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Gender and Menopause Impact on Recurrence and Cancer-Specific Mortality in Bladder Cancer After Radical Cystectomy: A Retrospective Cohort Study

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Purpose: Although bladder cancer occurs three to 4 times more frequently in men than in women, the relative number of deaths compared to incidence is higher in women, suggesting that women have a worse prognosis than men. Emerging evidence indicates that the activity of the sex steroid hormone pathway may play a role in bladder cancer development, with demonstrations that both androgens and estrogens have biological effects on bladder cancer *in vitro* and *in vivo*. This study investigates the influence of sex and menopausal status on recurrence and cancer-specific death (CSD) in bladder cancer patients undergoing radical cystectomy (RC).

Materials and Methods: This retrospective analysis included 3,913 patients from the Korean Bladder Cancer Study Group Database who underwent RC between 2010 and 2019. Patients were categorized based on gender and menopausal status (≤50 years: premenopausal; >50 years: postmenopausal). Pathological factors, neoadjuvant chemotherapy, recurrence, and CSD rates were analyzed using chi-square and Fisher exact tests.

Results: Among the 3,913 patients, 400 (10.2%) were female. Premenopausal females exhibited significantly lower recurrence rates (28.6%) compared to postmenopausal females (45.7%). CSD rates were similarly reduced in premenopausal females (12.0% vs. 22.2% in postmenopausal females). No significant sex differences in recurrence or CSD were observed among premenopausal patients. Pathological T stage, nodal status, and lymphovascular invasion were significantly associated with recurrence in males, while nodal status alone was significant in females. Neoadjuvant chemotherapy was significantly more frequently administered to male patients under the age of 50, while no difference was observed in the administration of neoadjuvant chemotherapy among female patients based on menopausal status.

Conclusion: Hormonal changes associated with menopause significantly influence bladder cancer outcomes in women. Premenopausal hormonal environments seem protective, underscoring the need for further research into hormone-driven mechanisms in bladder cancer.

Key Words: Urinary bladder neoplasms: Sex factors: Menopause: Neoplasm mortality: Cystectomy

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• **Research Ethics:** This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB No. SMC 2024-11-036-001). All procedures were conducted in accordance with the guidelines of the Declaration of Helsinki. Data confidentiality was maintained in compliance with the Data Protection Act 2016/679 (Spanish Government). Due to the retrospective nature of the study, written informed consent was waived.
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INTRODUCTION

Bladder cancer is a significant global health concern, ranking as the ninth most common malignancy and the thirteenth most common cause of cancer-related deaths [1]. Over recent years, a notable gender disparity has emerged in the incidence and outcomes of bladder cancer. While men exhibit a higher incidence of the disease, women often face poorer prognoses, as reflected in higher mortality-to-incidence ratios [2,3]. This discrepancy suggests that gender-related factors, beyond environmental risk factors such as smoking and occupational exposures, may contribute significantly to disease outcomes [4,5]. Despite environmental factors being well-documented contributors to bladder cancer risk, they do not fully explain the observed differences in prognosis between men and women [6].

Recent research has begun to uncover the involvement of sex steroid hormones, including androgens and estrogens, in the pathogenesis of bladder cancer. These hormones have been shown to have significant effects on cancer development, influencing both tumor progression and response to treatment. Androgens, which are more prevalent in men, and estrogens, which are more abundant in women, can affect the biology of bladder cancer in distinct ways. The influence of these hormones on cancer cells suggests that hormonal differences between genders may contribute to the disparity in bladder cancer outcomes [7,8]. Understanding how these hormones shape tumor behavior is crucial for developing targeted therapeutic strategies that consider the hormonal environment of the patient [9,10].

In addition to biological and hormonal factors, sex differences in the diagnosis and management of bladder cancer also play a critical role in the observed disparities. Women are more likely to present with advanced disease, often due to delays in the evaluation of hematuria, and lower rates of appropriate imaging and urologic referrals compared to men [11-13]. These diagnostic delays result in bladder cancer being diagnosed at a more advanced stage in women, which increases the risk of recurrence and cancer-specific mortality [14]. As a result, the combination of diagnostic challenges, biological differences, and hormonal influences contribute to the worse outcomes observed in women with bladder cancer [15,16].

This study aims to further investigate the sex-specific differences in bladder cancer, with a particular focus on how menopausal status may influence disease progression and patient outcomes.

MATERIALS AND METHODS

A retrospective analysis was conducted using the Korean Bladder Cancer Study Group Database, which included patients who underwent radical cystectomy (RC) for bladder cancer at 11 institutions from 2010 to 2019. In June 2024, following the systematic planning of a web-based electronic database by the Bladder Cancer Research Group of the Korean Urological Oncology Society, a dedicated database manager was responsible for collecting and validating the data. Adult patients who underwent RC for bladder cancer during the study period and whose follow-up examination results could be confirmed in the medical records of the hospital where the surgery was performed were included. Patients who underwent surgery for other reasons or whose follow-up examination results could not be confirmed were excluded.

This study was described followed by the STROBE

(Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. Menopausal status was determined based on age, with individuals aged 50 years or younger categorized as premenopausal and those older than 50 years categorized as postmenopausal, as menopause typically occurs around the age of 50. The study aimed to assess the impact of sex and postmenopausal status on the recurrence of bladder cancer and cancer-specific death (CSD) following RC. Several factors were analyzed, including pathological T stage, nodal status, lymphovascular invasion (LVI), carcinoma *in situ*, variant histologies, surgical margins, and the use of neoadjuvant chemotherapy (NAC).

Statistical analyses were performed using IBM SPSS Statistics ver. 27.0 (IBM Co., Armonk, NY, USA). The chi-square test and Fisher exact test were used to evaluate categorical variables. All statistical tests were 2-tailed, and a p-value of less than 0.05 was considered statistically significant.

RESULTS

The study analyzed a total of 3,913 patients, among whom 400 were female (10.2%). Female patients were further categorized based on menopausal status: premenopausal (≤50 years old) and postmenopausal (>50 years old). Differences in recurrence and CSD rates were evaluated in relation to these groups, alongside comparisons to male patients.

At the median follow-up of 39 months (interquartile range, 14–66), recurrence rates were found to vary significantly among the study groups. Although there were no significant differences in T stage (p=0.239), and nodal status (p=0.942) between pre- and postmenopausal females, premenopausal females demonstrated a recurrence rate of 28.6%, markedly lower than the 45.7% observed in postmenopausal females (Table 1). Similar trends were observed in CSD rates. Premenopausal females had a significantly lower CSD rate of 12.0% compared to 22.2% in postmenopausal females. Male patients under the age of 50 exhibited a CSD rate of 24.9%, which was slightly higher than the 22.8% observed in older males (Table 2).

Among premenopausal patients, no significant sex-based differences were identified in recurrence or CSD rates (Figs, 1 and 2). Pathological factors such as pathological T stage,

Table 1. Study population with or without recurrence after radical cystectomy according to sex and menopausal status

Variable	No recurrence	Recurrence	p-value*
Male sex			0.757
<50	112 (59.9)	75 (40.1)	
50≤	1,954 (58.7)	1,372 (41.3)	
Female sex			0.079
<50	20 (71.4)	8 (28.6)	
50≤	202 (54.3)	170 (45.7)	

Values are presented as number (%).
*Chi-square and Fisher exact test.

Table 2. Study population with or without cancer-specific death after radical cystectomy according to gender and menopausal status

Variable	No cancer-specific death	Cancer-specific death	p-value*
Male sex			0.527
<50	130 (75.1)	54 (24.9)	
50≤	2,319 (77.2)	684 (22.8)	
Female sex			0.231
<50	22 (88.0)	3 (12.0)	
50≤	238 (77.8)	68 (22.2)	

Values are presented as number (%).
*Chi-square and Fisher exact test.

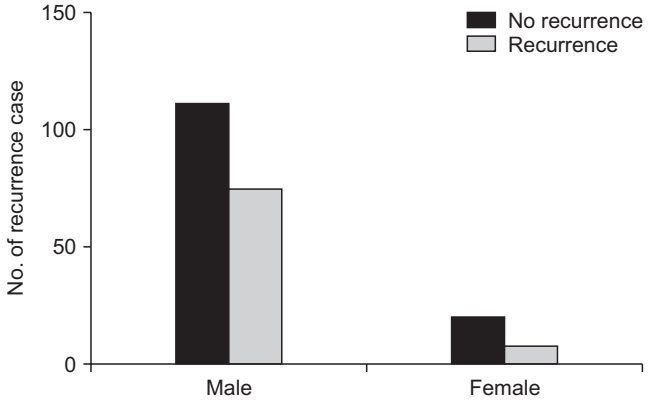

Fig. 1. Bar graphs showing the differences of recurrence cases at age under 50 according to sex (p=0.33).

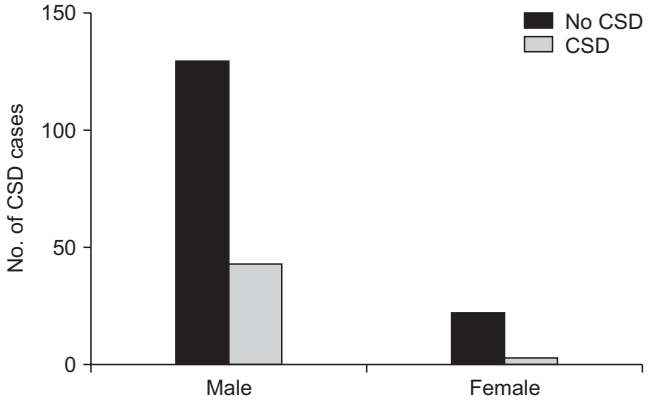

Fig. 2. Bar graphs showing the differences of cancer-specific death (CSD) cases at age under 50 according to sex (p=0.24).

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Table 3. Comparison of male and female patients age under 50 with or without recurrence after radical cystectomy

Variable	Male age <50		p-value*	Female age <50		p-value*
	Recurrence	No recurrence		Recurrence	No recurrence	
Pathology type			0.321			<0.001
UC	56/63 (88.9)	66/81 (81.5)		6/6 (100)	14/18 (77.8)	
Adenoca	7/63 (11.1)	15/81 (18.5)		0/6 (0)	4/18 (22.2)	
T stage			<0.001			0.458
T0,Tx	8/74 (10.8)	21/111 (18.9)		1/7 (0)	5/20 (25.0)	
Ta	0/74 (0)	2/111 (1.8)		1/7 (14.3)	0/20 (0)	
Tis	1/74 (1.4)	6/111 (5.4)		0/7 (0)	2/20 (10.0)	
T1	5/74 (6.8)	25/111 (22.5)		2/7 (28.6)	2/20 (10.0)	
T2	16/74 (21.6)	24/111 (21.6)		0/7 (0)	3/20 (15.0)	
T3	30/74 (40.5)	27/111 (24.3)		3/7 (42.8)	5/20 (25.0)	
T4	14/74 (18.9)	6/111 (5.4)		1/7 (14.3)	3/20 (15.0)	
N stage			<0.001			0.043
Nx	4/74 (5.4)	5/111 (4.5)		2/7 (28.6)	1/20 (5.0)	
N0	32/74 (43.2)	83/111 (74.8)		2/7 (28.6)	17/20 (85.0)	
N1	8/74 (10.8)	10/111 (9.0)		2/7 (28.6)	1/20 (5.0)	
N2	22/74 (29.7)	13/111 (11.7)		1/7 (14.3)	1/20 (5.0)	
N3	8/74 (10.8)	0/111 (0)		0/7 (0)	0/20 (0)	
Grade			0.766			0.897
Low	4/60 (6.7)	6/88 (6.8)		1/6 (16.7)	2/14 (14.3)	
High	56/60 (93.3)	82/88 (93.2)		5/6 (83.3)	12/14 (85.7)	
CIS	14/72 (19.4)	25/110 (22.7)	0.712	1/7 (14.3)	5/20 (25.0)	1.000
Variant histologies	16/70 (22.9)	22/104 (21.2)	0.130	1/7 (14.3)	2/19 (10.5)	1.000
LVI	42/74 (56.8)	41/110 (37.3)	0.011	3/7 (42.9)	5/19 (26.3)	0.635
Surgical margin	9/74 (12.2)	4/109 (3.7)	0.039	0/6 (0)	0/19 (0)	-

Values are presented as number (%).

UC, urothelial carcinoma; Adenoca, adenocarcinoma; CIS, carcinoma *in situ*; LVI, lymphovascular invasion.

*Chi-square and Fisher exact test.

nodal status, and LVI were significantly associated with recurrence in male patients (p<0.001). However, in females, only nodal status showed a significant correlation with recurrence (p=0.043) (Table 3).

NAC was more frequently administered to male patients under 50 years old (34.2%) compared to older males (22.4%). However, among female patients, no significant differences in NAC administration were observed between pre- and postmenopausal groups (Table 4).

Table 4. Study population with or without neoadjuvant chemotherapy according to gender and menopausal status

Variable	No neoadjuvant chemotherapy	Neoadjuvant chemotherapy	p-value*
Male sex			<0.001
<50	125 (65.8)	65 (34.2)	
50≤	2615 (77.6)	755 (22.4)	
Female sex			0.626
<50	21 (75.0)	7 (25.0)	
50≤	303 (78.9)	81 (21.1)	

Values are presented as number (%).

*Chi-square and Fisher exact test.

DISCUSSION

Emerging evidence suggests that the activity of the sex steroid hormone pathway may play a role in bladder cancer development [7-10]. Both androgens and estrogens have been shown to exert biological effects on bladder cancer *in vitro* and *in vivo* [11-13,17-20]. This study aims to elucidate sex-specific differences in bladder cancer and examine the influence of menopausal status on its prognosis.

Premenopausal females exhibited significantly lower recurrence rates (28.6%) compared to postmenopausal females (45.7%), indicating a potentially protective effect of premenopausal hormonal environments against bladder cancer recurrence. In contrast, male patients showed no clear hormonal distinctions, with recurrence rates remaining consistent across age groups.

Recurrence was significantly associated with pathologic

T stage, nodal status, and LVI in males, while in females, only nodal status was significantly associated. These findings suggest possible sex-specific biological mechanisms. Further investigation is needed to understand how these factors interact with hormonal changes. CSD rates were also lower in premenopausal females (12.0%) compared to postmenopausal females (22.2%). Among premenopausal patients, no significant sex-based differences were observed in recurrence or CSD rates, suggesting that hormonal factors may equalize outcomes in younger age groups.

Male patients under 50 were significantly more likely to receive NAC compared to females, although no significant differences in NAC use were observed within female subgroups. This discrepancy may reflect potential sex biases in treatment practices or differences in treatment eligibility based on clinical presentations [14,15]. Despite the lack of differences in the frequency of NAC administration, premenopausal female patients exhibited lower recurrence and CSD rates compared to their postmenopausal counterparts, reinforcing the protective role of hormonal environments in this subgroup. Conversely, male patients under 50, despite more frequent administration of NAC than older males, showed no significant differences in recurrence or CSD. This suggests that the effectiveness of NAC may vary depending on gender and menopausal status.

The results of this study underscore the complex interplay between sex, hormonal status, and bladder cancer outcomes. Premenopausal females demonstrated significantly better outcomes compared to postmenopausal females, with lower rates of recurrence and CSD, supporting the protective role of premenopausal hormonal environments. Both estrogen receptor and progesterone receptor have been suggested to be involved in bladder cancer tumorigenesis and progression. The significant association between nodal status and recurrence in females warrants further investigation into its underlying mechanisms.

This study is limited by its retrospective design and potential selection bias. Since it was not possible to confirm menopausal status in female patients, the age of 50 was used as a proxy for menopause. Additionally, the small number of female patients limited the ability to achieve statistical significance. Future research should focus on prospective studies and molecular analyses to further elucidate the role of hormonal influences in bladder cancer progression.

CONCLUSIONS

Hormonal changes associated with menopause significantly influence bladder cancer outcomes, with premenopausal women exhibiting reduced recurrence and CSD rates. These findings underscore the importance of integrating hormonal and sex-based considerations into future research and clinical practices for bladder cancer management.

NOTES

- **Author Contribution:** Conceptualization: JSP; Data curation: JSP; Formal analysis: JSP; Funding acquisition: WSJ, JH, KHK, JKN, BJL, BSH, WN, SL, JJO, SHJ, JHK, TIN, SGK, SHK, YSH, TGK, THK, JK, GS, HKS, WS, HHS; Methodology: JSP; Project administration: BCJ; Visualization: JSP; Writing - original draft: WSH; Writing - review & editing: JSP, WSH
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