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Bladder Cancer Highlights on UROPEDIA, Which is an E-Learning Platform of The Society of Urological Surgery in Turkiye

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Abstract

This study aimed to highlight the critical knowledge of bladder cancer education using UROPEDIA videos, an e-learning platform developed by the Society of Urological Surgery in Turkiye. We analyzed 90 educational videos on bladder cancer uploaded on UROPEDIA between January 2016 and October 2023. Two experienced urologists independently reviewed the videos, focusing on the essential information presented. Of the 90 videos, 43 (47.8%) addressed non-muscle-invasive bladder cancer, 39 (43.3%) focused on muscle-invasive bladder cancer, and 8 (8.9%) covered both. Key topics included Bacillus Calmette-Guerin (BCG) therapy, treatment options following BCG failure, and cystectomy procedures. UROPEDIA is an invaluable resource for urology residents and specialists, providing up-to-date information and expert insights.

Keywords: UROPEDIA, urology education, bladder cancer, e-learning

Introduction

Bladder cancer (BC) is the ninth most commonly diagnosed cancer and is up to 4 times more common in men. When focusing exclusively on males, the cancer ranked sixth most common. In terms of mortality, BC ranks sixth among men but falls outside the top ten when both genders are considered (1).

Although bladder cancer is the most costly per-patient malignancy, survival outcomes for patients with this malignancy have not improved adequately in recent decades (2). However, significant recent advances have been made in the management of BC. These advances include treatment alternatives for Bacillus Calmette-Guerin (BCG) failure, trimodal therapy for high-risk non-muscle-invasive (NMIBC) and MIBC, locally advanced and metastatic BC management, and immunotherapy for BC (3,4). Urology residents and urologists need to follow and adopt these developments to improve the oncological outcomes of BC.

In an interview study between urology residents and specialists, 45% of the participants indicated that they used online educational resources (5). Numerous studies have also shown that e-learning is a beneficial educational resource for urology residents and specialists (6-9). The rapid rise of e-learning occurred during the coronavirus disease 2019 pandemic when face-to-face education was impossible (10). However, in Turkiye, the foundations of e-learning were established much earlier, thanks to UROPEDIA, which was launched by the Society of Urological Surgery in 2016 (11). UROPEDIA is an online urology library created exclusively for medical professionals. This includes presentations for resident training, surgical procedure videos, video recordings of presentations from scientific congresses and meetings, podcasts, textbooks, and current articles (11,12). This review summarizes the key points from the BC videos uploaded during UROPEDIA's nearly 10-year e-learning experience and presents their general quantitative data.

Materials and Methods

Study Design and Data Collection

This review analyzed BC videos available on the UROPEDIA platform (https://uropedia.com.tr). A total of 93 videos were identified under the BC tab. The videos were uploaded between January 2016 and October 2023, with presentation dates from October 2012 to September 2023. Three videos were excluded

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from the analysis due to technical issues. Thus, 90 videos were included in the final evaluation. Descriptive quantitative data about the videos are given in the results section.

Two experienced urologists independently watched all 90 videos and evaluated and noted the essential and current knowledge presented. The key points of the videos will be highlighted in the discussion section. This information was synthesized and discussed to highlight critical advancements and recommendations in BC. We have also included links to relevant videos in the reference section to facilitate access for readers interested in specific information.

Ethical Considerations

This study involved analyzing educational videos and did not involve patient data or material. Thus, formal ethics committee approval was not deemed necessary. However, ethical research principles, including integrity and respect for intellectual property, were strictly adhered to. This study was performed with the knowledge and approval of The Society of Urological Surgery.

Results

A total of 90 videos were included in the study. Of these, 43 (47.8%) were about NMIBC, 39 (43.3%) were about MIBC, and 8 (8.9%) covered both topics. The primary focus of the videos concerning NMIBC and MIBC was on managing the disease. Among the NMIBC videos, the most common issues were discussions on BCG therapy and treatment options following BCG failure (n=11, 25.5%). On the MIBC side, the videos most frequently addressed cystectomy, its indications, timing, methods, and complications (n=17, 43.5%).

The video views ranged from 10 to 745, and the mean value was 100.3 views. Eighty-two (91.2%) of the academics presenting the videos were urologists. Moreover, 2 (2.2%) patients were medical oncologists, 2 (2.2%) were radiation oncologists, 3 (3.3) were radiologists, and 1 (1.1) was pathologist.

Discussion

UROPEDIA includes several videos that explain the etiology, epidemiology, diagnosis, classification-staging systems, and management alternatives for each stage of BC. Multiple videos cover the same topic. Although the information in these videos sometimes overlaps, they also provide different insights. Additionally, presentations on the same topic from different years emphasize updated information. In the continuation of our study, we will present the critical information compiled from UROPEDIA videos over the last ten years that urology residents and urologists should consider in BC practice. The videos featured esteemed academics that are experts in their fields. Hence, the authors proposed that reviewing the critical information, expert opinions, and experiences obtained from these videos in this manuscript would contribute to the literature. Readers can watch the reference video for more detailed information when they notice exciting sentences.

The association between smoking and bladder cancer is well demonstrated. Coffee consumption does not increase the risk of BC among non-smoking coffee consumers. Additionally, human papillomavirus (HPV) DNA has been detected in 2-35% of BC cases; however, a definitive relationship between HPV and BC has not been established.

The tumor-node-metastasis stage was revised in 2017, and T4a prostate involvement was redefined to include prostatic stroma and seminal vesicle involvement. Aydın Mungan stated that this change means that prostatic mucosal involvement is no longer considered T4a. Additionally, M1 was divided into two categories: M1a for nonregional lymph node metastasis and M1b for distant metastasis (14). Recently, a T1 subclassification based on muscularis mucosa invasion has been described (15). Sümer Baltacı pointed out that this classification might be essential in determining the treatment management [early cystectomy or transurethral resection of bladder (TUR-B)+BCG of NMIBC patients with T1 tumors in the high and very high-risk categories. Another critical issue is variant bladder cancer. A recently published meta-analysis reported a 14% detection rate of variant histology. (16). Variant pathology is associated with locally aggressive disease, upstaging, lymph node (LN) positivity, and a high rate of distant metastasis (17).

In the management of NMIBC, the presence of muscularis propria in the initial TUR-B indicates the quality of the operation, and the survival rates are better in these patients (18). In a study conducted in our country, the presence of residual tumor after TUR-B was shown to be 40% if there was muscle in the first specimen and 55% if there was no muscle, with an overall average of 47%. Moreover, 25% of the residual tumors are T1, the carcinoma *in situ* (CIS) accompanying rate is 18-20%, and the upstaging rate was 10% in reTUR-B (19). Incomplete TUR-B is a significant risk factor for early recurrence, and reTUR-B is not the completion of an incomplete TUR-B (20). İlker Tınay emphasized that in T1 patients, even if the specimen includes muscularis propria with no sign of invasion, re-TUR-B, including muscle tissue, should be performed within 14-42 days because it reduces progression and recurrence and increases survival (21).

The recommended treatment paradigm for managing patients with NMIBC based on risk groups is as follows. For low-risk and intermediate-risk patients with a European Organization for Research and Treatment of Cancer (EORTC) score <5 and a low recurrence rate (≤1/year) NMIBC: Early single-dose intravesical

chemotherapy (IVC). For other intermediate-risk NMIBC: Full-dose BCG administered for 1 year or 1 year of IVC. For high-risk NMIBC: Full-dose BCG for 1-3 years. For very high-risk NMIBC: Radical cystectomy (RCx) (21). Low-dose (1/3) BCG is more effective than 30 mg of mitomycin C (MMC) for preventing recurrence in the intermediate-risk group. As the BCG dose decreases, local and systemic toxicity also decreases. However, high-dose BCG is superior to low-dose BCG in preventing recurrence in high-risk patients (22). The Southwest Oncology Group (SWOG) study published in 2000 highlighted maintenance BCG treatment and found that the median RFS was 76.8 months in the maintenance versus 35.7% in the nonmaintenance arm. Three-year BCG maintenance treatment is superior to 1 year only in reducing recurrence in high-risk patients. Moreover, for high-risk patients, 3 years of maintenance BCG therapy does not provide advantages in terms of progression or survival (23). Thus, maintenance treatment can be limited to 1 year, especially in cases of BCG shortage.

For patients with CIS, if there is no response after a 6-week BCG induction, a second BCG induction can elicit a response in 40-60% of patients. However, if there is no response by the sixth month, RCx should be performed (24). Taner Divrik highlighted that if a T1HG tumor is present at the first evaluation after induction, further BCG should not be administered, and RCx should be recommended. In cases of BCG failure, the first choice is RCx. For patients unsuitable or unwilling to undergo cystectomy, the U.S. Food and Drug Administration (FDA) approved treatment alternatives include intravesical chemotherapy, chemo hyperthermia, immunotherapy, vaccines, gene therapy (Nadofaragene Firodenovac), and trimodal therapy (25). Evren Süer indicated that the FDA expects a 45-50% complete response rate for CIS at six months and a 30% recurrence-free survival (RFS) rate at 24 months for papillary tumors. Valrubicin, with a 10% complete response rate and a 10% 1-year RFS rate, became the first IVC agent approved by the FDA in 1998 for use in BCG failure (26). Other intravesical chemotherapy agents include gemcitabine, gemcitabine + docetaxel, and cabazitaxel + gemcitabine + cisplatin (25). Intravesical gemcitabine is superior to repeated BCG use in terms of 2-year RFS (19% vs. 3%) and progression rates (33% vs. 37%). Gemcitabine + docetaxel intravesically achieved 1-year and 2-year RFS rates of 60% and 47%, respectively (26). The use of intravesical gemcitabine + docetaxel is increasing. A study involving 18 patients receiving triple intravesical chemotherapy (cabazitaxel + gemcitabine + cisplatin) reported 1- and 2-year RFS rates of 80% and 65%, respectively (25). Pembrolizumab, an immunotherapy agent, received FDA approval for BCG failure based on the KEYNOTE-057 study (25,26). This study reported complete response rates of 41.2% at 3 months and 18.8% at 12 months for pembrolizumab administered at 200 mg intravenous (IV) every 3 weeks for 2 years. No progression to T2 disease was observed, but a 13% rate of adverse effects was noted (25). Another immunotherapy agent, atezolizumab, achieved complete response rates of 41.6% at 3 months and 26% at six months, with a 12% rate of grade 3-5 adverse effects. Oportuzumab monitor, a single-chain monoclonal antibody specific to EpCAM, is administered intravesically and has a complete response rate of 40% at 3 months and 17% at 12 months (26). Intravesical Nadofaragene Firadenovec achieved complete response rates of 50%, 70%, 21% for CIS, and 43% for papillary tumors at 12 months (26). The National Comprehensive Cancer Network (NCCN) recommends RCx as the first option for BCG failure. IV pembrolizumab is recommended if RCx is unsuitable or patients are unwilling to undergo cystectomy (25). Chang, Yariş, and İlker Tınay mentioned that in high-risk and very high-risk NMIBC patients, the presence of CIS in the prostatic urethra, lymphovascular invasion (LVI), variant histology, and BCG failure are indications of RCx (27-29). In patients who progress from NMIBC, the prognosis is worse than that of *de novo* MIBC (16). A study comparing early cystectomy with TUR + BCG reported 10-year cancer-specific survival (CSS) rates of 78% versus 51%, favoring early RCx (28). Additionally, BCG-unresponsive patients who undergo cystectomy within two years have a 15-year overall survival (OS) advantage of 43.2% compared with those undergoing cystectomy after two years (23). Thus, performing cystectomy within 2 years in patients with BCG failure improves survival.

Although the diagnosis of MIBC is made through pathological examination of tissue resected during TUR-B, recent advances have focused on multiparametric magnetic resonance imaging (MRI) for preoperative assessment of muscle invasion (30). The VI-RADS scoring system was developed, and recent studies have shown that it is an independent predictor of muscle invasion. Gökhan Pekindil reported that VI-RADS provides 83% sensitivity and 90% specificity for identifying invasive bladder cancer. VI-RADS scores of 1, 4, and 5 reach 90-95% accuracy in detecting muscle invasion, while VI-RADS 2 indicates non-invasive tumors with a 95% accuracy and a 5% false-negative rate. 66% of VI-RADS 3 reports were confirmed to be muscle-invasive, while 33% were non-invasive. Another parameter obtained from multiparametric MRI is the apparent diffusion coefficient (ADC). ADC is related to perfusion; a lower ADC indicates increased perfusion. An ADC value <0.63 is associated with chemosensitivity, while >0.84 indicates chemoresistance. Additionally, increased ADC values after chemotherapy suggest reduced perfusion and positive response to chemotherapy (31).

Maha Hussaın explained that neoadjuvant chemotherapy (NAC) should be standard practice. Because it does not increase morbidity, does not complicate surgery, does not delay surgery, or increases progression. Moreover, NAC usage has level-one evidence that it is well-tolerated by patients and leads to

downscaling (32). Aziz Karaoğlu stated that the advantages of NAC include early treatment of micrometastases, better tolerability compared with adjuvant chemotherapy, and the potential to simplify surgery by reducing the stage. The major disadvantage of NAC is that patients who do not benefit from NAC cause a delay in curative treatment (33). A reasonable protocol is to give two cycles of gemcitabine + cisplatin, evaluate the response, and administer two more cycles if there is a positive response. However, if there is no response, RCx should be immediately performed (34). Delaying cystectomy in patients with NAC resistance leads to poor oncological outcomes (35). The ideal RCx time after NACT is 4-6 weeks (36).

Patients with hydronephrosis, cT3b-T4a, LVI, and variant histology are appropriate candidates for NAC (37). Co-analyses of the Nordic 1 (cisplatin + docetaxel) and Nordic 2 (cisplatin + methotrexate) studies (n=620) showed an 8% improvement in 5-year OS with NAC (p=0.049) and a significant increase in pT0 rates in the NAC group (26% vs. 11%, p=0.001) (33). This benefit is more evident in T3 than in T2 tumors (38). A Phase III study using the CMV protocol (Cisplatin + Methotrexate + Vinblastine) as the NAC showed a 6% improvement in ten-year OS (p=0.037 HR 0.84) (33). The SWOG 8710 study (using methotrexate + vinblastine + adriamycin + cisplatin protocol) reported a 5-year OS rate of 57% vs. 43% (p=0.06), median OS was 77 vs. 46 months (p=0.001), and a pT0 rate was 38% vs 15% in favor of NAC, although with a 33% rate of grade 3-4 side effects (33,39). The EORTC/MRC study published in 2011 compared NAC (CMV) + local treatment vs. local treatment alone and reported significantly better outcomes for OS, metastasis-free survival (MFS), and disease-free survival (DFS) in the NAC group (32). The international collaboration of trials study (which includes T2-4 N0 M0 BC patients) reported better 10-year OS (36% vs. 30%), MFS, and progression-free survival (PFS) rates with NAC. Additionally, patients receiving NAC had a 16% lower mortality rate and higher rates of achieving pT0 (32.5% vs. 12.3%) without increased perioperative complications (39). Meta-analyses have reported that cisplatin-based NAC provides a 5% benefit in 5-year OS, a 9% benefit in RFS, and a 14% reduction in mortality risk. However, the authors suggested that carboplatin offers no survival benefit and that NAC should not be given to patients who cannot receive cisplatin (33).

Albers suggested that molecular subtyping can determine which patients will benefit from NAC. BC is molecularly classified as luminal (60%), basal-squamous (35%), and neuronal (5%). The luminal subtype is further divided into luminal papillary (35%), luminal infiltrative (19%), and luminal (6%). The luminal papillary subtype (type 1) includes an FGFR3 mutation and is characterized by poor response to NAC. Therefore, RCx should be considered as the primary treatment option. Luminal (type 2) tumors do not respond to platinum-based chemotherapy, and the potential treatment remains unclear. Luminal infiltrative (type 3) is characterized by p53 mutation and is resistant to platinum-based chemotherapy. Additionally, due to lymphocytic infiltration, luminal infiltrative (type 3) is the most suitable subtype for immunotherapy. The basal-squamous subtype can be identified histologically via cytokeratin staining and benefits from NAC containing cisplatin + gemcitabine. The neuronal type can be distinguished histologically by its small cells and benefits from NAC containing cisplatin + etoposide (40).

Ali Ferruh Akay reported that RCx was the most complex surgery performed by urologists. The 90-day morbidity and 30-day mortality rates are 64% and a 30-day mortality rate of 1.5 (41). Factors influencing mortality and morbidity include age, the American Society of Anesthesiologists score, and experience. Increased surgical volume reduces morbidity and mortality, with a threshold of approximately 20 cystectomies per year (42). Additionally, patients with hypoalbuminemia and low body mass index have an increased risk of complications (34). Preoperative bowel preparation is not recommended before RCx (43).

Female gender is associated with poor prognosis and higher 12-month post-diagnosis mortality (44). Additionally, BC tends to be more advanced at diagnosis in women. Witjes suggested that adnexal resection is unnecessary if it appears anatomically normal, and surgeons should avoid the sides of the vagina because this area is highly vascular and prone to excessive bleeding. Therefore, he recommends first excision of the urethra and then retrograde cystectomy. Witjes also stated that in cutaneous diversions, he does not remove the anterior vaginal wall but only excises the upper part of the vagina. This approach resulted in less bleeding and better preservation of pelvic floor innervation (45).

The oncological outcomes of robot-assisted radical cystectomy (RARC) and open cystectomy are similar. Güven Aslan stated that open RCx has an advantage in operative time, and RARC is superior in terms of blood loss, transfusion requirement, and lymph node count (46). Lymph node dissection (LND) improves prognosis and staging, with no difference between standard and extended LND. Aydın Mungan highlighted that some authors suggest that removing more than 15 lymph nodes during RCx positively impacts survival (43). The RAZOR study found shorter hospital stays, less blood loss, and fewer perioperative transfusions with RARC but similar 2-year PFS (70% for both) (47). Some studies have suggested that blood transfusions affect OS, CSS, and RFS; however, well-designed studies have shown that blood transfusion does not affect oncological outcomes (48). A study has shown that RARC is an independent risk factor for ureterointestinal anastomosis strictures. In the RARC series, more ureterointestinal anastomosis strictures were observed (13% vs. 25%), which did not change with increased experience. Sümer Baltacı mentioned that another issue with

RARC is atypical peritoneal metastases. One RCT reported more recurrences in the abdominal wall and loop site with RARC, suggesting a new recurrence pattern specific to RARC (48). The RAZOR study indicated that RARC does not contribute to quality of life (QoL), which should be explained to patients (49). RARC does not appear to have advantages over open RCx in terms of morbidity, oncological outcomes, or cost. The 10-year CSS for RCx is 79% for pT2, 43% for T3-4, and 29% for LN + patients (37). Systemic recurrence rates after RCx were 20-30% for pT2 disease: 20-30%, for pT3 disease: 40%, for pT4 disease: >50%, and for LN+ disease:%70 (37).

A study on long-term outcomes of trimodal therapy (n=348, median follow-up 7.7 years, cT2-4a) reported 5-year OS at 52%, 10-year OS at 35%, and 15-year OS at 22%, with bladder preservation rates of 60% at 5 years, 45% at 10 years, and 36% at 15 years. Approximately 29% of patients underwent RCx due to lack of response to treatment. A study using propensity score matching to compare RCx and trimodal therapy found that the two methods were similar for the first 2 years, but RCx had better mortality rates after 2 years. Another study found no difference in MFS or QoL between the methods, but RCx showed better local RFS and OS (50). Another series (475 cases, median follow-up 4.5 years) reported complete response rates of 75%, non-invasive recurrence at 10 years of 26%, invasive recurrence of 18%, regional nodal recurrence of 14%, and distant metastasis of 35%, with 27% of patients requiring RCx (half due to lack of complete response, half due to recurrence) (36). The bladder intact disease-specific survival (DSS) rate was 52% at 5 years, 46% at 10 years, and 40% at 15 years. For those undergoing salvage cystectomy, DSS was 58% at 5 years, 44% at 10 years, and 44% at fifteen years (51). Bossi stated that salvage cystectomy after RT provides survival outcomes similar to those of primary cystectomy. Ideal candidates for trimodal therapy must have not received prior pelvic RT, cT2-T3 N0, not extensive CIS, achieve microscopic complete TUR-B (the most critical factor for overall survival), minimal or no hydronephrosis, unifocal tumors, <7 cm tumors, good bladder function, and agree to regular follow-up (52).

The FDA approved atezolizumab, durvalumab, velum, nivolumab, and pembrolizumab in 2016 for the treatment of advanced and metastatic bladder cancer. KEYNOTE-045 showed that pembrolizumab reduces death risk by 27% in platinum-refractory patients, with a median OS of 10.3 months and a median PFS of 2.1 months, though grade 3-4 toxicity was 13%. KEYNOTE-52 evaluated pembrolizumab in first-line treatment for cisplatin-ineligible patients, showing a significant OS advantage for patients with PD-L1 expression ≥10 than patients with PD-L1 expression <10 (18.5 vs. 9.7 months). Studies investigating the addition of immunotherapy to first-line platinum-based chemotherapy (Imvigor130 with atezolizumab, DANUBE with durvalumab, KEYNOTE-361 with pembrolizumab) have found that this combination therapy does not provide any benefit. The Javelin bladder 100 study reported that adding maintenance velum to standard platinum-based chemotherapy improved survival (21.4 vs. 14.3 months, p=0.001), with a more pronounced advantage in PD-L1+ patients (12-month OS: 79% vs. 60%; 24-month OS: 70% vs. 48%). NCCN, European Society for Medical Oncology, and European Association of Urology guidelines recommend velum as maintenance therapy after chemotherapy.

Conclusion

UROPEDIA has contributed to bladder cancer education by offering a comprehensive collection of videos covering various aspects of the disease. This platform provides up-to-date information and expert insights to improve clinical practices and patient outcomes.

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Footnotes

Authorship Contributions

Concept: Y.M.A., N.A.M., Design Y.M.A., N.A.M., Data Collection or Processing: Y.M.A., N.A.M., Analysis or Interpretation: Y.M.A., Literature Search: Y.M.A., N.A.M., Writing: Y.M.A., N.A.M.

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