

Modern Applications and Factors Influencing Quality of Life and Functional Outcomes in Patients with Bladder Cancer

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Chen *et al.*: Factors Influencing Quality of Life and Functional Outcomes in Bladder Cancer

Here, we review quality of life and functional outcomes in bladder cancer patients after treatment and look for potential contributors. For the current scoring systems, we highlighted the specificity scales that are most commonly used in non-muscle invasive bladder cancer and muscle invasive bladder cancer. In addition, we go into the influence and bias of ileal conduit, robotic surgery, gender disparities, perioperative rehabilitation, bladder-preserving radiotherapy, pharmaceutical and immune chemotherapy, etc. on quality of life. Currently, although there are conflicts whether ileal conduit or orthotopic neobladder has a more positive impact on the prognosis of patients with bladder cancer, it is widely recognized that modern applications such as robotic surgery and pharmaceutical and immune chemotherapy improve the prognosis and quality of life of bladder cancer patients. Moreover, we discussed the differences in the adaptation of sex life quality between women and man after receiving various treatments. Surgical procedures that preserve organ integrity appear to improve patient's quality of sexual life. Through this review, clinicians will have a better understanding of how important modern applications can grasp to improve the quality of life of their patients, with the goal of restoring their patient's normal function and making it easier for them to re-join society.

Key words: Quality of life, bladder cancer, radical cystectomy, bladder urothelial carcinoma

Bladder cancer is a common malignant tumor with the highest morbidity and mortality in the urinary system tumors^[1,2], which is often accompanied by high treatment costs and medical burden^[3]. Bladder cancer can be divided into Non-Muscle Invasive Bladder Cancer (NMIBC) and Muscle Invasive Bladder Cancer (MIBC) according to whether the muscle layer is invaded or not. Urothelial carcinomas are divided into the bladder, renal pelvis, ureter and proximal urethra cancers. Bladder Urothelial Carcinoma (BLCA) accounts for 90 % to 95 % of urothelial cancers. Histologically, NMIBC accounts for 75 % of bladder cancer and MIBC accounts for 25 %^[4]. The complexity of cancer types increases the difficulty of bladder cancer treatment and management^[5]. Currently, for patients with NMIBC, the main treatment method includes a series of measures to preserve the bladder; for patients with muscle MIBC, radical cystectomy is the conventional treatment mode.

Complications and readmission rates are highly following bladder cancer interventions, which can severely compromise patient's quality of life and functional outcomes^[6]. This reduction in quality of life is manifested in many aspects such as urination, digestion and sexual function, and it also damages personal image and social behavior, ultimately leading to varying degrees of psychological problems in patients^[7,8]. The assessment of quality of life in patients with bladder cancer is diverse and complex. The heterogeneity of this disease makes it reasonable to combine cancer-specific and bladder cancer-specific scores. In addition to this, a detailed review of the potential impact of various interventions and population characteristics on quality of life and functional outcomes should be undertaken to inform clinicians and patients.

In this review article, we review research tools for quality of life in patients with bladder cancer and the impacts of various interventions on quality of life (fig. 1).

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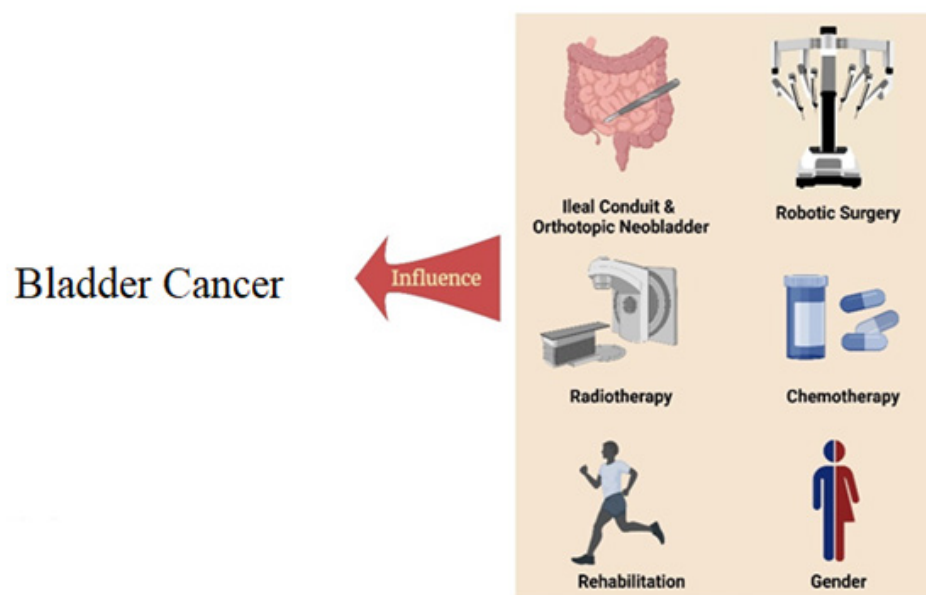


Fig. 1: Modern applications and factors influencing life quality of bladder cancer patients

ASSESSMENT OF QUALITY OF LIFE

It is undeniable that the estimation of survival time is very important for bladder cancer patients, but the quality of life involves whether the patient can retain the ability to live independently and the hope of returning to society. Measures of quality of life are important tools for assessing the clinical efficacy of cancer treatments. However, implementing quality of life measures in daily practice is challenging because measures of quality of life are far from standardized measures^[9].

Numerous measurement schemes have been developed over the past few decades. These protocols are broadly divided into bladder cancer specific scales and generic scales. However, many previously used or self-designed measurement protocols are considered as poorly reliable and have not been validated across a wide range of regions and populations, and are susceptible to bias. Clinicians should understand each routine measurement protocol and be familiar with the applicable scenarios and limitations.

Specific scale for NMIBC:

For patients with NMIBC, there are two scales available. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Bladder Cancer Superficial 24 (EORTC QLQ-BLS24) or EORTC Quality of Life Questionnaire Non-Muscle Invasive Bladder Cancer 24 (EORTC QLQ-NMIBC24)^[10] and Questionnaire of Quality of Life in patients with NMIBC (CAVICAVENMI)^[9].

In 1996, EORTC produced the QLQ-BLS24 scale for NMIBC. The scale consists of 24 questions, including urinary symptoms, chemotherapy tolerance, sexual and bowel function, and more. EORTC recommends the use of this questionnaire in addition to the EORTC QLQ-C30 questionnaire to evaluate quality of life for NMIBC^[11]. However, this questionnaire did not take into account local and systemic adverse effects of chemotherapy drugs.

In 2014, the researchers conducted the third stage of validation and reliability testing of this scale, provided evidence of reliability and validity. The information displays the EORTC QLQ-NMIBC24 module's evidence-based modified scale structure and psychometric data for the use in clinical studies of patients with high or intermediate-risk bladder cancer. The original scale was modified and the final scale's name was changed to EORTC QLQ-NMIBC24^[11]. However, data on the applicability of this latest scale in different countries and regions are lacking, although many studies have used this tool^[12,13].

CAVICAVENMI was designed in 2016 by a Spanish research team^[14]. Studies have demonstrated the scale's strong reliability and validity. There are 21 components in CAVICAVENMI, such as disease state, self-evaluation, emotional state, work state and sexual life. This questionnaire has the advantage of being simpler and shorter than the EORTC QLQ-NMIBC24 and QLQ-C30. At the same time, this questionnaire contains questions about the topical treatment of mesenteric and mitomycin. Unfortunately, this questionnaire is currently only available in Spanish and has not been

validated in a wide range of countries.

Specific scale for MIBC:

There are three questionnaires, which can be used to evaluate the quality of life of patients with MIBC. The initial aircraft is the EORTC QLQ-BLM30^[15]. It is intended to assess the quality of life of patients with MIBC and is appropriate to individuals having cystectomy and conservative treatment, but never to those receiving radiation therapies. Urinary issues, sexual functions, ureterostomy issues, catheter use, self-perception and gastrointestinal complaints are evaluated. In the sexual module, gender-specific questions tackle concerns that are unique to both men and women. The EORTC QLQ-BLM30 has been translated into eighteen different languages and is among the most frequently used instruments for evaluating the quality of life of patients with MIBC^[16].

The FACT-Bladder-Cystectomy (FACT-BI-Cys)/FACT-Vanderbilt Cystectomy Index is the second^[17]. In 2003, FACT-BI-Cys was developed exclusively for MIBC patients. This tool was like EORTC QLQ-BLM30, which has a specialized application and is not intended for use with radiation therapy patients^[18]. It assesses urinary function, sexual function, digestive function and body image. FACT-BI-Cys was validated in a retrospective clinical study of 50 patients in 2003, demonstrating its ability to objectively evaluate quality of life following radical cystectomy and urinary diversion^[19]. Currently, a prospective longitudinal research is still under implementation^[18]. According to preliminary findings, the FACT-BI-Cys is a viable and useful questionnaire for evaluating bladder cancer patient's quality of life.

The Ileal Orthotopic Neobladder-Pro Questionnaire (IONB-PRO) is the third instrument. This survey was created in 2014 to examine the effects of radical cystectomy and IONB^[20]. The material consists of everyday activities, emotional functioning, sleep disorders, social functioning and additional concerns. The IONB-PRO is available in one long-form (23 items) and two short-forms (12 items, 15 items) and research has demonstrated that it has high validity, internal consistency, reliability and discrimination^[20]. One study evaluated this questionnaire and showed that IONB-PRO is a viable tool for assessing patients with MIBC's quality of life^[21].

ILEAL CONDUIT vs. ORTHOTOPIC NEOBLADDER

Radical cystectomy often results in lifestyle changes

for the patient because the bladder is removed during this procedure. Patients who undergo the ileal conduit approach will have a colostomy, which increases care and cosmetic concerns, but patients do not experience problems associated with urinary retention or incontinence^[22]. In contrast, patients undergoing orthotopic neobladder do not require a colostomy and are capable to urinate *via* the urinary tract.

Since there is no distinction between ileal conduit and orthotopic neobladder in terms of tumor prognosis, the decision of treatment regimen is mostly determined by individual and physician desire. There is a considerable controversy in the academic community, to know which method of urinary diversion is more excellent. The academic community is deeply divided to know whether the type of urinary diversion is the most effective. According to Sultan *et al.* systematic evaluation, usage of the ileal conduit was related with a shorter length of hospital stay and lower rates of significant adverse events in patients following radical cystectomy and urinary diversion^[23]. However, they did not show clear advantages in terms of readmission rate, cardiovascular event rate and narcotic drug requirement, so they believe that ileal conduit is the most successful and safest way of urinary diversion.

Moreover, some researchers suggest that the orthotopic neobladder approach is related with higher quality of life scores. Ghosh *et al.* did a systematic study to investigate variations in life quality between neobladder surgery as well as other types of diversion surgery. Results showed that four out of six studies published upon 2011 supported the superior quality of life of the neobladder above other types of urinary diversions^[24]. Singh *et al.* conducted a recent prospective cohort study, wherein they concluded that orthotopic neobladder approach was associated with an improvement in quality of life^[25]. At all-time points in their study (6, 12 and 18 mo postoperatively), patients who received the orthotopic neobladder approach had significantly higher overall health status and wellbeing compared to those receiving the ileal conduit route. Due to research bias and lack of evidence, it is uncertain which surgery provides the best quality of life. More prospective studies with large samples are needed to validate these conclusions.

ROBOTIC SURGERY vs. OPEN SURGERY

The use of robots is an important way to achieve minimally invasive surgery. In developed countries, robotic surgery is an important method for performing

radical cystectomy^[26]. Robotic surgery is often accompanied by small incisions and shorter operative times, which may lower the incidence of complications and the duration of hospitalization. Most robotic-assisted radical cystectomies are performed in combination with open surgery. Noninvasive surgery is used for cystectomy and pelvic lymph node dissection, while open incision is used for urinary diversion^[27]. However, it has been demonstrated that the fully intracorporeal orthotopic neobladder approach offers advantages such as strong reproducibility, great surgical efficiency and excellent perioperative outcomes^[27,28]. Desai *et al.* reported on 132 patients who had totally intracorporeal robotic orthotopic ileal neobladder after radical cystectomy. The results showed that with experience, surgical time, loss of blood, duration of stay in the hospital and also the frequency of late complications improved, and the 5 y overall, cancer-specific, and recurrence-free survival rates were 72 %, 72 % and 71 %, respectively^[28].

Many investigators contributed to the study to determine whether patients who received most robotic-assisted radical cystectomy had higher postoperative quality of life than patients who underwent open surgery. Poch *et al.* investigated the patient's quality of life receiving robotic-assisted radical cystectomy in a small retrospective clinical research. They concluded that urine output and bowel function reverted to baseline after 1-2 mo and 2-4 mo, respectively. Quality of life scores for sexual function declined the most, but returned to normal within 16-24 mo after surgery^[29]. Sathianathan *et al.* found no differences in disease progression, significant complications or life quality comparing robotic-assisted and open radical cystectomy in a meta-analysis of five randomized controlled studies. However, robotic-related radical cystectomy has been proven to reduce the risk of perioperative blood transfusion and result in decreasing the length of hospital stay. Open radical cystectomy appears to have a lower rate of local recurrence^[30].

It must be pointed out that the above-mentioned meta-analyses used the extracorporeal urinary diversion method. The intracorporeal urinary diversion procedure has lately gained popularity due to the fact that it does not require additional surgeries to build a new bladder. There has been a 95 % rise in intracorporeal urinary diversion use since 2005 according to a research by the International robotic cystectomy consortium^[31]. However, patients with intracorporeal urinary diversion appeared to have more overall complications and

readmission rates, but high-grade complications did not show significant differences. Another study by this consortium noted that patients with intracorporeal urinary diversion showed shorter operative times, less blood loss and less blood transfusions, yet this subset of patients experienced more advanced complications^[32]. Despite the fact that intracorporeal urinary diversion was linked with more serious consequences than extracorporeal urinary diversion, the complications declined over time.

A well-designed open-label, randomized, phase 3, non-inferiority trial evaluating robotic surgical effectiveness was recently published^[33]. 350 individuals were randomly allocated to either robotic-assisted radical cystectomy or open radical cystectomy between July 1, 2011 and November 18, 2014. The 2 y progression-free survival rate in the robotic cystectomy group was 72.3 % against 71.6 % in the open cystectomy group, demonstrating that robotic cystectomy was not inferior. In addition, the authors used FACT-BI-Cys questionnaires to measure patient's quality of life at baseline, 3 mo and 6 mo postoperatively. The authors discovered no substantial change in FACT-BI-Cys in two different groups at any time point and the mean overall FACT-BI-Cys score improved considerably in both groups at 6 mo postoperatively. One possible explanation for this finding is that all urinary diversion procedures are extracorporeal, which might hide the potential advantages of robotic-assisted radical cystectomy^[34].

BLADDER-PRESERVING RADIOTHERAPY

Despite the fact that surgery is regarded as the standard of care for the majority of patients, radiation treatment has re-emerged as a viable alternative for patients who are not candidates for drastic surgery. Due to the inferior physical state of radiation treatment cohorts, it is sometimes difficult to compare the results of radiation therapy and surgery^[35,36].

Bowel discomfort is the life quality issue that individuals with bladder cancer report most commonly following radiation therapy whereas diarrhea/loose stools and fecal incontinence (20 %) were the most prevalent adverse events^[37]. In addition, unpleasant symptoms include frequent urination, sexual disturbance, fatigue and discomfort.

Several studies have compared bladder-sparing strategies with radical cystectomy. Botteman *et al.* demonstrate that bladder-sparing techniques had superior psychological, physical and sexual

performance outcomes in the near term^[38]. Perlis *et al.* conducted a systematic analysis of the quality of life of patients with bladder cancer treated with medical oncological therapy^[37]. They found that patients who got radiotherapy as a way to save their bladders had better bladder, bowel and sexual performance than those who had their bladders removed.

However, some authors reported different conclusions. Fokdal *et al.* discovered that following radical radiation, the majority of patients had normal bladder function, although 14 % of patients experienced moderate to severe bladder impairment. Due to the presence of the colon in the radiotherapy field, radiation therapy is invariably linked with long-term digestive adverse effects. Additionally, radiation therapy has the potential to cause sexual dysfunction^[39].

PHARMACEUTICAL AND IMMUNE CHEMOTHERAPY

The pharmaceutical and immune chemotherapy of bladder cancer has undergone a long exploratory process^[40-46]. Since 1970, cisplatin had gradually become the main drug for bladder cancer chemotherapy^[47-49]. When compared to surgery alone, neoadjuvant chemotherapy based on cisplatin has been demonstrated to minimize the chance of recurrence and enhance overall survival^[50,51]. Cisplatin-based neoadjuvant combination chemotherapy increased 5 y Overall Survival (OS) by 50 %, with a Hazard Ratio (HR) of 0.87, 95 % Confidence Interval (CI) of 0.78-0.98, which was greater than results from individuals treated with surgery alone^[44,50]. Although there is no uniform standard for cisplatin-based chemotherapy, there are currently two main treatment combinations: High-dose Methotrexate, Vinblastine, Doxorubicin and Cisplatin (MVAC) and Gemcitabine plus Cisplatin (GC)^[45]. Ineffective cases of cisplatin chemotherapy are mostly related to the patient's renal impairment, which restricts the administration of cisplatin, causing the dosage to fall short of the normal dose^[52]. Carboplatin is an alternative option within the constraints of this situation, however, it did not show a benefit in predictive survival statistics when compared to cisplatin-based regimens^[53,54].

Early studies on cancer mutations revealed that bladder cancer mutation rate ranked third among all malignancies^[54], after lung cancer and melanoma, indicating that bladder cancer immunotherapy has a lot of research potential. The United States Food and Drug Administration (USFDA) has approved a series of drugs targeting the Programmed Cell Death Ligand 1 (PD-

L1) pathway, including atezolizumab, pembrolizumab, avelumab, nivolumab and durvalumab, which have shown the ability to improve bladder cancer prognosis in repeated clinical trials^[55-59].

Notably, not all concomitant chemotherapy combined with drugs can clearly provide a better prognosis in bladder cancer patients. Robert *et al.* conducted a chemoradiotherapy phase III randomized controlled trial. The results show that adding 5-fluorouracil and mitomycin C to radiotherapy will first undergo a process of decline in organ prognostic function and can merely return patients quality of life scores to pre-treatment stages within 6 mo^[60].

GENDER DIFFERENCE

Most literature on life quality following surgery for bladder cancer excludes women. Nonetheless, women, particularly those with social demands or who engage in sexual activity, plays a premium on quality of life.

Smith *et al.* performed a comprehensive review evaluating the functional results of women in three categories, including voiding function, sexual function and quality of life^[61]. According to this report, 20 % of patients had daytime incontinence, 20 % had nocturnal incontinence and 10 % to 20 % had hypercontinence. The sexual function of patients who undergo genital-sparing radical cystectomy tends to improve. Furthermore, there were minor changes in quality of life between individuals following various urinary diversion treatments. In addition to comparing patients to the general population, the authors demonstrated significant disparities between patients in terms of emotional difficulties, performance role, weariness and appetite. All investigations included in this comprehensive study, however, had a significant potential bias and varied widely in sample size, inclusion criteria and duration of follow-up, so these findings should be interpreted with caution.

Several researchers have reported variations between male and female patient's quality of life. In a cross-sectional investigation, female patients appeared to have greater sexual function than male patients^[62]. In particular, female sexual performance may indeed impacted by body perception and self-image, whereas male patients may report difficulties with erection and ejaculatory function. The authors found that women who underwent the ileal conduit method had a lower cognitive function and outlook scores than men. However, men who received the approach of ileal conduit had lower sexual performance scores

than women. In terms of cognitive performance and attitude, female patients endure a greater psychological and social cost than male patients. In addition, the scientists compared the life quality effects of IONB and ileal conduit. In terms of median follow-up duration, pathological stage, tumor grade, adjuvant chemotherapy or radiotherapy and quality of life, the data showed no major disparities.

One of the key concerns for sexually active women is the recovery of sexual function. Damage towards neurovascular bundles found in the lateral wall of the vagina after radical cystectomy may result in reduced sexual function^[63]. Furthermore, since anterior vaginal wall is frequently removed together with the bladder during radical cystectomy, vaginal shortening or narrowing may ensue. Bhatt *et al.* performed a cohort research to investigate the effect of neurovascular preservation following radical cystectomy and neobladder creation^[64]. The authors analyzed six domains of sexual function (desire, arousal, lubrication, orgasm, satisfaction and pain) using the female sexual function index questionnaire. In the nerve-sparing group, scores at baseline and 1 y after surgery decreased little, but in the non-nerve-sparing group, baseline and postoperative ratings decreased dramatically. In the non-nerve-sparing group, 6 of 7 patients eventually stopped having sexual intercourse. The authors therefore concluded that patients who received neurovascular protection preserved female sexual function^[64].

Zippe *et al.* used a 10-item form of the self-administered index of female sexual function questionnaire to measure sexual dysfunction in 27 sexually experienced female patients treated with radical cystectomy from 1997 to 2002^[65]. The results revealed that the most often reported symptoms by patients were decreased ability or incapacity to attain orgasm (45 %), decreased lubrication (41 %), decreased libido (37 %) and dyspareunia (22 %). The authors imply that sexual dysfunction is a prevalent issue for women following radical cystectomy. The dysfunction manifests in a variety of ways, including diminished orgasm, decreased lubrication, lack of desire and dyspareunia. Female sexual functionality may be enhanced by surgical treatments such as urethra and vagina-sparing, neurovascular-sparing and tubular vaginal restoration.

PREHABILITATION AND POSTOPERATIVE REHABILITATION

Frailty is a complex, multifaceted state of diminishing physiological reserves, which leads to a decrease in

the patient's resilience and adaptability, and ultimately leads to an increase in physical vulnerability. In one study, 21.8 % of patients with urinary tract cancer over the age of 70 y were observed to be frail^[66]. Some scholars believe that preoperative and postoperative physical and dietary interventions can effectively eliminate frailty in this high-risk group^[67].

There is a growing desire to improve health through systematic rehabilitation interventions, consequently enhancing their quality of life and functional outcomes. Jensen *et al.* performed a research to determine if a standardized preoperative and postoperative exercise program influences the quality of life and patient's satisfaction following radical cystectomy^[13]. In areas such as dyspnea, constipation and abdominal bloating, the intervention group had considerably higher quality of life scores than the control group. Rehabilitation interventions did not affect hospital patient satisfaction. Another randomized controlled trial investigates the impact of a postoperative exercise program in patients with bladder cancer undergoing radical cystectomy^[68]. The intervention group included twice-weekly exercise training and daily walks, which used the 36-Item Short Form Survey (SF-36) scale to assess functional ability, balance, lower-body strength and health-related quality of life. Compared to the control group, the patients in the intervention group walked farther and had higher SF-36 scores.

Karl *et al.* examined the effect of the surgical recovery journey on patients receiving radical cystectomy^[69]. In the control group, quality of life was judged by the EORTC QLQ-30 questionnaire which did not alter substantially between postoperative d 3 and d 7 and upon hospital release, but it improved considerably in the recovery journey after the surgery group. In aspects of postoperative morbidity, life quality and analgesia usage, the authors found that early recovery, following surgery in patients receiving radical cystectomy is superior to conservative therapy. Sapre *et al.* believe that although there is insufficient evidence for the exact advantage of early recovery after surgery, the available evidence suggests that early recovery after surgery may hasten the recovery of patients receiving radical cystectomy, so clinicians must alter the standard perioperative management. Optimizing the rehabilitation of these patients requires a multifaceted approach combining surgeons, anesthesiologists, nurses, dietitians and allied health professionals^[70].

CONCLUSION

In addition to oncological outcomes, treatment burden

and quality of life are also top concerns for patients and physicians, and the primary goal of therapy for bladder cancer is changing from simple survival to a high life quality. Overall, researchers should gain a better understanding of the quality of life of bladder cancer patients to appropriately address this growing medical need. Several valid quality of life questionnaires have been produced over the past few decades, however no standard procedure has been established. In addition, longitudinal prospective large-scale cohort studies on the quality of life of patients with bladder cancer are still lacking and the part of this gap needs to be filled.

Author's contributions:

Qiu Chen and Yong Yang contributed equally to this work and they are co-first authors. Qiu Chen drafted the manuscript in detail. Qiu Chen, Yong Yang, Zhe Wang and Tianlin Jiang researched the literature. Qiu Chen, Yong Yang, Junran Yang and Simin Yuan revised the article. All authors have read and agreed to the published version of the manuscript.

Conflict of interests:

The authors declare that they have no competing interests.

REFERENCES

- Mossanen M. The epidemiology of bladder cancer. *Hematol Oncol Clin North Am* 2021;35(3):445-55.
- Cathomas R, Lorch A, Bruins HM, Comp rat EM, Cowan NC, Efstathiou JA, *et al.* The 2021 updated European association of urology guidelines on metastatic urothelial carcinoma. *Eur Urol* 2021;81(1):95-103.
- Svatek RS, Hollenbeck BK, Holm ng S, Lee R, Kim SP, Stenzl A, *et al.* The economics of bladder cancer: Costs and considerations of caring for this disease. *Eur Urol* 2014;66(2):253-62.
- Sylvester RJ, Rodr guez O, Hern ndez V, Turturica D, Bauerov  L, Bruins HM, *et al.* European Association of Urology (EAU) prognostic factor risk groups for non-muscle-invasive bladder cancer (NMIBC) incorporating the WHO 2004/2016 and WHO 1973 classification systems for grade: An update from the EAU NMIBC guidelines panel. *Eur Urol* 2021;79(4):480-8.
- Lobo N, Shariat SF, Guo CC, Fernandez MI, Kassouf W, Choudhury A, *et al.* What is the significance of variant histology in urothelial carcinoma? *Eur Urol Focus* 2020;6(4):653-63.
- Stimson CJ, Chang SS, Barocas DA, Humphrey JE, Patel SG, Clark PE, *et al.* Early and late perioperative outcomes following radical cystectomy: 90-day readmissions, morbidity and mortality in a contemporary series. *J Urol* 2010;184(4):1296-300.
- M nsson  , Davidsson T, Hunt S, M nsson W. The quality of life in men after radical cystectomy with a continent cutaneous diversion or orthotopic bladder substitution: Is there a difference? *BJU Int* 2002;90(4):386-90.
- Hedgepeth RC, Gilbert SM, He C, Lee CT, Wood Jr DP. Body image and bladder cancer specific quality of life in patients with ileal conduit and eobladder urinary diversions. *Urology* 2010;76(3):671-5.
- Zimmermann K, Mostafaei H, Heidenreich A, Schmelz HU, Shariat SF, Mori K. Health-related quality of life in bladder cancer patients: Bladder cancer-specific instruments and domains. Part 2. *Curr Opin Urol* 2021;31(4):304-14.
- Park J, Shin DW, Kim TH, Jung SI, Nam JK, Park SC, *et al.* Development and validation of the Korean version of the European organization for research and treatment of cancer quality of life questionnaire for patients with non-muscle invasive bladder cancer: EORTC QLQ-NMIBC24. *Cancer Res Treat* 2018;50(1):40-9.
- Blazeby JM, Hall E, Aaronson NK, Lloyd L, Waters R, Kelly JD, *et al.* Validation and reliability testing of the EORTC QLQ-NMIBC24 questionnaire module to assess patient-reported outcomes in non-muscle-invasive bladder cancer. *Eur Urol* 2014;66(6):1148-56.
- Kowalkowski MA, Goltz HH, Petersen NJ, Amiel GE, Lerner SP, Latini DM. Educational opportunities in bladder cancer: Increasing cystoscopic adherence and the availability of smoking-cessation programs. *J Cancer Educ* 2014;29(4):739-45.
- Jensen BT, Jensen JB, Laustsen S, Petersen AK, S ndergaard I, Borre M. Multidisciplinary rehabilitation can impact on health-related quality of life outcome in radical cystectomy: Secondary reported outcome of a randomized controlled trial. *J Multidiscip Healthc* 2014;7:301-11.
- Ab agar-Pedraza I, Megias-Garrigos J, S nchez-Pay  J. Quality-of-life survey for patients diagnosed with nonmuscle-invasive bladder cancer. *Actas Urol Esp* 2016;40(4):251-7.
- Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, *et al.* The European organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85(5):365-76.
- Danna BJ, Metcalfe MJ, Wood EL, Shah JB. Assessing symptom burden in bladder cancer: An overview of bladder cancer specific health-related quality of life instruments. *Bladder Cancer* 2016;2(3):329-40.
- Michels CT, Wijburg CJ, Abma IL, Witjes JA, Grutters JP, Rovers MM. Translation and validation of two disease-specific patient-reported outcome measures (Bladder cancer index and FACT-BI-Cys) in Dutch bladder cancer patients. *J Patient Rep Outcomes* 2019;3(1):1-7.
- Anderson CB, Feurer ID, Large MC, Steinberg GD, Barocas DA, Cookson MS, *et al.* Psychometric characteristics of a condition-specific, health-related quality-of-life survey: The FACT-Vanderbilt cystectomy index. *Urology* 2012;80(1):77-83.
- Cookson MS, Dutta SC, Chang SS, Clark T, Smith JA, Wells N. Health related quality of life in patients treated with radical cystectomy and urinary diversion for urothelial carcinoma of the bladder: Development and validation of a new disease specific questionnaire. *J Urol* 2003;170(5):1926-30.
- Siracusano S, Niero M, Lonardi C, Cerruto MA, Ciciliato S, Toffoli L, *et al.* Development of a questionnaire specifically for patients with Ileal Orthotopic Neobladder (IONB). *Health Qual Life Outcomes* 2014;12(1):1-2.
- Mason SJ, Catto JW, Downing A, Bottomley SE, Glaser AW, Wright P. Evaluating patient-reported outcome measures (PROM s) for bladder cancer: A systematic review using the CO nsensus-based Standards for the selection of health measurement instruments (COSMIN) checklist. *BJU Int* 2018;122(5):760-73.

22. Lee RK, Abol-Enein H, Artibani W, Bochner B, Dalbagni G, Daneshmand S, *et al*. Urinary diversion after radical cystectomy for bladder cancer: Options, patient selection and outcomes. *BJU Int* 2014;113(1):11-23.
23. Sultan S, Coles B, Dahm P. Alvimopan for recovery of bowel function after radical cystectomy . *Cochrane Database of Systematic Reviews*. 2017;5(5):Cd012111.
24. Ghosh A, Somani BK. Recent trends in postcystectomy health-related quality of life (QoL) favors neobladder diversion: Systematic review of the literature. *Urology* 2016;93:22-6.
25. Singh V, Yadav R, Sinha RJ, Gupta DK. Prospective comparison of quality-of-life outcomes between ileal conduit urinary diversion and orthotopic neobladder reconstruction after radical cystectomy: A statistical model. *BJU Int* 2014;113(5):726-32.
26. Marcus HJ, Hughes-Hallett A, Payne CJ, Cundy TP, Nandi D, Yang GZ, *et al*. Trends in the diffusion of robotic surgery: A retrospective observational study. *Int J Med Robot Comput Assist Surg* 2017;13(4):e1870.
27. Smith AB, Raynor M, Amling CL, Busby JE, Castle E, Davis R, *et al*. Multi-institutional analysis of robotic radical cystectomy for bladder cancer: Perioperative outcomes and complications in 227 patients . *J Laparoendosc Adv Surg Tech A* 2012;22(1):17-21.
28. Desai MM, Gill IS, de Castro Abreu AL, Hosseini A, Nyberg T, Adding C, *et al*. Robotic intracorporeal orthotopic neobladder during radical cystectomy in 132 patients. *J Urol* 2014;192(6):1734-40.
29. Poch MA, Stegemann AP, Rehman S, Sharif MA, Hussain A, Consiglio JD, *et al*. Short-term patient reported health-related quality of life (HRQL) outcomes after robot-assisted radical cystectomy (RARC). *BJU Int* 2014;113(2):260-5.
30. Sathianathan NJ, Kalapara A, Frydenberg M, Lawrentschuk N, Weight CJ, Parekh D, *et al*. Robotic assisted radical cystectomy vs. open radical cystectomy: Systematic review and meta-analysis. *J Urol* 2019;201(4):715-20.
31. Hussein AA, Elsayed AS, Aldhaam NA, Jing Z, Peabody JO, Wijburg CJ, *et al*. A comparative propensity score-matched analysis of perioperative outcomes of intracorporeal vs. extracorporeal urinary diversion after robot-assisted radical cystectomy: Results from the International robotic cystectomy consortium. *BJU Int* 2020;126(2):265-72.
32. Hussein AA, May PR, Jing Z, Ahmed YE, Wijburg CJ, Canda AE, *et al*. Outcomes of intracorporeal urinary diversion after robot-assisted radical cystectomy: Results from the International robotic cystectomy consortium . *J Urol* 2018;199(5):1302-11.
33. Parekh DJ, Reis IM, Castle EP, Gonzalgo ML, Woods ME, Svatek RS, *et al*. Robot-assisted radical cystectomy vs. open radical cystectomy in patients with bladder cancer (RAZOR): An open-label, randomised, phase 3, non-inferiority trial. *Lancet* 2018;391(10139):2525-36.
34. Seiler R, Thalmann GN. Robot-assisted versus open cystectomy. *Lancet* 2018;391(10139):2479-80.
35. Fossa SD, Aass N, Ous S, Wéhre H, Ilnér K, Hannisdal E. Survival after curative treatment of muscle-invasive bladder cancer. *Acta Oncol* 1996;35(8):59-65.
36. Rosenberg JE, Carroll PR, Small EJ. Update on chemotherapy for advanced bladder cancer . *J Urol* 2005;174(1):14-20.
37. Perlis N, Krahn M, Alibhai S, Finelli A, Ritvo P, Bremner KE, *et al*. Conceptualizing global health-related quality of life in bladder cancer . *Qual Life Res* 2014;23(8):2153-67.
38. Botteman MF, Pashos CL, Hauser RS, Laskin BL, Redaelli A. Quality of life aspects of bladder cancer: A review of the literature . *Qual Life Res* 2003;12(6):675-88.
39. Fokdal L, Høyer M, Meldgaard P, von der Maase H. Long-term bladder, colorectal and sexual functions after radical radiotherapy for urinary bladder cancer . *Radiother Oncol* 2004;72(2):139-45.
40. Malmstrom PU, Rintala E, Wahlqvist R, Hellstrom P, Hellsten S, Hannisdal E. Five-year follow up of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic cystectomy trial 1 . *J Urol* 1996;155(6):1903-6.
41. Sherif A, Rintala E, Mestad O, Nilsson J, Holmberg L, Nilsson S, *et al*. Neoadjuvant cisplatin-methotrexate chemotherapy for invasive bladder cancer-Nordic cystectomy trial 2. *Scand J Urol Nephrol* 2002;36(6):419-25.
42. Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MK. International phase III trial assessing neoadjuvant cisplatin, methotrexate and vinblastine chemotherapy for muscle-invasive bladder cancer: Long-term results of the BA06 30894 trial. *J Clin Oncol* 2011;29(16):2171-77.
43. Finnbladder NB, de Tratamiento Oncologico CU, EORTC Genito-Urinary Group, Australian Bladder Cancer Study Group, National Cancer Institute of Canada Clinical Trials Group. Neoadjuvant cisplatin, methotrexate and vinblastine chemotherapy for muscle-invasive bladder cancer: A randomised controlled trial. *Lancet* 1999;354(9178):533-40.
44. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, *et al*. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer . *N Engl J Med* 2003;349(9):859-66.
45. Choueiri TK, Jacobus S, Bellmunt J, Qu A, Appleman LJ, Tretter C, *et al*. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: Pathologic, radiologic, and biomarker correlates. *J Clin Oncol* 2014;32(18):1889-94.
46. Plimack ER, Hoffman-Censits JH, Viterbo R, Trabulsi EJ, Ross EA, Greenberg RE, *et al*. Accelerated methotrexate, vinblastine, doxorubicin and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: Results of a multicenter phase II study with molecular correlates of response and toxicity . *J Clin Oncol* 2014;32(18):1895-901.
47. Harker WG, Meyers FJ, Freiha FS, Palmer JM, Shortliffe LD, Hannigan JF, *et al*. Cisplatin, methotrexate and vinblastine (CMV): An effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. A Northern California Oncology Group study. *J Clin Oncol* 1985;3(11):1463-70.
48. Soloway MS, Ikard M, Ford K. Cis-diamminedichloroplatinum (II) in locally advanced and metastatic urothelial cancer. *Cancer* 1981;47(3):476-80.
49. Patel VG, Oh WK, Galsky MD. Treatment of muscle-invasive and advanced bladder cancer in 2020. *CA Cancer J Clin* 2020;70(5):404-23.
50. Vale C, Advanced Bladder Cancer (ABC) meta-analysis collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: A systematic review and meta-analysis. *Lancet* 2003;361(9373):1927-34.
51. Meeks JJ, Bellmunt J, Bochner BH, Clarke NW, Daneshmand S, Galsky MD, *et al*. A systematic review of neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer. *Eur Urol* 2012;62(3):523-33.
52. Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, *et al*. Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. *J Clin Oncol* 2011;29(17):2432-8.

53. Mertens LS, Meijer RP, Kerst JM, Bergman AM, van Tinteren H, van Rhijn BW, *et al.* Carboplatin based induction chemotherapy for nonorgan confined bladder cancer-A reasonable alternative for cisplatin unfit patients? *J Urol* 2012;188(4):1108-14.
54. Trump DL, Elson P, Madajewicz S, Dickman SH, Hahn RG, Harris JE, *et al.* Randomized phase II evaluation of carboplatin and CHIP in advanced transitional cell carcinoma of the urothelium. *J Urol* 1990;144(5):1119-22.
55. Rosenberg JE, Hoffman-Censits J, Powles T, van Der Heijden MS, Balar AV, Necchi A, *et al.* Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: A single-arm, multicentre, phase 2 trial. *Lancet* 2016;387(10031):1909-20.
56. Vaughn DJ, Bellmunt J, Fradet Y, Lee JL, Fong L, Vogelzang NJ, *et al.* Health-related quality-of-life analysis from KEYNOTE-045: A phase III study of pembrolizumab vs. chemotherapy for previously treated advanced urothelial cancer. *J Clin Oncol* 2018;36(16):1579-87.
57. Heery CR, O'Sullivan-Coyne G, Madan RA, Cordes L, Rajan A, Rauckhorst M, *et al.* Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN solid tumor): A phase 1a, multicohort, dose-escalation trial. *Lancet Oncol* 2017;18(5):587-98.
58. Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, *et al.* Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): A multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2017;18(3):312-22.
59. Powles T, O'Donnell PH, Massard C, Arkenau HT, Friedlander TW, Hoimes CJ, *et al.* Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: Updated results from a phase 1/2 open-label study. *JAMA Oncol* 2017;3(9):e172411.
60. Huddart RA, Hall E, Lewis R, Porta N, Crundwell M, Jenkins PJ, *et al.* Patient-reported quality of life outcomes in patients treated for muscle-invasive bladder cancer with radiotherapy+chemotherapy in the BC2001 phase III randomised controlled trial. *Eur Urol* 2020;77(2):260-8.
61. Smith AB, Crowell K, Woods ME, Wallen EM, Pruthi RS, Nielsen ME, *et al.* Functional outcomes following radical cystectomy in women with bladder cancer: A systematic review. *Eur Urol Focus* 2017;3(1):136-43.
62. Siracusano S, D'Elia C, Cerruto MA, Gacci M, Ciciliato S, Simonato A, *et al.* Quality of life following urinary diversion: Orthotopic ileal neobladder versus ileal conduit. A multicentre study among long-term, female bladder cancer survivors. *Eur J Surg Oncol* 2019;45(3):477-81.
63. Nandipati KC, Bhat A, Zippe CD. Neurovascular preservation in female orthotopic radical cystectomy significantly improves sexual function. *Urology* 2006;67(1):185-6.
64. Bhatt A, Nandipati K, Dhar N, Ulchaker J, Jones S, Rackley R, *et al.* Neurovascular preservation in orthotopic cystectomy: Impact on female sexual function. *Urology* 2006;67(4):742-5.
65. Zippe CD, Raina R, Shah AD, Massanyi EZ, Agarwal A, Ulchaker J, *et al.* Female sexual dysfunction after radical cystectomy: A new outcome measure. *Urology* 2004;63(6):1153-7.
66. Dal Moro F, Morlacco A, Motterle G, Barbieri L, Zattoni F. Frailty and elderly in urology: Is there an impact on post-operative complications? *Cent European J Urol* 2017;70(2):197-205.
67. Gadzinski AJ, Psutka SP. Risk stratification metrics for bladder cancer: Comprehensive geriatric assessments. *Urol Oncol* 2020;38(9):725-33.
68. Porsrud A, Sherif A, Tollbäck A. The effects of a physical exercise programme after radical cystectomy for urinary bladder cancer. A pilot randomized controlled trial. *Clin Rehabil* 2014;28(5):451-9.
69. Karl A, Buchner A, Becker A, Staehler M, Seitz M, Khoder W, *et al.* A new concept for early recovery after surgery for patients undergoing radical cystectomy for bladder cancer: Results of a prospective randomized study. *J Urol* 2014;191(2):335-40.
70. Sapre N, Murphy DG. Words of wisdom. Re: A new concept for early recovery after surgery in patients undergoing radical cystectomy for bladder cancer: Results of a prospective randomized study. *Eur Urol* 2014;66(2):392.

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