Advances in Radiation Oncology (2024) 9, 101302

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Dose-Escalated Radiation Therapy as Primary Treatment for Residual Bladder Cancer After Transurethral Resection

Yu-Chen Chang, MD,[a] Yao-Yu Wu, MD,[a] Din-Li Tsan, MD,[a,b] Wing-Keen Yap, MD,[a] Kan-Hsin Fan, MD,[c] Joseph Tung-Chieh Chang, MD, MHA,[a] and Eric Yi-Liang Shen, MD, PhD[a,d,e,*]

[a]Department of Radiation Oncology and Proton Therapy Center, Linkou Chang Gung Memorial Hospital and Chang Gung University, Taoyuan City, Taiwan; [b]Department of Radiation Oncology, Chang Gung Memorial Hospital, Keelung, Taiwan; [c]Department of Radiation Oncology, New Taipei Municipal Tucheng Hospital, New Taipei City, Taiwan; [d]Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, London, United Kingdom; and [e]Clinical Metabolomics Core Lab, Chang Gung Memorial Hospital at Linkou and Chang Gung University, Taoyuan, Taiwan

Received 28 November 2022; accepted 26 March 2023

Purpose: The aim of this study was to determine whether escalating the local radiation dose can improve the outcome of residual bladder cancer after transurethral resection of bladder tumor without increasing treatment-related toxicity.

Methods and Materials: The treatment plans and medical records of patients with bladder cancer treated with curative-intent radiation therapy between 2008 and 2020 were reviewed. Those who had residual tumors in the computed tomography simulation images were included. A cumulative radiation dose higher than 6600 cGy was defined as dose escalation. The effect of dose escalation on 3-year locoregional control, progression-free survival, and overall survival was evaluated.

Results: A total of 149 patients with residual tumors were identified. The median follow-up period was 27.5 months. Among them, 51 patients received an escalated radiation dose, and 98 received a standard dose in the residual tumor area. Patients in the dose-escalation group had higher 3-year locoregional control (65.6% vs 27.8%; $P < .001$) and progression-free survival (42.6% vs 18.2%; $P < .001$) than the standard-dose group. Overall survival also showed a trend favoring the dose-escalation group (54.9% vs 36.2%; $P = .059$). In the multivariate analyses, the differences between the dose-escalation and standard-dose groups were significant in terms of locoregional control (hazard ratio, 0.32; CI, 0.18-0.59; $P = <.001$) and progression-free survival (hazard ratio, 0.51; CI, 0.32-0.82; $P = .005$). There was no statistical difference in acute and chronic treatment-related toxicities between the 2 groups.

Conclusions: The outcome of residual bladder cancer after transurethral resection of bladder tumor could be improved by dose-escalated radiation therapy.

Introduction

Tri-modality therapy with transurethral resection of bladder tumor (TURBT) and concurrent chemoradiation has been proposed for organ preservation in muscle-invasive bladder cancer (MIBC).[1,2] While using this approach,

Sources of support: This work was supported by Chang Gung Memorial Hospital, Taiwan (No. CMRPG3G1211-3 and CLRPG3K0022) for data interpretation and proofreading. The funding source had no role in the design, practice, or analysis of this study.

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

*Corresponding author: Eric Yi-Liang Shen, MD, PhD; emails: patience.tw@gmail.com, pts@adm.cgmh.org.tw

https://doi.org/10.1016/j.adro.2023.101302

the treatment outcome is affected by the completeness of TURBT. In a previous study, a complete TURBT has been found to correlate with good tumor response.[3]

Since maximal TURBT is not always feasible when considering patient preference, suitability for surgery, tumor location, and tumor invasiveness, residual tumors after TURBT were reported in approximately 40% of patients before radical cystectomy.[4] Another retrospective study revealed pathologic upstaging from clinical staging in 42% of patients after radical cystectomy, implying the incompleteness of TURBT as well.[5] Furthermore, 1 study from the Surveillance, Epidemiology, and End Results registry found that 48% of TURBT sampling did not have detrusor muscle, which also indicates poor prognoses.[6] Therefore, repeat-TURBT is recommended in most MIBC treatment guidelines.

The effect of radiation dose escalation in the tumor bed in tri-modal treatment has been investigated. In a National Cancer Database study, dose-escalated radiation therapy was shown to improve overall survival (OS) in elderly patients receiving bladder-preserving treatment.[7] However, regarding the treatment-related toxicity, the dose-escalation strategy could have been limited owing to the challenges in preserving surrounding critical organs in the early radiation therapy era. Moreover, the efficacy of applying the dose-escalation strategy to residual tumors after TURBT has not been evaluated. In this study, we aimed to determine whether escalating radiation doses using modern radiation therapy techniques can improve treatment outcomes for patients with residual bladder tumors without increasing the treatment-related toxicities.

Methods and Materials

Patients

Data from the Cancer Registry of Chang Gung Memorial Hospital Linkou branch between March 2008 and December 2020 were reviewed. We included bladder cancer patients who underwent curative radiation therapy (≥5940 cGy to tumor areas) alone or combined with other treatments. Patients with residual tumors after TURBT were included, which incorporated incomplete TURBT in the cystoscope reports, or identified visible remnant tumors on magnetic resonance imaging or pre-radiation therapy computed tomography (CT) simulation images. The exclusion criteria were as follows: the presence of distant metastasis, palliative treatment for bladder cancer, previous radiation therapy for bladder cancer, or radical cystectomy. Associated data, including age, sex, comorbidities, body mass index, TURBT results, tumor grade and differentiation, tumor status in CT simulation, chemotherapy regimen, radiation therapy dose, dose-volume histogram of each radiation therapy plan, and post-treatment follow-ups such as cystoscopy and medical records, were collected. The protocol for this study has been approved by a suitably constituted ethics committee of the institution, and it conforms to the provisions of the Declaration of Helsinki by the Chang Gung Medical Foundation Institutional Review Board (IRB no. 202200049B0).

Treatment

According to the treatment guideline of the Chang Gung Memorial Hospital Linkou branch, radiation therapy was indicated for the purpose of organ preservation or for unresectable bladder tumors. Concurrent chemotherapy was suggested unless the general condition of patients precluded treatment, as judged by clinicians. The primary concurrent chemotherapy regimen was platinum-based. The irradiated field encompassed the entire urinary bladder and regional lymphatics. All patients underwent CT simulation for target volume delineation and radiation therapy treatment planning. Radiation therapy was delivered using a 6/10 MV x-ray via linear accelerators (Varian, Palo Alto, CA). Techniques of radiation therapy included 3-dimensional conformal radiation therapy (3DCRT), intensity modulated radiation therapy (IMRT), or volumetric-modulated arc therapy.

In the standard-dose group, the total radiation dose was 5940 to 6600 cGy in 30 to 36 fractions (180-200 cGy per fraction) to the whole bladder, whereas a radiation dose >6600 cGy was prescribed to residual tumors by either the simultaneous integrated boost or sequential boost techniques for the dose-escalation group. A minimum dose of 110% to 120% of the prescribed dose was delivered to residual tumors while using the simultaneous integrated boost technique. A planning target volume margin of 5 mm was established around the residual tumors for patients receiving radiation therapy using the sequential boost technique. Prophylactic lymphatic irradiation was applied with 4500 to 5040 cGy in 25 to 28 fractions. The constraints for both groups were the same. The regimens of concurrent chemotherapy included cisplatin, 5-fluorouracil, or gemcitabine.

Follow-up and treatment-related adverse events

The follow-up protocol after the completion of treatment included urine cytology, cystoscopy, and physical examination every 3 months in the first year, and then every 3 to 6 months. Imaging studies were performed 3 to 6 months after treatment completion and then yearly.

Genitourinary (GU) and gastrointestinal (GI) toxicity was graded according to the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE 4.03). The worst treatment-related adverse events during treatment or within 1 month after the end of treatment were graded and categorized as acute toxicity. Toxicity that happened 1 month after treatment completion was classed as late toxicity.

Endpoints and statistical analysis

The primary endpoint was the 3-year locoregional control rate (LRC), which was defined from the initiation of radiation therapy to the first detection of locoregional recurrence or death from any cause, whichever occurred first. The secondary endpoints were 3-year progression-free survival (PFS) and 3-year OS. PFS was defined as the time between the initiation of radiation therapy and tumor progression or death from any cause. OS was defined as the time from the initiation of radiation therapy to death from any cause. Patients who were lost to follow-up were censored at the time of the last follow-up.

Survival curves were estimated and compared using the Kaplan-Meier method and the log-rank test, respectively. The univariate and multivariate analyses were conducted using Cox proportional hazards regression. Pearson's χ^2 test was used for the comparison of adverse event numbers. The calculations were performed using SPSS Statistics version 22 (IBM, Armonk, NY) and the statistical programming language and environment R (version 4.2.2).[8] The survival plots were plotted using GraphPad Prism 9 (GraphPad, San Diego, CA).

Results

Patients

In total, 149 patients were identified with possible residual bladder tumors using preradiation therapy CT imaging. By examining the dose-volume histograms and treatment plans, 51 patients were found to receive doses higher than 6600 cGy for the residual bladder tumor (the dose-escalation group). The other 98 patients who received less than or equal to 6600 cGy were categorized as the standard-dose group. Among those who received concurrent chemotherapy, 90% (63/70) received platinum-based regimens. The patient- and tumor-associated characteristics between the dose-escalation and standard-dose groups were analyzed. No significant difference in those characteristics was found between these 2 groups. Detailed information is presented in Table 1.

Treatment results

The median follow-up time for the 149 patients was 27.5 months. Among them, 73 (49.0%) experienced local recurrence, and 19 (12.8%) had regional recurrences. Distant metastases developed in 43 (28.9%) patients. Eighty-five (57.0%) patients died during the follow-up period. The overall 3-year LRC, PFS, and OS were 40.0%, 23.0%, and 33.0%, respectively. The 3-year LRC, PFS, and OS of the dose-escalation and standard-dose groups were 65.6% and 27.8%, 42.6% and 18.2%, and 54.9% and 36.2%, respectively. Compared with the standard-dose group, the dose-escalation group had significantly higher LRC ($P < .001$) and PFS ($P < .001$) and a trend toward better OS ($P = .059$), implying improved outcomes by escalating radiation dose. The LRC, PFS, and OS of each group are shown in Fig. 1A-C, respectively.

Table 1 Patients and tumor characteristics at baseline

Characteristic	Dose escalation (n = 51)	Standard dose (n = 98)	*P* value*
RT dose (cGy), median (range)	6930 (6644-7326)	6300 (5940-6600)	<.001
Age (y), median (range)	74.2 (47.7-92.3)	77.5 (40.5-93.1)	.528
Male sex	35 (68.6%)	66 (67.3%)	.874
ECOG 0-1	43 (84.3%)	84 (85.7%)	.819
BMI ≥ 25	20 (40.0%)	31 (32.6%)	.377
Multimorbidity†	33 (64.7%)	58 (59.2%)	.512
T1-2‡	29 (56.9%)	62 (63.3%)	.447
N−‡	46 (90.2%)	85 (86.7%)	.538
Multi foci	24 (47.1%)	52 (53.1%)	.487
Hydronephrosis	18 (35.3%)	34 (34.7%)	.942
Hb (g/dL), median (range)	12.0 (5.1-16.0)	11.9 (4.4-16.3)	.720
Concurrent chemotherapy	29 (56.9%)	41 (41.8%)	.081

Abbreviations: BMI = body mass index; CCRT = concurrent chemoradiotherapy; ECOG = Eastern Cooperative Oncology Group; Hb = hemoglobin; RT = radiation therapy.
*By Pearson's χ^2 test.
†Charlson Comorbidity Index ≥3 points.
‡According to the American Joint Committee on Cancer−Clinical Staging eighth edition.

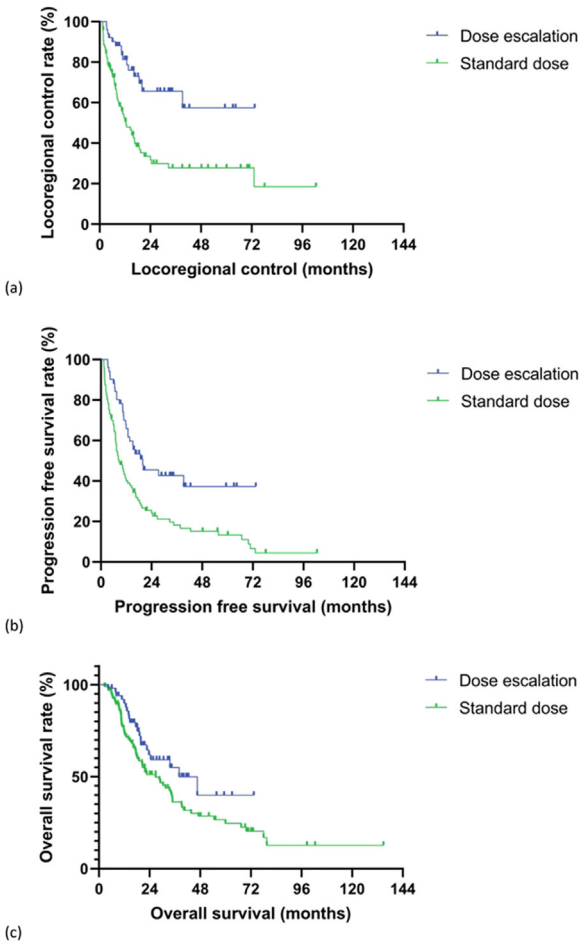

Figure 1 Treatment outcomes for the dose-escalation and standard-dose groups. These figures show the locoregional control (A), progression-free survival (B), and overall survival (C) of patients in the dose-escalation and standard-dose groups. The *P* values calculated by the log-ranked test were <.001, <.001, and .059 for locoregional control, progression-free survival, and overall survival, respectively.

Univariate and multivariate analyses

In the univariate analysis, the escalated dose and the presence of hydronephrosis were significantly associated with LRC. The multivariate analysis further confirmed the significance of the association of dose escalation and hydronephrosis with LRC (hazard ratio, 0.32; CI, 0.18-0.59; $P <$ .001 for dose escalation; hazard ratio, 1.99; CI, 1.22-3.23; $P = .005$ for hydronephrosis). The details of the univariate and multivariate analyses of LRC are shown in Table 2.

Regarding PFS, the escalated dose, nodal status, and presence of hydronephrosis showed statistical significance in the univariate analysis. The escalated dose and the presence of hydronephrosis were identified as significant parameters for PFS in the multivariate analysis. In the univariate analysis, OS was associated with age, performance status, tumor and nodal status, presence of hydronephrosis, and hemoglobin level. The multivariate analysis also showed the significance of sex, nodal status, presence of hydronephrosis, and hemoglobin level to OS. The details of the univariate and multivariate analyses of PFS and OS are shown in Table E1.

Treatment-related adverse events

Overall, approximately 50% of the study cohort experienced grades 1 to 2 acute GU and GI toxicity. In the dose-escalation group, no acute GU or GI toxicity higher than grade 3 was noted. A total of 3.1% (3/98) of the standard-dose group patients had grade ≥3 acute GU toxicity. No grade ≥3 acute GI toxicity was developed in the standard-dose group. No statistical significance in the numbers of acute toxicity was reached between the dose-escalation and standard-dose groups.

Regarding late toxicity, 43.1% (22/51) and 40.8% (40/98) patients had grade 1 to 2 late GU toxicity in the dose-escalation and standard-dose groups, respectively. Grade ≥3 late GU toxicity were developed in 17.6% (9/51) and 14.3% (14/98) patients in the dose-escalation and standard-dose groups, respectively. No statistical difference in the event number of late GU toxicity was found. Grades 1 to 2 late GI toxicities were reported in 5.9% (3/51) and 13.3% (13/98) of the dose-escalation and standard-dose groups, respectively. Less than 5% of patients had grade ≥3 late GI toxicity. The details of the treatment-related adverse events are shown in Table 3.

Discussion

Tri-modality therapy has been applied for organ preservation in bladder cancer.[9-11] However, the incompleteness of TURBT hampers the performance of tri-modality therapy.[12] This indicates the need for improving the treatment outcome for patients with residual bladder tumors after TURBT. The use of radiation dose escalation has been shown to improve the treatment outcome of muscle-invasive bladder cancer.[13] However, evidence of dose escalation for residual tumors after TURBT is scarce. This study demonstrates that the dose escalation strategy improves LRC and PFS for bladder cancer with incomplete TURBT. A dose higher than 6600 cGy also showed a trend toward better OS, providing an alternative salvage treatment for residual bladder tumors. Furthermore, the acute and late GU and GI toxicities were similar between patients who received escalated radiation doses and those who received standard doses, indicating the feasibility of dose escalation in the modern era.

In our study, the overall 3-year LRC, PFS, and OS were inferior to those in the available literature.[1,2,10,14,15] This

Table 2 Univariate and multivariable analysis for locoregional control

Locoregional control Characteristic	Univariate			Multivariable		
	HR	95% CI	*P* value*	HR	95% CI	*P* value*
Dose-escalation (vs standard-dose)	0.35	0.20-0.61	<.001	0.32	0.18-0.59	<.001
Age (y) ≥ 75 (vs <75)	0.83	0.53-1.30	.420	0.82	0.50-1.34	.427
Male (vs female)	1.20	0.72-1.90	.520	1.08	0.62-1.86	.785
ECOG 0-1 (vs ≥ 2)	0.61	0.28-1.30	.210	0.51	0.21-1.24	.138
BMI ≥ 25 (vs <25)	1.20	0.77-2.00	.400	1.50	0.90-2.50	.123
Multimorbidity†	0.74	0.47-1.20	.190	0.81	0.47-1.39	.450
T1-2 (vs T3-4) ‡	0.78	0.49-1.20	.290	0.82	0.46-1.45	.489
N− (vs N+)‡	0.54	0.29-1.00	.064	0.73	0.33-1.60	.432
Multi foci	1.40	0.90-2.30	.130	1.21	0.74-1.97	.457
Hydronephrosis	1.80	1.20-2.90	.009	1.99	1.22-3.23	.005
Hb (g/dL) ≥ 12.5 (vs <12.5)	0.75	0.47-1.20	.230	0.71	0.40-1.24	.226
CCRT (vs RT alone)	0.88	0.56-1.40	.600	0.76	0.44-1.34	.347

Abbreviations: BMI = body mass index; CCRT = concurrent chemoradiotherapy; ECOG = Eastern Cooperative Oncology Group; Hb = hemoglobin; HR = hazard ratio; RT = radiation therapy.
*By Cox proportional hazards regression.
†Defined by Charlson Comorbidity Index ≥3 points.
‡According to the American Joint Committee on Cancer—Clinical Staging eighth edition.

could be related to the study cohort's characteristics, including relatively older age, more multimorbidity, advanced tumor stage, multi foci, more hydronephrosis, low hemoglobin level, and lack of concurrent chemotherapy.[4,16] The inferior outcomes could be attributed to the inclusion criterion stipulating that only patients with residual tumors after TURBT were analyzed in our study. Nevertheless, despite the unsatisfactory nature, the treatment outcomes were significantly improved by increasing the radiation dose, suggesting that the dose escalation strategy holds the potential as a salvage treatment for patients with residual bladder tumors after incomplete TURBT.

The strategy of dose escalation has been investigated in bladder cancer. One study revealed an improved OS in patients who received radiation doses higher or equal to 6500 cGy. However, another report showed that the escalation of the dose to >6600 cGy was not associated with OS benefit.[7,13] Together with the 12% to 40% rate of incomplete TURBT,[4,7] this implies that the optimal

Table 3 Treatment-related toxicity

	Dose escalation (n = 51)	Standard dose (n = 98)	*P* value*
Acute toxicity			
Genitourinary, Gr 1-2	27 (52.9%)	45 (45.9%)	.416
Genitourinary, Gr 3+	0 (0.0%)	3 (3.1%)	.201
Gastrointestinal, Gr 1-2	30 (58.8%)	51 (52.0%)	.430
Gastrointestinal, Gr 3+	0 (0.0%)	0 (0.0%)	NA
Late toxicity			
Genitourinary, Gr 1-2	22 (43.1%)	40 (40.8%)	.097
Genitourinary, Gr 3+	9 (17.6%)	14 (14.3%)	.846
Gastrointestinal, Gr 1-2	3 (5.9%)	13 (13.3%)	.228
Gastrointestinal, Gr 3+	2 (3.9%)	3 (3.1%)	.937

Abbreviations: Gr = grade; NA = not applicable.
*By Pearson's χ^2 test.

radiation dose would be approximately 6600 cGy for patients who received complete TURBT or those who had only microscopic residual tumors. In our study, we provided evidence that increasing the radiation dose to higher than 6600 cGy may benefit patients with macroscopic residual bladder tumors after TURBT. In the multivariate analysis, the effect of this dose escalation remained statistically significant for LRC and PFS after adjustment for potential confounding factors, such as age, performance status,[17] tumor staging,[1,2] the presence of multiple foci,[4] the hydronephrosis status,[18,19] and the hemoglobin level.[20]

Regarding the possible treatment-related adverse effect, our study further confirmed the feasibility of delivering a dose higher than 6600 cGy to gross residual bladder tumors in the modern era of radiation therapy. The BC2001 study has shown that the focally escalated dose to 6400 cGy via 3DCRT was well tolerated, with 16.0% and 2.1% of grade ≥3 acute GU and GI toxicity, respectively.[21] When using IMRT, studies also revealed that a tumor bed boost to 6800 cGy did not significantly correlate with severe acute or late GU/GI toxicities,[22,23] which was consistent with our study.

Given the retrospective nature of this study, selection and information bias may have occurred, leading to overestimations of the oncological outcome and underestimations of the treatment-related toxicity. In addition, the radiation therapy techniques used in this study included 3DCRT in the earlier years, which might increase the acute and late toxicities found when compared with the IMRT technique.

Conclusions

This study demonstrated that a dose escalation higher than 6600 cGy to gross residual tumors improves the oncological outcome for patients with incomplete TURBT without increasing the treatment-related toxicity. This result supports integrating the dose escalation strategy into future studies of tri-modal therapy for bladder cancer.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank the Cancer Registry of the Department of Radiation Oncology and Proton Therapy Center, Linkou Chang Gung Memorial Hospital, Taoyuan City, Taiwan, for the data collection.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.adro.2023.101302.

References

1. Mak RH, Hunt D, Shipley WU, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: A pooled analysis of radiation therapy oncology group protocols 8802, 8903, 9506, 9706, 9906, and 0233. *J Clin Oncol*. 2014;32:3801-3809.
2. Giacalone NJ, Shipley WU, Clayman RH, et al. Long-term outcomes after bladder-preserving tri-modality therapy for patients with muscle-invasive bladder cancer: An updated analysis of the Massachusetts general hospital experience. *Eur Urol*. 2017;71:952-960.
3. Rodel C, Grabenbauer GG, Kuhn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: Long-term results. *J Clin Oncol*. 2002;20:3061-3071.
4. Zamboni S, Moschini M, Gallina A, et al. The impact of completeness of last transurethral resection of bladder tumors on the outcomes of radical cystectomy. *World J Urol*. 2019;37:2707-2714.
5. Shariat SF, Palapattu GS, Karakiewicz PI, et al. Discrepancy between clinical and pathologic stage: Impact on prognosis after radical cystectomy. *Eur Urol*. 2007;51:137-151.
6. Chamie K, Ballon-Landa E, Bassett JC, et al. Quality of diagnostic staging in patients with bladder cancer: A process-outcomes link. *Cancer*. 2015;121:379-385.
7. Korpics MC, Block AM, Martin B, et al. Concurrent chemotherapy is associated with improved survival in elderly patients with bladder cancer undergoing radiotherapy. *Cancer*. 2017;123:3524-3531.
8. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2022.
9. Garcia-Perdomo HA, Montes-Cardona CE, Guacheta M, et al. Muscle-invasive bladder cancer organ-preserving therapy: Systematic review and meta-analysis. *World J Urol*. 2018;36:1997-2008.
10. Royce TJ, Feldman AS, Mossanen M, et al. Comparative effectiveness of bladder-preserving tri-modality therapy versus radical cystectomy for muscle-invasive bladder cancer. *Clin Genitourin Cancer*. 2019;17:23-31 e3.
11. Gakis G, Efstathiou J, Lerner SP, et al. Icud-eau international consultation on bladder 2012: Radical cystectomy and bladder preservation for muscle-invasive urothelial carcinoma of the bladder. *Eur Urol*. 2013;63:45-57.
12. Divrik RT, Sahin AF, Yildirim U, et al. Impact of routine second transurethral resection on the long-term outcome of patients with newly diagnosed pT1 urothelial carcinoma with respect to recurrence, progression rate, and disease-specific survival: A prospective randomised clinical trial. *Eur Urol*. 2010;58:185-190.
13. Korpics M, Block AM, Harkenrider MM, et al. The impact of radiation therapy dose on survival in patients with muscle-invasive bladder cancer: A population-based analysis. *Int J Radiat Oncol Biol Phys*. 2016;96:S183.
14. James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med*. 2012;366:1477-1488.
15. Efstathiou JA, Spiegel DY, Shipley WU, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: The MGH experience. *Eur Urol*. 2012;61:705-711.
16. Roumiguie M, Xylinas E, Brisuda A, et al. Consensus definition and prediction of complexity in transurethral resection or bladder endoscopic dissection of bladder tumours. *Cancers (Basel)*. 2020;12:3063.

17. Zhong J, Switchenko J, Jegadeesh NK, et al. Comparison of outcomes in patients with muscle-invasive bladder cancer treated with radical cystectomy versus bladder preservation. *Am J Clin Oncol*. 2019;42:36-41.
18. Haleblian GE, Skinner EC, Dickinson MG, et al. Hydronephrosis as a prognostic indicator in bladder cancer patients. *J Urol*. 1998;160:2011-2014.
19. Kim DS, Cho KS, Lee YH, et al. High-grade hydronephrosis predicts poor outcomes after radical cystectomy in patients with bladder cancer. *J Korean Med Sci*. 2010;25:369-373.
20. Zhang J, Zhou X, Ding H, et al. The prognostic value of routine preoperative blood parameters in muscle-invasive bladder cancer. *BMC Urol*. 2020;20:31.
21. Huddart RA, Hall E, Hussain SA, et al. Randomized noninferiority trial of reduced high-dose volume versus standard volume radiation therapy for muscle-invasive bladder cancer: Results of the BC2001 trial (CRUK/01/004). *Int J Radiat Oncol Biol Phys*. 2013;87:261-269.
22. Murthy V, Masodkar R, Kalyani N, et al. Clinical outcomes with dose-escalated adaptive radiation therapy for urinary bladder cancer: A prospective study. *Int J Radiat Oncol Biol Phys*. 2016;94:60-66.
23. Murthy V, Gupta P, Baruah K, et al. Adaptive radiotherapy for carcinoma of the urinary bladder: Long-term outcomes with dose escalation. *Clin Oncol (R Coll Radiol)*. 2019;31:646-652.