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Bladder Cancer in Women

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to provide a critical assessment of the most recent literature on epidemiological trends in gender-specific differences in bladder cancer incidence, summarize how hormonal differences may affect urothelial cell neoplasia and carcinogenic metabolism, identify conflicting data on gender-specific differences in outcome and provide additional areas for further research, and support further research into gender-specific quality of life surgical techniques.

This AUA Update aligns with the American Board of Urology Module on Oncology, Urinary Diversion and Adrenal. Additional information on this topic can be found in the AUA Core Curriculum section on Oncology–Bladder.

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EPIDEMIOLOGY OF BLADDER CANCER IN WOMEN

Bladder cancer accounts for only 3% of new cancer diagnoses worldwide, with the 3 highest incidence rates of bladder cancer concentrated in Southern and Western Europe and North America.[1] In the U.S., approximately 81,400 new cases were estimated to occur in 2020, accounting for 22% of all new cancer diagnoses.[2] Among women, bladder cancer makes up only 2.1% of all new cancers, resulting in 1.7% of total cancer-related deaths.[2] **Bladder cancer is one of the few cancers with worse mortality among women than men (25.5% vs 21% bladder cancer-related deaths),[2] a phenomenon seen not only in the U.S. but globally.** In 2008, women were found to have a higher mortality/incidence ratio than men in 26 countries and a lower ratio in only 2 countries, implying either advanced diagnosis or inadequate treatment among women.[3] **Similarly a mortality/incidence ratio of 1.2 for bladder cancer-related deaths in women compared to men using 2018 GLOBOCAN data[4] suggests that although women have a much lower incidence of bladder cancer diagnoses, they are 20% more likely to die of bladder cancer than men.**

Regarding histological subtypes of bladder cancer, urothelial carcinoma is the most common subtype that occurs in women.[5] However, women are diagnosed with nonurothelial carcinoma variants more often than men.[6] **While histological variants may negatively impact prognosis, limited data are available to draw conclusions as to how variant histology might specifically impact women.[7]** Histological subtypes may relate to different risk factors in women compared to men. Risk factors for bladder cancer may be grouped as modifiable or nonmodifiable (table 1). Among modifiable factors, tobacco smoking is the most common. Historically, fewer women smoked tobacco and a higher risk of bladder cancer was attributed to longer duration of cigarette smoking among men. **However, adjustment for similar patterns of smoking among men and women results in the same risk of bladder cancer attributable to cigarette smoking.[8–11]** As in men, smoking cessation among women is inversely associated with risk of bladder cancer for each decade of cessation up to 30 years.[12]

Occupational exposure to carcinogens is an additional modifiable risk factor for bladder cancer (table 1). The most common occupations associated with increased bladder cancer among women in Finland were construction worker, waitress, health care worker, packer and clerk.[13] Additional modifiable risk factors included drinking water, which can contain contaminants like arsenic and nitrate, both of which associated with a higher risk of bladder cancer among women.[14,15] However, fluid intake itself showed no clear relationship with regard to risk of bladder cancer in women.[16] Other modifiable risk factors that have been investigated include body habitus and comorbidities. In contrast to men, body mass index is inversely associated with incident cases of bladder cancer among women.[17] In addition, women with hypertension were shown to have a 55% greater risk of bladder cancer than nonhypertensive women in a large, population-based study from Taiwan.[18]

Nonmodifiable risk factors include inflammation and hormonal influences. Chronic inflammation related to frequent urinary tract infections in postmenopausal women has been associated with increased risk of bladder cancer independent of the number of infections.[19] Low estrogen may also increase the risk of bladder cancer, as evidenced by a higher than expected incidence of bladder and urethral cancer in women with Turner syndrome, who have low serum estrogen concentration from infancy and a history of chronic urinary tract infections.[20] Several theories exist regarding the interactions between modifiable and nonmodifiable risk factors and gender-specific differences in bladder cancer risk, which are covered in the section below, "Theories of Gender Disparities."

RACIAL/ETHNIC DISPARITIES

Racial differences also exist among women at risk for bladder cancer. Black women present with higher stage and higher grade bladder tumors than white women as evidenced by reviewing the SEER (Surveillance, Epidemiology, and End Results) registry in 5-year time intervals from 1973 to 1999.[21] An updated analysis of the SEER registry was performed from 2004 to 2010 demonstrating that female gender, Black race and single/divorced/widowed status were independent predictors of presentation with metastatic bladder cancer at diagnosis.[22] **Review of the Kaiser Permanente Southern California health care delivery system's registry from 2001 to 2015, including members who are racially, ethnically and socioeconomically diverse, demonstrated that non-Hispanic Black women had a disproportionately higher presentation of muscle-invasive bladder cancer (MIBC) and metastatic bladder cancer than Hispanic, non-Hispanic white or Asian women.[23]** Differences in bladder cancer stage by race did not appear to be impacted by access to care as measured by duration of health plan membership or utilization of care, which were similar across racial/ethnic groups and between gender. However, differences were noted among neighborhood educational attainment and household incomes among groups. For example, Asian and non-Hispanic white patients were found to reside in neighborhoods with higher education and income.[23] The relationship between racial/ethnic disparities and low educational attainment is known but not well understood, specifically in health care and utilization of preventive health services. Although this SEER-Medicare study[24] places the onus of preventive services utilization on the patient, distrust of the medical community may play a larger role than socioeconomic factors.

PROGNOSIS AND OUTCOME

Nonmuscle-invasive bladder cancer (NMIBC). **The natural history of NMIBC (Ta, T1 or Tis) suggests that female gender or Black race is not associated with higher risk of bladder cancer recurrence. Rather, women of any race and Black individuals have a higher hazard of progression to MIBC and**

ABBREVIATIONS: AUA=American Urological Association, BCG=bacillus Calmette-Guérin, CSS=cancer-specific survival, MIBC=muscle-invasive bladder cancer, NMIBC=nonmuscle-invasive bladder cancer, SEER=Surveillance, Epidemiology, and End Results

bladder cancer-related death in comparison to male and white patients.[25] However, progression was indirectly defined by identification of subsequent treatment codes (radical cystectomy, radiation, chemotherapy) and was not confirmed by pathological review of tumor stages. Similarly, recurrence was defined by identification of codes related to endoscopic resection or biopsy of suspicious lesions and not confirmed with pathological review of all specimens.

MIBC. **Gender-specific differences regarding the outcomes of patients with MIBC are controversial.** This may be due to a disproportionately higher incidence and prevalence of bladder cancer in men than in women, and reported outcomes often cannot be balanced evenly on patient-specific and cancer-specific factors. For example, in a single institution study of 1,100 patients who underwent radical cystectomy with lymphadenectomy, of whom 19% were women, gender was not associated with overall survival.[26] In a retrospective review of 710 patients, of whom 19% were women, women experienced worse bladder cancer-specific survival (CSS) but not worse overall survival on univariate analysis.[27] Data from the California State Cancer Registry showed that female gender was associated with worse CSS compared to males, although details on potential confounders such as smoking status, occupational exposures and receipt of chemotherapy were unavailable.[28] Finally, worse CSS and overall survival were reported in women from population studies in the U.S.[29] and England,[30] in which patients received either neoadjuvant chemotherapy with radical cystectomy or radio-sensitizing chemotherapy and radiation treatment. However, no information on patient-specific and provider-specific factors was available in these studies.

Patient-specific factors were investigated in a large population-based study of 31,100 patients with invasive bladder cancer (25% of whom were women).[31] While there was similar median survival between men and women, Black women disproportionately experienced worse survival (26 months) compared to white women (63 months), with a similar but less substantial disparity in overall survival found in men (45 months). **Multivariate analyses adjusting for sociodemographic, clinical and treatment characteristics revealed that Black race, female gender and community poverty level >15% were independent predictors of overall survival among patients diagnosed with invasive bladder cancer.**

Specific cancer-related factors may also contribute to differential gender-specific outcomes. For example, a large single institution registry matched 414 women with bladder cancer undergoing radical cystectomy to men on cancer-specific factors such as tumor and nodal stage, lymphovascular invasion, surgical margin, administration of intravesical treatment, neoadjuvant chemotherapy, adjuvant chemotherapy, tumor grade, p53 expression of primary tumor, nodal yield during lymphadenectomy, ASA® score and presence of hydronephrosis. **No gender-specific differences in recurrence-free survival, CSS or overall survival were noted when cancer-specific factors were considered. The authors did note that women presented more frequently with ≥T3 disease (41% vs 34%), node-positive disease (26% vs 21%) and presence of hydronephrosis (27% vs 22%).[32] An additional study investigating cancer-specific factors between genders confirmed that women had a greater percentage of T2 and T3 disease at cystectomy than men, while men had a greater percentage of NMIBC including T1, but a similar percentage of T4.[33]** Reasons for worse cancer-specific factors among women are complex and poorly understood. **Two large contemporary cancer registries from Norway and the Netherlands demonstrate that relative survival rates were worse for women only in the first 2 years after initial diagnosis, and it was largely explained by worse stage at presentation.[34,35] Treatment of men and women within each group, NMIBC and MIBC, were approximately similar in terms of guideline-concordant care, and therefore the difference in relative survival within the first 2 years of diagnosis between men and women remains partially unexplained.**[35]

Additional studies for worse cancer-specific characteristics among women have investigated the role of molecular subtypes and differential gene expression of MIBC between men and women. The Cancer Genome Atlas previously reported that molecular subtyping of bladder cancer is different for men and women in that women are more likely to demonstrate basal/squamous subtypes than men.[36] **Among 1,000 patients with MIBC (24% of whom were women),[37] women had a greater percentage of basal/squamous subtype (47% vs 35%) and a lower expression of the luminal papillary subtype (15% vs 23%). In addition, basal tumors in women had a higher expression of inflammatory and keratinization genes, whereas luminal tumors in men had higher expression of androgen response pathway genes but not estrogen, suggesting that the luminal tumors in men may be driven by the androgen receptor.**[38] Interestingly, the keratinization gene signature of basal tumors in women supports the phenotype seen with loss of FOX1A expression in female radical cystectomy specimens.[39] Further investigation is necessary into the clinical significance of the variability in molecular subtypes between women and men, which may guide targeted therapy and therefore improve survival not just 2 years after treatment but at receipt of treatment.

RESPONSE TO TREATMENT

Intravesical bacillus Calmette-Guérin (BCG) and chemotherapy. **Several retrospective studies have not demonstrated conclusive gender-specific differences in response to BCG treatment.** Although a small retrospective review of patients with high-grade T1 disease treated with BCG (18/146 female) demonstrated shorter time to recurrence and increased rate of progression to MIBC in men vs women, this did not adjust for other contributory factors.[40] The CUETO (Club Urológico Español de Tratamiento Oncológico) group updated previous findings[41] regarding patients with high-grade NMIBC treated with BCG (24 female), demonstrating a shorter time to recurrence among women but no gender-specific differences in progression or cancer-specific mortality.[42] In a large study of 1,155 patients with high-grade T1 bladder cancer from 13 academic institutions across Europe, 182 women were treated with induction and maintenance BCG up to 3 years.[43] **In this study, female gender did not lead to a greater hazard of recurrence of T1 bladder cancer or progression to MIBC.** Regarding response to intravesical chemotherapy for low risk or intermediate risk NMIBC, a large study of 1,436 patients treated with mitomycin C, epirubicin or doxorubicin revealed an independent association of female gender with decreased cancer-specific mortality.[44]

Systemic chemotherapy and immunotherapy. **Response to neoadjuvant chemotherapy does not appear to be influenced**

by gender. A large study of 1,031 patients treated with neoadjuvant chemotherapy followed by radical cystectomy (22% of whom were female) demonstrated no differences in chemotherapy response between genders, although women were diagnosed with a higher percentage of cT3 but a lower percentage of cT4 than men.[45]

The influence of gender on response to adjuvant chemotherapy is unclear. Among a large population of patients who underwent cystectomy and adjuvant chemotherapy for MIBC from the National Cancer Database, female gender was a significant predictor of worse overall survival, although this result may have been influenced by the unbalanced proportion of female patients (16% of the sample) and additional predictors of poor outcomes, including health insurance and advanced pT3/T4 stage.[46]

Receipt of chemotherapy may differ based on gender. Women were less likely to receive adjuvant chemotherapy compared to cystectomy alone, but this may reflect other factors such as inaccurate clinical staging.[47]

Systemic immunotherapy with checkpoint inhibitors has recently changed the landscape of treatment for localized and advanced bladder cancer. **Gender-specific differences regarding response to immunotherapy are not yet understood, but future research will likely investigate these differential effects.**

ANATOMY AND STAGING DIFFERENCES IN WOMEN AND MEN

Staging differences between men and women diverge at T4a bladder cancer, characterized by invasion of neighboring organs: the uterus, fallopian tubes, ovaries and anterior vagina in women; and the prostate, seminal vesicles and vas deferens in men. These differences influence consideration in staging. For example, contiguous spread to the prostatic urethra may differ from contiguous spread to the anterior vagina and/or uterus, reflecting different cancer-specific outcomes due to differences in biological aggressiveness of T4a based on anatomy.[48] Differential bladder mucosal blood flow between males and females in animal studies[49] as well as patterns of angiolymphatic spread of cancer cells in anatomical mapping studies[50] suggest the need for further research into how this impacts advanced disease and metastasis. Theories of gender disparities are discussed below.

Access to care/delay in diagnosis. Higher incidence of bladder cancer in men compared to women may also be attributed to differences in access to care, or delay in diagnosis. **Hematuria referral patterns to urologists differ based on gender.[51–54] Although more than 80% of hematuria is reported by women, only 8% of women are referred to a urologist compared to 36% of men.[55]** Differences in referral patterns could be attributed to a higher incidence of urinary tract infections that may occur over a woman's lifetime. In men, as UTIs occur less frequently, this may prompt earlier evaluation with a referral to a urologist for men vs women. **An updated analysis of microhematuria referral patterns in the U.S. demonstrated that women were 30% less likely than men to undergo a complete microhematuria workup.[56] In patients with carcinoma in situ who undergo radical cystectomy, female gender was independently associated with worse cancer-specific mortality but similar cancer recurrence—suggesting a lag in referring women to the urologist for symptoms of recurrence such as gross hematuria.[57] However, timely diagnosis for women has likely improved over time.** The association of gender with CSS is stronger during earlier time periods, suggesting improvement in awareness and management of female urothelial cancer of the bladder in recent years.[58]

Different biology. There is evidence for interaction between modifiable and nonmodifiable factors in bladder cancer risk as observed by gender-specific differences in metabolic detoxication of carcinogens. **Polymorphism, or a sequence variation in gene expression, can produce different forms of an enzyme among men and women, and therefore infer a different risk of bladder cancer.** Glutathione S-transferase (GST) is one such family of enzymes that have been observed to be in the inactive form at different rates between men and women, and associated with an increased risk of bladder cancer in women smokers vs nonsmokers.[59] In addition, more women ever-smokers were observed to have the inactive form of GST enzyme vs never-smokers, suggesting an interaction between smoking and GST detoxification enzymes.[60] Occupational exposure and GST inactivation may also produce an additive risk of bladder cancer.[61] Interestingly, GST enzymes are also responsible for detoxifying estrogen compounds, and this may explain some of the differences observed in bladder cancer incidence between men and women.[62,63] Acetylation is another way to detoxify carcinogens, and polymorphism in the N-acetyltransferase 2 (NAT2) gene results in characterization of people as "slow acetylators." Exposure to aromatic amines from cigarette smoke may increase bladder cancer risk in women who smoke if they have a "slow acetylator" form of the protein.[64] At an epigenetic level, differential methylation of DNA in blood or "global DNA methylation" has previously been associated with modified bladder cancer risk in men who smoke.[65] Similarly, in postmenopausal women who were current smokers, low DNA methylation was associated with increased bladder cancer risk.[66] Additional gender-specific genetic variability occurring at different levels between men and women requires further investigation into the clinical significance (table 2).

Differential bladder cancer histology may also explain differences in outcomes based on gender. **A retrospective review of 485 patients who underwent radical cystectomy without neoadjuvant chemotherapy (of whom 21% were women) showed a differential distribution of variant histology (36% in women vs 15% in men), with the presence of variant histology associated with worse cancer-specific mortality on univariate but not multivariate analysis.[67]** Histological distribution differences were also seen in a contemporary Dutch study regarding squamous histology.[35]

Different treatment. **Treatment receipt may vary based on gender.** A Swedish review of a national bladder cancer registry revealed that women with NMIBC (23% of cohort) were less likely to undergo a second-look transurethral resection of bladder tumor and receive intravesical instillation therapy, contributing to a significantly reduced relative survival compared to men.[68] Women are less likely than men to receive systemic chemotherapy (RR 0.86, 95% CI 0.83–0.88).[69] In addition, women are more likely to receive an incontinent rather than continent urinary diversion compared to men (OR 2.4–6.9).[70–72] However, studies that delineate various diversions show women with 1.6-fold higher odds of receiving a continent cutaneous reservoir than their male counterparts ($p < 0.01$).[73] Gender-specific differences regarding orthotopic diversion may be related to a perceived increase in voiding dysfunction and urethral recurrence among women, which has been

disproven with contemporary series and thus may influence differences in treatment receipt with time.[74,75] **Additional surgical differences based on gender include technical approach, counseling and perioperative outcomes.** Men were more likely to undergo robot-assisted radical cystectomy than women, perhaps influenced by longer operative times among women, a higher proportion of advanced disease or the need for radical hysterectomy.[76,77] Women are also less likely to be counseled about sexual dysfunction after radical cystectomy than male patients.[78] Regarding perioperative complications, women are more likely to require a blood transfusion, have a longer hospital stay, experience a surgical site infection and be discharged to a nursing home or readmitted after surgery.[79–81] The influence of supportive care may also differentially impact outcomes. Interestingly, men who are widowed have worse outcomes than married men, a trend not seen among women.[82] Women also have a greater likelihood of readmission to the hospital within 30 days of radical cystectomy.[83]

Hormones, smoking and female gender. **A relationship between parity, smoking status and bladder cancer risk may exist in women.** Among women who were never-smokers, having at least 1 child appeared to be protective compared to women who were nulliparous, an effect that disappeared among current women smokers, suggesting a relationship between hormonal changes influenced by cigarette smoking. Levels of serum androgen increase among smokers, thus possibly diminishing estrogen's protective effect among nonsmokers in preventing bladder cancer.[84] Another explanation may be related to increased utilization of health services among parous women, as nulliparous women likely do not seek medical care to the same degree of frequency as pregnant women. Other contributory factors increase the complexity of these relationships. For example, the association between bladder cancer and dietary intake of nitrates and nitrites in meat preservatives is stronger among current smokers than nonsmokers, and unaffected by the amount of dietary antioxidant ingestion (vitamin C), although the sample was restricted to postmenopausal women to obviate the confounding of endogenous estrogen production.[15] Further adding to the complex interplay of hormones and cigarette carcinogens is that exogenous hormonal replacement of estrogen may postpone the carcinogenic effects of cigarette smoking in women.[85] This postponement may explain why women have a lower incidence of bladder cancer than men, but when they do succumb to bladder cancer the carcinogen is sensitized to lower doses of expectant estrogen and therefore primed to act more aggressively in postmenopausal women. A similar phenomenon is seen in castration-resistant prostate cancer, in which androgen receptor activity is stimulated by a smaller concentration of androgens.[86]

In one of the largest ongoing European cohort studies (more than 300,000 women), 529 cases of urothelial carcinoma were identified, with 43% of an aggressive tumor type. **Among the hormonal factors evaluated, only postmenopausal status (natural or surgical) was associated with at least an 88% increased risk of developing urothelial carcinoma in comparison to premenopausal status. In addition, estrogen-only but not combination estrogen/progestin hormone replacement therapy was associated with urothelial carcinoma risk, independent of duration of use and only among smokers.** Therefore, the authors postulate that this association is likely related to residual confounding from tobacco smoking. **Furthermore, number of full-term pregnancies was inversely associated with risk of bladder cancer.[87,88]**

MANAGEMENT ISSUES SPECIFIC TO WOMEN

Role of uterine sparing at cystectomy. In 2007, the Bern group described and illustrated a method for gynecologic organ-sparing radical cystectomy that included differences in anatomical and surgical technique compared to the traditional anterior exenteration, or classical radical cystectomy in a woman. **As Bhatta Dhar et al describe, uterine-sparing cystectomy includes 2 critical differences in dissection techniques: 1) the location of the peritoneal incision and 2) the location of bladder mobilization in reference to the parametrial structures containing the parasympathetic nerves and vessels.[89]** In uterine-sparing cystectomy, the peritoneal incision is more anterior in the vesico-uterine space and not as posterior as the pouch of Douglas (figs. 1 and 2). To optimize this dissection and have appropriate tension between tissue planes, borrowing from gynecologic oncology one may distend the bladder with normal saline and utilize an insulated transvaginal probe.

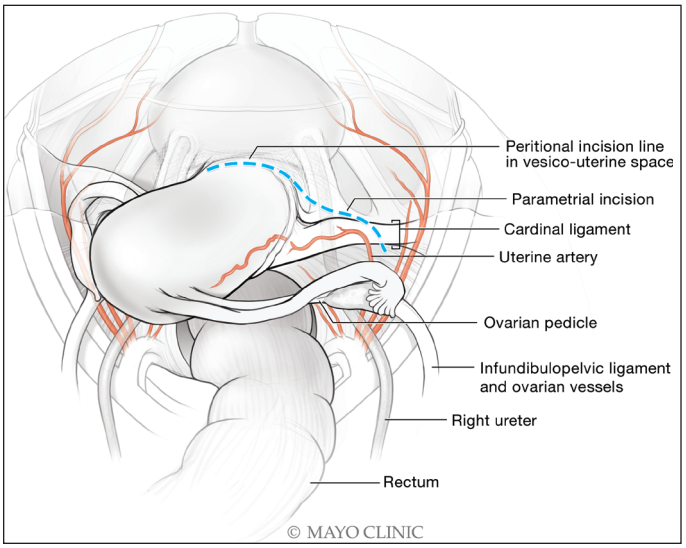

Figure 1. Peritoneal incision in uterine-sparing radical cystectomy. Reprinted with permission.

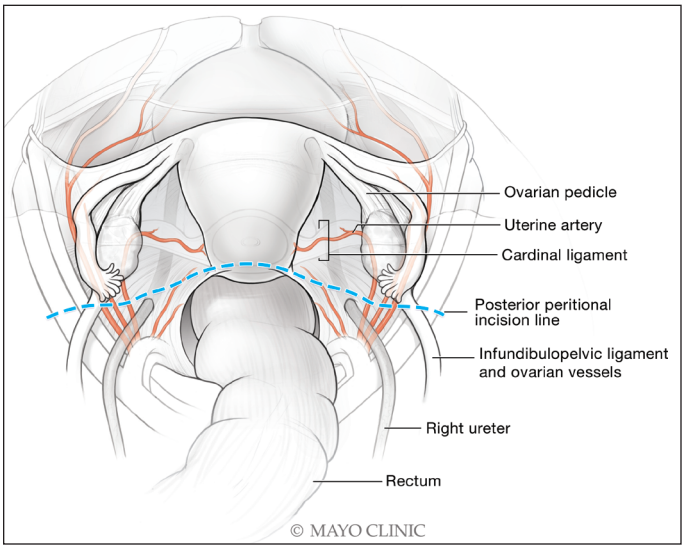

Figure 2. Peritoneal incision in classic radical cystectomy (nonuterine-sparing). Reprinted with permission.

Distension of the bladder should be gentle so as not to perforate the bladder and risk oncologic compromise from spillage of bladder cancer cells. In a completely gynecologic-sparing "radical" cystectomy, the parasympathetic nerves, ovarian pedicles and the uterine pedicles are preserved (fig. 3). The plane between the posterior bladder wall and the anterior vagina may be developed as distally as the posterior bladder neck (fig. 4). As Collins et al describe in the robotic approach, the anterior vaginal wall is opened between the cervical insertion proximally and the urethra distally to retrieve the bladder specimen transvaginally.[90] However, if an open approach is performed, the entire anterior vaginal wall may be spared and preserved without additional vaginal repair.[89]

The current AUA guidelines recommend that sexual-sparing techniques be applied in carefully selected patients in the absence of malignant disease at the bladder neck or urethra.[91] Similarly, a recent update of (European Association of Urology) guidelines reports that pelvic organ-sparing techniques are oncologically safe in well-selected patients and may be applied to prevent pelvic floor disorders and sexual dysfunction in women.[92] A recent review on the oncologic safety of organ-sparing cystectomy has outlined factors to consider when sparing pelvic organs for women and men in a radical cystectomy.[93] **For women specifically, the data are sparse and limited; however, the only clinical factor associated with disease recurrence was the presence of a palpable posterior bladder mass on preoperative examination.** Further study into long-term oncologic outcomes is long overdue and necessary.

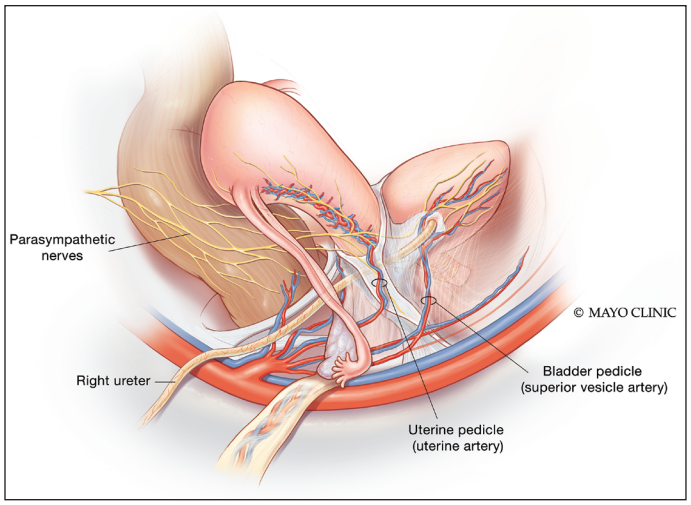

Figure 3. Parametrium including insertion of ureter into bladder and related structures to identify for completely gynecologic organ-sparing "radical" cystectomy. Reprinted with permission.

Ovary preservation. In terms of ovarian preservation, recent studies have questioned the utility of bilateral oophorectomy.[94] The American College of Obstetricians and Gynecologists no longer recommends routine prophylactic bilateral oophorectomy for prevention of ovarian cancer among women. Instead, there is strong evidence to support that the majority of ovarian cancer arises from the fallopian tubes, and therefore bilateral salpingectomy with ovarian preservation is recommended.[95] Long-term effects of oophorectomy include a 13% increase in all-cause mortality among women of all ages, specifically among women 60 years and older, and a trend toward higher risks of cancer and cardiovascular disease. Similarly, ovarian preservation may be protective of bone health as well as sexual health in postmenopausal women due to ovarian androgen production.[96] Ovarian preservation is safe and feasible in the immediate intraoperative and postoperative periods when compared to nonovarian-sparing radical cystectomy.[80]

Urinary diversion issues. With regard to urinary diversion and quality of life, a large number of retrospective studies exist that describe short- and long-term function. However, the majority of this literature focuses predominantly on men, with few studies focusing specifically on women. Quality of life was recently compared among women who underwent ileal conduit urinary diversion vs orthotopic neobladder. Women with an orthotopic neobladder were a decade younger, were more sexually active following surgery and reported higher physical functioning on self-administered quality of life questionnaires than women with an ileal conduit. However, on all other components of the global functioning and bladder cancer-specific questionnaire domains, including body image, no significant differences between groups were noted.[97,98]

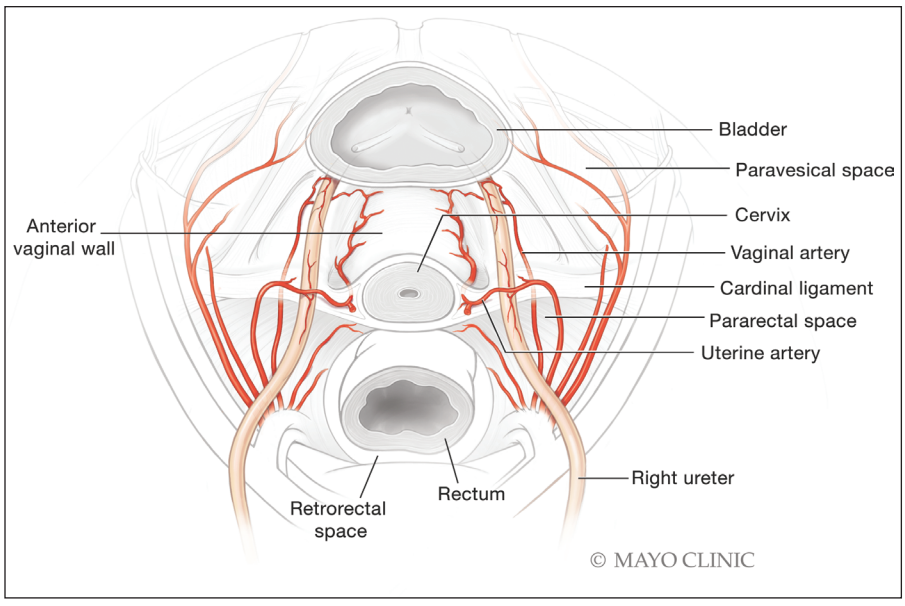

Figure 4. Cross-section of pelvic organs at bladder neck. Reprinted with permission.

CONCLUSION

The association of bladder cancer and gender is complex and requires further study. Future investigation should assess estrogen's protective effect in premenopausal women, the aggressive phenotype found in postmenopausal women, the influence of hormones on molecular subtypes of bladder cancer among women, improvement in referral patterns regarding gross hematuria, and consistent and thoughtful surgical techniques to optimize oncologic and functional outcomes among women. Studies to elucidate the association of these factors as they relate to bladder cancer in women should critically avoid perpetuating bias and results without a biological explanation.

DID YOU KNOW?

- Gender-specific hormonal differences may account for differences in bladder cancer incidence, molecular subtypes and adverse pathology in women.
- Women continue to experience inadequate evaluation of hematuria and timely referral to a urologist.
- Women continue to experience differences in treatment with regard to guideline-concordant care, utilization of continent urinary diversion and minimally invasive procedures, and preoperative sexual function counseling.
- Gender-specific surgical techniques should be considered and offered to women when oncologically appropriate, specifically ovarian preservation.
- Comparisons of oncologic outcomes between men and women should be done with caution to avoid perpetuating biases.

Table 1. Risk factors associated/suspected to be associated with bladder cancer

Modifiable	Nonmodifiable
Cigarette smoking[8–12]	Age
Occupational exposure (aromatic amines in dyes and organic chemicals in rubber, leather, textiles, paint, ink)[13]	Gender (hormonal differences, access to care and treatment differences)
Arsenic and nitrate in drinking water[14,15]	Genetic mutations (Lynch syndrome, Cowden syndrome, RB1, GST, NAT)
Body mass index[17]	Birth defects (bladder exstrophy, urachal cyst)
Hypertension[18]	
Medications/herbal supplements (pioglitazone,[99] aristolochic acid-containing)	Chronic inflammation (indwelling catheters or endemic schistosomiasis)
Low water consumption[16]	Radiation therapy/chemotherapy (cyclophosphamide)

Table 2. Genetic changes between men and women accounting for some differences in incidence of bladder cancer

Level of Genetic Modulation	Difference	Clinical Significance
Genotype	Polymorphisms in GSTM1, GSTT1 and NAT2 genes[59, 60,62–64,100]	Producing inactive forms of detoxifying enzymes may contribute to carcinogen buildup
	Mutation frequency of KDM6A gene, gene on X-chromosome coding for histone lysine demethylase[101]	Mutation frequency higher in women with low-grade tumors vs men with low-grade tumors
Epigenetic	DNA methylation, affected by carcinogenic exposure[65, 66, 102]	Smokers have lower DNA methylation ability than nonsmokers; invasive tumors have high DNA methylation from paraffin assessment
Phenotype	Loss of expression in FOXA1 protein specific to urothelial cell development[39]	In men → urothelial hyperplasia In women → keratinizing squamous metaplasia

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Study Questions Volume 40 Lesson 34

1. A 64-year-old woman was recently started on hormone replacement therapy for genitourinary symptoms of menopause, primarily hot flashes and vaginal atrophy. She is a smoker and has smoked 1 pack per day for the last 20 years. She was treated with antibiotics 1 month ago for symptoms of a UTI with gross hematuria and a urine culture positive for Escherichia coli $>10^5$. She has recurrent gross hematuria and is scheduled for a computerized tomographic urogram and a cystoscopy. She should be counseled that to lower her risk of bladder cancer, she should
   a. use cranberry supplementation to prevent future UTIs, which could contribute to bladder cancer
   b. continue hormone replacement therapy
   c. stop hormone replacement therapy
   d. stop smoking

2. The major differences in outcomes for bladder cancer between men and women are
   a. women present with higher stage bladder cancer and have worse survival only within the first 2 years of diagnosis
   b. women have worse cancer-specific and overall survival regardless of stage at presentation
   c. female gender is a nonmodifiable risk factor for poor bladder cancer survival compared to male gender
   d. men on average smoke for a longer duration than women, and therefore have worse overall survival

3. A 66-year-old woman recently diagnosed with invasive bladder cancer is interested in ovarian preservation. The main reason for ovarian preservation is
   a. decreased operative time
   b. decreased perioperative morbidity
   c. prevention of primary ovarian malignancy
   d. protection of bone health and sexual function

4. A 53-year-old woman is booked for radical cystectomy. She is interested in a uterine-sparing procedure. The 2 distinct differences in the surgical dissection during uterine-sparing cystectomy compared to nonuterine-sparing cystectomy in a woman are location of
   a. peritoneal incision and location of bladder mobilization in reference to the parametrium
   b. uterine artery ligation and location of infundibulopelvic suspensory ligament resection
   c. anterior vaginal wall incision and posterior bladder neck dissection
   d. cardinal ligament incision and parametrium ligation

5. A 62-year-old woman with muscle-invasive bladder cancer is scheduled for a radical cystectomy and desires all of her gynecologic organs to be preserved. The clinical factor shown to compromise oncologic safety of a gynecologic organ-preserving radical cystectomy is
   a. tumor involving the trigone
   b. pelvic lymphadenopathy on computerized tomography
   c. vaginal atrophy in a postmenopausal woman
   d. palpable posterior bladder mass on preoperative exam