemoradiation therapy results were superior, even though cisplatin-based chemotherapy was not used. In addition, the 5-year OS rates were 48% and 35% in the chemoradiation and radiation-alone arms, respectively.

For patients treated with radiation therapy alone, radiation doses in the range of 50 to 70 Gy, given in daily fractions of 1.8 to 2.5 Gy for 4 to 7 weeks, were used to treat the entire bladder and draining lymph nodes. Dose and fractionation in some of these studies were considered inadequate by current standards and resulted in 5-year OS rates of 10% to 40%.31 Factors contributing to these disappointing survival rates include failure to define the true extent of the tumor because of inadequate staging techniques, the inclusion of patients with a poor prognosis (patients treated with radiation therapy alone tend to have extensive comorbid disease or poor performance status), and the fact that most patients with high-grade, locally advanced bladder cancers have already developed occult metastases by the time of initial presentation.32

Radical Cystectomy With or Without Neoadjuvant Chemotherapy
Radical cystectomy involves the removal of the bladder, prostate, seminal vesicles, proximal vas deferens, and proximal urethra in men. By contrast, anterior pelvic exenteration involves removing the anterior vaginal wall, the bladder, ovaries, fallopian tubes, and urethra in women. Both of these surgeries are typically performed with a pelvic lymphadenectomy. Ileal conduit, orthotopic neobladder, and continent cutaneous reservoir are all options for urinary diversion. These operations can be performed open, laparoscopically, or with a robotic-assisted laparoscopic approach.

Several large series have evaluated the long-term results of radical cystectomy (Table 2).15,55-57 A series
of 181 patients with pT2 to T4a disease demonstrated a 5-year OS rate of 36%. Stein et al34 published an evaluation of 633 patients with pT2 to T4a disease and reported 5- and 10-year OS rates of 48% and 32%, respectively. For T2, T3a, T3b, and T4a disease, the 10-year recurrence-free survival rates were 87%, 76%, 61%, and 45%, respectively, for node-negative patients and 50%, 37%, 29%, and 33%, respectively, for node-positive patients. Similarly, Madersbacher et al38 found a 5-year recurrence-free survival rate of 73% for pT2N0M0 disease and 56% for disease stages higher than pT2N0M0 compared with 33% for pT1 to T4 node-positive disease. Five-year OS rates for these three groups were 62%, 49%, and 24%, respectively.

The worst recurrence-free and OS rates in patients with higher pathological T stage and node-positive invasive bladder cancer have been attributed to microscopic metastases at the time of surgery. Micrometastatic disease is found in regional lymph nodes in 25% of patients undergoing radical cystectomy. If the tumor has invaded into the perivesicular fat (pT3), that risk increases to 50%.39 Once metastatic disease is identified, median survival is 6 to 9 months. Due to this risk of microscopic disease, neoadjuvant cisplatin-based chemotherapy prior to radical cystectomy was evaluated.

Griffiths et al14 published long-term results of the MRC international randomized trial, BA06 30894, and evaluated 3 cycles of neoadjuvant methotrexate, vinblastine, and cisplatin chemotherapy or no neoadjuvant therapy prior to either surgery or radiation therapy for muscle-invasive urothelial carcinoma. A total of 976 patients were recruited between 1989 and 1995. At a median follow-up of 8 years, the investigators found a statistically significant 16% reduction in the risk of death (hazard ratio [HR], 0.84; 95% confidence interval, 0.72–0.99; \( P = .037 \)) in favor of neoadjuvant treatment. This risk reduction corresponded to an increase in 10-year survival rates from 30% to 36%. A similar trial, SWOG 8710 (INT-0080), was initiated in 1987.15 A total of 317 patients with pT2N0 to T4aN0 bladder cancer were randomized to cystectomy or 3 cycles of MVAC followed by cystectomy. The investigators observed a median survival rate of 46 months in patients treated with surgery alone compared with 77 months for those treated with neoadjuvant MVAC followed by surgery, resulting in a disease-specific HR of 1.66 (\( P = .002 \)) favoring neoadjuvant MVAC. Despite two large randomized trials showing a significant decrease in death due to pT2N0 to T4aN0 urothelial bladder cancer with cisplatin-based neoadjuvant chemotherapy, this approach was not widely adopted. In an evaluation of the Surveillance, Epidemiology, and End Result (SEER) registry, Schrag et al40 found that 11% of the 4,664 patients with stage III disease recorded in the SEER registry between 1991 and 1999 received perioperative chemotherapy. A multi-institutional trial conducted from 2003 to 2008 with 15 participating institutions found that 34% of patients received perioperative chemotherapy; however, 11% received neoadjuvant cisplatin-based chemotherapy as supported by the MRC and SWOG trials.

### Table 2. — Long-term Survival in Selected Studies of Radical Cystectomy and Bladder Preservation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Stage</th>
<th>No. of Patients</th>
<th>Overall Survival (%)</th>
<th>5-yr</th>
<th>10-yr</th>
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<tbody>
<tr>
<td>Stein34</td>
<td>pT2–pT4a</td>
<td>633</td>
<td>48</td>
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<tr>
<td>Dalbagni33</td>
<td>pT2–pT4a</td>
<td>181</td>
<td>36</td>
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<td>Grossman15</td>
<td>cT2–cT4a</td>
<td>307</td>
<td>50</td>
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<td>Bladder Preservation</td>
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<td></td>
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<td>Rödel35</td>
<td>cT2–cT4a</td>
<td>326</td>
<td>45</td>
<td>39</td>
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<tr>
<td>Efstathiou36</td>
<td>cT2–cT4a</td>
<td>348</td>
<td>52</td>
<td>35</td>
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<td>Shipley37</td>
<td>cT2–cT4a</td>
<td>123</td>
<td>49</td>
<td>N/A</td>
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</tbody>
</table>

N/A = not applicable.

### Maximal Transurethral Resection of Bladder Tumor Followed by Concurrent Chemotherapy and Radiotherapy

**Rationale**

The rationale for the addition of chemotherapy to radiation therapy is based on four main premises. First, clinical and autopsy data indicate that micrometastases are often present concurrently with invasive bladder cancer. One study reviewed the autopsies of 367 individuals with invasive bladder cancer and identified distant metastases in 68% of these cases.42 The frequencies of metastases increased with tumor stage (pT2, 36%; pT3a, 45%; pT3b, 69%; and pT4, 79%), supported by the high probability of subsequent distant metastasis after cystectomy or radiation therapy alone of approximately 50% at 2 years.44 Therefore, it is logical to assume that chemotherapy coupled with radiation therapy may reduce the likelihood of distant failure by eradicating occult micrometastatic disease. Second, the optimal time to treat potential micrometastatic cells is during radiation therapy and before the appearance of gross metastatic disease. Third, radiotherapy can induce vascular sclerosis over a period of months to years, thus reducing access of chemotherapeutic agents to tumors at later times.45 Fourth, certain conventional chemotherapy drugs such as 5-fluorouracil (5-FU), cisplatin, gemcitabine, and paclitaxel act as radiosensitizers that render cancer cells more sensitive to radiation therapy.44
Early Experiences

One of the earliest experiences using a combined modality approach occurred during the 1980s. Researchers treated patients with muscle-invasive bladder cancer with maximal TURBT followed by cisplatin and 5-FU chemotherapy concurrently with an accelerated course of radiation therapy.45 Patients received doses of 24 Gy twice daily in 8 treatments over 17 days. Biopsies were performed 6 weeks later. If no residual disease existed, then the patients continued chemoradiation therapy with an additional 8 doses of 20 Gy twice daily. Patients with residual carcinoma following the initial 24-Gy dose subsequently underwent cystectomy. The first 8 patients without residual tumor on repeat cystoscopy with biopsies underwent cystectomy. The pathological complete response in these patients was 100%, thus supporting bladder preservation. The 5-year OS rate in patients who were complete responders with bladder preservation was 63%.45,46 In addition, no difference existed in OS rates in complete responders to chemoradiation therapy with or without cystectomy.

Between 1980 and 1985, Shipley et al47 used a bladder-sparing approach to treat 70 patients with cT2 to cT4a muscle-invasive bladder cancer who were not surgical candidates. Patients received cisplatin chemotherapy concurrently with split-course radiation therapy using fields based on each patient’s bony anatomy rather than bladder plus nodal anatomy or bladder anatomy alone. Cystoscopy, cytology, and rebiopsy were performed 2 to 3 weeks into the treatment break to direct further therapy. Patients in whom repeat biopsy revealed persistent tumor invasion into or beyond the lamina propria (≥ T1 disease) underwent radical cystectomy, whereas patients who had T0 or Ta disease underwent consolidation therapy consisting of an additional dose of cisplatin and radiotherapy to the tumor using a 2.0- to 2.5-cm margin to the block edge to a total dose of 64.8 Gy. Normal areas of the bladder were excluded from the high-dose volume for the 25.2 Gy radiotherapy boost. In the 62 patients who completed the full course of induction and consolidation chemoradiation therapy, the complete response rate was 77%. Among the complete responders, the 4-year OS rate was 57%.

In another study, German patients were treated with radiation therapy and, after 1986, chemoradiation therapy.48 A total of 415 patients were treated with a radiation dose of 54 Gy. Those who had a cystoscopic complete response were observed while those who did not underwent salvage radical cystectomy. The clinical complete response rate was approximately 85% in patients receiving chemoradiation therapy. The 5-year OS rate in patients concurrently treated with cisplatin-based chemotherapy and radiation therapy was approximately 63%. The European and American experiences helped to define the current multimodality approach of maximal TURBT followed by cisplatin-based chemotherapy concurrently with radiation therapy.47,48

Modern Approaches

Although radical cystectomy remains the standard of care for muscle-invasive urothelial cancers, many patients are not candidates for curative surgery due to advanced age, poor nutrition, multiple comorbidities, or loss of cognitive function. In addition, some patients refuse to undergo surgery and instead opt for a bladder-sparing approach. Although bladder preservation strategies have often been perceived to result in inferior survival compared with radical cystectomy, no randomized trials support this bias. Five-year DFS rates of 61% to 71% have been achieved in appropriately selected patients who retain their bladders with modern bladder preservation approaches.

In general, patients with a solitary, clinical T2 to T4a transitional cell carcinoma smaller than 5 cm, with a Zubrod performance status of 0 to 1, a visibly and microscopically complete TURBT, absence of ureteral obstruction, and negative nodes (patients with radiographically positive nodes should have negative nodes by needle biopsy) are eligible for bladder preservation.49 Moreover, patients should have no associated carcinoma in situ, have a normally functioning bladder, and be amenable to lifelong bladder surveillance with prompt salvage cystectomy if local recurrence is present.31 The completeness of the TURBT is one of the strongest prognostic factors for OS.50 Patients with hydronephrosis, distant metastases, white blood cell counts below 4,000, absolute neutrophil counts below 1,800, hemoglobin levels below 10.0, platelet counts below 100,000, creatinine clearances below 60 mL/minute, serum creatinine levels above 1.5, serum bilirubin levels above 2.0 mg, or a history of prior pelvic radiotherapy are suboptimal candidates for a bladder-sparing treatment approach. Ideal candidates for bladder-sparing chemoradiotherapy are summarized in Table 3.

Table 3. — Ideal Candidates for Trimodality Bladder Preservation

| American Joint Committee on Cancer tumor stage T2–T3a, N0, M0 |
|——|——|
| No hydronephrosis or disease near ureteral orifices |
| No involvement of bladder trigone |
| Unifocal disease, absence of extensive invasive tumor-associated |
| Tis stage |
| Status post visibly and microscopically complete transurethral resection of the bladder tumor |
| Zubrod performance status ≤ 1 |
| No contraindications to concurrent chemotherapy |
| Good pretreatment bladder capacity and function |
| Understanding and acceptance by the patient regarding lifelong bladder surveillance with prompt salvage cystectomy if local recurrence is detected |
| No prior pelvic radiotherapy |
To keep radiotherapy field sizes as small as possible, patients should be simulated and treated to the whole bladder plus pelvic nodes or the whole bladder alone to between 39.6 Gy in 22 fractions and 50.4 Gy in 28 fractions with the bladder empty. The rectum should also be empty during simulation to maximize reproducibility of rectal volumes during treatment. Chemotherapy (eg, cisplatin on weeks 1 and 4) is given concurrently as a radiosensitizer with ≥ 10 MV external beam radiotherapy. In patients with low or moderate renal function, 5-FU and mitomycin C or paclitaxel chemotherapy can be used in place of cisplatin. In general, patients should be treated with four, not two, radiotherapy fields if three-dimensional conformal radiation therapy (3D-CRT) is used. Intensity-modulated radiation therapy (IMRT) reduces the radiation dose delivered to adjacent normal organs such as the rectum relative to 3D-CRT. With IMRT, the bladder with or without adjacent lymph nodes (initial clinical target volume) can be contoured on a treatment-planning computed tomographic scan and used instead of bony anatomy to determine radiotherapy field borders. A 2.0- to 2.5-cm margin is created in all directions on the initial clinical target volume for the initial planning target volume. A 0.5- to 0.7-cm margin beyond the planning target volume is added for penumbra. Patients should be treated to a cumulative radiation dose between 63.0 Gy in 35 fractions and 66.6 Gy in 37 fractions. The more recent use of continuous-course chemoradiation seen in Radiation Therapy Oncology Group (RTOG) protocol 05-24, rather than the more traditional split-course chemoradiation, may help improve outcomes by not providing tumor cells with the time to repopulate during a planned treatment break.

Close coordination among all specialties is required to achieve optimal results with bladder preservation. Radiotherapy predominantly causes genitourinary (eg, urinary frequency, burning) and gastrointestinal (eg, diarrhea) acute toxicity, and cisplatin-based chemotherapy mainly causes hematological (eg, neutropenia, anemia, thrombocytopenia), gastrointestinal (eg, nausea, vomiting), and neurological (eg, paresthesias, sensory ataxia, loss of vibration sense) acute toxicity.

The incidence of significant late pelvic toxicity with a bladder-sparing approach is low. On RTOG protocols 89-03, 95-06, 97-06, and 99-06, the incidence of late grade 3 genitourinary and gastrointestinal toxicities was 6% and 2%, respectively, based on a median follow-up of 5 years (range, 2 to 13 years). Late grade 3 toxicity persisted in 1 of the 9 patients. No patients experienced late grade 4 or 5 toxicity. None of the clinical variables studied predicted for late toxicity. QOL and quality of bladder function were satisfactory in 67% of patients who underwent bladder preservation.

Results
During the past two decades, bladder preservation has been investigated in prospective series from single centers and cooperative groups, with more than 1,000 patients with transitional cell carcinoma provided with treatment. Complete response rates have ranged from 47% to 87%, and 5-year OS rates have ranged from 30% to 70%. Three- to 5-year survival rates with an intact bladder have ranged from 37% to 66%. Level 2 evidence suggests that the outcomes with chemoradiation may be better than those with external beam radiotherapy alone, realizing that selection bias may play a role in these findings.

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Controversies Regarding Primary Treatment of Muscle-Invasive Urothelial Carcinoma of the Bladder
Radical cystectomy remains the standard of care in the United States for the primary treatment of muscle-invasive urothelial bladder cancer in patients who are medically operable. However, prospective results from multi-institutional bladder preservation trials suggest that this is also a reasonable approach. Table 3 shows equivalent long-term survival with radical cystectomy compared with bladder preservation. When comparing studies of each approach, there are two main caveats. First, surgical series involve pathologically staged tumors as opposed to clinically staged tumors in the chemoradiation trials, favoring the surgical series because many cancers are upstaged at the time of surgery. Second, retrospective radical cystectomy series do not report an intent-to-treat analysis, which is in contrast to prospective chemoradiation trials. Randomized trials comparing these two treatments are unlikely to be forthcoming in the near future and are based, in part, on physician biases.

Inappropriate surgical candidates include patients who have poor nutrition, high anesthesia risk, multiple comorbidities, and loss of cognitive function. However, age alone should not necessarily rule out surgery because the rates of major and minor surgical complications are no different in patients with bladder cancer who are 80 years of age compared with those who are younger. Treatment decisions should be based on patient preferences and an understanding of the QOL issues associated with each treatment modality.

Quality of Life
For patients undergoing radical cystectomy, three sur-
gical urinary reconstructions have been developed to eliminate urine. Typically, the preferred method is to construct an orthotopic neobladder. In this procedure, a neobladder is created from the small bowel and subsequently connected to the ureters and urethra in an attempt to maintain continence via the urethra. Urination is performed similarly to an intact bladder, although catheterization of the urethra is sometimes necessary for emptying. A second approach is an ileal conduit (urostomy) in which the bladder is removed.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Phase (No. of Patients)</th>
<th>Clinical Tumor Stage</th>
<th>RT and CT Following Maximal TURBT</th>
<th>Outcomes</th>
<th>Median Follow-up (mos)</th>
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<tbody>
<tr>
<td>Shipley47</td>
<td>II (70)</td>
<td>T2–T4</td>
<td>64.8 Gy 45 Gy pelvis plus 19.8 Gy boost plus cisplatin</td>
<td>CR: 70% 4-yr OS: 35% 4-yr OS advantage for CR: 57% vs 11%; P &lt; .01 73% bladder preservation</td>
<td>24</td>
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<tr>
<td>Tester58</td>
<td>II (42)</td>
<td>T2–T4</td>
<td>64 Gy (40 Gy pelvic field; if CR: 24 Gy boost) plus cisplatin on weeks 1 and 3</td>
<td>CR: 67% 3-yr OS: 64% 40% bladder preservation with CR 12% bladder preservation with superficial recurrence treated with TURBT + Bacillus-Calmette-Guérin 26% cystectomy rate</td>
<td>36</td>
</tr>
<tr>
<td>Coppin27</td>
<td>III (99)</td>
<td>T2–T4b</td>
<td>60 Gy (40 Gy pelvis plus 20 Gy tumor boost) with or without cisplatin on weeks 1, 3, and 5</td>
<td>CR: 47% (CRT) vs 31% (RT); P = .16 3-yr OS: 47% (CRT) vs 33% (RT); P = .34 Better pelvic PFS with CRT (P = .038) At 5 yrs, 7/8 CRT patients with CRT had intact bladder vs 3/7 RT patients (P = .2)</td>
<td>78</td>
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<tr>
<td>Chauvet55</td>
<td>II (109)</td>
<td>T2–T4</td>
<td>60 Gy (40 Gy pelvic field plus 20 Gy tumor boost) with or without cisplatin on weeks 1 and 5</td>
<td>CR: 65% 4-yr survival: 41.9% for all patients, 51.4% for CR patients 4-yr locoregional control rate: 47.6% for all patients, 61.2% for patients with CR 4-yr survival with intact bladder: 37%</td>
<td>55</td>
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<tr>
<td>Kaufman60</td>
<td>I/II (34)</td>
<td>T2–T4a</td>
<td>24 Gy in 3 Gy fx twice daily on days 1, 3, 15, and 17 to pelvis plus 5-FU/cisplatin If CR: additional 20 Gy in 2.5 Gy fx twice daily boost with 5-FU/cisplatin on weeks 1 and 3; higher biologically effective dose overall</td>
<td>CR: 67% 3-yr OS: 83% 3-yr survival with intact bladder: 66%</td>
<td>29</td>
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<tr>
<td>Hagan54</td>
<td>I/II (52)</td>
<td>T2–T4a</td>
<td>64.8 Gy (44 Gy to pelvis twice daily; if CR: additional 24 Gy) RT with cisplatin weeks 1–3, followed by adjuvant methotrexate, cisplatin and vinblastine for 3 cycles</td>
<td>CR: 74% 3-yr OS: 61% 3-yr survival with intact bladder: 48% 20% acute grade 3 and 4 toxicity with induction CRT</td>
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<td>Gogna57</td>
<td>II (113)</td>
<td>T2–T4</td>
<td>63–64 Gy RT and weekly cisplatin</td>
<td>CR: 70% 5-yr OS: 50% Salvage cystectomy: 13% Survival with intact bladder: 61%</td>
<td>60</td>
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<td>Kaufman61</td>
<td>I/II (50)</td>
<td>T2–T4a</td>
<td>64.3 Gy RT (40 Gy days 1–5, 8–17 twice daily) with weekly cisplatin plus paclitaxel If CR: additional 24 Gy with weekly cisplatin plus paclitaxel, followed by adjuvant gemcitabine and cisplatin</td>
<td>CR: 87% 5-yr OS: 56% 5-year disease-specific survival: 71% 26% acute grades 3 and 4 toxicity with induction chemoradiation</td>
<td>49</td>
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<tr>
<td>James30</td>
<td>III, 2 × 2 factorial (360)</td>
<td>T2–T4</td>
<td>55 Gy in 20 treatments vs 64 Gy in 32 treatments with (n = 178) or without (n = 182) 5-FU and mitomycin C</td>
<td>RT alone vs CRT: 5-yr OS: 35% vs 48% 2-yr bladder preservation: 83% vs 89% 2-year locoregional relapse-free survival: 68% vs 82%</td>
<td>69.9</td>
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</table>

5-FU = 5-fluorouracil, CR = complete response, CRT = conformal radiation therapy, CT = computed tomography, fx = fractions, OS = overall survival, PFS = progression-free survival, RT = radiation therapy, TURBT = transurethral resection of the bladder tumor.
or bypassed and a conduit is constructed of small bowel or colon that carries urine to an opening on the abdominal wall. The urine is collected in a drainable pouch secured to the abdomen. A third approach involves a continent urinary diversion. This reconstruction involves the creation of an internal pouch from loops of the intestine connected to the abdominal wall. There is a “one-way” passage between the opening on the abdominal wall (stoma) and the internal pouch so that urine is contained within the pouch. Urine is drained by passing a catheter through the stoma and into the pouch every 3 to 4 hours.

Several QOL studies have evaluated these reconstructive methods. A study in Japan assessed 85 patients following radical cystectomy, 48 with an orthotopic neobladder (26 with an ileal neobladder and 22 with a colon neobladder) and 37 with an ileal conduit. QOL was evaluated using the Short Form-36 survey that contains 36 questions assessing physical functioning, role-physical functioning, bodily pain, general health, vitality, social functioning, role-emotional functioning, and mental health. No significant difference existed in any scale scores between the neobladder and ileal conduit groups. However, general health and social functioning in both the neobladder and ileal conduit groups were significantly lower than those in the United States general population. Another study evaluated QOL in 49 neobladder and 23 ileal conduit patients. The researchers found on multivariate analysis that no significant difference was present in QOL between the two groups \((P = .09)\). A third study evaluated 224 patients following radical cystectomy and also found no difference regarding the type of diversion used.

In addition to urinary function, erectile function is a major concern following radical cystectomy. One study evaluated 49 sexually active men who underwent radical cystectomy; 33% of those had undergone a nerve-sparing procedure. With a median follow-up of 47 months, the mean sexual health inventory scores decreased from 22 to 4 \((P < .05)\), with 86% of men unable to perform vaginal penetration. This is supported by a Swedish cross-sectional comparison study that found 13% of patients receiving radical cystectomy had intercourse in the previous month compared with 38% of patients receiving chemoradiation therapy. In an Italian series, 8% of patients who underwent radical cystectomy had erectile function. This is in contrast to a Massachusetts QOL study of chemoradiation therapy that revealed that 8% of men reported dissatisfaction with their sex lives and 50% of men had normal erectile function.

**Toxicity**

A surgical series involving 1,142 patients reported that 64% of patients had more than one complication in the 90 days following surgery. Of those patients, 13% had major complications (grades 3 to 5). In addition, the readmission rate was 26% with a 90-day mortality of 2%. The perioperative morbidity and mortality rates of salvage cystectomy after previous bladder chemoradiation therapy were no different from primary cystectomy.

A major criticism of maximal TURBT followed by chemoradiation therapy is that the preserved bladder ultimately becomes a poorly functioning bladder. However, a group in Massachusetts published results of QOL and urodynamic studies on 71 patients with intact bladders after chemoradiation therapy. With a median follow-up of 6.3 years, they found that 75% of patients had normally functioning bladders based on urodynamic studies, and 85% reported no urgency or occasional urgency. In addition, 22% had a reduced bladder capacity, with 7 of the patients reporting significant symptoms. Efthathiou et al published late pelvic toxicity from 157 prospectively followed patients from an RTOG protocol after bladder preservation treatment with a median follow-up of 5.2 years. They reported a 6% grade 3 or higher genitourinary system toxicity. This report is consistent with findings by Weiss et al who found that 4% of patients were dissatisfied with their bladder function following chemoradiation therapy. In addition, Rödel et al reported that 2% of patients experienced unacceptable bladder toxicity requiring palliative cystectomy. Ultimately, patient preference should drive modality selection.

**Future Directions of Chemoradiation Therapy**

**Altered Fractionation**

In an effort to improve on the 67% likelihood of having a bladder free of invasive tumor that functions well at an initial evaluation following 3 months of treatment, the RTOG protocol 07-12 studied the use of maximal TURBT followed by concurrent cisplatin-based chemotherapy with twice-daily radiation treatment, also known as hyperfractionation. Regional lymph nodes were excluded from the radiotherapy fields. Complete response rates were reported above 85%. However, longer follow-up is necessary. In a randomized trial comparing chemoradiation vs radiation alone, two fractionation schemes were administered: 55 Gy in 20 fractions (39%) and the more standard regimen of 64 Gy in 32 fractions (61%). The researchers found no differences in the HR for locoregional DFS between the two groups.

**Lipiodol for Image-Guided Radiation Therapy**

Technological advances in radiotherapy over the past decade lend themselves to a bladder-sparing approach. For example, image-guided radiation therapy (IGRT) can more accurately target tumors in organs that move, especially the bladder. Approximately three to four radio-opaque gold markers can be im-
planted in the bladder wall surrounding the tumor using a rigid cystoscope during TURBT and then used for online image tracking during radiation therapy to account for tumor movement. Disadvantages of this approach are that it can be painful, and approximately one-half of the markers can fall out during radiotherapy. Alternatively, 0.3 to 0.4 cc of the contrast agent lipiodol can be injected three to five times under the urothelium of the bladder wall around the tumor at the time of TURBT using a flexible cystoscope. Use of more than 0.4 cc of lipiodol per injection can result in diffusion of the contrast outward through the bladder wall, making it difficult to precisely define the tumor bed. With IGRT, the patient is prepared for radiotherapy each day based on the location of the fiducial markers on orthogonal radiography or cone-beam computed tomography. The bladder moves based on factors such as urine filling and bowel distention. By allowing a therapist to set up the patient based on the location of the tumor rather than bony anatomy, lipiodol-based IGRT significantly improves treatment accuracy while decreasing the dose delivered to adjacent normal tissues (Fig 1). Lipiodol also allows for the use of smaller tumor margins of 0.6 to
1.0 cm rather than 2.0 to 2.5 cm during the boost, and washout of lipiodol is minimal during IGRT.77

Intra-Arterial Chemotherapy, HER2/Neu, and Epidermal Growth Factor Receptor

Several novel agents are being evaluated for use in combination with radiation therapy. Azuma et al79 reported a prospective, nonrandomized, single-institutional study of 192 cT2 to cT4, N0 to N1 patients who initially underwent maximal TURBT. Of these patients, 96 then underwent radical cystectomy. If radical cystectomy was not feasible or if patients refused radical cystectomy, they underwent balloon-occluded arterial infusion of cisplatin chemotherapy with concomitant hemodialysis and radiation therapy (referred to as the OMC regimen; n = 96). Arms were unequal in that the patients receiving the OMC regimen had more high-grade tumors (P = .004), worse performance status (P = .03), more T4 tumors (16.7% vs 0%), and a higher prevalence of node-positive disease (10% vs 0%). Despite these selection biases, the 5- and 15-year OS rates favored the chemoradiation therapy arm at 91% and 81% vs 60% and 40%, respectively (P < .001). No grade 3 or higher toxicity was reported. However, these results require further investigation to determine whether they can be reproduced in a multi-institutional setting.

Biological agents such as trastuzumab are currently under investigation for use with radiation therapy. Chakravarti et al80 reported on a pathological evaluation of four bladder-sparing RTOG protocols. They described a significant correlation between HER2/neu overexpression and decreased complete response rates. This finding led to the development of the ongoing RTOG trial 05-24. In this phase II study, patients who overexpressed HER2/neu were treated with trastuzumab and concomitant paclitaxel. Nguyen et al81 demonstrated that tumor overexpression of epidermal growth factor receptor was associated with worse clinical outcomes. Cell culture studies have revealed that cetuximab, an epidermal growth factor receptor inhibitor, is limited in its ability to halt growth of bladder cancer cells.82 However, despite this in vitro data, phase II studies of cetuximab and radiation therapy for locally advanced disease and as monotherapy for stage I disease are currently underway.

Conclusions

Although no randomized trials exist that compare radical cystectomy with maximal transurethral resection of the bladder tumor followed by chemoradiation therapy, the 5- and 10-year OS rates are comparable, even though undergoing cystectomy and those undergoing chemoradiation therapy were pathologically and clinically staged, respectively. Bladder-sparing therapy helps to achieve a disease-free survival rate and preserves a functional bladder in approximately two-thirds of patients. In addition, quality-of-life studies demonstrate that the bladder functions well, and sexual function is also favorable with bladder preservation. The incidence of grade 3 or higher toxicity is low with a bladder-sparing approach. Furthermore, the incidence of radical cystectomy performed for palliation of treatment-related toxicity has been low, and the morbidity of salvage cystectomy may be comparable with primary cystectomy. Selective bladder-sparing therapy represents an opportunity for radiation oncologists, urological surgeons, and medical oncologists to work together to equally contribute to the quality of life for patients with bladder cancer. Surgical techniques continue to evolve, and the optimal combination of systemic therapy and radiotherapy continues to be investigated.

References


