ARS Appropriate Use Criteria

Radiation Therapy for Muscle-Invasive Lymph Node-Negative Bladder Cancer

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Methodology

A systematic literature review using the PubMed (Medline) and Embase (Elsevier) databases was completed between January 18, 2019 to March 18, 2019 per the Preferred Reporting Items for Systematic

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Reviews and Meta-Analyses (PRISMA) declaration\(^1\). The search strategy was developed based on National Library of Medicine\(^\text{®}\) Medical Subject Headings (MeSH\(^\text{®}\)) with addition of subject-specific keywords. References were sequentially screened by title, abstract, and full text for relevance. Articles included for full review were assessed for quality according to relevance, study design, sample size, generalizability of endpoints, follow-up time, and assessment protocols. Up to three additional references were included for review at the discretion of the senior authors. An expert panel consisting of 14 radiation oncologists, one medical oncologist, and one urologist from 14 US institutions was assembled. After reviewing available evidence, key clinical questions were addressed utilizing a modified Delphi consensus framework\(^2\).

**Summary of Literature Review**

**Introduction/Background**

An estimated 80,470 Americans were diagnosed with bladder cancer in 2019, associated with 17,670 deaths \(^3\). Approximately 25% of bladder cancers are muscle-invasive (MIBC) at diagnosis, for which radical cystectomy (RC) is the most common treatment in the United States\(^4\)-\(^6\). RC results in 5-year recurrence-free and overall survival of 53-89% and 44-77%, respectively. However, surgery can be associated with peri-operative risks in addition to severe urinary, gastrointestinal, and sexual dysfunction that may lead to poor quality of life \(^7\),\(^8\). Radiation therapy (RT), with concurrent chemotherapy when possible, commonly referred to as bladder preservation or conservation (BP), is an established treatment for patients who are medically unfit for RC or who seek a non-surgical alternative\(^9\),\(^10\). For well-selected patients who are operative candidates, BP preserves function and may result in similar oncologic outcomes as compared to RC. However, the only contemporary randomized trial attempting to compare outcomes between RC and RT failed to accrue\(^11\). Here, we present a systematic review of the appropriate use of RT in the management of MIBC using the Preferred Reporting of Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline\(^1\). This guideline will focus on lymph node-negative MIBC, as there is a paucity of clinical data regarding the use of definitive-intent radiotherapy in patients with node-positive MIBC. For patients with node-positive MIBC, we strongly encourage clinical trial participation, as available, to help address this evidence gap. In this regard, a large prospective North American cooperative group trial ECOG/NRG 8185 is currently in development.

**Clinical Condition: Patients with MIBC who are operative candidates.**

**Subtopic 1: Who can be offered bladder preservation therapy?**

Appropriate patient selection is paramount for bladder preservation. For patients who are deemed medically fit for cystectomy but desire BP, multimodality treatment consisting of maximal trans-urethral resection of bladder tumor (TURBT), followed by concurrent chemotherapy and radiation therapy (CCRT), has been the most commonly studied approach\(^9\),\(^10\),\(^12\),\(^13\). Close coordination by an experienced multi-disciplinary team is strongly recommended. Clinical outcomes for operable patients in community practices appear comparable to the outcomes on RTOG protocols and in centers of expertise \(^14\), supporting BP as a feasible treatment strategy for patients in multi-disciplinary community practices that use appropriate techniques and abide by national treatment guidelines.

Nearly all studies reviewed included patients with cT2-T4 cN0 cM0 disease (see Evidence Table). Some series included node-positive patients\(^15\)-\(^21\), but most contemporary trials have excluded clinically- or pathologically-confirmed lymph node metastases \(^22\)-\(^25\). There are no published studies comparing the effectiveness of RT versus lymphadenectomy for patients with grossly-involved nodes.
Patients who are otherwise fit for RC should ideally be candidates for chemotherapy as a part of BP. Numerous phase II and phase III prospective trials have demonstrated superior local control (LC), disease free survival (DFS), and overall survival (OS) following CCRT when compared to historical series of RT monotherapy. While radical RT alone demonstrated 5-year overall survival (OS-5y) ranging from 16% - 28% 15,26–30, combined chemotherapy regimens have resulted in notably better survival, ranging from 52% -74% 16,25,31–34. A randomized, phase 3 trial demonstrated that concurrent cisplatin and RT improved locoregional control over RT alone: pelvic failure rates were 29% and 52% (p=0.036) with and without concurrent cisplatin, respectively 19. This trial only accrued 99 out of a planned 160 patients and the numerical improvement in OS-3y (47% vs. 33%) was not statistically significant. BC2001 was another randomized, phase 3 trial that included 360 mostly operable patients with cT2-4aN0 MIBC. This multicenter study showed that the addition of concurrent 5-FU and mitomycin C improved DFS at 2 years (67% vs. 54%, p=0.03), and salvage cystectomy rate (11.4% vs. 16.8%, p=0.07). Again, there was a non-statistically significant improvement in OS at 2 years: 48% vs. 35% (p=0.16).

Patients should undergo an attempted maximally complete TURBT, defined as no visible tumor on cystoscopy and negative urine cytology. In a large, prospective CCRT cohort from Germany, Rodel and colleagues found that OS-5y for R0, R1, and R2 status after initial TURBT was 76%, 52%, and 34%, respectively (p=0.003) 35. Further, complete response (CR) after CCRT—which was the strongest prognostic factor for both DFS and OS—was 90%, 77%, and 54% in these groups respectively (p=0.002). Similarly, in a combined analysis of the BP experience at the Massachusetts General Hospital (MGH), extent of TURBT was prognostic for both OS (p=0.003) and disease-specific survival (p=0.03). Salvage cystectomy was required in 22% of patients who underwent a complete TURBT, as compared to 42% who had incomplete TURBT (p<0.001) 36. Among patients with MIBC treated with radical RT alone at the MD Anderson Cancer Center (MDACC), complete TURBT was prognostic for distant metastasis-free survival (DMS, p=0.02), OS (p=0.0008), and clinical CR (p=0.004) 28. In the Trans-Tasman Radiation Oncology Group (TROG) trials, patients with maximal or complete TURBT had a LC-5 of 44-53%, compared to 18% for patients with partial TURBT (p=0.12); though not statistically significant, it should be noted that the TROG patient cohort was significantly smaller to the University of Erlangen and MGH cohorts 32.

Ureteral obstruction leading to hydronephrosis may be a negative prognostic factor for outcomes after BP. In the MGH cohort, the presence of hydronephrosis was associated with decreased CR rate (68% vs. 37%, p=0.002) 37. With longer follow up, hydronephrosis was also associated with a 79% increased risk of death (p<0.001) and two-fold increased risk of disease specific mortality (p=0.001) 38. Hydronephrosis was not significantly associated with either outcome after adjusting for other prognostic covariates such as T-stage, however. The MDACC radical RT series showed that hydronephrosis was prognostic of clinical CR (p=0.02), but not of OS (p=0.18) 28. Hydronephrosis became an exclusion criteria in the RTOG studies after 1993, but was permitted in most subsequent European and Australasian studies 17,32.

There is weak evidence to suggest that multifocal disease portends poor outcomes after BP. Rodel reported that multifocal disease was prognostic of lower rates of local control (52% vs. 39%, p=0.08) 35. However, multifocality was not associated with CR, DMS, or OS.

The significance of carcinoma-in-situ (CIS) is also uncertain, though CIS is an exclusion criterion in many trials. In the MDACC radical RT series, the presence of CIS was associated with a 52% and 57% increased hazard of OS and LC, respectively 15. However, CIS was not shown to impact outcomes in the MGH or German experiences, in which patients received concurrent chemotherapy 35,36.

Hydronephrosis, multi-focal disease, CIS as well as tumor size and T-stage are interrelated and are likely proxies for the underlying cancer biology. As such, these covariates also negatively impact outcomes after RC 4–6. When multiple risk factors suggest a high likelihood of local failure after MMT, neoadjuvant chemotherapy with immediate RC may be more appropriate for surgical candidates.

Patient-specific factors are also important in the selection process for BP in operable candidates. As RT to the whole bladder is known to alter bladder function 38, candidates for organ preservation should
Subtopic 2: What are the optimal neoadjuvant, concurrent, or adjuvant chemotherapy options?

CCRT is the most widely adopted regimen for BP. Cisplatin has been the most commonly used agent in North American, Australasian, and German studies. Typical regimens using cisplatin alone consist of 100 mg/m² every 3 weeks or 35-40 mg/m² weekly during RT. Because many patients with MIBC are ineligible for cisplatin due to poor renal function, non-platinum CCRT regimens have been explored. BC2001 used combined 5-FU and mitomycin-C as part of their CCRT regimen. More recent RTOG trials have employed combinations of cisplatin with either paclitaxel or 5-FU for CCRT. Outcomes for these regimens are comparable, with CR rates of approximately 70%. Two prospective trials showed that paclitaxel-based CCRT resulted in a CR rate of 48 to 65%. In the University of Erlangen study, carboplatin was used for patients who were ineligible to receive cisplatin. With the caveat of confounding factors, carboplatin CCRT produced inferior CR and OS rates as compared to cisplatin CCRT: 66% vs. 82% (p=0.001) and 45% vs. 62% (p<0.001), respectively.

More recently, gemcitabine-based CCRT has resulted in even higher CR rates, reaching up to 93%. Given encouraging activity, several trials compare gemcitabine- to cisplatin-based CCRT regimens. RTOG 0712 was a randomized phase 2, multicenter study that evaluated concurrent CCRT with either 5-FU/Cisplatin or low-dose gemcitabine. The rates of CR were 88% and 78%, respectively. DMS at 3 years was 78% and 84%, respectively. The ongoing phase 2 trial GETUG V04 will also compare these agents as part of multiagent CCRT.

Neoadjuvant chemotherapy prior to RT for BP has been explored in two randomized trials. BA-06 randomized patients to neoadjuvant methotrexate, cisplatin, and vinblastine (MCV) followed by radical local therapy (RT or cystectomy) versus radical local therapy alone. Importantly, CCRT was not used. Neoadjuvant MCV was shown to improve OS at 5 years by 6% (39% vs. 43%, p=0.037). RTOG 8903 compared neoadjuvant MCV followed by cisplatin-based CCRT versus CCRT alone. There were no significant differences in CR, OS, DM, or BP rates. This trial closed early, however, due to high rates of neutropenia and sepsis leading to three treatment-related deaths. The high rates of MCV-related toxicity recapitulated results of an earlier phase 2 study, in which there were four sepsis-related deaths during neoadjuvant treatment.

There are important caveats related to interpretation of the toxicity results of RTOG 8903. The initial eligibility criteria included patients with 24-hr creatinine clearance as low as 50 mL/min and serum creatinine up to 2.0 mg/dL. After significant toxicity with neutropenia and sepsis was observed, the protocol was modified to adjust these eligibility criteria to 60 mL/min and 1.7 mg/dL, respectively. Following this modification, no further toxicity was seen in subsequent patients. Moreover, despite these changes in eligibility criteria, patients were also treated with cisplatin 100 mg/m² x 3 cycles concurrently with pelvic RT. Treatment-related toxicities may have been mitigated if patients with impaired renal function had not been treated with cisplatin-based neoadjuvant chemotherapy and subsequent cisplatin-based CCRT.

Further, several retrospective reports have indicated the safety of neoadjuvant chemotherapy regimens, followed by CCRT, with excellent outcomes: CR, OS, and cancer-specific survival (CSS) rates range from 73-86%, 68-72%, and 76-79%, respectively. Neoadjuvant chemotherapy is thus considered
standard in the UK, where National Institute for Health and Care Excellence recommends that all patients with MIBC should be offered neoadjuvant chemotherapy, regardless of the modality of local treatment. This approach is also used in some centers in North America.

The benefit of adjuvant chemotherapy therapy is unclear, and to date there are no published randomized trials comparing CCRT with and without adjuvant chemotherapy. RTOG 9706, a non-randomized phase I/II trial, included 3 cycles of adjuvant MCV resulting in an OS and local recurrence (LR) at 3 years of 83% and 45%, respectively. RTOG 9906 included adjuvant gemcitabine and cisplatin in a phase 2 trial that resulted in OS and CSS at 5 years of 56% and 71%, respectively. This regimen was tolerable with 46% and 26% grade 3 and 4 toxicities during adjuvant chemotherapy, respectively. RTOG 0233 added adjuvant gemcitabine, cisplatin, and paclitaxel after CCRT. This regimen resulted in OS at 5 years of >70%, with more than 75% of patients experiencing Grade 3 or 4 toxicities during the adjuvant chemotherapy phase.

Subtopic 3: What radiation dose and fractionation is most appropriate?

RT can be delivered as a continuous course or split course, the latter allowing for response assessment in patients who would be medically fit for immediate salvage radical cystectomy in case of an incomplete response to RT. For operable patients who refuse response-adapted cystectomy, continuous course radiotherapy is acceptable and recommended. In the largest series using continuous course, RT was delivered to a maximum dose of 55.8 to 65 Gy in 1.8 to 2.0 Gy daily fractions to the whole bladder or tumor, with the majority of patients receiving at least 63 Gy. Outcomes are not clearly better with higher dose: in one series where patients received less than 60Gy, the CR rate was 88.4% whereas CR was 70% in a separate series in which patients received 63-64 Gy. Nonetheless, these results are confounded by differences in patient selection, chemotherapy regimens and small overall differences in prescribed radiation dose.

Split-course treatment has the advantage of response-adapted, immediate salvage cystectomy before completion of a definitive course of radiation therapy. This can be advantageous given the increased morbidity with cystectomy performed after high dose pelvic RT. Additionally, CR after RT is a strong predictor of overall survival, and early salvage for patients without CR after induction RT may be beneficial. In the MGH selective bladder sparing protocol, 39.6 Gy was delivered in 1.8 Gy fractions to the entire pelvis, with a planned break to evaluate for response, followed by an additional 25.2 Gy to the tumor plus margin for complete responders.

A potential disadvantage to split-course RT is that the prolonged total treatment time can result in decreased biological effectiveness. In a large retrospective Dutch study, there was a trend towards inferior locoregional control with longer total treatment times (47% for greater than 75 days versus 63% for less than 75 days, p=0.08). There was no difference in OS. Maciewjewski and colleagues generated a statistical model based upon clinical data that predicted a LC probability of 50% if a total of 63.3 Gy were delivered within 40 days versus only 5% if the same were delivered in 55 days. The authors suggested increasing the total dose by 0.36 Gy for every incremental treatment day beyond 40 days. These two studies examined RT alone; it is unknown whether time effects remain relevant with the addition of systemic therapy. On RTOG protocols with concurrent chemoRT and mandated treatment break of several weeks for cystoscopic assessment, patients had dramatically higher LC rates, suggesting that systemic therapy may compensate for a protracted treatment course.

Altered fractionation has been incorporated into various bladder preservation regimens. Hypofractionation increases convenience and can potentially enhance tumor control by increasing the fractional dose and/or decreasing the overall treatment time. In BC2001, patients were treated with a continuous course of 64 Gy in 2 Gy fractions or a hypofractionated course of 55 Gy in 2.75 Gy fractions, at the discretion of the treating physician. While outcomes between these two RT regimens were not directly compared, the added benefit of concurrent chemotherapy was not different between these two
fractionation schedules (p=0.59). Patients received similar, hypofractionated regimens in two other phase 2 trials. Fifty-five Gy in 2.75 Gy per fraction is a preferred fractionation scheme in UK centers.

Hyperfractionation can potentially overcome treatment failures as a result of accelerated repopulation. Housset and colleagues first proposed a split-course, hyperfractionated regimen of 24 Gy in 3 Gy, twice-daily (BID) fractions (every other day at the beginning of weeks 1 and 3), followed by consolidation treatment for complete responders of 20 Gy in 2.5 Gy, BID fractions (every other day at the beginning of weeks 9 and 11). 5-FU and cisplatin were given concurrently. CR was achieved in 74% of patients. OS at 3 years was 59% and not significantly different between patients who underwent cystectomy compared to consolidation CCRT. A modified version of this regimen was adopted in RTOG 9506, resulting in a 67% CR rate and OS at 3 years of 83%. The regimen was accelerated by using a concomitant BID boost to the bladder field during induction in RTOG 9706, resulting in a 74% CR rate and OS at 3 years of 61%. This accelerated, hyperfractionated regimen with concomitant boost was further refined in RTOG 9906, RTOG 0233, and RTOG 0712, resulting in a total of 44.8 Gy to the pelvis and 64.3 Gy to the tumor. RTOG 0712 compared this accelerated, hyperfractionated regimen (with concurrent cisplatin and 5-FU) to a standard fractionation regimen to 64 Gy (with concurrent gemcitabine). Early results of this trial indicate comparable efficacy of both regimen, with 3-year DMS rates of 78% and 84%, respectively, but fewer toxicities in the daily RT and gemcitabine arm. Logistically, BID treatment is challenging for many patients and cancer centers, and most prefer once-daily RT.

Subtopic 4: What are the most appropriate RT fields?

RT treatment volumes vary significantly between clinical trials, but typically include the entire bladder, with or without pelvic lymph nodes. In RTOG and University of Erlangen studies, the pelvic lymph nodes are usually treated to elective doses during the induction phase of the split-course regimen. Elective pelvic lymph node irradiation was incorporated into RTOG protocols based on surgical series showing approximately a 25% risk of LN-involvement in clinically node-negative patients. A full pelvic volume (extending to the L5/S1 interspace superiorly) was treated in earlier RTOG trials and a small pelvic volume (extending to S2/3 superiorly) was treated in later RTOG trials. The whole bladder or bladder tumor was then boosted to the maximum dose during the consolidation phase (in earlier trials) or as a concomitant boost during induction (in later trials). Patients treated in BC2001, TROG 97.01, and many European trials were treated to the whole bladder plus a 1.5 to 2.0 cm margin. These trials excluded clinically node-positive patients, and all had rates of pelvic control comparable to trials which included pelvic nodal irradiation. Despite the significant risk of nodal upstaging after surgery in clinically node-negative patients, the rates of pelvic nodal failure in BC2001 and the TROG trials were low: 5.8% and less than 9%, respectively. A randomized trial including 230 patients with cN0 MIBC compared CCRT with elective whole pelvic RT versus same with bladder plus 2cm margin only. At a median follow up of 5 years, there was no difference in DFS (47% vs. 47%), OS (53% vs. 51%), or rate of bladder preservation (59% vs. 57%). Acute Grade 3 or 4 diarrhea was higher in patients receiving whole pelvic RT with CCRT (3.9% vs. 2%, p=0.05). There were no differences in late effects.

Inclusion of the entire bladder within the clinical target volume is motivated by surgical series revealing a high rate of discordance between urologists’ preoperative identification of a primary lesion location and pathological analysis of the RC specimen. In a nested comparison within BC2001, patients were randomized to whole bladder irradiation or whole bladder irradiation to 80% prescription dose plus boost to the tumor volume. While a reduction in bladder volume receiving full dose was shown to be non-inferior with regards to LC, there was no demonstrated advantage in toxicity. Similarly, a trial conducted at Christie Hospital in the UK randomized 149 patients to either whole bladder or partial bladder (tumor+1.5 cm margin) RT. 5-year local control, DFS, OS and toxicities were no different between the two arms.
Clinical Condition/Topic 2: Patients with MIBC who are not operative candidates or who refuse salvage cystectomy.

The previous discussion also pertains to management of medically inoperable patients or those who refuse upfront RC, with the exception that a split-course regimen to assess for CR is unnecessary for medically inoperable patients, but should be discussed with potentially operable patients who refuse upfront RC.

Subtopic 1: In patients who cannot receive chemotherapy, can definitive RT alone be offered?

Historically, radical RT alone was reserved for non-operative candidates and demonstrated 5-year OS rates ranging from 16% - 28%\(^{15,26-30}\). Total dose ranged from 60 Gy to 70 Gy in 2 Gy fractions and pelvic radiation was typically included. Many non-operative candidates are also cisplatin-ineligible. In such cases, alternative chemotherapy agents should be considered (e.g. MMC/5FU, low dose gemcitabine). The randomized clinical trial BC2001 revealed statistically significant improvements in LC and salvage rates, but not OS, between RT and CRT\(^{22}\). RT alone is a curative treatment modality, and patients who are not able to receive concurrent chemotherapy should be offered definitive RT alone.

In Europe and some North American centers, concurrent carbogen and nicotinamide (CON, a hypoxia modifier) are used with RT in patients who are not candidates for CCRT. The BCON trial randomized 333 patients to either RT alone or RT with carbogen gas (2% CO2 and 98% O2 at 15 L/min and nicotinamide (40-60 mg/kg)\(^{69}\). Addition of CON resulted in an 11% and 13% improvement in RFS and OS at 3 years, respectively. This improvement was even more dramatic in patients with necrosis present in the TURBT specimen, based on post-hoc, histopathologic analysis\(^{70}\). Although experience using RT with CON is limited in North America, this approach may be considered standard for patients with MIBC who are ineligible for RC and cannot receive concurrent chemotherapy with RT.

Special Technical Considerations:

1. Appropriate bladder filling during bladder RT.

Patients can be treated with either full or empty bladder, depending on anatomic variation and patient-specific factors. Most RTOG protocols have mandated empty bladder during the irradiation of small pelvic fields, to minimize field size and to ascertain that the dome of the bladder would not extend outside of the pelvic field borders. The decision regarding bladder filling during the bladder tumor boost would often be dictated by the location of the tumor. However, for best treatment outcomes the techniques must be individualized for each patient. For some patients, small bowel extends into the lower pelvis around an empty bladder, and a full bladder allows for more normal tissue sparing. For others, a full bladder pushes the dome into small bowel, and an empty bladder is more favorable with respect to sparing of small bowel. Patients with mild lower urinary symptoms at baseline may either have difficulty maintaining a reproducibly full or empty bladder throughout treatment. The radiation oncologist should evaluate these factors, keeping in mind the tradeoff between reproducibility of daily treatments and minimization of dose to normal tissues. A dual CT simulation, one with full and another with empty bladder, may be useful in this evaluation.

2. 3D conformal versus intensity modulated RT.

Nearly all trials reviewed used 3D conformal RT (3D-CRT) technique (see Evidence Table), however, use of IMRT is also appropriate. A retrospective Danish study compared outcomes from 116 patients who received CCRT for MIBC with either 3D-CRT (46 Gy to pelvis, followed by cone-down to bladder to 60 Gy in 2 Gy fractions) or IMRT (48 Gy to pelvis and simultaneous integrated boost to bladder to 60 Gy in 2 Gy fractions)\(^{71}\). IMRT significantly reduced dose to the small bowel, resulting in a decrease in Grade 2 diarrhea during treatment (30% vs. 56%, p=0.008). There was no difference in OS or late toxicity.
The quantitative analysis of normal tissue effects in the clinic (QUANTEC) recommends a maximum dose to the bladder of 65 Gy to maintain a late RTOG grade 3 bladder toxicity below 6%\(^2\). For 55 Gy in 20 fractions, a linear-quadratic calculation using an \(\alpha/\beta\) ratio of 3 estimates that the maximum, biologic equivalent dose to bladder should be 56 Gy to achieve a similar outcome. Below is a table that summarizes these dose constraints for normal tissues at risk, all using an \(\alpha/\beta\) ratio of 3.

<table>
<thead>
<tr>
<th>Organ at Risk</th>
<th>Constraint in 2 Gy Fractions</th>
<th>Constraint in 2.75 Gy Fractions</th>
<th>Endpoint (RTOG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>D(_{\text{max}}) &lt; 65 Gy</td>
<td>D(_{\text{max}}) &lt; 56 Gy</td>
<td>Grade (\geq) 3 late toxicity &lt;10%</td>
</tr>
<tr>
<td>Rectum/Large Bowel</td>
<td>V50 &lt; 50%</td>
<td>V44 &lt; 50%</td>
<td>Grade (\geq) 3 late toxicity &lt;10%</td>
</tr>
<tr>
<td></td>
<td>V60 &lt; 35%</td>
<td>V52 &lt; 35%</td>
<td>Grade (\geq) 2 late toxicity &lt;15%</td>
</tr>
<tr>
<td></td>
<td>V65 &lt; 25%</td>
<td>V56 &lt; 25%</td>
<td></td>
</tr>
<tr>
<td>Small Bowel (Individual loops)</td>
<td>V15 Gy &lt; 120 cc</td>
<td>V14 Gy &lt; 120 cc</td>
<td>Grade (\geq) 3 late toxicity &lt;10%</td>
</tr>
</tbody>
</table>

**Areas of Non-Uniform Recommendations**

The committee was unable to reach internal consensus on the use of split-course radiation therapy. RTOG protocols in North America have always included a split course, in order to re-assess bladder tumor cystoscopically at 40 Gy of chemoRT and offer patients who did not achieve a complete response early salvage RC. However, in the UK, Australasia, and parts of Europe, both cystectomy candidates and non-cystectomy candidates, are treated without a planned break or interim cystoscopic evaluation. Some committee members argue that the latter achieve similar oncologic outcomes. Furthermore, the current SWOG/NRG protocol S1806 of bladder preservation with and without atezolizumab does not allow split course XRT. Other committee members base practice upon RTOG protocols argue that excellent outcomes achieved with bladder preservation on these trials require adherence to RTOG protocols and incorporate split course – both for interim response assessment and to mitigate toxicity. Overall, split-course treatment was felt to be more appropriate in patients who are good cystectomy candidates but less appropriate in non-surgical candidates. The panel agreed that for patients who develop RTOG Grade 2 or higher acute toxicity during pelvic chemoRT, introducing a treatment break until the toxicity subsides is a reasonable clinical decision.

The issue of elective pelvic nodal irradiation was another area of divergent recommendations. Heterogeneity in panel recommendations followed differences between RTOG trials and the University of Erlangen studies, in which the pelvic lymph nodes were typically and in BC2001, TROG 97.01, and many European trials, in which patients were treated to the whole bladder plus margin. The latter trials excluded clinically node-positive patients, and all had rates of pelvic control comparable to trials which included pelvic nodal irradiation. Panelists in favor of omitting elective pelvic irradiation note that in clinically node-negative patients, the rates of pelvic nodal failure in BC2001 and the TROG trials were low: 5.8% and less than 9%, respectively. Members of the ARS GU panel felt that elective pelvic nodal RT was either usually or sometimes appropriate in managing patients with MIBC.

The appropriateness of bladder preservation in surgical candidates with unilateral hydronephrosis was also debated. Hydronephrosis is associated with worse local control and survival, both in bladder preservation series and in surgical series. Previous RTOG protocols excluded hydronephrosis, in part, to demonstrate bladder preservation outcomes competitive with surgical series. Henceforth, some radiation
oncologists were taught that hydronephrosis was a contraindication for bladder preservation. However, the current SWOG/NRG protocol S1806 enrolls patients who are both cystectomy candidates and non-candidates and allows patients to present with unilateral hydronephrosis prior to treatment. For patients with unilateral hydronephrosis and who are otherwise surgical candidates, the panel disagreed on whether bladder preservation should be considered usually appropriate or may be appropriate.

The committee did not reach a uniform recommendation on the use of concurrent carbogen and nicotinamide in patients who are not candidates for cisplatin chemotherapy. In Europe, concurrent carbogen and nicotinamide (CON, a hypoxia modifier) is a standard of care for patients who are not able to receive concurrent chemotherapy with RT, based on an overall survival benefit seen in the BCON trial (see above). Panel members argued that there is no experience with carbogen and nicotamide in the United States and this regimen is not yet included in the NCCN bladder cancer guidelines. However, several centers in North America (OHSU, UPenn to our knowledge) have been able to implement this treatment and it could be considered a standard of care in patients not fit for concurrent chemotherapy. Panel members also felt that patients who are not candidates for cisplatin chemotherapy could tolerate low-dose gemcitabine with radiation therapy, and this would be preferable to RT with carbogen/nicotinamide based on clinical experience in the United States.

Summary of Recommendations

1. The panel strongly recommends that definitive radiotherapy (with or without concurrent chemotherapy) is usually appropriate for patients with MIBC who are ineligible for radical cystectomy.

2. The panel conditionally recommends that response-adapted, selective bladder preservation (i.e. definitive radiotherapy for patients with CR after induction phase of (chemo)RT or salvage cystectomy otherwise) is usually appropriate for patients with MIBC who are eligible for radical cystectomy but have adequate baseline bladder function and wish to pursue organ preservation. Organ preservation may be appropriate in the subset of these patients with unilateral hydronephrosis.

3. The panel strongly recommends that maximal TURBT before definitive (chemo)RT is usually appropriate for patients with MIBC who are ineligiblle for radical cystectomy.

4. The panel strongly recommends that concurrent chemotherapy (cisplatin alone, 5-FU/MMC, or low-dose gemcitabine) is usually appropriate for patients undergoing bladder-preserving RT for MIBC.

5. The panel conditionally recommends that neoadjuvant chemotherapy (MCV or gemcitabine/cisplatin) before (chemo)RT may be appropriate for patients undergoing bladder-preserving RT for MIBC. Candidates for cisplatin should have adequate renal function.

6. The panel conditionally recommends that adjuvant chemotherapy after (chemo)RT may be appropriate for patients undergoing bladder-preserving RT for MIBC, if patients have not received neoadjuvant chemotherapy.

7. The panel strongly recommends that a maximal dose of 60-66 Gy in 2Gy daily fractions is usually appropriate for definitive (chemo)RT given as a continuous treatment course with no planned breaks.

8. The panel conditionally recommends that a maximal dose of 60-66 Gy in 2Gy daily fractions given as a split-course is usually appropriate for definitive (chemo) RT for patients who are candidates for cystectomy in order to evaluate the response and offer early salvage cystectomy in case of non-response.

9. The panel conditionally recommends that elective pelvic nodal irradiation may be appropriate for patients undergoing bladder-preserving RT for MIBC.

10. The panel strongly recommends that 3D-conformal RT or IMRT are both usually appropriate for patients undergoing bladder-preserving RT for MIBC. IMRT may provide better sparing of organs at
risk, while 3D-conformal RT may be preferred if there is concern for significant target motion or lack of image guidance capabilities.

11. The panel conditionally recommends that addition of concurrent carbogen/nicotinamide to radiation therapy may be appropriate for patients with MIBC who are not candidates for concurrent chemotherapy.

Summary of Evidence

Of the 61 evidence references cited in the ARS Appropriateness Criteria for Muscle-Invasive Bladder cancer document, there are 50 therapeutic references including 7 well-designed studies, 20 good quality studies, 28 quality studies that may have design limitations, and 6 references that may not be useful as primary evidence. Two references were added, at the authors’ discretion to the literature review (Siegel et al., and Hall et al.). References were published from 1975 to 2019. These are summarized in the supplementary Evidence Table document.

Supporting Documents

For additional information on the ARS-ACR Appropriate Use Criteria methodology and other supporting documents go to http://www.americanradiumsociety.org/page/aucmethodology.

References


ARS Appropriate Use Criteria 11 Radiation Therapy for Muscle-Invasive Lymph-Node Negative Bladder Cancer
The ARS Appropriate Use Criteria® and its expert panels have developed criteria for determining appropriate radiologic procedures for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient’s clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient’s condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.
**Clinical Condition:** Muscle invasive bladder cancer

**Variant 1:** 67 year old, current smoker, sexually active man with a recent diagnosis of a 3cm cT2 cN0 M0 transitional cell carcinoma of the posterior wall of bladder who is fit for radical cystectomy, but would like to avoid RC due to concerns regarding erectile dysfunction after surgery.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Rating Category</th>
<th>Final Tabulation</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>References</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
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<tr>
<td>External beam radiotherapy</td>
<td>A</td>
<td>1 1 1 3 5 8</td>
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<td>16-19,21-29,31,34-55,57-61</td>
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<td>↑</td>
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<tr>
<td>Split course XRT</td>
<td>A*</td>
<td>2 2 3 5 1 1 5</td>
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<td>35-36,39,42,45-49,51,53</td>
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</tr>
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<td>Neoadjuvant chemotherapy</td>
<td>M</td>
<td>1 1 4 3 1 5</td>
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<td>39,41-46,48,61</td>
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<tr>
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<td>Adjuvant chemotherapy, in absence of neoadjuvant chemotherapy</td>
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<td>37,38,47,49</td>
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<tr>
<td>IMRT</td>
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<td>56</td>
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<tr>
<td>3D Conformal radiotherapy</td>
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**Rating:** A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

**Strength of Evidence:** S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

**Study Quality:** 1-Well designed; 2-Good quality; 3-Good quality with limitations; 4-May not be useful as primary reference

**Strength of Recommendation:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation
**Variant 2:** 80 year old, female patient with COPD and CAD with a 4 cm cT3 cN0 M0 TCC of the bladder dome, who is determined by urology team to be medically unfit for radical cystectomy.

<table>
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<th>Procedure</th>
<th>Rating Category</th>
<th>Final Tabulation</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>References</th>
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<td>M</td>
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<td>3 M</td>
<td>↑</td>
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<td>2 S</td>
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**Rating:** A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

* Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

**Strength of Evidence:** S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

**Study Quality:** 1-Well designed; 2-Good quality; 3-Good quality with limitations; 4-May not be useful as primary reference

**Strength of Recommendation:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation
**Variant 3:** 67 year-old male previous smoker with Stage 3 chronic kidney disease and a new diagnosis of a 3 cm cT2 cN0 M0 TCC of the right wall of bladder. Patient was deemed unable to receive cisplatin by medical oncology team because of his poor renal function.

<table>
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<th>Final Tabulation</th>
<th>Group Median Rating</th>
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<td>21,24,50,55</td>
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<td>8</td>
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<td>22-30,32-34,44,50</td>
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<td>56</td>
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<tr>
<td>3D Conformal radiotherapy</td>
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<td>7.5</td>
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<td>6</td>
<td>21,30,44</td>
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</table>

**Rating:** A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

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**Strength of Evidence:** S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion

**Study Quality:** 1-Well designed; 2-Good quality; 3-Good quality with limitations; 4-May not be useful as primary reference

**Strength of Recommendation:** ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel’s recommendation

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**Variant 4:** 80 year-old woman with diabetes and hypertension with a 6 cm cT3 cN0 M0 TCC of the left and posterior walls of the bladder with obstruction of the left ureteral orifice, resulting in left-sided hydronephrosis, with normal renal function.
<table>
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<th>Procedure</th>
<th>Rating Category</th>
<th>Final Tabulation</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>References</th>
<th>SQ</th>
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<tr>
<td>Bladder preservation if patient is a good candidate for RC, but desires bladder preservation</td>
<td>M*</td>
<td>1 3 5 4 1</td>
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<td>5</td>
<td>16-19,21-29,31,34-55,57-61</td>
<td>1</td>
<td>S</td>
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<tr>
<td>Bladder preservation if patient is a good candidate for RC, but refuses surgery</td>
<td>A</td>
<td>1 1 2 6 7</td>
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<td>16-19,21-29,31,34-55,57-61</td>
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<tr>
<td>Bladder preservation if patient is not a RC candidate</td>
<td>A</td>
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<td>13-61</td>
<td>1 S</td>
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<td>Neoadjuvant chemotherapy</td>
<td>M</td>
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<td>39,41-46,48,61</td>
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<td>M</td>
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<tr>
<td>Adjuvant chemotherapy, in absence of neoadjuvant chemotherapy</td>
<td>M</td>
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<td>56</td>
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<td>3D Conformal radiotherapy</td>
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<tr>
<td>Elective Pelvic Nodal XRT</td>
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<td>4 5 4 1 5 X</td>
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<td>21,22,30,35,36,38-40,42,44,45,47-49,54,56,57,61</td>
<td>2</td>
<td>M</td>
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Rating: A-Usually appropriate; M-May be appropriate; U-Usually not appropriate
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Strength of Evidence: S-Strong; M-Moderate; L-Limited; EC-Expert consensus; EO-Expert opinion
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Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; + Additional considerations do not strengthen or weaken the panel’s recommendation