Public Comment DRAFT

Radiation Therapy for Bladder Cancer: An ASTRO/AUA/SUO Clinical Practice Guideline

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Preamble

As a leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision-making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

Disclosure Policy—ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before the initiation of the writing effort. Disclosures for the chair and vice chair go through a review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. Peer reviewer disclosures are also reviewed and included (Supplementary Materials, Appendix E1). The complete disclosure policy for Formal Papers is online.

Selection of Task Force Members—ASTRO strives to avoid bias and is committed to creating a task force that includes a diverse and multidisciplinary group of experts. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force.

Methodology—ASTRO's task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.[1,2] The evidence identified from key questions (KQs) is assessed using the **P**opulation, **I**ntervention, **C**omparator, **O**utcome, **T**iming, **S**etting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system. See Appendix E2 in Supplementary Materials for a list of abbreviations used in the guideline.

Consensus Development—Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from "strongly agree" to "strongly disagree". A prespecified threshold of ≥75% (≥90% for expert opinion recommendations) of raters who select "strongly agree" or "agree" indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submitting for approval.

Annual Evaluation and Updates—Guidelines are evaluated annually beginning 2 years after publication for new, potentially practice-changing studies that could result in a guideline update. In addition, ASTRO's Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

Table 1 ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE and panel consensus, which, among other considerations, inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.

Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/ Should"
Conditional	• Benefits are finely balanced with risks and burden, or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"

Overall QoE Grade	Type/Quality of Study	Evidence Interpretation
High	• 2 or more well-conducted and highly generalizable RCTs or well-conducted meta-analyses of such randomized trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.
Moderate	• 1 well-conducted and highly generalizable RCT or a meta-analysis including such a trial **OR** • 2 or more RCTs with some weaknesses of procedure or generalizability **OR** • 2 or more well-conducted and highly generalizable observational or single-arm prospective interventional studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.
Low	• 1 RCT with some weaknesses of procedure or generalizability **OR** • 1 or more RCTs with serious deficiencies of procedure or generalizability **OR** • 1 well-conducted observational or single-arm prospective interventional study **OR** • 2 or more observational or single-arm prospective interventional studies with some weaknesses of procedure or generalizability.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.
Expert Opinion*	• Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect.

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCT(s) = randomized controlled trial(s).

*A lower QoE, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

ASTRO's methodology allows for use of implementation remarks meant to convey clinically practical information that may enhance the interpretation and application of the recommendation. Although each recommendation is graded according to recommendation strength and QoE, these grades should not be assumed to extend to the implementation remarks.

1. Introduction

Bladder cancer is the tenth leading cause of cancer death in the United States and the fifth leading cancer diagnosis amongst men. In 2025, there will be an estimated 85,000 new cases of bladder cancer (approximately 65,000 in men and 20,000 in women) and an estimated 17,000 deaths from bladder cancer.[3] A standard treatment for muscle-invasive bladder cancer (MIBC) has been cystectomy with or without neoadjuvant chemotherapy; however, cystectomy is not being performed in up to 50% of patients with MIBC and as such, there is an undertreated and underserved population of patients who are not getting optimal curative-intent treatment.[4,5] An alternative to this approach is trimodal therapy (TMT), which includes transurethral resection of bladder tumor (TURBT) followed by chemoradiation for bladder preservation. Despite multiple prospective trials dating back to the 1980s, TMT has not historically had widespread acceptance. However, with consistently favorable and mature outcome data and large cooperative group trials using TMT, there has been growing interest in and greater adoption of TMT.[6-11]

A multidisciplinary approach to MIBC is required to appropriately select patients for TMT and optimally individualize patient care. It is essential to understand the indications for TMT, how outcomes following TMT compare with radical cystectomy (RC),[11] how to integrate radiation therapy (RT) with systemic therapy, and the technical aspects of how RT is performed. Additionally, the use of RT in the postoperative and metastatic bladder cancer setting is an important tool in the treatment of this disease, especially as systemic therapies have improved overall survival (OS) in this patient population. ASTRO commissioned a task force to review published literature on the use of RT across the clinical spectrum for bladder cancer to create evidence-based recommendations that address 5 clinical KQs.

2. Methods

2.1. Task force composition

The task force consisted of a multidisciplinary team of radiation, medical, and urologic oncologists; a medical physicist; and a patient representative. This guideline was developed in partnership with the American Urological Association (AUA) and the Society for Urologic Oncology (SUO) and in collaboration with the American Society of Clinical Oncology (ASCO), European Association of Urology (EAU), and European Society for Radiotherapy and Oncology, who provided representatives and peer reviewers.

2.2. Document review and approval

The guideline was reviewed by XX official peer reviewers (Appendix E1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment from January to February 2026. The final guideline was approved by the ASTRO Board of Directors and endorsed by the TBD.

2.3. Evidence review

KQs were developed by the ASTRO guideline subcommittee in conjunction with the guideline chairs and then reviewed by the full task force. Using the PICOTS framework (Table 2), a systematic search of human participant studies retrieved from Ovid MEDLINE and Embase databases was conducted for English-language publications between January 2009, through November 18, 2024. Allowable publication types comprised prospective studies including randomized controlled trials (RCTs), meta-analyses (of RCTs and prospective studies only), retrospective studies, and dosimetric/contouring studies. The population of interest was adults (age ≥18 years) who received a diagnosis of bladder cancer and were treated with RT. The following requirements for study size were applied: (1) for retrospective studies, KQ1 was limited to ≥65 patients and KQ2 was limited to ≥100 patients but no threshold was used for KQs 3 and 4; (2) for dosimetric studies with validated clinical endpoints, ≥10 patients were required and only included for KQ3. Universal exclusion criteria included preclinical and nonhuman studies; publication types including abstract only, review articles, comments, or editorials; study types such as health economics/cost analysis studies and treatment of secondary primaries. For specific subquestions where limited data were available, expert opinion was relied on to support recommendations. Full-text articles were assessed by the task force to determine the final included study list resulting in 153 studies (see the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] flow diagram showing the number of articles screened, excluded, and included in the evidence review) and Appendix E3 in Supplementary Materials for the literature search strategy, which includes the evidence search parameters and inclusion/exclusion criteria.

The data used by the task force to formulate recommendations are summarized in evidence tables available in Supplementary Materials, Appendix E4. References selected and published in this document are representative and not all-inclusive. Additional ancillary articles not in the evidence tables are included in the text; these were not used to support the evidence-based recommendations but may have informed expert opinion.

2.4. Scope of the guideline

This guideline only addresses the topics specified in the KQs (Table 2). The scope includes the use of RT in bladder cancer in the upfront, definitive setting and in the postoperative and metastatic settings. Discussions of indications for RT, integration of systemic therapies, and RT techniques in these settings are also included. This guideline is not intended to address surgical management of MIBC, detailed discussion of systemic therapy, targeted therapies, intravesical or local therapy options, and bladder preservation techniques that do not incorporate RT. The key outcomes of interest are oncologic results including OS, disease-specific survival, metastasis-free survival, progression-free survival, locoregional control, and bladder-intact event-free survival.

Table 2 KQs in PICO format

KQ	Population	Intervention	Comparator	Outcomes
1	**What are the indications and contraindications for bladder preservation with curative-intent RT, with or without systemic therapy, for patients with nonmetastatic bladder cancer?**			
	• Adults with nonmetastatic bladder cancer	• RT +/- systemic therapy	• Cystectomy +/- neoadjuvant systemic therapy • Systemic therapy alone • TURBT alone or observation • RT alone	• Bladder-intact event-free survival • Complete response rates • Cystectomy-free rate • Disease-specific survival • Locoregional control • Metastasis-free survival • Overall survival • NMIBC recurrence rates • Patient- and provider-reported QoL, adverse events, toxicities
2	**What are appropriate RT techniques (eg, target volumes, modalities, simulation, image guidance) and dose-fractionation regimens for patients with intact, nonmetastatic bladder cancer being treated with curative intent?**			
	• Same as KQ1	• RT/trimodal therapy • Hypofractionated RT • Bladder only RT • Adaptive RT • Bladder tumor boost • IMRT • Proton therapy	• Whole pelvis RT, small pelvis RT, mini-pelvis RT, or pelvic RT • Conventionally fractionated RT • 3-D CRT • Photon therapy	• Patterns of failure • Safety, feasibility • Toxicity
3	**What are the indications, appropriate RT techniques (eg, target volumes, modalities, simulation, image guidance), and dose-fractionation regimens for postoperative RT, with or without systemic therapy, for patients with nonmetastatic bladder cancer status postcystectomy or partial cystectomy?**			
	• Same as KQ1	• +/- RT (postoperative, adjuvant, salvage) +/- systemic therapy	• Cystectomy +/- systemic therapy without RT	• Disease-specific survival • Locoregional control • Metastasis-free survival • Overall survival • Patient- and provider-reported QoL, adverse events, toxicities • Patterns of failure

4	What are indications and appropriate dose-fractionation regimens for RT to the bladder or sites of metastases for patients with metastatic or symptomatic bladder cancer being treated with noncurative intent?			
	• Adults with metastatic or symptomatic bladder cancer OR nonmetastatic bladder cancer treated with noncurative intent	• RT to bladder +/- systemic therapy • RT to metastatic disease +/- systemic therapy • Stereotactic body RT	• Observation or best supportive care • Systemic treatment alone	• Locoregional control/palliation • Metastasis-free survival • Overall survival • Patient- and provider-reported QoL, adverse events, toxicities • Patterns of failure • Progression-free survival • Safety, feasibility

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; KQs = key questions; MIBC = muscle-invasive bladder cancer; NMIBC = non-muscle invasive bladder cancer; PICO = Population, Intervention, Comparator, Outcome; QoL = quality of life; RT = radiation therapy; TURBT = transurethral resection of bladder tumor.

3. KQs and Recommendations

3.1. KQ1: Indications and contraindications for bladder preservation with curative-intent RT (Table 3)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ1 and Fig 1.

What are the indications and contraindications for bladder preservation with curative-intent RT, with or without systemic therapy, for patients with nonmetastatic bladder cancer?

Table 3 Indications and contraindications for bladder preservation with RT

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with cT2-4aN0M0 muscle-invasive bladder cancer, trimodal therapy or radical cystectomy is recommended. Implementation remarks: • Trimodal therapy includes TURBT followed by chemoradiation. • Favorable prognostic features for bladder-preserving RT include: ○ cT2 disease ○ solitary tumors ○ tumors <7cm ○ predominant urothelial carcinoma ○ absence of extensive carcinoma in situ ○ absence of bilateral hydronephrosis	Strong	High [7,9,11-15]
2. For patients with high-grade, cT1N0M0 non-muscle invasive bladder cancer with a recurrence despite available intravesical or systemic therapies (or are not candidates for those options)	Conditional	Low [16]

and decline or are ineligible for cystectomy, trimodal therapy is conditionally recommended.		
3. For patients with cN1-3 bladder cancer, trimodal therapy or radical cystectomy is recommended after neoadjuvant or induction systemic therapy without progression.	Strong	Low [17-19]
4. For patients with bladder cancer undergoing trimodal therapy, concurrent radiosensitizing systemic therapy is recommended. Implementation remarks: Concurrent systemic therapy options include: • Chemotherapy (preferred) (ideally cisplatin +/- 5-FU, 5-FU + mitomycin-C, or low-dose gemcitabine); OR • Carbogen and nicotinamide; OR • Anti PD-1/PD-L1 therapy (for those who are not candidates for the above or as part of a clinical trial)	Strong	High (chemotherapy) [7,9,12,15,20,21] Moderate (carbogen/ nicotinamide) [22-24] Low (anti PD-1/PD-L1) [18,25-27]
5. For patients with bladder cancer at a higher risk of distant metastatic progression (eg, cT3-4 and/or N+) who plan to receive trimodal therapy, neoadjuvant systemic therapy is recommended.	Strong	Low [28-35]
6. For patients with bladder cancer planning to receive trimodal therapy, attempting a maximal TURBT is recommended.	Strong	Low [7,9,12,36]
7. For patients with bladder cancer post trimodal therapy, surveillance with axial imaging of the chest, abdomen and pelvis; cystoscopy; and urine cytology is recommended.	Strong	Low [7,9,12,37]
8. For patients with bladder cancer post trimodal therapy who have residual disease or develop a recurrence in the bladder, urologic evaluation is recommended.	Strong	Low [11,14,38]

Abbreviations: 5-FU = 5-fluorouracil; KQ = key question; PD-1 = programmed cell death protein 1; N+ = node-positive; PD-L1 = programmed cell death ligand 1; RT = radiation therapy; TURBT = transurethral resection of bladder tumor.

TMT, which consists of maximal TURBT followed by concurrent chemoradiation, is an established alternative to RC for appropriately selected patients with localized MIBC (Figure 1).[11] Multiple RCTs[7,9,15,22] have demonstrated that TMT achieves long-term OS and disease-specific survival rates similar to RC in appropriately selected patients, while maintaining quality of life and urinary function. Ideally, TMT is part of a multidisciplinary framework that emphasizes shared decision making and is a curative treatment alongside RC.

Use of TMT has been most extensively studied in cT2-4aN0M0 bladder cancer yet select patients with cT4bN0M0 disease may also be candidates. Additionally, patients with cT1N0M0, non-muscle invasive bladder cancer (NMIBC), who are not candidates for or have recurred despite available intravesical or systemic therapy options and decline or are ineligible for cystectomy may be candidates for TMT based on a prospective trial that demonstrates efficacy and safety to this approach.[16] Similarly, both TMT and RC are options for patients who have clinical regional node-positive disease (any T-classification, cN1-3M0) who do not have distant progression after neoadjuvant or induction systemic therapy (Figure 1).[17,39,40]

Favorable prognostic features for TMT include cT2 disease, solitary tumors, tumors <7 cm in size, predominant urothelial histology, and the absence of extensive carcinoma in situ or bilateral hydronephrosis.[7,9,11-14,20,21,23-25,28,37,41-52] Patients with extensive carcinoma in situ, multifocal tumors, generally have inferior outcomes with TMT, although these are also poor prognostic features in the setting of RC as well. While not absolute contraindications to TMT, caution is advised for patients with active inflammatory bowel disease, unresolved grade 2 to 4 gastrointestinal (GI) toxicity from prior pelvic RT, or severely reduced bladder capacity, as toxicity risk may outweigh the benefit. Patients with poor performance status, inability to complete a full RT course, poor baseline bladder function and/or continence, or lack of access to close follow-up are less ideal candidates for bladder preservation.

Maximal TURBT should be performed before TMT whenever feasible, as complete macroscopic tumor resection strongly correlates with complete response rates and bladder-intact event-free survival.[6,7,9,12,15,20,23,24,49,50,52,53] Where available, advanced imaging such as multiparametric magnetic resonance imaging (MRI) (using Vesical Imaging Reporting and Data System [VI-RADS] scoring) or positron emission tomography/computed tomography (PET/CT) scan can refine local and nodal staging, particularly for cT3 disease, and may help identify candidates most likely to benefit from bladder preservation.[54,55] Other emerging tools for patient selection include circulating tumor DNA and molecular classifiers, but these remain investigational and should not yet guide therapy outside clinical trials.

Most evidence supporting TMT derives from patients with pure urothelial carcinoma.[7] Nevertheless, these recommendations extend to urothelial carcinomas exhibiting limited squamous or glandular histologic subtypes, which have shown comparable outcomes.[43,44,56] Data for rarer variants including plasmacytoid, sarcomatoid, micropapillary, or nested subtypes are extremely limited, and management should be individualized based on multidisciplinary discussion. Given the paucity of prospective data, a recommendation on strict exclusions based on histology is not included but documentation of histological subtype in clinical trials and registries is encouraged to inform future guidance.

Concurrent chemotherapy is the preferred radiosensitizing approach for patients undergoing TMT.[9,12-14,20,23,28,37,41,42,48,52,57-59] Standard systemic therapy regimens include cisplatin with or without 5-fluorouracil (5-FU), 5-FU plus mitomycin C, or low-dose gemcitabine, each of which has demonstrated improved efficacy compared with RT alone. For patients who are ineligible for these chemotherapy agents, alternative radiosensitizing chemotherapy options include single-agent 5-FU or capecitabine, either alone or combined with mitomycin C or paclitaxel, although data supporting these regimens are more limited.[60] The addition of carbogen and nicotinamide to RT, provides another radiosensitizing strategy by improving tumor oxygenation;[23,24,26] however, its clinical use is largely confined to select centers in the United Kingdom and has not been widely adopted in the United States.

For patients who decline or are ineligible for chemotherapy, emerging data support the investigational use of immune checkpoint inhibitors such as anti-programmed cell death protein-1 programmed cell death ligand 1 agents (durvalumab, pembrolizumab, nivolumab) concurrently with RT, ideally in the context of a prospective trial.[18,25-27] Early-phase studies suggest safety and promising efficacy for these regimens in patients unable to undergo conventional chemoradiation.[18,25-27]

For patients with higher-risk features such as cT3-4 or N1-3 disease, neoadjuvant cisplatin-based chemotherapy before TMT is recommended.[28-35] One trial demonstrated an OS benefit for neoadjuvant chemotherapy before either RC or RT, irrespective of treatment modality.[61] However, most patients in this study received RC. Similarly, in another RCT,[31] patients who received neoadjuvant chemotherapy continued to derive additional benefit from concurrent radiosensitization, implying complementary mechanisms. These studies were not powered to detect small (5%) OS differences, and definitive evidence supporting neoadjuvant chemotherapy in the RT cohort remains limited. Therefore, by analogy to surgical paradigms, neoadjuvant therapy should be discussed in a multidisciplinary setting and offered selectively to patients, acknowledging the limited direct data.[61,62] There is an ongoing single arm trial evaluating risk-adapted bladder preservation with immunotherapy and RT in patients with a ≤T1 response to neoadjuvant therapy (*NCT07061964*).

Following completion of TMT, patients should undergo rigorous surveillance to ensure early detection of recurrence.[7,9,12,15,20,23,24,49,50,52,53] Follow-up ideally includes cystoscopic evaluation with urine cytology every 3 months and axial imaging of the chest, abdomen, and pelvis every 3-6 months for the first 2 years, then at gradually increasing intervals.[7,9,12,37] If cystoscopy reveals a suspicious residual lesion or equivocal abnormality, a targeted rebiopsy may be performed to confirm complete response. Patients with NMIBC recurrences can generally be managed with TURBT with or without intravesical therapy, whereas MIBC relapses are best treated with salvage RC, which achieves oncologic outcomes comparable to upfront surgery in contemporary series.[11,14,38]

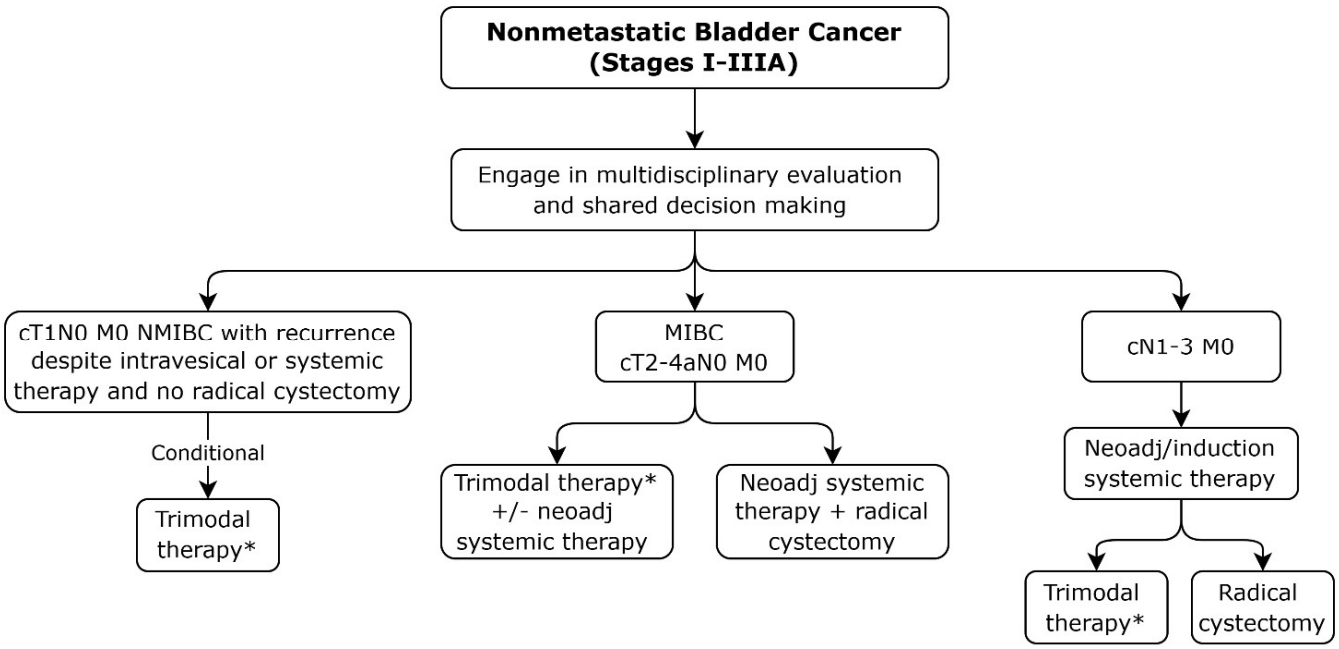

Figure 1 Management of nonmetastatic bladder cancer (stages I-IIIA)

Abbreviations: MIBC = muscle-invasive bladder cancer; neoadj = neoadjuvant; NMIBC = non-muscle invasive bladder cancer; TURBT = transurethral resection of bladder tumor.

*Attempt maximal TURBT followed by RT-based bladder preservation with concurrent radiosensitization.

3.2. KQ2 Appropriate RT techniques and dose-fractionation for intact nonmetastatic disease (Table 5)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ2.

What are appropriate RT techniques (eg, target volumes, modalities, simulation, image guidance) and dose-fractionation regimens for patients with intact, nonmetastatic bladder cancer being treated with curative intent?

Table 4 Appropriate RT techniques and dose-fractionation regimens for intact nonmetastatic disease

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
Volumes		
1. For patients with intact cT2-4N0M0 bladder cancer receiving RT, elective RT to pelvic lymph nodes is conditionally recommended based on tumor characteristics (eg, T3-4 disease).	Conditional	Moderate 9,28,38,49,63-66
2. For male patients with intact cT2-4N0-3M0 bladder cancer including the prostate in the target volume is conditionally recommended for tumors at the base or neck of the bladder, T4 disease, or tumors with prostatic urethral involvement receiving RT.	Conditional	Moderate 15,24

3. For patients with intact cT2-4N0-3M0 bladder cancer receiving RT, whole bladder RT to full dose or reduced dose to uninvolved bladder with a partial tumor boost is recommended.	Strong	High [9,15,24]
Dose-Fractionation		
4. For patients with intact, cT1-4N0-3M0 bladder cancer receiving RT, daily RT without a mid-treatment break for cystoscopic response assessment is recommended.	Strong	Moderate [9,24,50]
5. For patients with intact, cT1-4N0M0 bladder cancer receiving RT to the bladder alone, a dose of 5500 cGy in 20 fractions or 6400-6480 cGy in 32-36 fractions is recommended. Implementation remark: A lower dose of 6120 cGy in 180 cGy fractions may be an option for cT1N0M0 bladder cancer.	Strong	High [9,15,16,24,67]
6. For patients with intact, cT2-4N0M0 bladder cancer receiving RT to the bladder and lymph nodes, a dose of 4000-4600 cGy in 20-25 fractions to the elective lymph nodes and bladder, with a boost to the bladder to a total dose of 6400-6480 cGy in 32-36 fractions is recommended. Implementation remark: If treating with a 20-fraction regimen, a dose of approximately 4400 cGy to the elective lymph nodes may be an option.	Strong	Low [9,24]
7. For patients with cT2-4N1-3M0 bladder cancer, a focal boost to gross nodal disease is conditionally recommended with the dose dependent on normal tissue tolerance. Implementation remark: A BED up to 6400-6480 cGy in 180-200 cGy fractions to gross disease and ≥4500 cGy to elective nodes may be reasonable.	Conditional	Low [19]
8. For patients with intact, cT2-4N0-3M0 bladder cancer receiving RT, dose escalation to the bladder is **not** recommended outside of a clinical trial or multi-institutional registry.	Strong	Moderate [15,68-71]
Techniques		
9. For patients with intact cT1-4N0-3M0 bladder cancer receiving RT, IMRT (including VMAT) using daily image guidance with cone-beam CT to verify bladder volume is recommended.	Strong	Moderate [72,73]
10. For patients with intact cT1-4N0-3M0 bladder cancer receiving RT, adaptive RT is conditionally recommended where target coverage and OAR constraints cannot be met and/or daily setup is not reproducible with traditional treatment planning.	Conditional	Moderate [15,70,74,75]

Abbreviations: BED = biologically equivalent dose; CT = computed tomography; IMRT = intensity modulated radiation therapy; KQ = key question; OAR = organ(s) at risk; RT = radiation therapy; VMAT = volumetric modulated arc therapy.

RT techniques have improved globally since the first trials of TMT in the 1980s and this has allowed for more conformal treatment with fewer side effects for patients with bladder cancer. While no RCT comparing intensity modulated radiation therapy (IMRT) and 3-dimensional conformal radiation therapy (3-D CRT) for bladder cancer exists, data in other pelvic disease sites with concurrent chemotherapy identify

IMRT as reducing bowel toxicity.[76,77] Several series demonstrate a reduction in acute bowel toxicity with the use of IMRT compared with 3-D CRT.[72,73] When IMRT is used, daily image guidance with cone-beam CT is recommended to verify bladder filling and target localization.[72,73] Historically, TMT trials incorporated interim treatment response evaluation with cystoscopy during an RT break to avoid exposure of small bowel to additional RT, if a salvage cystectomy was required. [20,49,51,52,78-80] This practice has been replaced by continuous complete course RT because salvage cystectomy rates have similar complication rates and similar outcomes to upfront cystectomy.[11,12,49,51,81] While hyperfractionated twice daily RT has been used in clinical trials of localized bladder cancer, once daily RT (with biweekly gemcitabine) showed no difference in 3-year metastasis-free survival compared with twice daily RT (with 5-FU/cisplatin) and no difference in OS.[50,82] Therefore, once daily, continuous course RT remains the preferred RT delivery regimen.

The ideal dose and fractionation regimen for patients with localized bladder cancer remains controversial. An individual patient meta-analysis of 2 RCTs found moderately hypofractionated RT (5500 cGy in 20 fractions) was superior to conventionally fractionated RT (6400-6480 cGy in 32-36 fractions) for locoregional control with no differences in late GI or genitourinary toxicity.[67] However, few patients on these trials received hypofractionated RT with concurrent chemotherapy and no patients received pelvic nodal RT, thus limiting the conclusion for patients who receive concurrent chemoradiation or those receiving treatment to the pelvic lymph nodes. Data incorporating hypofractionated RT and concurrent chemotherapy showed similar toxicity compared with conventionally fractionated RT.[15] For patients with T1N0M0 NMIBC and a recurrence despite available intravesical or systemic therapies (or who are not candidates for those options) and decline or are ineligible for cystectomy, a dose of 6120 cGy in 34 fractions to the bladder alone resulted in a 3-year cystectomy-free rate of 88%.[16] Limited data exist on hypofractionated RT for NMIBC.[83] One ongoing RCT is investigating the use of immunotherapy with RT (and allows hypofractionated RT) compared with chemoradiation in T1 high-grade NMIBC (*NCT06770582*).

There is insufficient data to support dose escalation beyond 5500 cGy in 20 fractions or 6400 to 6480 cGy in 32 to 36 fractions, therefore, these techniques are not recommended outside of a clinical trial.[15,68-71] A randomised phase II trial of adaptive image-guided standard or dose-escalated tumour boost radiotherapy in the treatment of transitional cell carcinoma of the bladder investigated dose-escalated, adaptive RT in its 2-stage randomization and at 3.5 years follow up, no oncologic benefit was demonstrated; although, there was no signal for increased toxicity.[15] Adaptive techniques may be suitable for patients with bowel anatomy that compromises tumor coverage or for patients with bladder filling challenges. Adaptive RT has been studied for bladder cancer with a plan-of-the-day approach that allows adjustment of the RT plan based on the daily bladder filling variations with a library of preset RT plans.[15,71,84] A more advanced form of adaptive RT called online adaptive RT uses customized patient-specific treatment plans created in real-time based on CT or MRI visualized patient anatomy and allows for the most accurate

plan delivery but has limited data to support routine use in bladder cancer.[85-87] There is an ongoing phase III RCT designed to evaluate the utility of adaptive 5-fraction ultrahypofractionated RT compared with moderately hypofractionated RT (both with concurrent chemotherapy) for localized bladder cancer (*NCT07097142*).

Elective treatment of the lymph nodes remains a controversial topic in bladder cancer. There are no validated prospective randomized trial results comparing elective pelvic nodal RT with bladder-only RT. While 3 trials delivered bladder-only RT, many of the RTOG studies used a mini-pelvis field treating from S2-3 junction at mid-sacrum to the lower pole of the obturator foramen using 3-D CRT.[9,20,23,24,47,79,80] Many of the studies using bladder-only RT demonstrated low rates (~7%) of pelvic nodal recurrences suggesting bladder-only RT is sufficient.[12,49,67,88] One RCT attempted to compare whole pelvis versus bladder-only RT in node-negative MIBC; however, concerns with the results require careful consideration.[89,90] A multicenter retrospective Canadian series with inverse probability treatment weighting demonstrated a cancer-specific and OS benefit for whole pelvis RT over bladder only.[64] Arguments in favor of elective nodal RT for MIBC include high rates of occult pathologic nodal involvement, especially in patients with T3 or T4 primary disease, and low toxicity rates with IMRT when including elective nodes.[19,91]

Most prospective studies in bladder cancer target the whole bladder as a single clinical target volume instead of treating the whole bladder to a lower dose with a higher dose delivered to the tumor/tumor bed (bladder tumor boost).[7,16,49] Two RCTs investigated whether partial bladder boost would reduce treatment-related toxicity over whole bladder RT.[12,88] Neither study demonstrated a significant reduction in toxicity with partial bladder boost RT. Despite these results, there remains a strong clinical rationale for its continued use because the majority of recurrences after TMT occur at the original tumor site.[38,92] Bladder tumor boost may be particularly beneficial where bowel anatomy is dosimetrically unfavorable allowing for a partial bladder boost to best spare dose to the bowel. Careful treatment planning based on patient anatomy is critical to maintain excellent target coverage and minimize dose to neighboring organs at risk (Tables 5 and 6).

Prior RTOG and NRG studies included the prostate in the RT fields for men with bladder cancer based on 3-D CRT treatment planning.[7] With the use of IMRT, the prostate has not been included in the clinical target volume unless there is prostatic urethral involvement, low-lying bladder tumors located in the bladder neck or trigone, or T4 bladder cancer. For female patients with bladder cancer, proximal urethra should be included in the setting of T4 disease or low-lying tumors in the bladder neck or trigone.

Interstitial brachytherapy may be an option as part of a bladder-preserving strategy in carefully selected patients with solitary, small (<5 cm), muscle-invasive T2 tumors without carcinoma in situ. Although not routinely performed, series from specialized European centers have shown good local control,

low toxicity, and high rates of bladder preservation when brachytherapy is combined with TURBT and external beam RT.[93-97]

Table 5 Guidance on normal tissue goals for conventionally fractionated regimens (1.8 or 2 Gy per fraction to 64-64.8 Gy, nodes treated to 40-46 Gy)*

Organ/Target	Metric	Primary Goal	Secondary Goal	Deviation	Notes
Rectum	V30 Gy	<50%†	≤80%[19,23]	>80%	
	V55 Gy	≤10%†	≤15%†	>15%	
Femoral heads	V45 Gy	≤50%†	≤55%†	>55%	
	D0.03 cc	≤50 Gy†	≤55 Gy†	>55%	
Bowel bag	V30 Gy	≤150 cc†	170 cc†	>170 cc	
	V40 Gy	≤130 cc†	150 cc†	>150 cc	
	V45 Gy	<100 cc†	≤139 cc[19,23]	>139 cc	
	V50 Gy	<15 cc†	≤127 cc[23]	>127 cc	
	D0.03 cc	≤55 Gy	≤57.5 Gy	>57.5 Gy	PTV coverage should be compromised to meet bowel bag, especially small bowel
PTV	V100 Gy	≥95%	---	<95%	OARs have priority over PTV coverage when close in proximity

Abbreviations: PTV = planning target volume; OARs = organs at risk.
*This table is a combination of evidence-based constraints and expert opinion.
†*NCT03775265* (SWOG NRG1806).

Table 6 Guidance on normal tissue goals for hypofractionation (2.75 Gy per fraction to 55 Gy, nodes treated to 40-44 Gy)*

Organ/Target	Metric	Primary Goal	Secondary Goal	Deviation	Notes
Rectum	V25 Gy	<80%[23]	≤85%†	>85%	
	V41.7 Gy	<60%[23]	≤65%	>65%	
	V50 Gy	<50%[23]	≤55%†	>55%	
	V54.2 Gy	<30%[23]	≤35%†	>35%	
	V58.3 Gy	<15%[23]	≤20%†	>20%	
Femoral heads	V41.7 Gy	<50%[23]	---	≥50%	
	V44 Gy	≤8 cc[23]	---	>8 cc	
	D0.03 cc	≤47 Gy†	>47 to 50 Gy	>50 Gy	
Bowel bag	V37.5 Gy	<116 cc[23]	≤139 cc†	>139 cc	
	V41.7 Gy	<104 cc[23]	≤127 cc†	>127 cc	
	V45.8 Gy	<91 cc[23]	---	≥91 cc	
	V50 Gy	<73 cc[23]	---	---	
	V54 Gy	<0.03 cc	---	>0.03cc	
PTV	V100 Gy	≥95%	---	<95%	OARs have priority over PTV coverage when close in proximity

Abbreviations: PTV = planning target volume; OARs = organs at risk.
*This table is a combination of evidence-based constraints and expert opinion.
†*NCT07097142* (NRG GU015).

3.3. KQ3 Indications, dose-fractionation, and techniques for postoperative RT for nonmetastatic disease (Table 4)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ3.

What are the indications, appropriate RT techniques (eg, target volumes, modalities, simulation, image guidance), and dose-fractionation regimens for postoperative RT, with or without systemic therapy, for patients with nonmetastatic bladder cancer status postcystectomy or partial cystectomy?

Table 7 Indications, dose-fractionation, and techniques for postoperative RT for nonmetastatic disease

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
Indications & Timing		
1. For patients with (y)pT3-4M0 or positive margins or (y)pN1-3M0 urothelial carcinoma of the bladder postcystectomy, adjuvant RT is conditionally recommended for locoregional control. Implementation remark: Neobladder reconstruction is not a contraindication for adjuvant RT.	Conditional	High 98-103
2. For patients with (y)pT3-4N0-3M0 pure squamous cell carcinoma of the bladder postcystectomy, adjuvant RT is conditionally recommended for locoregional control.	Conditional	Moderate 101,104
3. For patients with (y)pT3-4N0-3M0 bladder cancer post cystectomy receiving adjuvant immunotherapy and RT, RT is conditionally recommended before or during immunotherapy treatment.	Conditional	Expert Opinion
4. For patients with (y)pT3-4N0-3M0 bladder cancer, initiating adjuvant RT within 2-3 months postcystectomy or within 8 weeks of completing adjuvant chemotherapy is recommended. Implementation remark: Initiating RT up to 4 months postcystectomy is acceptable.	Strong	Moderate 98-101
Volumes		
5. For patients with (y)pT3-4N0-3M0 bladder cancer postcystectomy, pelvic lymph nodes and cystectomy bed should routinely be included when receiving adjuvant RT. Implementation remark: For neobladder diversions or concern for higher risk of bowel toxicity, it is acceptable to omit the cystectomy bed and treat only the pelvic lymph nodes for those with negative margins.	Strong	High 91,98-103,105
Dose-fractionation		
6. For patients with (y)pT3-4N0-3M0 bladder cancer postcystectomy and negative margins, a dose of 4400-5040 cGy in 180-200 cGy fractions is recommended.	Strong	High 98,100

7. For patients with (y)pT3-4N0-3M0 bladder cancer postcystectomy and positive margins receiving a dose of 4400-5040 cGy in 180-200 cGy fractions to the pelvic lymph nodes and cystectomy bed, an SIB to the site of positive margin to a total dose of 5400 cGy is conditionally recommended.	Conditional	Moderate [98]
8. For patients with (y)pT3-4N0-3M0 bladder cancer postcystectomy and residual gross disease, an SIB to gross disease is recommended with the dose dependent on normal tissue tolerance. Implementation remark: A BED up to 6400-6480 Gy in 180-200 cGy fractions to gross disease may be an option.	Strong	Low [99]
Techniques		
9. For patients with (y)pT3-4N0-3M0 bladder cancer postcystectomy, IMRT (including VMAT) using daily image guidance with cone-beam CT to reduce dose to the rectum, bowel, and urinary diversion is recommended.	Strong	Moderate [98,100,106]
10. For patients with (y)pT3-4N0-3M0 bladder cancer postcystectomy receiving adjuvant RT, simulation and treatment with an empty urostomy bag is recommended.	Strong	Low [98,99]

Abbreviations: BED = biologically equivalent dose; CT= computed tomography; IMRT = intensity modulated radiation therapy; KQ = key question; RT = radiation therapy; SIB = simultaneous integrated boost; VMAT = volumetric modulated arc therapy.

Locoregional failure is relatively high for patients with locally advanced disease post RC, with approximately one third of patients with (y)pT3-4N0-3 disease developing locoregional failure.[91,102,103,107] Importantly, local failures are rarely salvageable, and the morbidity and mortality from local failure is high.[91] Furthermore, perioperative chemotherapy has not been shown to reduce the risk of locoregional failure.[107] Consequently, interest in adjuvant RT as a means to reduce pelvic recurrences and potentially change the patterns of failure postcystectomy has increased.

Adjuvant RT has been assessed in 3 RCTs (based on the risk stratification factors previously noted) with all showing a clinically meaningful and statistically significant improvement in local control with the addition of adjuvant RT.[98,100,101] One phase II trial enrolled 120 patients who underwent RC and pelvic lymph node dissection with negative margins and any of the following: (y)pT3b-4, pathologically node positive, or grade 3 disease (91% had ≥[y]pT3 disease and 53% had urothelial carcinoma).[101] Patients were randomized to adjuvant chemotherapy versus adjuvant chemotherapy with adjuvant RT. The addition of RT to adjuvant chemotherapy significantly improved 2-year locoregional failure-free survival (96% vs 69%) with an improvement in local control seen in the urothelial cohort on subgroup analysis.[100] The follow-up study was limited to urothelial histology only and showed that adjuvant RT significantly improved local control versus observation in this RCT.[100] The largest and most recent RCT included patients with nonmetastatic urothelial carcinoma who had ≥1 of the following after RC with lymph node dissection: (y)pT3-4, pN1-3, <10 lymph

nodes removed, positive margin, or ≥(y)cT3 downstaged with neoadjuvant chemotherapy, and reported a statistically significant improvement in the primary endpoint of locoregional failure-free survival.[98]

Identifying patients most likely to benefit from adjuvant RT is critical. A risk stratification tool was developed using data from SWOG 8710 and the retrospective experience to help identify patients at highest risk for locoregional recurrence who would benefit most from adjuvant RT.[107,108] Patients at highest risk included those with (y)pT3-4 disease and positive margins or (y)pT3-4 disease and <10 lymph nodes removed with 5-year cumulative incidence of local failure of 41%.[107,108] Patients with intermediate-risk were those with (y)pT3-4 disease and ≥10 nodes removed and negative margins with a 5-year local failure rate of 19% to 20%.[107,108] The risk stratification was subsequently validated,[109,110] however, questions remain on the importance of node-positive disease as an independent predictor of locoregional failure given the high competing risk of distant disease.

Based on available prospective and retrospective data, patients most likely to benefit from adjuvant RT are those with (y)pT3-4 or node-positive disease or with positive margins.[91,98-103,105,111-115] When considering whether to offer adjuvant RT to patients with (y)pT3-4 disease, the extent of the lymph node dissection has been shown to be an independent factor and can be taken into consideration, with <10 nodes removed associated with higher risk of locoregional failure. The extent of lymph node involvement was included in the validated risk stratification tool and was also used as an independent selection criterion in the Bladder Cancer Adjuvant Radiotherapy Trial (BART) trial.[98]

Adjuvant RT may be an option for (y)pT1-2 disease with a positive margin, though it is relatively rare. There are no data to guide decisions on the use of adjuvant RT after partial cystectomy. However, adjuvant RT may be reasonable in selected cases if the patient meets criteria for adjuvant RT as defined for the RC patient population.[116]

For patients with neobladders, adjuvant RT is not contraindicated with data showing the safety and effectiveness of adjuvant RT in this patient population.[117] The timing of adjuvant RT in the setting of a neobladder should take into account the patient's recovery of urinary continence. Close collaboration with urologists to determine optimal timing is important and longer delays (≥3 months) may be appropriate to allow for continence recovery. Referral for pelvic floor physical therapy may also be reasonable.

Adjuvant RT is generally contraindicated for patients with bladder cancer who have active inflammatory bowel disease, prior pelvic RT, and ongoing grade ≥2 GI symptoms that do not respond to medical management. For patients with prior prostate-only RT, adjuvant RT may be an option in select cases, though overlap with prior RT should be minimized and the cystectomy bed omitted from the RT field.

For patients with pure squamous cell carcinoma (with no urothelial component), adjuvant RT improved local control and disease-free survival in an RCT from Egypt in which 80% of the patients had squamous cell carcinoma.[118] An RCT from Egypt randomizing patients to adjuvant RT and adjuvant

chemotherapy versus adjuvant chemotherapy alone reported a significant improvement in local control in a cohort in which >40% of the patients had squamous cell carcinoma. Adjuvant RT improved local control in the squamous cell subgroup.[101] Given the reduced effectiveness of chemotherapy for squamous cell carcinoma of the bladder relative to urothelial carcinoma, adjuvant RT remains a reasonable option.

With the emergence of adjuvant immunotherapy as a treatment option for patients with locally advanced disease after cystectomy, the role of adjuvant RT in addition to immunotherapy should be further studied. Since adjuvant immunotherapy is typically given for a period up to 1 year, it is usually not feasible to delay adjuvant RT until after completion of immunotherapy. Early toxicity results from SWOG/NRG 1806 (*NCT03775265*) have demonstrated the safety and feasibility of this approach for chemoradiation plus immunotherapy for intact bladder cancer.[119] Additional research is needed to confirm the safety and efficacy of combination therapy and to determine optimal timing. Given limited data on the toxicity of concurrent adjuvant immunotherapy and RT in the postcystectomy setting, treating patients with adjuvant RT first (when feasible) may be preferred.

With respect to the timing of adjuvant RT, the BART trial required that patients start adjuvant RT within 8 weeks of RC or within 8 weeks of completing adjuvant chemotherapy.[98] The Egyptian trials had similar requirements.[100,101] Given the recovery from cystectomy in an elderly population, it is reasonable to delay adjuvant RT up to 4 months after cystectomy, though 2 to 3 months after cystectomy is preferred based on expert opinion of the task force.

The target volumes for postcystectomy RT should typically include the cystectomy bed and the pelvic lymph nodes up to the aortic bifurcation, including the common iliac, internal/external iliac, and obturator nodes. A patterns of failure analysis reported low rates of cystectomy failures for patients with margin-negative resections with most of the recurrences occurring in the pelvic nodes.[91] Based on this study, the initial NRG consensus contouring atlas recommended omitting the cystectomy bed for patients with margin-negative resections given concerns about the potential toxicity of irradiating the cystectomy bed.[120] Subsequent studies have reported higher rates of cystectomy bed failures even for margin negative patients. Three trials included the cystectomy bed routinely for all patients and reported low rates of locoregional failure and a favorable toxicity profile.[98,100,101] Omitting the cystectomy bed is reasonable for patients with neobladders or with a higher risk of GI toxicity if they are margin-negative. Consensus guidelines for contouring the cystectomy bed and pelvic nodes are available.[120,121]

The dose for adjuvant RT is typically 5000 to 5040 cGy in 25 to 28 fractions using conventional fractionation.[98-100,122] Lower doses (eg, 4400-4500 cGy) can be used for patients where there is greater concern for bowel toxicity/patient tolerance (eg, patients receiving concurrent adjuvant RT and immunotherapy). With the exception of a focal SIB (to positive margin or gross local or nodal disease), there is not sufficient safety/tolerability data to support hypofractionation in the adjuvant setting.[99]

Dosimetric studies have shown that IMRT (including volumetric modulated arc therapy can achieve lower doses to the rectum, bowel, and urinary diversion compared with 3-D CRT.[123] IMRT is particularly important to limit dose to the urinary diversion (eg, ileal conduit or neobladder). Daily imaging with cone-beam CT is recommended to assess changes in bowel anatomy and confirm safety/efficacy of daily setup.[98,100,106]

For CT simulation, supine position is generally preferred and the urostomy bag should be emptied prior to simulation and each treatment to reduce uncertainty as the beams may go through the urostomy bag, creating a bolus effect on the skin and introducing greater uncertainty with dose delivery to the targets and organs at risk if there is a clinically meaningful volume of urine in the urostomy bag.[98,99] Similarly, for patients with continent urinary diversions or orthotopic neobladders, emptying the reservoir immediately prior to CT simulation and before each daily treatment session to optimize reproducibility and attempt to minimize toxicity is appropriate.[98,99]

3.4. KQ4: Indications for RT and dose-fractionation for metastatic or symptomatic disease (Table 6)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ4 and Fig 2.

What are indications and appropriate dose-fractionation regimens for RT to the bladder or sites of metastases for patients with metastatic or symptomatic bladder cancer being treated with noncurative intent?

Table 8 Indications for RT and dose-fractionation regimens for metastatic or symptomatic disease

KQ4 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with (a) high-burden metastatic and locally symptomatic bladder cancer, or (b) localized or locoregional disease being treated with noncurative intent, bladder-directed RT is recommended for local control and/or palliation as follows: • 2100 cGy in 3 fractions every other day, OR • 3450-3600 cGy in 6 weekly fractions Implementation remarks: • Other dose-fractionation regimens may be appropriate depending on clinical scenario. • High burden is defined as ≥5 metastatic sites and/or presence of liver metastases. • For locoregional disease treated with noncurative intent, design the RT field to encompass all gross disease.	Strong	Moderate 75,124-129

2. For patients with low-burden metastatic bladder cancer at diagnosis, bladder-directed consolidative RT or chemoradiation with a BED of ≥4500 cGy after systemic therapy is conditionally recommended. Implementation remark: Low burden is defined as <5 metastatic sites other than pelvic lymph nodes and no presence of liver metastases.	Conditional	Low 130-132
3. For asymptomatic patients with high-burden metastatic bladder cancer, bladder-directed consolidative RT is **not** recommended. Implementation remark: High burden is defined as ≥5 metastatic sites and/or presence of liver metastases.	Strong	Low 132
4. For patients with low-burden metastatic bladder cancer (oligometastatic or oligoprogressive), ablative RT to metastatic sites, with or without systemic therapy, is conditionally recommended. Implementation remark: Low burden is defined as <5 metastatic sites and no presence of liver metastases.	Conditional	Low 133-135
5. For patients with metastatic bladder cancer being treated with noncurative intent, RT is recommended for palliation of symptomatic or potentially symptomatic metastases following a multidisciplinary, patient-centered discussion.	Strong	Expert Opinion

Abbreviations: BED = biologically equivalent dose; KQ = key question; RT = radiation therapy.

RT is used differently based on metastatic burden of disease, response to initial systemic therapy and for symptom management (Figure 2). RT is highly efficacious in palliating or preventing local symptoms from bladder cancer, including hematuria, dysuria, and irritative bladder symptoms. The only RCT in this setting, published outside the date range for this guideline's evidence review, established 2100 cGy in 3 fractions every other day as the preferred schedule for local symptom control in bladder cancer.[136] Six weekly fractions of 575 to 600 cGy is also effective and well tolerated.[75,124-129] Other palliative schedules that can be used based on the clinical context and patient preference include 1 fraction of 600 to 800 cGy, 5 fractions of 400 cGy over 7 days, and 10 fractions of 300 cGy over 14 days. For patients with nonmetastatic bladder cancer (ie, those with localized or locoregional disease) who are not candidates for curative treatment (eg, because of age and/or comorbidities), encompassing all gross disease is advised to achieve durable long-term local or locoregional control.

In patients with metastatic bladder cancer, there is increasing interest in the subgroup with low burden or oligometastatic disease. While not as established for bladder cancer as in other disease sites (eg, prostate), there is growing evidence that patients with <5 metastases (defined as non-pelvic lymph nodes or distant metastases) and without liver disease may benefit from a more aggressive local approach, both to the bladder and metastatic sites.[137,138] Ablative metastasis-directed RT may be an option, although evidence is limited.[133-135] Available data do not support specific regimens, but a sufficiently ablative RT dose and the potential combination with systemic agent(s) is imperative.[133-135]

Based on limited data in patients with metastatic disease who have responded well to systemic therapy, ablative consolidation RT to the bladder improves OS.[130-132] When treating the bladder for consolidation, it is important to prescribe a sufficient dose to the bladder (≥4500 cGy biologically equivalent dose) and to examine the possibility of combining RT with a radiosensitizing systemic agent.[130-132]

For patients with high-burden metastatic disease, defined as ≥5 metastases and/or liver disease, there are no data to support ablative RT to the bladder or metastases. While consolidation RT to the bladder in this setting is not recommended,[132] these patients benefit from palliative RT to the bladder and/or metastatic sites to prevent or alleviate symptoms. There are no data to suggest that patients with bladder cancer and brain metastases benefit less than other cancer patients from RT.[139] In fact, there is some evidence specific to bladder cancer that clearly supports the use of stereotactic radiosurgery.[140-142]

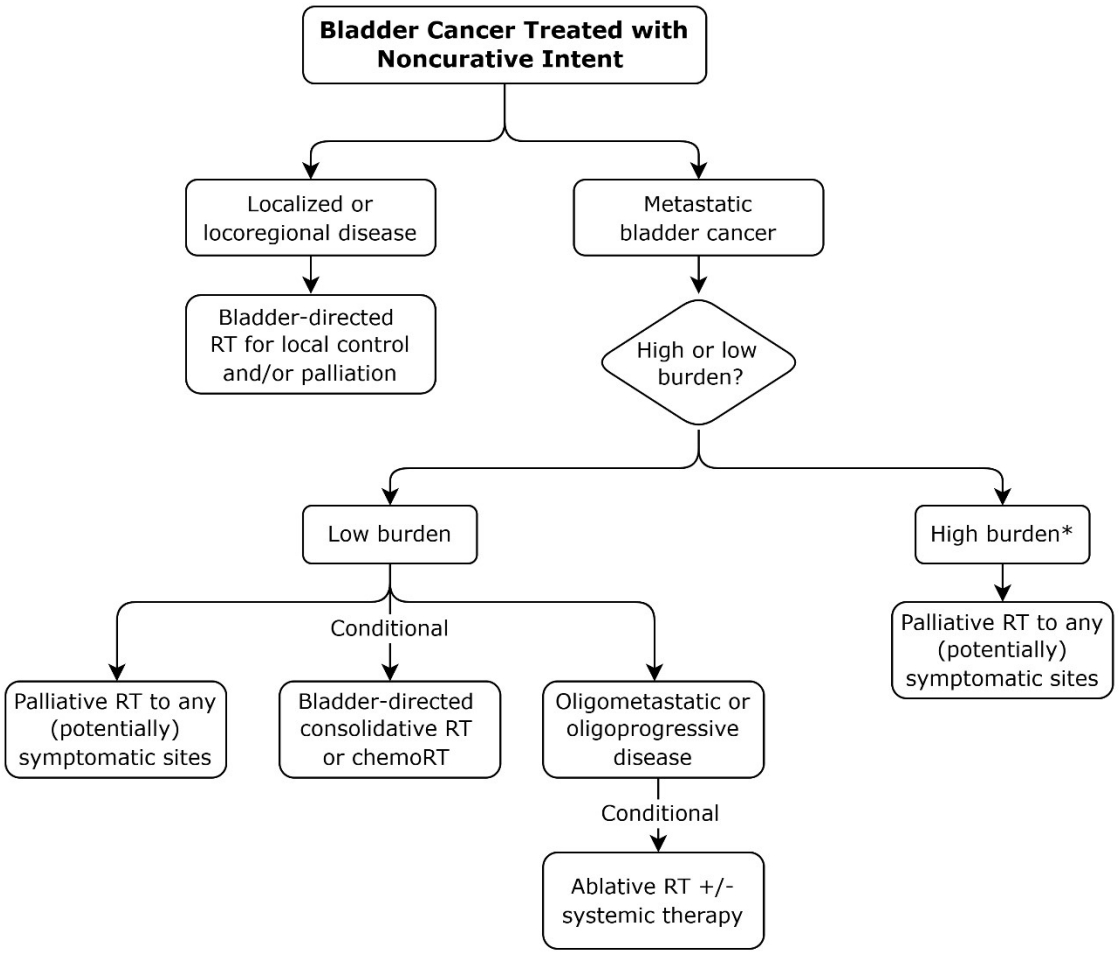

Figure 2 Management of bladder cancer treated with noncurative intent

Abbreviations: chemoRT = chemoradiation; RT = radiation therapy.

*High-burden disease is defined as ≥5 metastatic sites and/or presence of liver metastasis.

4. Conclusions and Future Directions

RT is a critical component of bladder cancer care across the spectrum of disease, including definitive TMT, postoperative therapy in high-risk patients, and palliation and symptom control in advanced and metastatic disease. Successful use of RT in these clinical scenarios requires coordinated multidisciplinary care with shared decision making, careful patient selection, and integration with systemic therapy. While the role for RT in bladder cancer has expanded, real-world disparities in treatment access, multidisciplinary care, and clinical trial access continues to exist, highlighting the need for more equitable evidence-based care delivery.[143-145]

Several areas of investigation hold promise for future practice. Validation of biomarkers, including circulating tumor DNA, genomic classifiers, and imaging such as multiparametric MRI and PET, may allow for improved staging, risk stratification, personalized treatment selection (including identifying patients most likely to benefit from RT), and posttreatment surveillance. As the systemic therapy landscape in bladder cancer continues to rapidly evolve, further studies are needed to define the optimal integration of immunotherapy (and other novel systemic therapies) with RT, both in the intact and postcystectomy settings. Ongoing trials will further clarify the role of ultrahypofractionation and adaptive RT, and future work should look to further improve access and convenience while decreasing treatment burden. Additionally, the role of metastasis-directed therapy in oligometastatic and oligoprogressive disease in the setting of improved systemic therapies will require continued study.

Future research must also focus on patient-centered outcomes with special emphasis on populations traditionally underrepresented in bladder cancer studies, including female patients.[144,146] Collection of quality of life metrics and survivorship endpoints will help ensure that any advances in treatment are put into the context of the patient experience.

These research priorities will further advance our understanding of optimal treatment strategies for a range of patients with bladder cancer while helping ensure continued innovation, improved selection, optimized integration of RT with systemic therapies, and a focus on patient-centered and evidence-based care.

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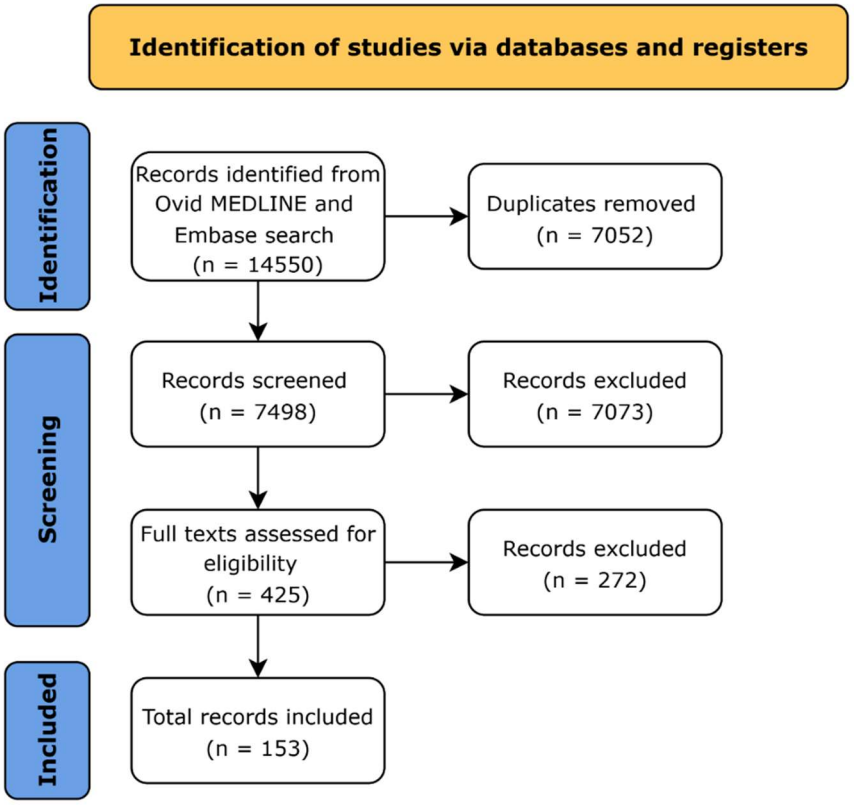

PRISMA 2020 study selection diagram[147,148]

Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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Appendix E1 Peer Reviewers and Disclosures (Comprehensive)

Added to the draft prior to publication.

Appendix E2 Abbreviations

3-D CRT = 3-dimensional conformal radiation therapy
5-FU = 5-fluorouracil
cGy = centigray
CT = computed tomography
CTV = clinical target volume
GI = gastrointestinal
IMRT = intensity modulated radiation therapy
KQ = key question
MRI = magnetic resonance imaging
MIBC = muscle-invasive bladder cancer
NMIBC = non-muscle invasive bladder cancer
OS = overall survival
PET = positron emission tomography
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RC = radical cystectomy
RCT = randomized controlled trial
RT = radiation therapy
SIB = simultaneous integrated boost
TMT = trimodal therapy
TURBT = transurethral resection of bladder tumor
VMAT = volumetric modulated arc therapy

Appendix E3 PICOTS Questions / Literature Search Strategy

Search Limits:

Search Date(s):	November 18, 2024
Age Range	Adults (≥18 years old)
Language	English only
Species	Humans
Publication Types	• RCTs • Meta-analyses • Prospective trials (phase 2/3, prospective cohort studies) • Retrospective studies (KQ 1 ≥65 pts; KQ 3 ≥100 pts) • Dosimetric studies with validated clinical endpoints (KQ3 only, ≥10 pts)
Timeframe	• January 1, 2009 – November 18, 2024 – All study types

Key Inclusions:
Histology terms: Urothelial (transitional) cell carcinoma, variant histology (squamous cell carcinoma, adenocarcinoma, neuroendocrine, plasmacytoid, sarcomatoid)
Anatomic location terms**:** Bladder

Universal Exclusion Criteria:

1. Preclinical/nonhuman studies (phase I)
2. Health economics/cost analysis studies
3. Studies available in abstract only
4. Guidelines, review articles, case reports, comments, or editorials
5. Pediatric patients
6. NCDB/SEER data
7. Otherwise not relevant or out of scope

Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 1: What are the indications and contraindications for bladder preservation with curative-intent RT, with or without systemic therapy, for patients with nonmetastatic bladder cancer?**
Definitions	Nonmetastatic defined as stage I-IIIB, (cT1-T4aN0-3) (excluding M1 disease)
Participants/ population	Nonmetastatic bladder cancer (clinical T1-T4aN0-3)
Intervention(s)/ exposure(s)	• RT +/- systemic therapy
Comparator(s)/ control	• Cystectomy (surgery) +/- neoadjuvant systemic therapy • Systemic therapy alone • TURBT alone or observation • RT alone
Outcomes: primary/critical	**Primary**: • Bladder intact event-free survival • Cystectomy-free rate • Disease-specific survival • OS • PFS • NMIBC/MIBC/pelvic recurrence rates • Complete response rates • Locoregional control/locoregional disease-free survival • Distant metastasis-free survival **Secondary**: • Patterns of failure • Patient and provider-reported QoL/adverse events/toxicities • Biomarkers (prognostic and predictive) • Posttreatment response assessment • Surveillance imaging modality (eg, MRI vs CT) • Urine cytology • Surveillance timing or intervals • Posttreatment cystoscopy • Posttreatment biopsy
Timing	Definitive
Setting/context	Any
Study design	• RCTs • Prospective • Retrospective (≥65 patients)
Health disparity considerations	Age/elderly; racial/ethnic disparities; gender; sociodemographic factors; insurance status; Latino/Hispanic; social determinants of health; time to treatment; access to care; income level; rural setting; smoking status; occupation

Key search selection criteria	Inclusion criteria: • Trimodal therapy/trimodality therapy (TURBT+ RT + chemotherapy) • Neoadjuvant chemotherapy + RT +/- systemic therapy • Bladder preservation therapy/bladder-sparing therapy/chemoRT Exclusion criteria: • Palliative intent • Prior cystectomy (salvage cystectomy is okay) • General exclusion criteria listed above
Validation set (PMID)	30433852, 35577644, 37187202, 25366678, 33689854, 19636019, 30712971, 27727064, 28081860, 28040351, 34337540, 33294644, 31400946 ,39226514, 27720221, 37478391, 38387404, 28125821, 28400426, 37870965, 36383379, 38641541

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Item	Details
	Key Question and PICO(TSS) Framework
Key clinical question(s)	**Key Question 2:** What are appropriate RT techniques (eg, target volumes, modalities, simulation, image guidance) and dose-fractionation regimens for patients with intact, nonmetastatic bladder cancer being treated with curative intent?
Definitions	Nonmetastatic defined as stage I-IIIB, (cT1-T4aN0-3) (excluding M1 disease) Other potentially relevant definitions for this KQ: • Conventional fractionation (180-200 cGy/fx) • Hypofractionation >200 cGy/fx • Hyperfractionation (≥2 fractions daily of smaller than conventional fraction size) or accelerated fractionation (dosing more than once daily to shorten total treatment time) • GTV, PTV, OAR, CTV
Participants/ population	MIBC and NMIBC (cT1-T4aN0-3)
Intervention(s)/ exposure(s)	• RT/Trimodal therapy • Hypofractionated RT • Bladder only RT • Adaptive RT • Bladder tumor boost • IMRT • Post-cystectomy/adjuvant/salvage RT • Proton therapy
Comparator(s)/ control	• Whole pelvis RT/small pelvis RT/mini pelvis RT/pelvic RT • Conventionally fractionated RT • 3-D CRT • Photon therapy
Outcomes: primary/critical	**Primary**: • Toxicity • Patterns of failure • Safety/feasibility • Dosimetric comparison **Secondary:** • Cystectomy free rate • Disease-specific survival • OS • PFS • NMIBC/MIBC/pelvic recurrence rates • Complete response rates • Locoregional control / locoregional disease-free survival • Metastasis-free survival
Timing	Any

Setting/context	Any
Study design	• RCTs • Prospective • Retrospective (>100 pts) • Dosimetric studies with validated clinical endpoints (≥10 pts)
Health disparity considerations	N/A
Key search selection criteria	**Inclusion criteria**: • Trimodal therapy/trimodality therapy (TURBT+ RT + chemotherapy) • Bladder preservation therapy/bladder-sparing therapy/chemoRT **Exclusion criteria**: • Palliative intent • General exclusion criteria listed above
Validation set (PMID)	36725382, 26547385, 38047218, 37803392, 33316362, 31301959, 29655582, 28249609, 27026308, 37931278, 37225552, 33539743, 30433852, 37730609, 35691760, 33343830, 25445550, 31400946, 37478391, 26323390, 28558986, 37185773, 27737963

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Item	Details
	Key Question and PICO(TSS) Framework
Key clinical question(s)	**Key Question 3:** What are the indications, appropriate RT techniques (eg, target volumes, modalities, simulation, image guidance), and dose-fractionation regimens for postoperative RT, with or without systemic therapy, for patients with nonmetastatic bladder cancer status post cystectomy or partial cystectomy?
Definitions	Nonmetastatic post-cystectomy or post-partial cystectomy pT1-T4apN0-3M0 with ≥1 risk factors (≥pT3, grade 3, positive nodes, positive margins)
Participants/ population	Nonmetastatic bladder cancer (pT1-T4aN0-3)
Intervention(s)/ exposure(s)	+/- RT (postoperative, adjuvant, salvage) +/- chemotherapy or other systemic therapy
Comparator(s)/ control	Cystectomy (surgery) +/- systemic therapy without RT
Outcomes: primary/critical	**Primary**: • Locoregional control / locoregional disease-free survival / locoregional failure / locoregional relapse (recurrence)-free survival / pelvic recurrence rates • Patient and provider-reported QoL/adverse events/toxicities (acute and late) • Patterns of failure • Disease-specific survival • OS • PFS • Metastasis-free survival **Secondary**: • Safety/feasibility • Surveillance imaging modality (eg, MRI vs CT) • Urine cytology • Surveillance timing or intervals • Posttreatment cystoscopy (partial cystectomy) • Posttreatment biopsy (partial cystectomy)
Timing	Postoperative, adjuvant, salvage
Setting/context	Any
Study design	• RCTs • Prospective • Retrospective

Health disparity considerations	Age/elderly; racial/ethnic disparities; gender; sociodemographic factors; insurance status; Latino/Hispanic; social determinants of health; time to treatment; access to care; income level; rural setting; smoking status; occupation
Key search selection criteria	**Inclusion criteria:** • Radical or partial cystectomy +/- systemic therapy • Postoperative/adjuvant/salvage RT +/- systemic therapy **Exclusion criteria:** • Palliative intent • General exclusion criteria listed above
Validation set (PMID)	29188298, 34893458, 38879088, 28384195, 25506244, 33573998, 27026309, 24390799, 27020106, 22543204, 22658217, 25663359, 31119885, 38994178

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Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 4:** What are indications and appropriate dose-fractionation regimens for RT to the bladder or sites of metastasis for patients with metastatic or symptomatic bladder cancer being treated with noncurative intent?
Definitions	See participants
Participants/ population	Metastatic bladder cancer (any T Any N, M1a or M1b) OR Patients with nonmetastatic bladder cancer ineligible for definitive therapy, symptomatic bladder cancer being treated with noncurative intent
Intervention(s)/ exposure(s)	• RT to bladder +/- systemic therapy • RT to metastatic disease +/- systemic therapy • SBRT
Comparator(s)/ control	• Observation/best supportive care • Chemotherapy alone/immunotherapy alone/systemic treatment alone
Outcomes: primary/critical	• Palliation • Patient and provider-reported QoL/adverse events/toxicities • Patterns of failure • Safety/feasibility • Disease control/PFS/metastasis-free survival/OS
Timing	Any
Setting/context	Any
Study design	•RCTs •Prospective •Retrospective
Health disparity considerations	Age/elderly; racial/ethnic disparities; gender; sociodemographic factors; insurance status; Latino/Hispanic; social determinants of health; time to treatment; access to care; income level; rural setting; smoking status; occupation
Key search selection criteria	**Inclusion criteria:** RT for hematuria RT for pelvic pain RT for urinary/bladder symptoms Bladder RT Pelvic RT Hypofractionated RT Palliative RT Metastasis-directed RT Metastatic bladder cancer/advanced bladder cancer Oligometastatic/oligoprogressive/oligorecurrent bladder cancer Oligometastatic genitourinary cancer RT to metastases (including stereotactic body RT) **Exclusion criteria:**

	General exclusion criteria included above
Validation set (PMID)	25975677, 28586948 ,31283979, 32723486, 36831503, 34215505, 30509099, 28465049, 30851645, 35249864, 27269944, 26421586

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; chemoRT = chemoradiation; CT = computed tomography; CTV = clinical target volume; fx = fraction(s); GTV = gross tumor volume; IMRT = intensity modulated radiation therapy; MIBC = muscle-invasive bladder cancer; MRI = magnetic resonance imaging; NCDB = national cancer database; NMIBC = non-muscle invasive bladder cancer; OAR = organ(s) at risk; OS = overall survival; PFS = progression free survival; PTV = planning target volume; QoL = quality of life; RCT = randomized controlled trial; RT = radiation therapy; SBRT = stereotactic body radiation therapy; SEER = Surveillance, Epidemiology, and End Results; TURBT = transurethral resection of bladder tumor.