Review article

Women with bladder cancer: an underserved population due to a faulty health care system or in a biological disadvantage?

Cáncer de vejiga en mujeres, ¿población vulnerable en el sistema de salud o en desventaja biológica?

Regina Barragán-Carrillo,[1] Yuly Andrea Remolina-Bonilla,[1] Rosa Elena Caballero-Landinez,[1] María Teresa Bourlon de los Ríos.[1*]

Abstract

Although men are four times more frequently diagnosed than women with urothelial bladder cancer, clinical outcomes greatly differ between both genders, as women present a higher lethality rate, as well as a greater loss of life expectancy. At diagnosis, women present more advanced clinical stages, situation which has led to many efforts to elucidate the social determinants of health and the biological factors implied. Women face different challenges associated with a delay in both, diagnosis and treatment, a more limited access to systemic treatment, and lower response rates associated with immunotherapy. Women are underrepresented in the main chemotherapy, immunotherapy, and other systemic treatment trials, as they comprise only 15 to 25% of the overall population, limiting the possibility of drawing any definitive conclusions. Furthermore, through gene expression analysis, women have been linked to a more aggressive biological subtype of bladder cancer (basal), a higher rate of *FGFR* 1-4 mutated tumors, lower rate of NECTIN-4 expression, and a higher prevalence of germline mutations. Despite the worse prognosis, sex-based recommendations have not been developed. Cancer care teams must not hinder access to treatment options based on sex and should strive for an equitable cancer care.

Keywords: bladder cancer, women, gender-gap, disparities, gender- inequality

Corresponding author: *Maria T. Bourlon. Av. Vasco de Quiroga No. 15, ZIP code 14080 Ciudad de México, México. Email: maitebourlon@gmail.com

Citation: Barragán-Carrillo R., Remolina-Bonilla Y. A., Caballero-Landinez R. E., Bourlon de los Ríos M. T. *Women with bladder cancer: an underserved population due to a faulty health care system or in a biological disadvantage?. Rev Mex Urol.* 2022;81(6):pp. 1-11

[1] Secretaría de Salud, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México, México.

Received: October 5, 2021
Accepted: December 16, 2021

Resumen

A pesar de que los hombres se diagnostican cuatro veces más frecuentemente con cáncer urotelial de vejiga, las mujeres presentan una mayor tasa de letalidad y menor expectativa de vida. Al diagnóstico, las mujeres se presentan con etapas clínicas más avanzadas, lo cual ha llevado a múltiples esfuerzos para elucidar los determinantes sociales y biológicos relacionados. Las mujeres se enfrentan a retos diferentes, asociados con el retraso tanto al diagnóstico como al inicio de tratamiento, acceso más limitado a tratamiento sistémico y menores respuestas con el uso de inmunoterapia. En los principales ensayos clínicos de uso de quimioterapia, inmunoterapia y otras estrategias de tratamiento sistémico, las mujeres están subrepresentadas dado que conforman del 15 al 25% de la población, limitando la generación de conclusiones definitivas. Adicionalmente, a través de análisis de expresión génica, las mujeres se han asociado a un subtipo biológico más agresivo de cáncer (basal), una mayor tasa de tumores *FGFR* 1-4 mutados, una menor expresión de NECTINA 4 y una mayor prevalencia de mutaciones germinales. A pesar del peor pronóstico, no se han desarrollado recomendaciones basadas en género. Los equipos dedicados al cuidado de cáncer no deben retrasar el acceso a las opciones de tratamiento basados en género, y deben procurar un tratamiento de cáncer equitativo.

Palabras clave:
cáncer de vejiga, mujeres, brecha de género, disparidades, inequidad de género

Introduction

Bladder cancer is the fourth most common cancer diagnosed in men, and the eighth leading cause of cancer related death in this group. Compared to their female counterparts, male patients are at a 3 to 4 times higher risk of developing urothelial bladder carcinoma during their lifetime.[1,2] Despite the higher incidence of bladder cancer in men, women are more likely to face worse outcomes compared to their male counterparts. The 5-year overall survival for men is 5-12% higher than for women, with an adjusted hazard ratio for bladder cancer mortality of 1.15 (95% CI 1.08-1.23), and a case fatality rate for women of 0.25, and of 0.19 for men, per each diagnosed individual.[3] Furthermore, women diagnosed with bladder cancer are older, are more frequently diagnosed with non-urothelial histology, including adenocarcinoma and squamous cell carcinoma, loose more years of life (6.5 vs. 3.9 years), and a greater fraction of their life expectancy (47% vs. 33%).[4,5]

It has been hypothesized that the mortality excess in females is a direct consequence of a delay in bladder cancer diagnosis, as females

have a higher chance of presenting high-grade or muscle invasive tumors (64% vs 52% in males), and node-positive locally advanced disease (13% vs 9% in males).[6–8] Contemporary analyses adjusted for clinical stage at presentation have proven, that when comparing stage by stage, women still have a shorter 5-year overall survival, and a higher cancer specific mortality.[3,5]

These dissimilar outcomes are most likely multifactorial; however, in many cases, they may be based on modifiable approaches to screening, diagnosing, and treating patients.[8] The aim of this review was to provide an updated comprehensive review of the interplay of social determinants of health, as well as to address potential biological dependent factors for the worse prognosis associated to female-sex, and its impact on outcomes on specific therapies. As this manuscript is mainly focused on the effect of the different modalities of systemic therapy, we will not provide a comprehensive review on the differences on anatomy and cystectomy related outcomes.

Diagnosis delay

Gross hematuria is the most common symptom of bladder cancer for both men and women, presenting in 85% of cases.[9] Female patients experience longer delays for diagnosis, as they report twice as long wait-times for urologic care than men (56 vs. 23 days), a 17.3% lower rate of self-directed referrals to a urology consultation, and even longer time before treatment initiation, reflected in a higher number of pre-treatment clinic visits (>2 vs 1).[10,11] On average, men undergo a cystoscopy examination 58.9 days after presenting to their primary care physician, in contrast to women that present with the same tumor related symptoms accessing a cystoscopy examination on average 13.3 days later. The overall impact on bladder cancer prognosis from these variations is unknown; mainly, it can contribute to stage migration in female patients.[8] Furthermore, some diagnostic tools for early bladder cancer, tend to yield a lower accuracy for women, as a consequence of higher rate of urothelial inflammation due to benign conditions. Blue light cystoscopy yields a cancer detection rate significantly higher in men than in women (91.1% vs. 86.7%, respectively) (p=0.035), with a higher false positive rate in women (35.9% vs 28.5%) (p=0.008).[12]

Socio-economic barriers

When calculated as health care cost per-patient, from diagnosis to death, urothelial bladder carcinoma is the costliest neoplasia per patient.[4] Considering the financial burden of bladder cancer diagnosis and treatments, the association between socio-economic status and survival is of utmost importance. It is noteworthy that women of African American descent have the lowest socio-economic status reported, and experienced worse bladder cancer overall survival (60%), whilst white males have the highest 5-year overall survival (83%).[13] When taking into account white females and African American men also in the analysis, women have a 30 to 50% greater chance than men of their respective races, of dying from bladder cancer, if they develop it.[14]

Even when comparing between only female patients, the social environment can have a negative impact on outcomes. This has been reported in a British observation study that

included female patients with newly diagnosed urothelial cancer, and described a 6-month survival rate of 52.3% for women that lived in a deprived area, contrasting with a 73.5% survival in those women who did not, reaching statistical significance ($p<0.05$).[15]

Genitourinary microbiome

Data providing the characterization of the bladder cancer microbiome is limited, especially according to sex; therefore, the role of the urobiome in bladder cancer carcinogenesis in females, remains to be further understood. Using next-generation DNA sequencing, urine samples from a group of bladder cancer patients have been examined and compared to samples from healthy individuals. This analysis found an enrichment in *Klebsiella* spp in the urine of females with bladder cancer, when compared with controls. One hypothesis for this association is the release of colibactin toxin by *Klebsiella* spp, directly damaging DNA, and leading to genomic instability through DNA strand breaks.[16]

Estrogen exposure

As postmenopausal women are more frequently affected with muscle invasion than their premenopausal counterparts, one could argue that this association could be only age dependent.[17,18] Nonetheless, after a 26-year follow-up in the US Nurses' Health Study cohort among postmenopausal women, early age at menopause (at 45 years or younger), compared with late age at menopause (50 years or older), was associated with a statistically significant increased risk of bladder cancer.[19] In the tissue analysis, the relationship between estrogen receptor (ER) alpha and beta activity and urothelial cancer outgrowth, there have been conflicting results, partially explained by the fact that many molecular mechanisms of the hormone receptors in urothelial cancer cells have not been fully uncovered. The upper third of the vagina and the trigone and posterior bladder neck share common embryonic origin, which explains why the normal urothelial tissue of the female bladder expresses ER on its surface. The expression of the ER beta has been reported to be positive in 27-100% of urothelial tumors, in contrast with the limited expression of ER alfa in bladder neoplasm, ranging from 0 to 38%.[20,21] A positive correlation between the expression of a tumor suppressor (UDP Glucuronosyltransferase Family 1 Member A or UGT1A) and ER alfa levels in a urothelial bladder cancer line have been observed, while the UGT1A and ER beta expression were inversely correlated.[17,20] These findings conclude on inhibitory functions of ER alfa, and enhancing functions of ER beta, during urothelial carcinogenesis.[22]

Local treatment

Currently, radical cystectomy is the cornerstone treatment for non-metastatic muscle invasive bladder cancer. Several inequalities in care between men and women undergoing cystectomy have been described. Women undergoing radical cystectomy, irrespective of clinical stage, present a 20% higher risk of 90-day mortality, while also reporting worse surgical related outcomes, such as longer operative time, greater blood loss, higher need for blood

transfusions, and more frequent perioperative complications, as well as lower rates of pelvic node dissection.[5,6,23]

Evidence on the benefit of either, radiation therapy or trimodal therapy, in a female predominant population is scarce. In a 2012 population-based analysis which included 386 male and 105 female patients, sex was found to be a potential prognostic factor on the overall- and cancer-specific survival, after treatment with either transurethral resection and radiotherapy, or chemoradiotherapy. After a 5-year follow up, female sex was independently associated with poorer overall- and cancer specific outcomes, with a median survival of 2.3 years vs. 5.1 years for male patients ($p = 0.045$).[24]

Systemic treatment

As it has been previously stated, women are more frequently diagnosed at a scenario that requires platinum-based chemotherapy in the perioperative setting, as they are more frequently diagnosed with locally advanced disease. In a pooled analysis which included 8 phase II and III clinical trials, with a total of 543 patients (18% female), no differences were observed between overall survival of male and female patients who underwent platinum-based systemic cytotoxic therapy, with a similar safety profile.[7] Despite a similar tolerability in both sexes, real world data suggest that women are less likely to receive systemic treatment, as a National Cancer Data Base proved, after adjusting for confounders, that women have a relative risk of 0.86 of receiving systemic chemotherapy, and consequently a 1.8-month lower overall survival ($p<0.001$).[25] To this date, data on treatment patterns in resource-limited settings is lacking. Data arising from a German cohort shows no differences in first line treatment patterns between males and females, as 62 and 66% receive a gemcitabine and cisplatin based first line treatment, and a numerical advantage for women in respect to access to a second line in 26.6 and 34%.[26]

In the recently presented VESPER trial, locally advanced bladder cancer patients were randomized to receive two different systemic therapies (gemcitabine and cisplatin vs. dose-dense methotrexate vinblastine doxorubicin and cisplatin) in the perioperative setting. Among the whole cohort, 15% were female. This rate is 11% lower than the expected accrual for clinical stage, in comparison to the Swedish cohort, where the rate of women diagnosed with a locally advanced disease was 26.9%. A subgroup analysis has not been published at the time of the elaboration of this manuscript, but female underrepresentation could represent an area of opportunity for this trial.[27]

Based on the National Comprehensive Cancer Network's (NCCN) guidelines, systemic therapy for advanced urothelial cancer includes platinum-based cytotoxic chemotherapy with or without an anti-PD-L1 maintenance therapy, non-platinum-based chemotherapy, immunotherapy, tyrosine kinase inhibitors and antidrug-antibodies conjugates for later lines.[28] Currently, the first line of systemic treatment comprises an induction platinum-based chemotherapy, followed by maintenance treatment with the anti-PD-L1 monoclonal antibody avelumab, based on the phase 3 JAVELIN 100 Bladder trial. Overall, the trial included a 22.7% of female patients, from which 52.8% were PD-L1 positive (PD-L1 positivity was present in 50.6% of the male population). Even though women presented a numerically higher

prevalence of PD-L1 positivity, in a post-hoc subgroup analysis, the women subgroup did not reach a statistical significance (hazard ratio 0.89 with a 95% CI 0.56-14.1), in contrast with the men subgroup (hazard ratio 0.64 with a 95% CI 0.5- 0.83). As this was not a preplanned analysis, these differences should be taken only as hypothesis generating.[29]

When assessing response and efficacy for immunotherapy as the sole treatment modality in advanced urothelial cancer, a pooled analysis which included 6 different clinical trials found a non-significant higher response rates in men compared to women, without survival differences noted.[30] This trend towards lesser responses in women, is particularly present in the IMvigor210 cohort, with an overall response rate in women of 6%, contrasting with the male cohort reaching a response of 20%.[31]

These findings partially contradict some previously published data, as the prevalence of basal tumors has been described more frequently in females than in men. Population-wise, basal-like bladder cancer presents in 33% of women and 21% of men (p=0.024), and when correlating demographical characteristics of a basal vs. a luminal cluster, female patients with high-grade urothelial carcinoma have a higher incidence of basal like tumors (p=0.0203).[20,32,33] With the higher frequency of basal tumors in this subpopulation, one would expect a higher response rate to immunotherapy when compared to males. The former conclusion is supported by the findings present in the CheckMate 275 trial, where patients with basal tumors contained the highest proportion of responders (30%), after second line treatment with nivolumab.[34]

Fibroblast growth factor receptor (FGFR) 1-4 mutations are present in as many as 20% of patients with advanced urothelial carcinoma (and 37% in patients with upper tract urothelial carcinoma), and is currently a well described treatment target for advanced urothelial cancer after progression to at least a first line treatment with chemotherapy.[35] A tendency towards a higher incidence of mutations has been described in females, when comparing to males, of up to 27.8 vs 17%, without reaching statistical significance.[36] The latter has been previously described in other populations, with numerical tendency for a higher incidence of mutations in women (44.6 vs. 40.2%).[37] When analyzing for other clinical characteristics associated with *FGFR* 1-4 mutations, some paradoxical information is present. These mutations are more common at low pathological stages, low-grade tumors, and well-differentiated tumors (32.6%), in comparison to moderately differentiated tumors (11.3%) and poorly differentiated tumors (0%) (p = .007).[36]

In the clinical setting, in a phase 2 trial comparing second or later line treatment with a tyrosine kinase inhibitor of the FGFR 1-4, erdafitinib, differences between the male and female cohort are also noteworthy mentioning. Firstly, as the trial was designed as a phase 2 trial, only a total of 99 patients were included, from which 23 (23%) were women. When assessing for overall treatment response, the complete cohort reported a 40% comprised by women 43% and men 39%, presenting a favorable tendency in the female subgroup, nevertheless without sufficient statistical power to draw any definitive conclusions.[35]

As novel therapies have been developed, the adoption of antibody-drug conjugates have been more widely used in the treatment of advanced bladder cancer. Currently, two antibody-drug conjugates have been tested in

phase II/III trials: enfortumab-vedotin and sacituzumab-govitecan. The enfortumab-vedotin complex binds to the Nectin-4-expressing cells, resulting in the internalization of the antibody-drug conjugate Nectin-4 complex and the release of the toxin monomethyl auristatin E by proteolytic cleavage. Nectin-4 expression has been identified by immunohistochemistry analysis in around 80% of bladder cancer, making it an attractive therapeutic target.[38] In the EV-301 trial, advanced bladder cancer patients after progression to platinum-based chemotherapy and immunotherapy were randomized to receive enfortumab-vedotin or chemotherapy as a third line therapy.[39] From the total accrued population, 24% were females, with a numerical difference between the chemotherapy and enfortumab vedotin allocation arms (24.4 vs. 20.9%). When analyzing for only the female patients, a tendency for worse overall survival was observed when comparing to males, as the hazard ratio for death in women was 1.17 (0.72-1.89) and males 0.61 (0.47-0.79).[39] Additionally, a statistically significant lower Nectin-4 mRNA expression has been observed in female patients, with approximately 50% vs. 70% in males ($p<0.001$).[40] As this was only a post-hoc analysis, no definitive conclusions could be drawn, but considering the lower mRNA expression, and the lack of a beneficial tendency of enfortumab-vedotin when comparing to chemotherapy, further sex-directed analyses are warranted.

Sacituzumab-govitecan, another novel antigen-drug conjugate, has been adapted in the heavily pretreated advanced disease setting of the TROPHY-U-01 trial. Overall, the trial included 22% of female patients with positive results reported for the whole cohort.[41] Until the date of elaboration of this manuscript, no sex-based subgroup analysis has been reported.

Germline mutations are present more frequently in women than in men, as it has been recently reported, that up to 20% of women with high-risk bladder cancer carry a germline mutation, reaching a statistical difference when comparing to the incidence of this alterations in their male counterparts (13.3%). The spectrum of germline mutations in female patients is subdivided in 15% DNA damage repair genes, 13% genes of moderate or high penetrance and 4% genes associated with an increased risk of ovarian and endometrial cancer.[42] Therapeutic strategies based on polyADP-ribose polymerase inhibition are being explored to this date, mainly in phase I/II trials, and are not currently supported by NCCN guidelines, given a lack of sufficient evidence on efficacy.[28,43] The main message is that women with high-risk bladder cancer should receive a comprehensive cancer risk assessment, especially those who desire any pelvic organ preservation at the time of radical cystectomy, as they might be carriers for a pathological variant associated with other pelvic neoplasia.[42]

Strive for an equitable cancer care

Bladder cancer awareness remains a key tool to eradicate disparities. The formulation of prespecified endpoints in clinical studies based around sex can help better describe this field of study and lead to a meaningful impact on outcomes for women and ensure the best care for all our patients.[8]

Independently of the underlying factors associated with the development of a bladder

malignancy in women, these patients should be addressed for their particular care-needs. It has been observed through quantitative analysis, that the role of family in the decision-making process is a dominant theme for women, who describe family members as facilitators for cancer treatment–related decisions, which is in contrast with men, who described family in a less supportive role.[44]

The exploration of these disparities, to understand their role and influence on bladder cancer survival, must be prioritized, as well as the development of sex-specific outlines for the care of a highly underserved population. Clinicians must ensure an adequate evaluation when presented with either hematuria and/or lower urinary tract symptoms and adhere to international guidelines to shorten the gap between symptom onset and treatment. Also, cancer care teams must not hinder access treatment options based on sex and should strive for an equitable cancer care.

CRediT Taxonomy

RBC: Conceptualization, Investigation, Visualization, Writing – original draft
YARM: Writing – review & editing
RECL: Writing – review & editing
MTB: Conceptualization, Supervision, Writing – review & editing

Financial support: The authors received no financial support for the research, authorship, and/or publication of this manuscript.

Conflict of interest: The authors declare no conflicts of interest for the elaboration of this manuscript.

References

1. **Mancini M, Righetto M, Baggio G.** Spotlight on gender-specific disparities in bladder cancer. Urologia. 2020 Aug;87(3):103–14. doi: https://doi.org/10.1177/0391560319887327
2. **Siegel RL, Miller KD, Fuchs HE, Jemal A.** Cancer Statistics, 2021. CA Cancer J Clin. 2021 Jan;71(1):7–33. doi: https://doi.org/10.3322/caac.21654. Radkiewicz C, Edgren G, Johansson ALV, Jahnson S, Häggström C, Akre O, et al. Sex Differences in Urothelial Bladder Cancer Survival. Clin Genitourin Cancer. 2020 Feb;18(1):26-34.e6. doi: https://doi.org/10.1016/j.clgc.2019.10.020
4. **Mossanen M, Gore JL.** The burden of bladder cancer care: direct and indirect costs. Curr Opin Urol. 2014 Sep;24(5):487–91. doi: https://doi.org/10.1097/mou.0000000000000078
5. **Dobruch J, Daneshmand S, Fisch M, Lotan Y, Noon AP, Resnick MJ, et al.** Gender and Bladder Cancer: A Collaborative Review of Etiology, Biology, and Outcomes. Eur Urol. 2016 Feb;69(2):300–10. doi: https://doi.org/10.1016/j.eururo.2015.08.037
6. **Patafio FM, Robert Siemens D, Wei X, Booth CM.** Is there a gender effect in bladder cancer? A population-based study of practice and outcomes. Can Urol Assoc J. 2015;9(7–8):269–74. doi: https://dx.doi.org/10.5489%2Fcuaj.2927
7. **Haines L, Bamias A, Krege S, Lin C-C, Hahn N, Ecke TH, et al.** The impact of gender on outcomes in patients with metastatic urothelial carcinoma. Clin Genitourin Cancer. 2013 Sep;11(3):346–52. doi: https://doi.org/10.1016/j.clgc.2013.04.010
8. **Hoffman-Censits J, Kanesvaran R, Bangs R, Fashoyin-Aje L, Weinstock C.** Breaking Barriers: Addressing Issues of Inequality in Trial

Enrollment and Clinical Outcomes for Patients With Kidney and Bladder Cancer. Am Soc Clin Oncol Educ Book. 2021 Jun;41:e174–81. doi: https://doi.org/10.1200/edbk_320273

9. **Garg T, Pinheiro LC, Atoria CL, Donat SM, Weissman JS, Herr HW, et al.** Gender disparities in hematuria evaluation and bladder cancer diagnosis: a population based analysis. J Urol. 2014 Oct;192(4):1072–7. doi: https://doi.org/10.1016/j.juro.2014.04.101
10. **Henning A, Wehrberger M, Madersbacher S, Pycha A, Martini T, Comploj E, et al.** Do differences in clinical symptoms and referral patterns contribute to the gender gap in bladder cancer? BJU Int. 2013 Jul;112(1):68–73. doi: https://doi.org/10.1111/j.1464-410x.2012.11661.x
11. **Cohn JA, Vekhter B, Lyttle C, Steinberg GD, Large MC.** Sex disparities in diagnosis of bladder cancer after initial presentation with hematuria: a nationwide claims-based investigation. Cancer. 2014 Feb 15;120(4):555–61. doi: https://dx.doi.org/10.1002%2Fcncr.28416
12. **Regmi S, Kalapara A, Alford A, Daneshmand S, Porten S, Pohar K, et al.** Mp24-06 gender based variations in the detection of bladder cancer with blue light cystoscopy: insights from a multicenter registry. J Urol. 2020 Apr 1;203(Supplement 4):e349–e349. doi: https://doi.org/10.1097/JU.0000000000000857.06
13. **Prout GR, Wesley MN, Greenberg RS, Chen VW, Brown CC, Miller AW, et al.** Bladder cancer: race differences in extent of disease at diagnosis. Cancer. 2000 Sep 15;89(6):1349–58. doi: https://doi.org/10.1002/1097-0142(20000915)89:6%3C1349::aid-cncr20%3E3.0.co;2-d
14. **Madeb R, Messing EM.** Gender, racial and age differences in bladder cancer incidence and mortality. Urol Oncol. 2004 Apr;22(2):86–92. doi: https://doi.org/10.1016/s1078-1439(03)00139-x
15. **Moran A, Sowerbutts A-M, Collins S, Clarke N, Cowan R.** Bladder cancer: worse survival in women from deprived areas. Br J Cancer. 2004 Jun 1;90(11):2142–4. doi: https://dx.doi.org/10.1038%2Fsj.bjc.6601847
16. **Kaur CP, Vadivelu J, Chandramathi S.** Impact of Klebsiella pneumoniae in lower gastrointestinal tract diseases. J Dig Dis. 2018 May;19(5):262–71. doi: https://doi.org/10.1111/1751-2980.12595
17. **Godoy G, Gakis G, Smith CL, Fahmy O.** Effects of Androgen and Estrogen Receptor Signaling Pathways on Bladder Cancer Initiation and Progression. Bladder Cancer. 2016 Apr 27;2(2):127–37. doi: https://doi.org/10.3233/blc-160052
18. **Dietrich K, Demidenko E, Schned A, Zens MS, Heaney J, Karagas MR.** Parity, early menopause and the incidence of bladder cancer in women: a case-control study and meta-analysis. Eur J Cancer. 2011 Mar;47(4):592–9. doi: https://doi.org/10.1016/j.ejca.2010.10.007
19. **Abufaraj M, Shariat S, Moschini M, Rohrer F, Papantoniou K, Devore E, et al.** The impact of hormones and reproductive factors on the risk of bladder cancer in women: results from the Nurses' Health Study and Nurses' Health Study II. Int J Epidemiol. 2020 Apr 1;49(2):599–607. doi: https://doi.org/10.1093/ije/dyz264
20. **Goto T, Miyamoto H.** The Role of Estrogen Receptors in Urothelial Cancer. Front Endocrinol (Lausanne). 2021;12:643870. doi: https://doi.org/10.3389/fendo.2021.643870
21. **Ide H, Miyamoto H.** Sex Hormone Receptor Signaling in Bladder Cancer: A Potential Target for Enhancing the Efficacy of Conventional Non-Surgical Therapy. Cells. 2021 May 11;10(5):1169. doi: https://doi.org/10.3390/cells10051169

22. **Ou Z, Wang Y, Chen J, Tao L, Zuo L, Sahasrabudhe D, et al**. Estrogen receptor β promotes bladder cancer growth and invasion via alteration of miR-92a/DAB2IP signals. Exp Mol Med. 2018 Nov 20;50(11):1–11. doi: https://doi.org/10.1038/s12276-018-0155-5
23. **Kyritsi F, Loffredo CA, Zheng Y-L, Philips G, Amr S.** Urinary Bladder Cancer in Egypt: Are There Gender Differences in Its Histopathological Presentation? Adv Urol. 2018;2018:3453808. doi: https://doi.org/10.1155/2018/3453808
24. **Keck B, Ott OJ, Häberle L, Kunath F, Weiss C, Rödel C, et al.** Female sex is an independent risk factor for reduced overall survival in bladder cancer patients treated by transurethral resection and radio- or radiochemotherapy. World J Urol. 2013 Oct;31(5):1023–8. doi: https://doi.org/10.1007/s00345-012-0971-5
25. **Rose TL, Deal AM, Nielsen ME, Smith AB, Milowsky MI.** Sex disparities in use of chemotherapy and survival in patients with advanced bladder cancer. Cancer. 2016 Jul 1;122(13):2012–20. doi: https://doi.org/10.1002/cncr.30029
26. **Niegisch G, Gerullis H, Lin S-W, Pavlova J, Gondos A, Rudolph A, et al.** A Real-World Data Study to Evaluate Treatment Patterns, Clinical Characteristics and Survival Outcomes for First- and Second-Line Treatment in Locally Advanced and Metastatic Urothelial Cancer Patients in Germany. J Cancer. 2018;9(8):1337–48. doi: https://doi.org/10.7150/jca.23162
27. **Pfister C, Gravis G, Flechon A, Chevreau CM, Mahammedi H, Laguerre B, et al.** 652O Dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC) or gemcitabine and cisplatin (GC) as perioperative chemotherapy for patients with muscle-invasive bladder cancer (MIBC): Results of the GETUG/AFU VESPER V05 phase III trial. Ann Oncol . 2021 Sep 1;32:S678. doi: https://doi.org/10.1016/j.annonc.2021.08.048
28. **Flaig TW, Spiess PE, Agarwal N, Bangs R, Boorjian SA, Buyyounouski MK, et al.** Bladder Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020 Mar;18(3):329–54. doi: https://doi.org/10.6004/jnccn.2020.0011
29. **Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, et al.** Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2020 Sep 24;383(13):1218–30. doi: https://doi.org/10.1056/nejmoa2002788
30. **Hoffman-Censits J, Rosenberg JE, Heijden M van D, Dreicer R, Gracia JLP, Petrylak DP, et al.** Clinical outcomes by sex with atezolizumab (atezo) monotherapy in patients (pts) with locally advanced/metastatic urothelial carcinoma (mUC). Annals of Oncology. 2019 Oct 1;30:v372–3. doi: https://doi.org/10.1093/annonc/mdz249.026
31. **IMvigor 210, a phase II trial of atezolizumab (MPDL3280A) in platinum-treated locally advanced or metastatic urothelial carcinoma (mUC).** J Clin Oncol. 2016 Jan 10;34(2_suppl):355–355. doi: http://dx.doi.org/10.1200/jco.2016.34.2_suppl.355
32. **Robertson AG, Kim J, Al-Ahmadie H, Bellmunt J, Guo G, Cherniack AD, et al.** Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer. Cell. 2017 Oct 19;171(3):540-556.e25. doi: https://doi.org/10.1016/j.cell.2017.09.007
33. **Williams SB, Huo J, Dafashy TJ, Ghaffary CK, Baillargeon JG, Morales EE, et al.** Survival differences among patients with bladder cancer according to sex: Critical evaluation of radical cystectomy use and delay to treatment. Urol

Oncol. 2017 Oct;35(10):602.e1-602.e9. doi: https://doi.org/10.1016/j.urolonc.2017.05.022

34. **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 Mar;18(3):312–22. doi: https://doi.org/10.1016/s1470-2045(17)30065-7
35. **Loriot Y, Necchi A, Park SH, Garcia-Donas J, Huddart R, Burgess E, et al.** Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2019 Jul 25;381(4):338–48. doi: https://doi.org/10.1056/nejmoa1817323
36. **Ahmad F, Mahal V, Verma G, Bhatia S, Das BR.** Molecular investigation of FGFR3 gene mutation and its correlation with clinicopathological findings in Indian bladder cancer patients. Cancer Rep (Hoboken). 2018 Oct;1(3):e1130. doi: https://doi.org/10.1002/cnr2.1130
37. **Tomlinson DC, Baldo O, Harnden P, Knowles MA.** FGFR3 protein expression and its relationship to mutation status and prognostic variables in bladder cancer. J Pathol. 2007 Sep;213(1):91–8. doi: https://doi.org/10.1002/path.2207
38. **Challita-Eid PM, Satpayev D, Yang P, An Z, Morrison K, Shostak Y, et al.** Enfortumab Vedotin Antibody-Drug Conjugate Targeting Nectin-4 Is a Highly Potent Therapeutic Agent in Multiple Preclinical Cancer Models. Cancer Res. 2016 May 15;76(10):3003–13. doi: https://doi.org/10.1158/0008-5472.can-15-1313
39. **Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Durán I, Lee J-L, et al.** Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. N Engl J Med. 2021 Mar 25;384(12):1125–35. doi: https://doi.org/10.1056/nejmoa2035807
40. **Chu C, Sjöström M, Egusa EA, Gibb E, Badura ML, Koshkin VS, et al.** Heterogeneity in Nectin-4 expression across molecular subtypes of urothelial cancer mediates sensitivity to enfortumab vedotin. J Clin Oncol. 2021 Feb 20;39(6_suppl):463–463. doi: http://dx.doi.org/10.1200/JCO.2021.39.6_suppl.463
41. **Tagawa ST, Balar AV, Petrylak DP, Kalebasty AR, Loriot Y, Fléchon A, et al.** TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. J Clin Oncol. 2021 Aug 1;39(22):2474–85. doi: http://dx.doi.org/10.1200/JCO.20.03489
42. **Truong H, Sheikh R, Khurram A, Kemel Y, Lenis AT, Reisz P, et al.** Germline alterations in cancer susceptibility genes in women with high-risk bladder cancer: Implications for germline testing and clinical management. J Clin Oncol. 2021 Feb 20;39(6_suppl):418–418. doi: http://dx.doi.org/10.1016/S1096-7192(21)00133-5
43. **Sweis RF, Heiss B, Segal J, Ritterhouse L, Kadri S, Churpek JE, et al.** Clinical Activity of Olaparib in Urothelial Bladder Cancer With DNA Damage Response Gene Mutations. JCO Precis Oncol. 2018 Nov 1;(2):1–7. doi: http://dx.doi.org/10.1200/PO.18.00264
44. **Pozzar RA, Berry DL.** Gender Differences in Bladder Cancer Treatment Decision Making. Oncol Nurs Forum. 2017 Mar 1;44(2):204–9. doi: https://doi.org/10.1188/17.onf.204-209