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Research Article

Bladder-sparing trimodal therapy in elderly patients with muscle-invasive bladder cancer: a real-world single-center experience

Yaşlı kas invaziv mesane kanseri hastalarında mesane koruyucu trimodal tedavi: tek merkez gerçek yaşam deneyimi

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Abstract

Aim: This study aimed to evaluate survival outcomes and potential prognostic indicators in a real-world cohort of elderly patients diagnosed with early-stage muscle-invasive bladder cancer (MIBC) who underwent trimodal therapy (TMT).

Material and Methods: This retrospective study included 23 patients with a mean age of 70 years diagnosed with stage T2N0–T2N1 MIBC and treated with TMT, which comprised maximal transurethral resection, chemotherapy, and radiotherapy. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method, and the impact of clinical and laboratory variables on survival was assessed through multivariable Cox regression analysis. Inflammatory biomarkers such as the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) were also evaluated for their prognostic significance.

Results: The median OS was 22 months (95% CI: 12.5–31.5), and the median PFS was 19 months (95% CI: 14.5–47.4). Patients receiving platinum-based chemotherapy had significantly improved OS (HR: 0.041; p = 0.015). Higher platelet-to-lymphocyte ratio (PLR) and advanced nodal stage (N stage) were negatively associated with OS. Although no factor was significantly associated with PFS, a trend toward decreased survival was observed with increasing T stage. Radiotherapy dose did not have a significant impact on survival outcomes.

Conclusion: This study highlights the efficacy and tolerability of TMT in elderly, comorbid patients with early-stage MIBC who are candidates for bladder preservation. Platinum-based regimens appear to confer a survival advantage, while PLR and nodal stage may serve as practical prognostic markers. Given the acceptable survival outcomes and favorable toxicity profile, TMT should be considered a promising bladder-sparing option for appropriately selected elderly patients.

Keywords: urinary bladder neoplasms, combined modality therapy, aged

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Öz

Amaç: Bu çalışmada, erken evre kas invaziv mesane kanseri (MIBC) tanısı almış ve trimodal tedavi (TMT) uygulanmış ileri yaşlı hasta grubunda, gerçek yaşam verileri kullanılarak sağkalım sonuçları ile prognostik belirteçlerin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif analizde, yaş ortalaması 70 olan ve evre T2N0–T2N1 MIBC tanısı alarak TMT (maksimal transüretral rezeksiyon, kemoterapi ve radyoterapi) uygulanmış 23 hasta değerlendirilmiştir. Genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) Kaplan-Meier yöntemiyle hesaplanmış; prognostik faktörler çok değişkenli Cox regresyon analiziyle incelenmiştir. Ayrıca, PLR ve NLR gibi sistemik inflamatuar belirteçlerin prognostik rolü de değerlendirilmiştir.

Bulgular: Ortanca OS süresi 22 ay (%95 GA: 12,5–31,5), ortanca PFS süresi ise 19 ay (%95 GA: 14,5–47,4) olarak hesaplanmıştır. Platin bazlı kemoterapi uygulanan hastalarda OS anlamlı şekilde daha uzun bulunmuştur (HR: 0,041; p = 0,015). Yüksek PLR ve ileri N evresi OS ile negatif yönde ilişkili bulunmuştur. PFS açısından anlamlı bir değişken saptanmamış olmakla birlikte, T evresindeki artış sağkalımda azalma eğilimi göstermiştir. Radyoterapi dozunun sağkalım üzerinde anlamlı bir etkisi gözlenmemiştir.

Sonuç: Bu çalışma, komorbiditesi yüksek yaşlı MIBC hastalarında TMT'nin etkin ve tolere edilebilir bir tedavi seçeneği olduğunu göstermektedir. Platin temelli rejimlerin sağkalım avantajı sağladığı; PLR ve nodal evrenin ise potansiyel prognostik belirteçler olarak öne çıktığı belirlenmiştir. Kabul edilebilir toksisite oranları ve sağkalım verileri göz önünde bulundurulduğunda, TMT yaşlı bireyler için mesane koruyucu umut verici bir alternatif olarak değerlendirilmelidir.

Anahtar kelimeler: kas invaziv mesane tümörü, trimodal tedavi, yaşlı hasta

Introduction

Muscle-invasive bladder cancer (MIBC) is a biologically aggressive malignancy that typically necessitates radical treatment upon diagnosis. According to current international guidelines, radical cystectomy (RC) combined with neoadjuvant chemotherapy is considered the standard curative approach for patients with MIBC [1,2]. However, RC is associated with substantial perioperative morbidity and mortality, especially among elderly patients with significant comorbid conditions [3]. Trimodal therapy (TMT), a bladder-sparing alternative, consists of maximal transurethral resection of the bladder tumor (TURBT) followed by concurrent chemoradiotherapy. TMT has demonstrated promising outcomes in terms of local disease control and overall survival, yet it is utilized in only 10% to 20% of eligible patients in real-world settings [4, 5]. This limited adoption is largely attributed to the absence of large-scale randomized trials and limited familiarity among clinicians with bladder-preserving protocols [6]. Prospective data from RTOG trials and the phase III BC2001 study have validated the efficacy of TMT in achieving satisfactory oncologic outcomes while preserving bladder function [7]. More recent retrospective and comparative studies have further suggested that, with appropriate patient selection, TMT may offer survival rates comparable to those of RC. Nonetheless, uncertainties remain regarding the optimal components of TMT, particularly with respect to chemotherapy agents and radiotherapy dose. Randomized trials such as BC2001 and RTOG 0712 have demonstrated the effectiveness of various radiosensitizing agents including mitomycin C plus 5-fluorouracil and gemcitabine [8, 9]. However, real-world evidence assessing these regimens - particularly in elderly populations - remains limited.

In this retrospective study, we aimed to evaluate overall and progression-free survival in a real-world cohort of early-stage MIBC patients with a mean age of 70 years treated with TMT. We further investigated the prognostic impact of chemotherapy regimen (platinum-based vs. gemcitabine-based), nodal stage, platelet-to-lymphocyte ratio (PLR), and other clinical variables.

Material and Methods

This retrospective observational study analyzed data from 23 elderly patients diagnosed with MIBC who underwent TMT at our institution between 2016 and 2024. Eligible patients had clinical stages ranging from T1 to T3, with nodal status N0 to N2, and no evidence of distant metastasis (M0). All patients had opted for bladder-preserving therapy as an alternative to radical cystectomy.

The study protocol was approved by the Ethics Committee of the University of Health Sciences, Gülhane Faculty of Medicine (Approval No: 2025/192, dated April 8, 2025). All procedures were conducted in accordance with the ethical standards of

the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. Patient data were anonymized to ensure confidentiality. Due to the retrospective nature of the study, the requirement for informed consent was waived by the Ethics Committee.

Patient characteristics and treatment

Demographic data including age, sex, and Eastern Cooperative Oncology Group (ECOG) performance status were collected, along with clinical staging parameters (T and N stages), chemotherapy regimen (platinum-based vs. gemcitabine-based), radiotherapy dose, and the completeness of TURBT. All patients received concurrent chemoradiotherapy, using either a platinum-based or gemcitabine-based regimen. The administered radiotherapy doses ranged from 23 Gy to ≥60 Gy, tailored according to clinical factors and institutional protocols.

Variables

Systemic inflammatory markers, including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), were calculated for each patient based on pre-treatment laboratory values. These markers were categorized using clinically relevant median thresholds (NLR ≥3 and PLR ≥157). During follow-up, data were collected on local and distant disease progression, survival status, toxicity events, and date of last follow-up.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 25.0. Descriptive variables were summarized as frequencies and percentages. Survival outcomes, including overall survival (OS) and progression-free survival (PFS), were estimated using the Kaplan–Meier method, and group comparisons were performed with the log-rank test. Prognostic factors were analyzed using both univariable and multivariable Cox proportional hazards models. A p-value of <0.05 was considered statistically significant. Forest plots were generated to illustrate hazard ratios (HRs) and 95% confidence intervals (CIs)

Study population characteristics

A total of 23 patients diagnosed with early-stage MIBC and treated with TMT were included in the study. The median age was 73 years (range: 43–90), and the majority were male (95.7%). Only one patient had an Eastern Cooperative Oncology Group (ECOG) performance status of 0; the remaining patients had ECOG 1. T2 tumors were the most prevalent, representing 78.3% of cases. According to nodal staging, 65.2% of patients were classified as N0, 26.1% as N1, and 8.7% as N2. Complete TURBT was achieved in 91.3% of patients.

Regarding chemotherapy, 12 patients (52.2%) received platinum-based regimens (cisplatin or carboplatin), while 11 patients (47.8%) received gemcitabine-based protocols. The median radiotherapy dose was 60 Gy (range: 30–64.8 Gy), with 13 patients (57%) receiving high-dose radiotherapy (≥60 Gy). The median follow-up duration was 18 months (range: 0–70 months). Grade ≥3 treatment-related toxicity was observed in only one patient (4.3%) (Table 1).

Table 1. Baseline demographic and clinical characteristics of the patients (n = 23).

Variable	n (%) or Median (Range)
Age, years	73 (43–90)
Sex	
Male	22 (96)
Female	1 (4)
ECOG Performance Status	
0	1 (4)
1	22 (96)
≥2	0
Clinical T Stage	
T1	3 (13)
T2	18 (78)
T3	2 (9)
Clinical N Stage	
N0	15 (65)
N1	6 (26)
N2	2 (9)
Chemotherapy Regimen	
Platinum-based (cisplatin or carboplatin)	12 (52)
Gemcitabine-based	11 (48)
Complete TURBT performed	21 (91)
Radiotherapy dose, Gy	60 (30–65)
Grade ≥3 toxicity	1 (4)

ECOG, Eastern Cooperative Oncology Group; TURBT, transurethral resection of bladder tumor; RT, radiotherapy; Gy, gray.

Results

Based on Kaplan–Meier analysis, the median overall survival (OS) was 22 months (95% CI: 12.5–31.5), and the mean OS was 30.7 ± 6.6 months. At the time of analysis, survival data were not yet mature for 47.8% of patients. The estimated 1-year OS rate was 63.6%, while the 2-year and 3-year OS rates were approximately 30–35% and 27%, respectively. The median progression-free survival (PFS) was 19 months (95% CI: 14.5–47.4). The estimated 1- and 2-year PFS rates were 61.8% and 22.9%, respectively. In multivariate Cox regression analysis, patients who received platinum-based chemotherapy exhibited significantly better overall survival compared to those treated with gemcitabine-

based regimens (HR: 0.04; 95% CI: 0.003–0.50; p = 0.015). This finding was consistent with the univariate analysis, which also demonstrated improved survival outcomes in the platinum-based group (HR: 0.18; p = 0.013).

Furthermore, both the PLR (p = 0.054) and clinical N stage (p = 0.076) approached statistical significance, suggesting potential prognostic relevance for overall survival (Table 2, Figure 1).

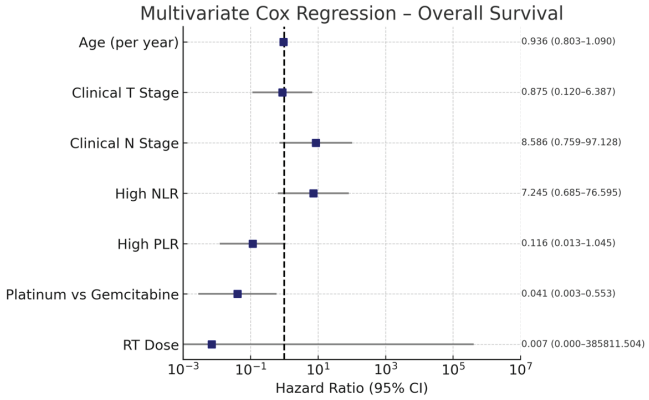

Figure 1. Forest plot for overall survival (OS) according to multivariate Cox regression analysis.

In the Multivariate Cox regression analysis for PFS, none of the examined variables demonstrated statistically significant associations. Nonetheless, clinical T stage exhibited a trend toward worse prognosis (HR: 3.37; 95% CI: 0.54–20.91; p = 0.192) (Table 3, Figure 2).

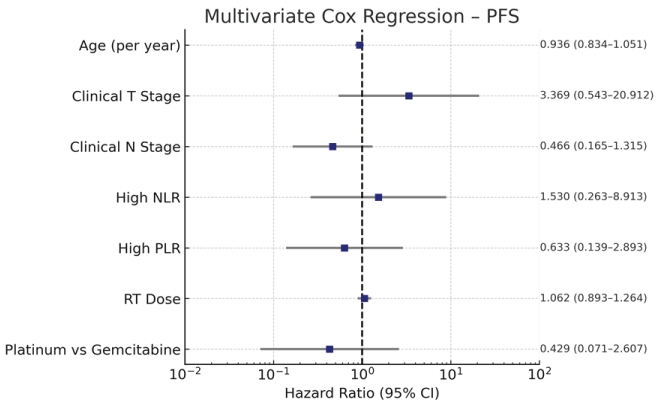

Figure 2: Forest plot for progression-free survival (PFS) according to multivariate Cox regression analysis

Table 2. Risk Factors for Overall Survival Based on Univariate and Multivariate Cox Proportional Hazards Models

Clinical Variable	Univariate analyses			Multivariate analyses		
	HR	95% CI	p	HR	95% CI	p
Age	0.9	(0.9-1)	0.19	0.9	(0.8-1.1)	0.38
T stage	1.6	(0.3-6.9)	0.51	0.8	(0.1-6.2)	0.89
N stage	0.8	(0.4-1.9)	0.72	8.5	(0.7-93)	0.07
NLR	0.6	(0.2-2)	0.47	7.2	(0.6-76)	0.1
PLR	0.5	(0.1-1.7)	0.29	0.1	(0.01-1)	0.054
RT dose	1	(0.9-1.1)	0.46	0.007	(0-3800)*	0.58
Platinum vs.Gemcitabine	0.2	(0.05-0.7)	0.013	0.04	(0.003-0.5)	0.015

Reference categories: T1 for T stage; N0 for N stage, * RT dose CI is extremely wide; interpret with caution due to likely model instability or low event count.

Table 3. Risk factors for PFS based on univariate and multivariate cox proportional hazards models.

Clinical Variable	Univariate analyses			Multivariate analyses		
	HR	95% CI	p	HR	95% CI	p
Age	0.9	(0.8-1)	0.13	0.93	(0.8-1.1)	0.26
T stage	3.8	(0.7-21)	0.11	3.3	(0.5-21)	0.19
N stage	0.8	(0.3-2)	0.74	0.5	(0.1-1.3)	0.14
NLR	0.5	(0.1-1.8)	0.37	1.5	(0.2-8.9)	0.63
PLR	0.7	(0.2-2.3)	0.62	0.6	(0.1-2.8)	0.55
RT dose	1.1	(0.9-1.2)	0.20	1	(0.8-1.2)	0.49
Platinum vs. Gemcitabine	0.3	(0.08-1)	0.057	0.4	(0.07-2.6)	0.35

Reference categories: T1 for T stage; N0 for N stage, Wide CIs may be due to small sample size and few progression events.

Discussion

Our study presents real-world data from a cohort of 23 elderly patients with early-stage MIBC who received trimodal therapy. TMT has emerged as a key bladder-sparing approach, offering favorable oncologic outcomes while preserving quality of life in appropriately selected patients [9]. Previous studies have reported that a substantial proportion of patients aged 70–80 years are often not offered curative-intent treatment, highlighting the importance of bladder-preserving alternatives such as TMT for this age group [10].

A recent meta-analysis demonstrated that TMT and RC yield comparable 5- and 10-year OS and disease-specific survival (DSS) outcomes [6]. Although RC may provide superior oncologic control in select patients, our findings support the notion that MT provides a meaningful balance between organ preservation between organ preservation and survival, particularly in carefully selected elderly individuals.

Despite mounting evidence of trimodal therapy's effectiveness and tolerability, TMT remains underutilized in clinical practice, with reported adoption rates ranging from 10% to 20%. This underuse likely reflects multiple contributing factors, including the absence of randomized controlled trials, heterogeneity in institutional protocols, and ongoing skepticism among clinicians [9].

The BC2001 trial confirmed that chemoradiotherapy (CRT) significantly improves locoregional control compared to radiotherapy alone (HR 0.61; 95% CI 0.43–0.86; p = 0.004) [8]. Likewise, the NRG-RTOG 0712 phase II trial demonstrated that gemcitabine-based CRT yields acceptable toxicity and distant metastasis-free survival rates comparable to platinum-based regimens [11].

In our real-world cohort, platinum-based chemotherapy was significantly associated with improved overall survival (HR: 0.041; 95% CI: 0.003–0.553; p = 0.016), aligning with prior studies that emphasize the efficacy of platinum-based CRT in bladder preservation [12, 13]. This survival advantage can be explained by the radiosensitizing properties of cisplatin, which enhance the cytotoxic effects of radiotherapy through multiple mechanisms including DNA crosslinking, inhibition of DNA repair, and apoptosis promotion. These mechanisms lead to improved local control and potentially lower micrometastatic spread, thereby translating into better long-term survival outcomes [14]. Current guidelines recommend platinum-based agents as first-line radiosensitizers, especially for patients with preserved renal function and good performance status. Our results reinforce the value of chemotherapy regimen selection and suggest that, with appropriate clinical judgment, elderly patients can safely receive platinum-based CRT. Notably, recent studies have shown that older patients with adequate organ function may tolerate such regimens with acceptable toxicity and achieve outcomes comparable to younger populations [8, 15, 16].

Multiple retrospective and prospective studies have shown that carefully selected patients undergoing TMT can achieve oncologic outcomes similar to those receiving RC. One large multi-institutional analysis using propensity score matching reported equivalent 5-year metastasis-free survival (74%) for both groups, with a modest overall survival advantage in favor of TMT [17]. These findings highlight the potential of TMT as a curative-intent alternative in appropriately selected patients.

Among systemic inflammatory markers, the NLR and PLR have emerged as significant prognostic indicators in various malignancies. Elevated PLR, in particular, has been associated with adverse outcomes, especially in the presence of lymph node metastasis and systemic inflammation [18-20]. In a study by Hurmuz et al., high NLR and PLR were significantly correlated with worse overall survival (OS), DSS, and local recurrence-free survival in patients undergoing gemcitabine-based TMT [21]. Similarly, in our cohort, elevated PLR (observed in 57% of patients) and advanced nodal stage showed a strong trend toward poorer OS and PFS outcomes.

Beyond treatment-specific factors, we identified both PLR and nodal stage as independent prognostic indicators for OS in elderly patients undergoing TMT. Nodal involvement reflects higher tumor burden and greater metastatic potential, while an elevated PLR likely represents a pro-tumorigenic state marked by thrombocytosis and impaired immune surveillance[22]. In contrast, lower PLR may signal preserved host immunity and reduced systemic inflammation. These markers could thus serve as accessible, low-cost tools for risk stratification and individualized treatment planning in elderly patients with MIBC[23].

In addition to oncologic efficacy, TMT offers meaningful quality-of-life benefits. Bladder preservation has been associated with improved body image, sexual function, and emotional well-being compared to RC, particularly among elderly patients who value functional independence [24]. Prospective studies have reported 5-year OS rates between 50% and 70% for TMT [25]. Our study reported a 2-year OS rate of 69%, reinforcing its effectiveness in real-world elderly populations.

Despite evidence supporting its clinical utility, TMT remains underutilized, largely due to institutional variability and the absence of randomized trials [9]. Nevertheless, evidence from real-world retrospective studies, including our own, suggests that TMT offers comparable oncologic outcomes to RC in appropriately selected elderly patients [15].

There remains ongoing debate regarding the optimal radiotherapy (RT) dose in the context of TMT for muscle-invasive bladder cancer. In our study, RT dose was not found to be a significant prognostic factor for overall survival or progression-free survival (PFS HR = 1.062; $p > 0.05$ for OS). This observation aligns with previous findings suggesting that, within standard therapeutic ranges, dose escalation alone may not significantly enhance long-term oncologic outcomes.

For instance, the BC2001 trial demonstrated that improvements in locoregional control and survival were primarily attributable to the addition of concurrent chemotherapy, rather than to increases in RT dose [8]. Similarly, the BCON trial emphasized the therapeutic value of hypoxia modification strategies—such as the use of carbogen and nicotinamide—over conventional RT dose intensification in improving treatment response [26]. Taken together, these data suggest that beyond a certain threshold, further escalation of RT dose offers limited incremental benefit. Instead, optimizing treatment through multimodal synergy—including the integration of effective radiosensitizers—appears to be the more impactful approach. Our findings reinforce the critical role of concurrent radiosensitizing agents in enhancing the efficacy of TMT and underscore the importance of biologically tailored treatment strategies to maximize therapeutic outcomes in elderly MIBC patients [27]. Although radiotherapy dose was included in the multivariate analysis, its hazard ratio and confidence interval suggested model instability (CI: 0–3800), likely due to limited sample size and low number of events. Therefore, its prognostic relevance should be interpreted cautiously.

Treatment-related toxicity in our cohort was notably low, with grade ≥3 adverse events reported in only one patient (4.3%). This finding is consistent with previous studies demonstrating that both gemcitabine- and platinum-based regimens used in the context of TMT are generally well tolerated, with a relatively low incidence of severe toxicities [8, 28].

Importantly, nearly all patients in our study (91%) underwent complete TURBT prior to initiating chemoradiotherapy. As emphasized in earlier literature, achieving a complete TURBT is a crucial component of bladder-preserving strategies and has been associated with improved oncologic outcomes [6].

This study is subject to several limitations that must be considered when interpreting the results. Some hazard ratios yielded in the multivariable Cox regression model, such as those for PLR and N stage, exhibited extreme values with wide confidence intervals. These findings should be interpreted with caution, as they likely reflect statistical variability stemming from the small sample size and limited number of events. Although the retrospective design and relatively small cohort limit the generalizability of our findings, the study provides meaningful insights into the real-world effectiveness and safety of TMT in elderly patients. Moreover, the inherent subjectivity in patient selection likely reflects the nuanced clinical decision-making processes required for this vulnerable population.

In conclusion, our findings support the use of TMT as a feasible, effective, and well-tolerated bladder-preserving option in elderly patients with early-stage MIBC and comorbid conditions. Platinum-based chemotherapy was significantly associated with improved overall survival, while elevated PLR and nodal involvement (N stage) emerged as potentially relevant prognostic indicators. While NLR and age showed borderline associations, radiotherapy dose was not found to influence survival outcomes.

TMT represents a valuable strategy for patients who prioritize bladder preservation and quality of life. Optimal patient selection, tailored chemotherapy protocols, and multimodal integration remain key to maximizing clinical benefit. Given its favorable toxicity profile and promising survival outcomes, TMT warrants broader consideration in routine oncology practice, particularly for elderly individuals who may not tolerate radical cystectomy.

Furthermore, emerging data from ongoing trials such as ANZUP-1502 and DUART suggest that combining immune checkpoint inhibitors with chemoradiotherapy may enhance response rates and survival, potentially expanding the scope of TMT in future treatment paradigms [29].

As large-scale prospective trials and biomarker-driven selection strategies advance, TMT is likely to secure a more standardized role in early-stage MIBC treatment algorithms.

Institutional Review Board Statement

The study protocol was approved by the Ethics Committee of the University of Health Sciences, Gülhane Faculty of Medicine (Approval No: 2025/192, dated April 8, 2025).

Conflicts of Interest

The authors declare no conflicts of interest.

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Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Volkan ASLAN], [hüseyin Atacan], [Aybala NUR ÜÇGÜL], [Gül Sema Yıldıran Keskin], [İsa DEDE], [Doğan BAYRAM], [Musa Barış Aykan],[İsmail Ertürk], [Nuri Karadurmuş], The first draft of the manuscript was written by [volkan Aslan], and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. Kamat AM, Hahn NM, Efstathiou JA, Lerner SP, Malmström PU, Choi W et al. Bladder cancer. Lancet 2016; 388: 2796-810.
2. Compérat E, Larré S, Rouprêt M, Neuzillet Y, Houédé N, Roy C et al. Current best practice for bladder cancer: a narrative review of diagnostics and treatments. Lancet 2022; 400: 1712-21.
3. Ramakrishnan VM, Eswara JR. The timing of radical cystectomy following neoadjuvant chemotherapy. Transl Androl Urol 2018; 7(Suppl 6): S758-62.
4. Fahmy O, Khairul-Asri MG, Schubert T, Renninger M, Malek R, Kübler H et al. A systematic review and meta-analysis on the oncological long-term outcomes after trimodality therapy and radical cystectomy with or without neoadjuvant chemotherapy for muscle-invasive bladder cancer. Urol Oncol 2018; 36: 43-53.
5. Ploussard G, Daneshmand S, Efstathiou JA, Herr HW, James ND, Rodel CM et al. Critical analysis of bladder sparing with trimodal therapy in muscle-invasive bladder cancer: a systematic review. Eur Urol 2014; 66: 120-37.
6. Vashistha V, Wang H, Mazzone A, Bandyopadhyay D, Gupta A, Dynda D et al. Radical cystectomy compared to combined modality treatment for muscle-invasive bladder cancer: a systematic review and meta-analysis. Int J Radiat Oncol Biol Phys 2017; 97:1002-20.
7. Mak RH, Hunt D, Shipley WU, Efstathiou JA, Tester WJ, Hagan MP 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. J Clin Oncol 2014; 32: 3801-9.
8. James ND, Hussain SA, Hall E, Jenkins P, Tremlett J, Rawlings C et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med 2012; 366: 1477-88.
9. Wang SJ. Trimodality therapy in the modern era for management of bladder cancer. Transl Cancer Res 2024; 13: 3935-45.
10. Turgeon GA, Souhami L. Trimodality therapy for bladder preservation in the elderly population with invasive bladder cancer. Front Oncol 2014; 4: 206.
11. Coen JJ, Zhang P, Saylor PJ, Lee CT, Wu CL, Parker W et al. Bladder preservation with twice-a-day radiation plus fluorouracil/cisplatin or once daily radiation plus gemcitabine for muscle-invasive bladder cancer: NRG/RTOG 0712—a randomized phase II trial. J Clin Oncol 2019; 37: 44-51.
12. Aluwini S, Pos F, Schimmel E, Krol S, van der Voort van Zyp J, Moonen L et al. Bladder function preservation with brachytherapy, external beam radiation therapy, and limited surgery in bladder cancer patients: long-term results. Int J Radiat Oncol Biol Phys 2014; 88: 611-7.
13. Giacalone NJ, Shipley WU, Clayman RH, Niemierko A, Drumm M, Heney NM 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: 952-60.
14. Lawrence TS, Blackstock AW, McGinn C. The mechanism of action of radiosensitization of conventional chemotherapeutic agents. Semin Radiat Oncol 2003; 13: 13-21.
15. Hall E, Hussain SA, Porta N, Lewis R, Birtle AJ, Nicholson S et al. Chemoradiotherapy in muscle-invasive bladder cancer: 10-yr follow-up of the phase 3 randomised controlled BC2001 trial. Eur Urol 2022; 82: 273-9.
16. Miyamoto DT, Mouw KW, Harshman LC, Niemierko A, Drumm MR, Wu CL et al. Outcomes and tolerability of selective bladder preservation by combined modality therapy for invasive bladder cancer in elderly patients. Int J Radiat Oncol Biol Phys 2017; 99(2 Suppl): S120.
17. Zlotta AR, Lajkosz K, Efstathiou JA. Radical cystectomy vs trimodality therapy for muscle-invasive bladder cancer: further extensive evaluation needed – Authors' reply. Lancet Oncol 2023; 24: e325-6.
18. Black AJ, Zargar H, Zargar-Shoshtari K, Fairey AS, Mertens LS, Dinney CP et al. The prognostic value of the neutrophil-to-lymphocyte ratio in patients with muscle-invasive bladder cancer treated with neoadjuvant chemotherapy and radical cystectomy. Urol Oncol 2020; 38: 77.e11-9.
19. Chen H, Chen H, Liang L, Liu J, Wang J, Gao Y et al. The clinicopathological and prognostic value of NLR, PLR and MLR in non-muscular invasive bladder cancer. Arch Esp Urol 2022; 75: 467-71.

20. Bizzarri FP, Di Meo S, Zamparella C, Pecoraro M, Merola R, Pierconti F et al. Prognostic Value of PLR, SIRI, PIV, SII, and NLR in Non-Muscle Invasive Bladder Cancer: Can Inflammatory Factors Influence Pathogenesis and Outcomes? Cancers (Basel) 2025; 17: 2189.
21. Hurmuz P, Bozkurt O, Keskin S, Kucukarda A, Bilici A, Oksuzoglu B. Gemcitabine based trimodality treatment in patients with muscle invasive bladder cancer: May neutrophil lymphocyte and platelet lymphocyte ratios predict outcomes? Urol Oncol 2021; 39: 370.e9-15.
22. Karl A, Carroll PR, Gschwend JE, Knuchel R, Montorsi F, Stenzl A et al. The impact of lymphadenectomy and lymph node metastasis on the outcomes of radical cystectomy for bladder cancer. Eur Urol 2009; 55: 826-35.
23. Wang X, Ni X, Tang G. Prognostic role of platelet-to-lymphocyte ratio in patients with bladder cancer: a meta-analysis. Front Oncol 2019; 9: 757.
24. Jo Y, Yuk HD. Trimodal therapy in the treatment of muscle-invasive bladder cancer. J Urol Oncol 2024; 22: 256-67.
25. Mak RH, Hunt D, Shipley WU, Tester WJ, Hagan MP, Kaufman DS et al. Long-term outcomes in patients with muscle-invasive bladder cancer after bladder-preserving combined-modality therapy: a pooled analysis of RTOG protocols. J Clin Oncol 2012; 30(5 Suppl): 264.
26. Song YP, Choudhury A, Nelson M, Hoskin P, James ND. Long-term outcomes of radical radiation therapy with hypoxia modification with biomarker discovery for stratification: 10-year update of the BCON phase 3 randomized trial. Int J Radiat Oncol Biol Phys 2021; 110: 1407-15.
27. Choudhury A, Porta N, Hall E, Song Y, Bahl A, Parmar M, et al. Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials. Lancet Oncol 2021; 22: 246-55.
28. Kobayashi K, Saito Y, Kawai K, Takahashi R, Yoshino T, Otsuka H et al. The efficacy of trimodal chemoradiotherapy with gemcitabine and cisplatin as a bladder-preserving strategy for the treatment of muscle-invasive bladder cancer: a single-arm phase II study. Jpn J Clin Oncol 2022; 52: 1201-7.
29. Weickhardt A, Tan A, Yip S, Kichenadasse G, McKendrick J, Lawrentschuk N et al. Pembrolizumab with chemoradiation as treatment for muscle-invasive bladder cancer: analysis of safety and efficacy of the PCR-MIB Phase 2 Clinical Trial (ANZUP 1502). Eur Urol Oncol 2024; 7: 469-77.