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Fast progression in non-small cell lung cancer: results from the randomized phase III OAK study evaluating second-line atezolizumab versus docetaxel

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Critical Review

Executive Summary of the American Radium Society Appropriate Use Criteria for Radiation Treatment of Node-Negative Muscle Invasive Bladder Cancer

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Purpose: Definitive radiation therapy (RT), with or without concurrent chemotherapy, is an alternative to radical cystectomy for patients with localized, muscle-invasive bladder cancer (MIBC) who are either not surgical candidates or prefer organ preservation. We aim to synthesize an evidence-based guideline regarding the appropriate use of RT.

Methods and Materials: We performed a Preferred Reporting Items for Systematic Reviews and Meta-analyses literature review using the PubMed and Embase databases. Based on the literature review, critical management topics were identified and reformulated into consensus questions. An expert panel was assembled to address key areas of both consensus and controversy using the modified Delphi framework.

Results: A total of 761 articles were screened, of which 61 were published between 1975 and 2019 and included for full review. There were 7 well-designed studies, 20 good quality studies, 28 quality studies with design limitations, and 6 references not suited as primary evidence. Adjuvant radiation therapy after cystectomy was not included owing to lack of high-quality data or clinical use. An expert panel consisting of 14 radiation oncologists, 1 medical oncologist, and 1 urologist was assembled. We identified 4 clinical variants of MIBC: surgically fit patients who wish to pursue organ preservation, patients surgically unfit for cystectomy, patients medically unfit for cisplatin-based chemotherapy, and borderline cystectomy candidates based on age with unilateral hydronephrosis and normal renal function. We identified key areas of controversy, including use of definitive radiation therapy for patients with negative prognostic factors, appropriate radiation therapy dose, fractionation, fields and technique when used, and chemotherapy sequencing and choice of agent.

Conclusions: There is limited level-one evidence to guide appropriate treatment of MIBC. Studies vary significantly with regards to patient selection, chemotherapy use, and radiation therapy technique. A consensus guideline on the appropriateness of RT for MIBC may aid practicing oncologists in bridging the gap between data and clinical practice.

Introduction

An estimated 80,470 Americans received a diagnosis with bladder cancer in 2019, and there were 17,670 deaths related to this disease.[1] 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.[2-4] RC results in 5-year recurrence-free and overall survival of 53% to 89% and 44% to 77%, respectively. However, surgery can be associated with significant perioperative risk as well as diminished quality of life due to urinary, gastrointestinal, and sexual dysfunction.[5,6] Radiation-based therapy (RT), with concurrent chemotherapy when possible, commonly referred to as bladder preservation (BP), is an established treatment option for patients who are medically unfit for RC or who seek a nonsurgical alternative.[7,8] Indeed, the National Comprehensive Cancer Network guidelines has evolved to incorporate chemoradiation-based BP as a category 1 recommendation for primary treatment in 2020.[9] For well-selected patients who are otherwise surgical candidates, bladder conservation preserves function and may result in similar oncologic outcomes compared with RC. However, the only contemporary randomized trial attempting to compare outcomes between RC and RT failed to accrue.[10]

Despite the lack of randomized data demonstrating the superiority of surgery versus RT, bladder preservation accounts for only 7% to 9% of treatments for MIBC in the United States.[11] The complexity and multidisciplinary nature of MIBC treatment can result in widely disparate management decisions,[12] and there exists a pressing need for evidence-based treatment criteria. Here, we present an executive summary of the American Radium Society (ARS) appropriate use guideline for RT for MIBC based upon a systematic review of the evidence. This guideline will focus on lymph node-negative MIBC, as there is a paucity of clinical data on the use of definitive-intent radiation therapy in patients with node-positive MIBC. Similarly, management in the palliative setting, including many well-described hypofractionated RT regimens,[13,14] were beyond the scope of this panel. Little data exist for postoperative treatment of MIBC, which is not widely adopted nationally. For patients with node-positive MIBC, we strongly encourage clinical trial participation as available (eg, NRG 8185). Consistent with previous guidelines, this ARS panel recommends that patients be evaluated and advised of their treatment options in a multidisciplinary manner.[8]

Methods and Materials

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

Table 1 Literature search strategy

Search index	Search terms	No. of references
1	Bladder cancer[title] OR bladder carcinoma[title]	21,282
2	1 OR transitional cell carcinoma[title] OR urothelial carcinoma[title]	28,636
3	2 AND "invasive" [title/abstract])	7740
4	3 AND "radiation[title/abstract] OR radiation therapy[title/abstract] OR radiation therapy[title/abstract] OR chemorad*[title/abstract]	997
5	Limit 4 to English language	901
6	Limit 5 to human subjects	761

Reporting Items for Systematic Reviews and Meta-Analyses declaration.[15] The search strategy is presented in Table 1 and the literature review flowchart is presented in Fig. 1. 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. Three additional references were included for review at the discretion of the senior authors.

An expert panel consisting of 14 radiation oncologists, 1 medical oncologist, and 1 urologist from 14 US institutions was assembled. After reviewing available evidence, key clinical questions were addressed using a modified Delphi consensus framework.[16]

Results

Fifty-eight studies were included, with an addition of 3 reference sources, to create an evidence table (Table E1). Of these, there are 7 well-designed randomized trials, 20 good quality trials, 28 quality studies with design limitations, and 6 references that may not be useful as primary evidence. Each study is summarized in the evidence table, which can be found in the Supplementary Materials. Two rounds of voting were completed pertaining to the appropriateness of key management decisions for 4 clinical variants of MIBC that encompass an inclusive range of scenarios.

Who can be offered bladder preservation therapy?

Patient selection is paramount for bladder preservation. Nearly all studies reviewed included patients with cT2-T4 cN0 cM0 disease (Table E1). Some series included node-positive patients,[17-23] but most contemporary trials have excluded clinically or pathologically confirmed lymph node metastases.[24-27]

Patients who are otherwise fit for RC should typically also be candidates for chemotherapy as a part of BP. Although radical RT alone demonstrated 5-year overall survival (OS-5y) ranging from 16% to 28%,[17,28-32] combined chemoradiotherapy regimens resulted in OS-5y ranging from 52% to 74%.[18,27,33-36] Patients should undergo an attempted maximally complete trans-urethral resection of bladder tumor (TURBT), defined as no visible tumor on cystoscopy and negative urine cytology. A number of analyses of large prospective studies from Germany, the United States, and Australia have demonstrated that the extent of TURBT is a strong prognostic factor for survival.[30,34,37,38] Ureteral obstruction leading to hydronephrosis may be a negative prognostic factor for outcomes after BP. In the Massachusetts General Hospital (MGH) experience, the presence of hydronephrosis was associated on univariable analysis with decreased CR rate (68% vs 37%, $P = .002$), a 79% increased risk of death ($P < .001$), and 2-fold increased risk of disease specific mortality ($P = .001$).[38,39] Hydronephrosis became an exclusion criteria in the RTOG studies after 1993, although patients with hydronephrosis were included in most subsequent European and Australasian studies.[19,34]

Discussion

There is weak evidence to suggest that multifocal disease portends poor outcomes after BP. Rodel et al reported that multifocal disease was prognostic of lower rates of local control (LC, 52% vs 39%, $P = .08$).[37] However, multifocality was not associated with CR, distant metastasis (DM), or OS. Although carcinoma-in situ (CIS) is an exclusion criterion in many trials, the prognostic significance of CIS is also uncertain. In the MD Anderson Cancer Center radical RT series, the presence of CIS was associated with a 52% and 57% hazard of poorer OS and LC, respectively.[17] However, CIS was not shown to effect outcomes in the MGH or German experiences, in which patients received chemotherapy.[37,38]

Patient-specific factors are important in the selection process for BP in operable candidates. Some patients with MIBC previously have undergone many sequential TURBTs and intravesical instillation therapies, which can negatively affect baseline bladder function. Because RT to the whole bladder is known to further diminish function, baseline bladder performance should be adequate enough to attempt BP.[40] In the case of in-bladder recurrence, salvage cystectomy often is effective and should be promptly considered.[24,35,41-43] Patients must be motivated to participate in routine surveillance to detect in-bladder recurrences early.

In cases where patients who are not surgical candidates or decline RC, there was consensus to strongly recommend RT-based treatment (Tables 2-4). Hydronephrosis, multifocal disease, CIS, tumor size, as well as T-stage are

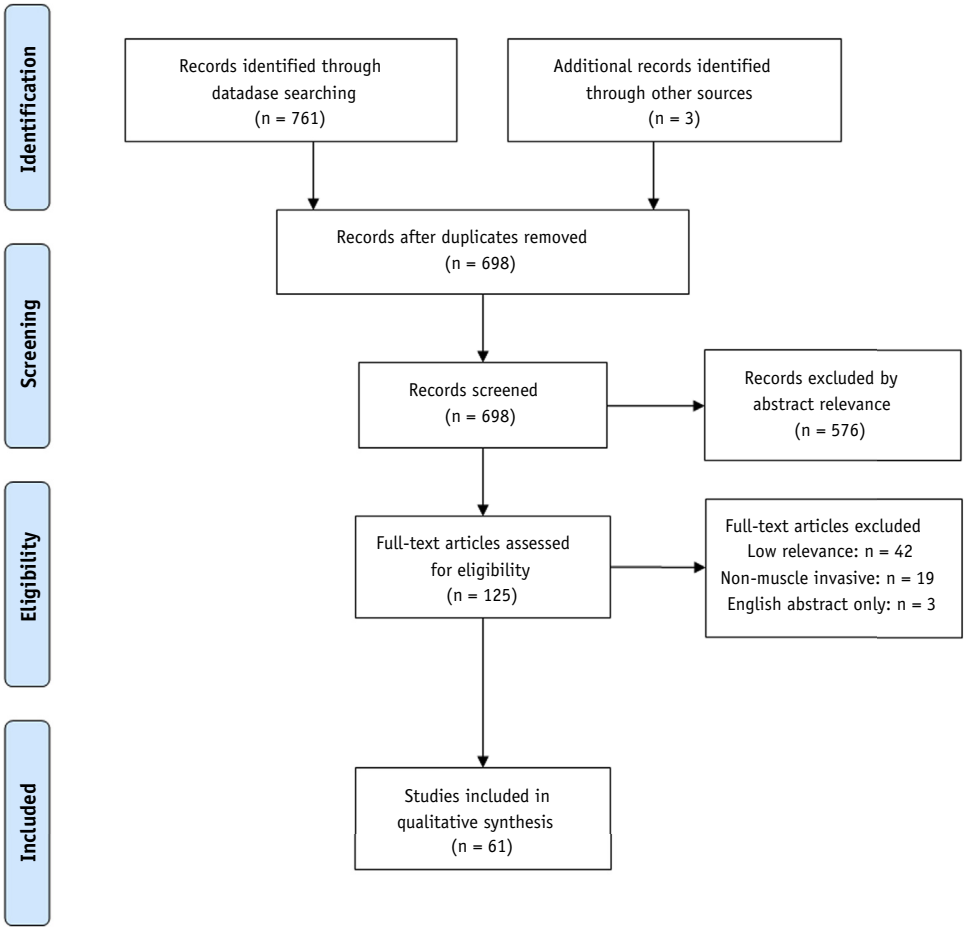

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart.

interrelated and are likely proxies for the underlying cancer biology. As such, these covariates also negatively affect outcomes after radical cystectomy.[2-4] When multiple risk factors suggest a high likelihood of local failure after MMT, neoadjuvant chemotherapy with immediate radical cystectomy may be more appropriate for surgical candidates (Table 5).

What are the optimal neoadjuvant, concurrent, or adjuvant chemotherapy options?

Concurrent chemotherapy with RT (CCRT) is the most widely adopted regimen for BP.[7,8] Cisplatin has been the most commonly used agent in North America, Australia, and Germany.[21,34,43] Cisplatin can often be combined with either paclitaxel or 5-FU as part of CCRT.[25,44,45] For patients ineligible for cisplatin due to poor renal function or hearing impairment, alternate CCRT regimens include 5-FU plus mitomycin-C,[24] paclitaxel,[46,47] or carboplatin.[37] Outcomes for these regimens are comparable, with CR rates of approximately 70%. More recently, gemcitabine-based CCRT have resulted in even higher CR rates reaching up to 93%.[19,27,36,48-53] RTOG 0712 is a randomized phase 2, multicenter study that evaluated concurrent CCRT with either 5-FU/cisplatin or low-dose gemcitabine.[26] The rates of CR were 88% and 78%, respectively. Distant-metastasis free survival at 3 years was 78% and 84%, respectively. The ongoing phase 2 trial GETUG V04 compares cisplatin and gemcitabine-based CCRT.[52] Cisplatin-based CCRT was preferred by the panel for patients undergoing BP with adequate renal function, however, nonplatinum CCRT also was deemed appropriate (Tables 2-4).

Neoadjuvant chemotherapy before RT for BP has been explored in 2 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.[42] CCRT was not used. Neoadjuvant MCV was shown to improve OS at 5 years by 6% (39% vs 43%, $P = .037$). RTOG 8903 compared neoadjuvant MCV followed by cisplatin-based CCRT versus CCRT alone.[54] There were no significant differences in CR, OS, DM, or bladder conservation rates. This trial closed early owing to high rates of neutropenia and sepsis leading to 3 treatment-related deaths. The high rates of MCV-related toxicity recapitulated results of an earlier phase 2 study, in which there were 4 sepsis-related deaths during neoadjuvant treatment.[55] As a caveat, the

Table 2 Clinical variant 1, a 67-year-old, current smoker, sexually active man with a recent diagnosis of a 3 cm 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

Procedure	Rating category	Group median rating	Disagree	References	SQ	SOE	SOR
External beam RT	A	8		16-19,21-29,31,34-55,57-61	1	S	↑
Split course XRT	A*	5	X	35,36,39,42,45-49,51,53	1	S	↓
Continuous course XRT	A	8.5		23-34,37,40,41,43,44,50-52,54-56,58,59,61	1	S	↑
Neoadjuvant chemotherapy	M	5		39,41-46,48,61	1	M	↓
Concurrent cisplatin-based chemotherapy	A	9		20,22-24,31,35-40,42-49,53-56,61	1	S	↑
Concurrent noncisplatin-based chemotherapy	A	7		25-30,32-34,44,46,50	1	S	↑
Adjuvant chemotherapy, in absence of neoadjuvant chemotherapy	M	4.5		37,38,47,49	2	L	↓
Maximal TURBT	A	9		22-61	1	S	↑
IMRT	A	7		56	3	M	↑
3D conformal RT	A	8		16-19,21-29,31,34-55,57-61	1	S	↑
Elective pelvic nodal XRT	M*	5	X	21,22,30,35,36,38-40,42,44,45,47-49,54,56,57,61	2	M	↓

Abbreviations: 3D = 3-dimensional; IMRT = intensity-modulated radiation therapy; RC = radical cystectomy; RT = radiation therapy.
Rating: A = usually appropriate; M = may be appropriate; U = usually not appropriate.
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.
* Disagreement (ie, 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.

Table 3 Clinical variant 2, an 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

Procedure	Rating category	Group median rating	Disagree	References	SQ	SOE	SOR
External beam RT	A	8.5		13-61	1	S	↑
Split course XRT	M*	5	X	35,36,39,42,45-49,51,53	1	S	↓
Continuous course XRT	A	9		23-34,37,40,41,43,44,50-52,54-56,58,59,61	1	S	↑
Neoadjuvant chemotherapy	M	5		39,41-46,48,61	1	M	↓
Concurrent cisplatin-based chemotherapy	A	8		20,22-24,31,35-40,42-49,53-56,61	1	S	↑
Concurrent noncisplatin-based chemotherapy	A*	5	X	25-30,32-34,44,46,50	1	S	↑
Adjuvant chemotherapy, in absence of neoadjuvant chemotherapy	M	4		37,38,47,49	2	L	↓
Maximal TURBT	A	9		22-61	1	S	↑
IMRT	A	7		56	3	M	↑
3D conformal RT	A	8		13-61	1	S	↑
Elective pelvic nodal XRT	M*	5	X	21,22,30,35,36,38-40,42,44,45,47-49,54,56,57,61	2	M	↓

Abbreviations: 3D = 3-dimensional; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; IMRT = intensity-modulated radiation therapy; RC = radical cystectomy; RT = radiation therapy.
Rating: A = usually appropriate; M = may be appropriate; U = usually not appropriate.
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.
* Disagreement (ie, 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.

Table 4 Clinical variant 3, a 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

Procedure	Rating category	Group median rating	Disagree	References	SQ	SOE	SOR
External beam RT	A	8		14-19,21,25-30,32-34,44,50	1	S	↑
Split course XRT	M*	5	X	46	3	S	↓
Continuous course XRT	A	8.5		25-30,32-34,44,50	1	S	↑
Concurrent carbogen and nicotinamide	M*	5	X	59,60	1	M	↓
Concurrent 5-FU/MMC chemotherapy	A	7.5		21,24,50,55	1	S	↑
Concurrent gemcitabine-based chemotherapy	A	8		25-30,32-34,49	2	S	↑
Maximal TURBT	A	7.5		22-30,32-34,44,50	1	S	↑
IMRT	A	8		56	3	M	↑
3D conformal RT	A	7.5		14-19,21,25-30,32-34,44,50	1	S	↑
Elective pelvic nodal XRT	M	6		21,30,44	2	M	↓

Abbreviations: 3D = 3-dimensional; IMRT = intensity-modulated radiation therapy; RC = radical cystectomy; RT = radiation therapy.
Patient was deemed unable to receive cisplatin by medical oncology team due to his poor renal function.
Rating: A = usually appropriate; M = may be appropriate; U = usually not appropriate.
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.
* Disagreement (ie, 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.

initial eligibility criteria for RTOG 8903 included patients with 24-hour creatinine clearance as low as 50 mL/min and serum creatinine up to 2.0 mg/dL. After the protocol was modified to require better baseline renal function, no additional grade 4 or 5 toxicity was seen in subsequent patients. 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% to 86%, 68% to 72%, and 76% to 79%, respectively.[56-59] Neoadjuvant chemotherapy was rated as potentially appropriate, with a weak recommendation (Tables 2, 3, and 5).

The benefit of adjuvant chemotherapy therapy after CCRT is unclear and to date, there are no published randomized trials comparing CCRT with and without adjuvant chemotherapy. RTOG 9706, 9906, and 0233 were nonrandomized phase 1 or 2 trials adding MCV or cisplatin/gemcitabine as adjuvant therapy, resulting in 5-year OS ranging from 56% to more than 70%.[25,44,45] As expected, adjuvant treatments came at the expense of more than 50% to 70% of patients in these trials experiencing acute grade 3 to 4 toxicities. Adjuvant chemotherapy was rated as potentially appropriate, with a weak recommendation (Tables 2, 3, and 5).

What radiation dose and fractionation are most appropriate?

Radiation therapy can be delivered as a continuous or a split course—the latter to allow for response assessment for potential immediate salvage cystectomy. For operable patients who refuse surgery, continuous course RT 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 standard fractions to the tumor or whole bladder.[24,34,35,60] Outcomes were not clearly better with higher dose: in one series where patients received less than 60 Gy, the CR rate was 88.4%, whereas CR was 70% in a separate series in which patients received 63 to 64 Gy. However, these comparable results are confounded by differences including patient selection, chemotherapy regimens, and radiation therapy techniques.

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 potentially increased morbidity of cystectomy after high dose pelvic RT.[41,61] Additionally, CR after RT is a strong predictor of overall survival, and early salvage for patients without CR after induction RT may be beneficial.[17,37] In the MGH selective bladder sparing protocol, 39.6 Gy was delivered in 1.8 Gy fractions to the entire pelvis, followed by a break to evaluate for response, followed by an additional 25.2 Gy to the tumor plus margin for complete responders.[54]

A potential disadvantage to split-course RT is that the prolonged total treatment time can result in decreased biological effectiveness.[62] In a large retrospective Dutch study, there was a trend toward inferior locoregional control with longer total treatment times (47% for greater than 75 days vs 63% for less than 75 days, $P = .08$).[22] There was

Table 5 Clinical variant 4, an 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

Procedure	Rating category	Group median rating	Disagree	References	SQ	SOE	SOR
Bladder preservation if patient is a good candidate for RC, but desires bladder preservation	M*	5	X	16-19,21-29,31,34-55,57-61	1	S	↓
Bladder preservation if patient is a good candidate for RC, but refuses surgery	A	7		16-19,21-29,31,34-55,57-61	1	S	↑
Bladder preservation if patient is not a RC candidate	A	9		13-61	1	S	↑
Neoadjuvant chemotherapy	M	5.5		39,41-46,48,61	1	M	↓
Concurrent cisplatin-based chemotherapy	A	7.5		20,22-24,31,35-40,42-49,53-56,61	1	S	↑
Concurrent noncisplatin-based chemotherapy	A	8		25-30,32-34,44,46,50	1	S	↑
Adjuvant chemotherapy, in absence of neoadjuvant chemotherapy	M	4		37,38,47,49	2	L	↓
Maximal TURBT	A	8.5		22-61	1	S	↑
IMRT	A	8		56	3	M	↑
3D conformal RT	A	8		16-19,21-29,31,34-55,57-61	1	S	↑
Elective pelvic nodal XRT	M*	5	X	21,22,30,35,36,38-40,42,44,45,47-49,54,56,57,61	2	M	↓

Abbreviations: 3D = 3-dimensional; IMRT = intensity-modulated radiation therapy; RC = radical cystectomy; RT = radiation therapy.
Rating: A = usually appropriate; M = may be appropriate; U = usually not appropriate.
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.
* Disagreement (ie, 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.

no difference in overall survival. Maciejewski et al generated a statistical model based on clinical data that predicted a local control 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.[63] These 2 studies examined RT alone; it is unknown whether time effects remain as influential with concurrent chemotherapy. RTOG protocols with split-course and concurrent chemotherapy resulted in relatively high local control rates despite treatment breaks. However, the currently enrolling SWOG/NRG S1806 trial does not allow for split-course RT. The panel did not reach a uniform decision on the appropriateness of split-course RT, but generally felt that this approach was more appropriate in patients for whom cystectomy is an option (Tables 2-4).

What are the most appropriate RT fields?

RT treatment volumes vary significantly between clinical trials. In RTOG trials and the University of Erlangen studies, the pelvic lymph nodes are usually treated to elective doses during the induction phase of the split-course regimen.[34,54,60,64] Elective pelvic lymph node irradiation (PLNI) was incorporated into RTOG protocols based on surgical series showing approximately a 25% risk of LN-involvement in clinically node-negative patients.[4,64] 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.[44] The tumor or whole bladder was then boosted to the maximum dose during the consolidation phase (in earlier trials) or as a concomitant boost during induction (in later trials). In comparison, patients in BC2001, TROG 97.01, and many European trials were treated to the whole bladder plus a 1.5 to 2.0 cm margin.[24,27,34] These trials excluded clinically node-positive patients, and all had rates of pelvic control comparable to trials which included pelvic nodal irradiation. The rates of pelvic nodal failure in BC2001 and the TROG trials were less than 10%. A randomized trial including 230 patients with cN0 MIBC compared CCRT with elective whole pelvic RT versus same with bladder plus 2cm margin only.[60] 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 and concurrent chemotherapy (3.9% vs 2%). There were no

differences in late effects. Due to significant differences in practices between North American and European clinicians, and historical use of elective pelvic LN fields, members of the ARS bladder panel felt that elective PLNI can be appropriate for patients with cT2-T4 cN0 M0 MIBC (Tables 2-5).

Inclusion of the entire bladder within the clinical target volume is partly motivated by surgical series revealing a high rate of discordance in the primary tumor location between urologists' preoperative identification and that of the actual cystectomy specimen.[65] In BC2001, patients were also randomized to whole bladder irradiation or whole bladder irradiation to 80% prescription dose plus boost to the tumor volume.[66] Although a reduction in bladder volume receiving full dose was shown to be noninferior with regards to local control, there was no demonstrated advantage in toxicity. Similarly, a trial conducted at Christie Hospital in the United Kingdom randomized 149 patients to either whole bladder or partial bladder (tumor plus 1.5 cm margin) RT; disease control and toxicities were not different.[67] Both of the trials used 3-dimensional (3D) approaches for RT, and it is unknown whether more conformal techniques, such as intensity-modulated radiation therapy (IMRT), would be able to produce clinically relevant differences in toxicity by better sparing uninvolved bladder.

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 radical cystectomy, with the exception that a split-course regimen to assess for CR is typically unnecessary for medically inoperable patients (Table 3).

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

Historically, radical RT alone was reserved for nonoperative candidates and demonstrated 5-year overall survival rates ranging from 16% to 28%.[17,28-32] Total dose ranged from 60 Gy to 70 Gy in 2 Gy fractions and PLNI was typically used. Many nonoperative candidates are also cisplatin-ineligible. In such cases, alternative chemotherapy agents should be considered (eg, 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.[24] 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).[68] 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.[69] Although experience with RT + CON is limited in North America, this approach is evidence-based and should be strongly considered in patients with MIBC who are ineligible for RC and cannot receive concurrent chemotherapy with RT.

3D conformal versus intensity modulated RT

Nearly all trials reviewed used 3D conformal RT (3D-CRT) technique (4- or 3-field box, see evidence table). 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).[70] IMRT significantly reduced dose to the small bowel, resulting in a decrease in grade 2 diarrhea during treatment (30% vs 56%, $P = .008$), but there was no difference in late toxicity. The panel recommends both 3D-CRT and IMRT as being appropriate (Tables 2-5).[15]

Conclusions

1. Patients with MIBC should be evaluated in a multidisciplinary tumor board, including a urologic oncologist, medical oncologist, and radiation oncologist.

2. The panel strongly recommends that definitive radiation therapy (with concurrent chemotherapy if tolerable or as monotherapy) usually is appropriate for patients with MIBC who are ineligible for radical cystectomy.

3. The panel conditionally recommends that response-adapted, selective bladder preservation (ie, definitive radiation therapy 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.

4. The panel strongly recommends that maximal TURBT before definitive (chemo)RT usually is appropriate for patients undergoing bladder-preserving RT for MIBC.

5. The panel strongly recommends that concurrent chemotherapy (cisplatin alone, 5-FU/MMC, or low-dose

gemcitabine) usually is appropriate for patients undergoing bladder-preserving RT for MIBC.

6. 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.

7. 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.

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

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

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

11. 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.

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

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