International Journal of Urology Sciences

ISSN Print: 2664-9306
ISSN Online: 2664-9314
Impact Factor: RJIF 5.22
IJUS 2024; 6(1): 01-05
www.urologyjournal.net
Received: 03-05-2024
Accepted: 07-06-2024

Dr. Abdul Sabooh Rizvi
Specialist Urologist, Prime Health Care Group, Dubai, United Arab Emirates

Dr. Sanchit Gupta
Specialist Urologist, Prime Health Care Group, Dubai, United Arab Emirates

Corresponding Author:
Dr. Abdul Sabooh Rizvi
Specialist Urologist, Prime Health Care Group, Dubai, United Arab Emirates

Bladder preservation protocol in muscle-invasive transitional cell carcinoma of the bladder: A comprehensive review

Dr. Abdul Sabooh Rizvi and Dr. Sanchit Gupta

DOI: https://doi.org/10.33545/26649306.2021.v3.i1a.7

Abstract
Muscle-invasive transitional cell carcinoma (TCC) of the bladder poses a considerable therapeutic challenge, traditionally managed by radical cystectomy. However, bladder preservation protocols have gained prominence as feasible alternatives, aiming to maintain the patient's quality of life without compromising oncological outcomes. This comprehensive review delves into the current bladder preservation strategies, scrutinizing their efficacy, patient selection criteria, treatment modalities, and overall outcomes. We discuss the integration of multimodal approaches, including transurethral resection of the bladder tumor (TURBT), chemotherapy, and radiotherapy, highlighting their synergistic potential in achieving local control and long-term survival. The review examines the criteria for patient selection, emphasizing the importance of tumor staging, patient comorbidities, and bladder function in determining the suitability for bladder-preserving strategies. We explore the therapeutic impact and side effect profiles of various chemotherapeutic agents and radiation techniques, and the role of concurrent chemoradiotherapy in enhancing treatment efficacy. Furthermore, we investigate the emerging role of novel therapies and biomarkers in bladder preservation. Advances in immunotherapy, targeted therapies, and molecular markers hold promise for more personalized treatment approaches, potentially improving outcomes and reducing treatment-related toxicity. The integration of these novel therapies with traditional multimodal approaches is also discussed, providing insights into future directions in bladder preservation. Our analysis includes a critical evaluation of clinical trials and real-world studies, presenting evidence on survival rates, recurrence patterns, and quality of life metrics. The review aims to furnish an updated perspective on bladder preservation, offering guidance for clinical decision-making and highlighting areas where further research is needed. By optimizing bladder preservation protocols, we can enhance patient outcomes, achieving a balance between effective oncological control and preservation of bladder function.

Keywords: Bladder, MIBC, TURBT, chemotherapy, carcinoma, review

Introduction
Muscle-invasive bladder cancer (MIBC) constitutes approximately 25% of all bladder cancer cases and is associated with a poor prognosis if not treated aggressively. Traditionally, the gold standard treatment for MIBC has been radical cystectomy with pelvic lymph node dissection. However, the procedure carries significant morbidity and impacts quality of life due to the loss of bladder function. Bladder preservation protocols offer an alternative that aims to maintain bladder function while providing effective oncologic control. This review examines the various bladder preservation strategies, their implementation, and outcomes.

Bladder cancer ranks as the second most prevalent genitourinary malignancy and the ninth most prevalent cancer globally [1]. Approximately 70% of bladder cancer cases are non-muscle invasive at the time of presentation, while 30% are muscle-invasive [2]. In contrast to non-muscle invasive bladder cancer (NMIBC), which is typically managed with bladder-conserving first-line treatments, muscle-invasive bladder cancer (MIBC) is typically treated with bladder excision and bilateral pelvic lymph node dissection. By decreasing micro-metastatic disease at the time of surgery, the addition of neoadjuvant chemotherapy to MIBC treatment increases 5-year survival by 5% absolute [3]. Numerous regimens incorporate cisplatin-based chemotherapy, such as cisplatin [4, 5].

Despite the standard treatment for MIBC being radical cystectomy with neoadjuvant chemotherapy, substantial concerns continue to exist regarding the associated morbidity and mortality [6]. Trimodality therapy (TMT) and partial cystectomy with neoadjuvant chemotherapy are two bladder conserving interventions that have garnered increasing attention due to the morbidity associated with cystectomy. Pooled analyses of prospective cohort studies revealed that patients who underwent trimodality therapy achieved a 5-year overall survival (OS) of 57% and a 5-year disease-specific survival (DSS) of 71% [7]. In line with this, a 2015 meta-analysis revealed that TMT exhibited a 5-year OS of 56%, which is similar to the OS observed subsequent to RC [8]. In comparison to patients who underwent RC, TMT also has a connection with higher overall quality of life scores, including improved interpersonal, bodily, sexual, along with cognitive abilities [9].

Patient Selection Criteria

Effective bladder preservation begins with careful patient selection. Ideal candidates typically exhibit the following characteristics:

- Single, unifocal tumor
- Tumor size less than 5 cm
- No extensive carcinoma *In Situ*
- Absence of hydronephrosis
- Good bladder function
- Patient preference for bladder preservation
- Adequate renal function for chemotherapy

Patient selection is crucial, as inappropriate candidates may not achieve optimal outcomes and could experience disease progression, necessitating delayed cystectomy under less favorable conditions.

Treatment Modalities

Cancer of the bladder is treated in accordance with the lesion's stage. Transurethral resection of bladder tumor (TURBT) is the prevailing treatment approach for early-stage bladder cancer (Ta, T1, and carcinoma *In Situ*). In patients with advanced-stage disease, adjuvant intravesical administration of Bacillus Calmette-Guérin is commonly administered. The type of surgery and the severity of the disease have a direct bearing on the overall prognosis of MIBC. Once bladder wall cancer (MIBC) has invaded (stage T2 or later), TURBT is typically the initial treatment of choice; its primary purpose is to assess the extent of the invasion, not to treat the cancer. The gold standard treatments for patients with MIBC (stages T2–T4a, N0, and M0) are radical cystectomy (RC) and pelvic lymph node dissection. Numerous clinical studies and series have provided evidence of RC's efficacy and sustained positive results. Neo-adjuvant/adjuvant chemotherapy is occasionally administered prior to surgery, especially in instances involving T4a and T4b.

A substantial cohort of 1054 patients diagnosed with MIBC who underwent RC with bilateral pelvic iliac lymphadenectomy from July 1971 to December 1997 demonstrated an overall recurrence-free survival rate of 68% at 5 years and 66% at 10 years, as reported in one of the largest series [11]. The 5-year and 10-year recurrence-free survival rates for patients diagnosed with organ-confined, lymph node-negative tumors (P0, Pis, Pa, and P1) were 83%, 92%, 79%, and 83%, respectively. These rates were 86%, 89%, 74%, and 78% [11] At five and ten years, patients with stages P2 and P3a and negative lymph nodes had recurrence-free survival rates of 89% and 87%, 78% and 76%, respectively. The corresponding rates for P3b and P4 tumors were 62% and 61%, and 50% and 45%, respectively [11]. In comparison to other urological and nonurological procedures, RC has the second highest readmission rate, according to another study by Goodney *et al*. [12]. Bowel preservation may be considered for patients who are ineligible for cystectomy or unwilling to undertake the procedure. It is critical that patients and their family members are informed that cystectomy may have adverse effects on bowel and sexual functions.

Transurethral Resection of Bladder Tumor (TURBT)

TURBT is the cornerstone of bladder preservation, involving the resection of visible tumor tissue from the bladder wall. Complete resection is essential for staging and for reducing tumor burden before additional treatments. Repeated TURBT may be necessary to ensure thorough removal.

In the event that the tumor is confined to the superficial muscle layer and subsequent biopsies of the site of the initial resection rule out an invasive tumor (i.e., absence of residual T1 or higher stage disease), TURBT in isolation may only serve as a therapeutic option. Solsona *et al*. reported on a phase II study for MIBC that examined 133 highly-selected patients who underwent a complete TURBT with a negative biopsy post-treatment over a 15-year follow-up period (13). Overall survival (OS) and cancer-specific survival (CSS) rates at 5, 10, and 15 years were, respectively, 73.7%, 39.8%, and 24.8% and 81.9%, 79.5%, and 76.7%. A 30% proportion of patients experienced disease progression, including 7.7% who developed metastases. Notably, all patients who experienced metastasis did so within the initial 36 months following TURBT. Furthermore, between 36 and 180 months, only 30% of patients encountered local progression; none did so beyond this timeframe. The established follow-up schedule entails systemic and endoscopic evaluation every three months for the initial three years, after which systemic evaluation may be omitted and endoscopic interval may be extended to every six months for five years, followed by annual evaluation for the remaining fifteen years. Herr (2014) documented comparable survival rates, including a 10-year CSS of 76%, for 99 patients diagnosed with MIBC who were treated exclusively with TURBT. The survival rate of patients with T0 disease was found to be substantially higher than that of patients with T1 disease on restaging TUR (82% vs. 57%, P=0.003). The ideal criteria for patients who are exclusively treated with TURBT in MIBC are as follows: a tumor location that is easily accessible, a TURBT that has been resected completely with negative restaging, a tumor size of less than 2-3 cm, the absence of multi-focal carcinoma in-situ (CIS), hydronephrosis, and satisfactory bladder function [13, 14].

Performing a partial cystectomy. It has been reported that in carefully chosen patients, partial cystectomy alone can yield satisfactory oncological results for MIBC. This approach offers the added benefit of precise staging through lymphadenectomy and full-thickness resection, which includes sufficient evaluation of surgical margins, in comparison to TURBT alone. Capitanio *et al*. reported comparable 5-year OS and CSS for partial cystectomy and

RC of 57% and 70%, respectively, when patients were matched for age, race, TNM stage, tumor grade, and number of lymph nodes removed [15]. These values were compared to 55% and 69%, respectively, when patients were matched. Nevertheless, the literature has documented recurrence rates following partial cystectomy ranging from 38% to 49%, with as many as 30% of patients ultimately undergoing RC [15, 17].

Patients who are considered ideal candidates have a single lesion measuring less than 3-4 cm in diameter, can be excisiond with 2-cm margins (such as the bladder dome), do not have a concurrent CIS, do not require ureteral reimplantation, and do not have hyper-contractility of the bladder. The proportion of MIBC patients who satisfy the requirements for partial cystectomy is below 5% [16]

Chemotherapy

Chemotherapy (CT) has a restricted application when used as the exclusive treatment for MIBC. Chemotherapy is commonly administered through RC as a neo-adjuvant component of standard non-preservation therapy for bladder cancer. cisplatin-based chemotherapy improves survival when combined with RC and PLND [5], with the greatest benefit observed in patients who attain complete pathological response subsequent to NAC [17]. Post-RC adjuvant chemotherapy may also serve a purpose [18, 19].

In recent times, research has been prompted to examine the potential of specific DNA damage response (DDR) gene mutations, which are linked to reactivity to cisplatin-based chemotherapy, as predictive biomarkers of chemotherapy response in bladder preservation [20]. At this time, a phase II trial at Memorial Sloan Kettering is being conducted by the Alliance for Clinical Trials in Oncology to determine whether patients with DDR mutations can be treated with cisplatin-based chemotherapy exclusively, without the need for RC and PLND [21, 22]. Further analysis of chemotherapy in the context of BPT will be provided in the following sections of this review.

Chemotherapy plays a pivotal role in bladder preservation, either as neo-adjuvant, concurrent, or adjuvant therapy. Common regimens include:

- **Cisplatin-based combinations:** The most effective and widely used, particularly cisplatin, methotrexate, and vinblastine (CMV), or gemcitabine and cisplatin (GC).
- **Non-cisplatin alternatives:** For patients who are cisplatin-ineligible, combinations such as gemcitabine and carboplatin are used.

Radiotherapy

Radiotherapy is typically used concurrently with chemotherapy to enhance local control of the tumor. The radiation dose and fractionation schedules are tailored to maximize tumor control while minimizing toxicity to surrounding tissues.

Research has demonstrated that external beam radiotherapy (EBRT) can induce complete regression of malignant ileary cell carcinoma (MIBC) in as many as 70% of patients, with a sustained local response of 30–50%. Nevertheless, over 50% of patients will develop metastatic disease, and the 5-year overall survival rate is a mere 20–30% [26]. In the radiotherapy-only cohort, James *et al*. [23] documented a 2-year disease-free survival rate of 54% and a 5-year OS of 35%. A T3−4 disease, extravesical mass, large tumor size (>5 cm), hydronephrosis, or both were associated with an increased risk of incomplete response or local recurrence in patients. Conversely, maximal TURBT prior to radiotherapy and the absence of CIS served as favorable prognostic indicators. A reduction in the incidence of radiotherapy-induced toxicity can be attributed to advancements in computer technology and modern radiotherapy apparatus, which have enhanced the precision of treatment delivery and the accuracy of treatment planning. Intensity modulated and image-guided EBRT have been found to cause minor late genitourinary or gastrointestinal toxicities in less than 10% of cases [24, 25]. Doses ranging from 50 to 70 Gy are typically administered to bladder tumors in 1.8 to 2.5 Gy daily fractions over a period of 4 to 7 weeks. In contrast, pelvic lymph nodes typically receive 40 to 50 Gy.

Multimodal Therapy

The combination of TURBT, chemotherapy, and radiotherapy (trimodal therapy) has shown promising results. The approach generally involves:

1. Initial TURBT to remove as much of the tumor as possible.
2. Concurrent chemoradiation to target residual microscopic disease.
3. Adjuvant chemotherapy to address potential micro-metastatic disease.

Studies have demonstrated that trimodal therapy can achieve survival rates comparable to radical cystectomy, with 5-year overall survival rates around 50-60% and bladder-intact survival rates around 30-40%.

"Maximal TURBT" is the initial stage of any multimodal treatment; it entails the secure removal of the maximum amount of tumor feasible. Eliminating all visible disease while maintaining the procedure's safety is the objective. The achievement of a complete resection has been associated with a 20% increase in the rate of local control, according to multiple prospective studies [26, 27]. Patients with large T3/T4 lesions or multifocal CIS, which are difficult to completely resec via TURBT, have a reduced prognosis for cure when utilizing this multimodal approach [28].

Outcomes

Oncological Outcomes: The success of bladder preservation protocols is measured by cancer-specific survival (CSS), overall survival (OS), and bladder-intact survival (BIS). The rates of complete response (CR) to chemoradiation are high, often exceeding 70-80% in well-selected patients. Patients achieving CR have a good prognosis, with long-term survival comparable to those undergoing radical cystectomy.

Functional Outcomes

A significant advantage of bladder preservation is the maintenance of bladder function and quality of life. Most patients retain a functional bladder, although some may experience irritative or obstructive urinary symptoms. Long-term follow-up is necessary to monitor for late toxicity and secondary malignancies.

Complications and Management

Complications from bladder preservation protocols can include urinary incontinence, bladder dysfunction, and

radiation cystitis. Management involves supportive care, pharmacotherapy, and, in severe cases, surgical intervention.

Emerging Therapies and Future Directions

Immunotherapy

Checkpoint inhibitors, such as pembrolizumab and atezolizumab, have shown efficacy in metastatic bladder cancer and are being investigated in the bladder preservation setting. Combining immunotherapy with chemoradiation holds promise for enhancing local and systemic control.

Biomarkers

The development of biomarkers to predict response to bladder preservation therapies is an area of active research. Identifying patients most likely to benefit from bladder-sparing approaches could personalize treatment and improve outcomes.

Personalized Medicine

Advances in genomic profiling and molecular characterization of tumors are paving the way for personalized medicine. Tailoring treatment based on individual tumor biology could optimize therapeutic efficacy and minimize unnecessary toxicity.

Future Directions

In the context of metastatic urothelial carcinoma following cisplatin-based chemotherapy, the recent development of immune checkpoint inhibitors that target programmed death-1 (PD-1) and programmed-death ligand-1 (PDL-1) improved survival in the second line setting. These inhibitors were also approved in the first line for patients who were ineligible for cisplatin chemotherapy. A biologic justification exists for integrating immunotherapy with existing BSP. The synergistic impact of immunotherapy and BSP in augmenting abscopal antitumor effects and attaining maximum tumor inhibition is corroborated by our recent preclinical discoveries [29]. Recent findings from a phase III trial comparing durvalumab after definitive chemoradiotherapy to chemoradiotherapy alone for locally advanced non-small-cell lung cancer indicate that the immunotherapy arm had a substantially prolonged OS and progression-free survival [30]. These results lend great credence to the viability of this concept. Presently, there are ongoing and multiple phase I to III trials that have been approved to use immune checkpoint inhibitors as neo-adjuvant or adjuvant therapy in combination with radiotherapy or TMT for patients diagnosed with bladder cancer.

Conclusion

Bladder preservation protocols offer a viable alternative to radical cystectomy for selected patients with muscle-invasive transitional cell carcinoma of the bladder. Multimodal approaches, particularly trimodal therapy, provide effective oncologic control while preserving bladder function. Ongoing research into novel therapies and biomarkers will likely enhance the efficacy and applicability of bladder preservation strategies. Multidisciplinary collaboration and careful patient selection remain key to successful outcomes. Recent years have seen a substantial increase in interest in bladder preservation techniques (BPTs), owing to the fact that technological advances have enhanced BPT outcomes and the emphasis has increased on enhancing quality of life. The most evidence supports the use of trimodal therapy; more recent series have shown encouraging oncologic outcomes, such as overall and cancer-specific survival. Prospective avenues for development and noteworthy developments encompass the application of tetramodal therapy, predictive biomarkers including DDR gene mutations, and the potential of immunotherapy (10), which can be followed by bladder preservation. In the realm of immunotherapy, a number of immune checkpoint inhibitors have been granted approval in recent years.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34.
2. Ro JY, Staerkel GA, Ayala AG. Cytologic and histologic features of superficial bladder cancer. Urol Clin North Am. 1992;19(3):435-453.
3. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol. 2005;48(2):202-205; discussion 205-6.
4. Witjes JA, Lebret T, Compérat EM, Cowan NC, De Santis M, Bruins HM, *et al*. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Eur Urol. 2017;71(3):462-475.
5. Herr HW, Dotan Z, Donat SM, Bajorin DF. Defining optimal therapy for muscle invasive bladder cancer. J Urol. 2007;177(2):437-443.
6. Rosario DJ, Becker M, Anderson JB. The changing pattern of mortality and morbidity from radical cystectomy. BJU Int. 2000;85(4):427-430.
7. Mitin T, George A, Zietman AL, Heney NM, Kaufman DS, Uzzo RG, *et al*. Long-Term Outcomes Among Patients Who Achieve Complete or Near-Complete Responses After the Induction Phase of Bladder-Preserving Combined-Modality Therapy for Muscle-Invasive Bladder Cancer: A Pooled Analysis of NRG Oncology/RTOG 9906 and 0233. Int. J Radiat. Oncol Biol. Phys. 2016;94(1):67-74.
8. Arcangeli G, Arcangeli S, Strigari L. A systematic review and meta-analysis of clinical trials of bladder-sparing trimodality treatment for muscle-invasive bladder cancer (MIBC). Crit Rev Oncol Hematol. 2015;94(1):105-15.
9. Mak KS, Smith AB, Eidelman A, Clayman R, Niemierko A, Cheng JS, *et al*. Quality of Life in Long-term Survivors of Muscle-Invasive Bladder Cancer. Int J Radiat Oncol Biol Phys. 2016;96(5):1028-36.
10. Chemoradiotherapy With or Without Atezolizumab in Treating Patients With Localized Muscle Invasive Bladder Cancer [Internet]. ClinicalTrials.gov. 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT03775265 Accessed November 23, 2019.
11. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, *et al*. Radical cystectomy in the treatment of invasive bladder cancer: Long-term results in 1,054 patients. J Clin Oncol. 2001;19(3):666-675.
12. Goodney PP, Stukel TA, Lucas FL, Finlayson EV, Birkmeyer JD. Hospital volume, length of stay, and

readmission rates in high-risk surgery. Ann Surg. 2003;238(2):161-167.
13. Solsona E, Iborra I, Collado A, Rubio J, Casanova JL, Ricós JV, *et al*. Feasibility of radical transurethral resection as monotherapy for selected patients with muscle invasive bladder cancer. J Urol. 2010;184(2):475-480.
14. Herr HW. Transurethral resection of muscle-invasive bladder cancer: 10-year outcome. J Clin Oncol. 2001;19(1):89-93.
15. Capitanio U, Isbarn H, Shariat SF, Lutke RJ, Nini A, Terrone C, *et al*. Partial cystectomy does not undermine cancer control in appropriately selected patients with urothelial carcinoma of the bladder: a population-based matched analysis. Urology. 2009;74(4):858-864.
16. Kassouf W, Swanson D, Kamat AM, Siefker-Radtke A, Grossman HB, Dinney CP. Partial cystectomy for muscle invasive urothelial carcinoma of the bladder: A contemporary review of the M. D. Anderson Cancer Center experience. J Urol. 2006;175(6):2058-2062.
17. Eswara JR, Efstathiou JA, Heney NM, Luongo T, Richie JP, Shipley WU. Complications and long-term results of salvage cystectomy after failed bladder sparing therapy for muscle invasive bladder cancer. J Urol. 2012;187(2):463-468.
18. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, *et al*. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol. 2001;19(3):666-675.
19. Kaufman DS, Shipley WU, Feldman AS. Bladder cancer. Lancet. 2009;374(9685):239-249.
20. 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(16):1477-1488.
21. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, *et al*. Neo-adjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl. J Med. 2003;349(9):859-866.
22. Plimack ER, Guadagnolo BA, Yuh B, Smith A, Bass P, Hartke C, *et al*. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive bladder cancer (PURE-01): an open-label, single-arm, phase II study. J Clin Oncol. 2020;38(17):1819-1828.
23. 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(16):1477-1488.
24. Søndergaard J, Holmberg M, Jakobsen AR, Muren LP, Petersen JB, Alsner J. A comparison of morbidity following conformal versus intensity-modulated radiotherapy for urinary bladder cancer. Acta Oncol. 2014;53(10):1321-1328.
25. Turgeon GA, Souhami L, Cury FL, Rajan R, Faria S, Bahoric B, *et al*. Hypofractionated intensity-modulated radiation therapy in combined modality treatment for bladder preservation in elderly patients with invasive bladder cancer. Int. J Radiat. Oncol. Biol. Phys. 2014;88(2):326-331.
26. Kaufman DS, Winter KA, Shipley WU, Heney NM, Chetner MP, Heney NM, *et al*. The initial results in muscle-invading bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. Oncologist. 2000;5(6):471-476.
27. Kaufman DS, Winter KA, Shipley WU, Heney NM, Lee CT, Tester WJ, *et al*. Phase I-II RTOG study (99-06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twice-daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. Urology. 2009;73(4):833-837.
28. Giacalone NJ, Shipley WU, Clayman RH, Niemierko A, Drumm MR, Althoff AL, *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(6):952-960.
29. Rompré-Brodeur A, Shinde-Jadhav S, Ayoub M, Ayari C, Hovington H, Péloquin L, *et al*. PD-1/PD-L1 Immune Checkpoint Inhibition with Radiation in Bladder Cancer: *In Situ* and Abscopal Effects. Mol Cancer Ther. 2020;19(1):211-220.
30. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, *et al*. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl. J Med. 2018;379(24):2342-2350.