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Over-expression of Long Non-coding RNA Urothelial Cancer-associated 1 as a Predictive Marker for Prostate Cancer

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Abstract. *Background/Aim: To determine the expression of long non-coding RNA urothelial cancer-associated 1 (UCA1) by performing array-based quantitative polymerase chain reaction (PCR) and to identify the clinicopathological significance of UCA1 expression in prostate cancer using in situ hybridization (ISH) of surgically resected specimens. Materials and Methods: Array-based quantitative PCR was performed using 10 pairs of fresh malignant (prostate cancer) and normal tissue samples to determine UCA1 expression. Single-color RNA ISH of surgically resected prostate cancer specimens was performed using 70 formalin-fixed, paraffin-embedded tissue specimens to examine the clinicopathological significance of UCA1. Results: Prostate cancer tissues exhibited higher levels of UCA1 expression than paired benign tissues. Furthermore, a correlation between high UCA1 expression and unfavourable clinicopathological characteristics, including advanced pathologic T stage, extraprostatic extension, presence of Gleason pattern 5, and involvement of the resection margins was observed. Notably, increased UCA1 expression significantly correlated with high- or very-high-risk patients, as defined by the 2023 National Comprehensive Cancer Network guidelines. Conclusion: UCA1 could be used as a novel diagnostic and prognostic biomarker for establishing an effective treatment protocol for prostate cancer.*

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Prostate cancer is the second most common cause of cancer-associated mortality among men, and its incidence is gradually increasing (1). According to comprehensive cancer statistics in 2008, patients with newly diagnosed prostate cancer accounted for 14% of all new cancer cases, and prostate cancer deaths accounted for 6% of all cancer-related deaths (2). Despite the increasing incidence and mortality rates, prostate cancer screening is only performed by measuring serum prostate cancer antigen (PSA) levels, which has a limited ability for disease detection. Moreover, approximately two-third of PSA-detected cases are false positives, thereby resulting in overdiagnosis. Consequently, an invasive prostate biopsy is necessary to confirm the diagnosis of prostate cancer (3, 4). However, this procedure can be burdensome for patients and provides limited data. Additional tests are required to further stratify the risk in patients clinically diagnosed with prostate cancer. According to the 2023 National Comprehensive Cancer Network (NCCN) guidelines, risk stratification relies on serum PSA level, grade group, presence of Gleason pattern 5, or extraprostatic extension (5). There is an urgent need for alternative biomarkers since neither the grade group nor Gleason pattern of the entire prostate cancer or extraprostatic extension can be determined using needle biopsy.

Over the years, research related to prostate cancer has focused primarily on the functions of protein-coding genes. However, the use of next-generation sequencing technology in studying human and cancer genomes has been transformative and has increased the attention on non-protein coding genes, which have been suggested to have a critical role in the development of human diseases and cancer biology (6). Non-coding RNAs are divided into two groups on the basis of their length: long and small non-coding RNAs. Long non-coding RNAs (lncRNAs) are defined as RNA transcripts longer than 200 nucleotides that do not encode proteins, while small non-coding RNAs are RNA transcripts shorter than 200 nucleotides (2, 7). Small non-coding RNAs include microRNAs, small nuclear RNAs, small interfering RNAs, transfer RNAs, and ribosomal RNAs. Among these, the role of microRNAs in prostate cancer biology has been extensively

studied (8). Even though lncRNAs remain relatively less scrutinized, their influence on gene expression has been suggested. Not only normal biological processes, including cellular differentiation, development, and reprogramming of stem cells, but also pathologic cancer processes, such as tumorigenesis, apoptosis, metastasis, chemoresistance, and angiogenesis, have been suggested to be affected by lncRNAs (2). Studies on lncRNAs involved in prostate cancer have revealed that various lncRNAs played important roles in prostate cancer; lncRNA prostate cancer antigen 3, which is highly expressed in prostate cancer tissue compared with normal tissue, was the first identified lncRNA in prostate cancer (9). It has the potential to be the most specific prostate cancer biomarker because it can be detected in the urine samples of patients with prostate cancer, thus enabling non-invasive diagnostic testing for prostate cancer. However, further studies are needed to determine its clinical utility for diagnosis and treatment.

Similarly, several other lncRNAs have also been suggested to be associated with prostate cancer. LncRNA urothelial cancer-associated 1 (UCA1) is a 1.4 kb lncRNA located on chromosome 19p13.12, which was initially identified in urinary bladder urothelial cancer (10, 11). Although UCA1 is highly expressed during the early (5-10) weeks of gestation and remains upregulated in certain adult tissues, such as the urinary bladder, heart, and uterus, it is generally downregulated in most adult tissues (10, 11). UCA1 over-expression has been documented in a wide range of human malignancies (12), including oesophageal squamous cell carcinoma (13), colorectal cancer (14, 15), and ovarian cancer (16). UCA1 over-expression has been strongly associated with poor prognosis in bladder, pancreatic, and ovarian cancers (11, 17-20), which suggests an oncogenic function associated with this lncRNA. Collectively, these findings indicate the potential of UCA1 as a prognostic biomarker and therapeutic target.

However, several studies assessing the clinicopathological significance of UCA1 in prostate cancer have presented conflicting results. Although most of the studies indicate that high UCA1 expression can be associated with poor prognosis (21-23), an opposing function of this lncRNA has also been reported (24). Therefore, in this study, we aimed to determine UCA1 expression by performing array-based quantitative polymerase chain reaction (PCR) and to identify the clinicopathological significance of UCA1 expression using *in situ* hybridization (ISH) of surgically resected specimens.

Materials and Methods

Ethical considerations. The study was conducted in accordance with the tenets of Declaration of Helsinki and was approved by the Institutional Review Board of the Korea University Anam Hospital (IRB No. 2018AN0108). The requirement for patient consent was waived owing to the retrospective nature of the research without risk to subjects.

RNA purification from fresh tissues. Ten pairs of fresh prostate cancer and normal tissue samples were obtained and immediately preserved in liquid nitrogen. These samples were collected *via* needle biopsy, performed by a urologist at the Department of Urology of Korea University Anam Hospital. Five fresh tissue sections, 10-μm thick and a surface area of approximately 100 mm^2, were used for total RNA extraction. Tissue sections were completely lysed using 0.8 ml of Trizol reagent (Invitrogen, Carlsbad, CA, USA) and incubated at room temperature for 10 min. After adding 0.2 ml of chloroform, the samples were vortexed and centrifuged for 15 min at 14,000 rpm. The aqueous phase was transferred to a new 1.5-ml tube, followed by ethanol precipitation. After suspending in 20 μl of RNase-free deionized water, the quality and quantity of isolated total RNA were measured using an Eppendorf BioPhotometer Plus (Eppendorf, Hamburg, Germany) spectrophotometer. Purified total RNA samples were stored at –80˚C for further use.

Array-based quantitative PCR (qPCR). Expression profiling of 90 human lncRNAs was performed by real-time PCR using the LncProfiler qPCR Array Kit (System Biosciences, Mountain View, CA, USA) in accordance with the manufacturer's instructions. Real-time PCR was performed using Maxima SYBR Green/ROX qPCR Master Mix 2X (Thermo Scientific, Pittsburgh, PA, USA). The number of cycles at which the reaction crossed the threshold (CT) was determined for each gene. Raw CT values were normalized to the median CT value (ΔCT=CTLnc–CTmedian). The expression of 90 human lncRNAs, including UCA1, was evaluated using the comparative ΔCT method. For each lncRNA, the expression level in prostate cancer tissue relative to that in normal tissue (fold change) was quantified using the equation $2^{-\Delta\Delta CT}$, where ΔΔCT=ΔCTprostate cancer–ΔCTnormal tissue. Tail and tag complementary DNAs (cDNAs) were synthesized according to the manufacturer's protocol. Real-time PCR was performed using Maxima SYBR Green/ROX qPCR Master Mix 2X (Thermo Scientific).

Sample collection and tissue microarray (TMA) production. The TMA samples included prostate cancer tissue specimens from 70 patients with prostate cancer. We included patients who were diagnosed with acinar adenocarcinoma and underwent radical prostatectomy at the Korea University Anam Hospital between 2009 and 2013. We incorporated patients whose follow-up data were identifiable and patients with other cancers or later additional cancers. Patients with insufficient or inappropriate formalin-fixed, paraffin-embedded (FFPE) samples to produce two TMA cores were excluded. Two tissue cores, 3-mm in diameter, obtained from FFPE tissue blocks of prostate cancer specimens were used to generate the TMA. Single-color RNA ISH was performed to examine the clinicopathological significance of UCA1.

Single-color RNA ISH. ISH was performed in accordance with the manufacturer's instructions using the RNAscope® 2.0 HD Red Chromogenic Reagent Kit (Advanced Cell Diagnostics, Newark, CA, USA). Briefly, 4 μm-thick TMA sections from FFPE samples were used for ISH. The sections were baked in a dry oven for 1 h at 60˚C. After deparaffinization, dehydration, and air-drying, the sections were incubated with hydrogen peroxide for 10 min at room temperature. Next, the slides were submerged in boiling pre-treatment solution for 15 min, followed by application of Protease Plus and incubation at 40˚C for 30 min. The target probes, including positive and negative controls, were hybridized for 2 h using the HybEZ™ Oven (Advanced Cell

Diagnostics), Amplifier 1 (30 min), Amplifier 2 (15 min), Amplifier 3 (30 min), Amplifier 4 (15 min) at 40˚C, Amplifier 5 (30 min), and Amplifier 6 (15 min) at room temperature. A fast red substrate was added to facilitate RNA visualization as red chromogenic dots.

The probes used were Hs-UCA1, Hs-PPIB (positive control, housekeeping gene cyclophilin B), and DapB (negative control, probe targeting the bacterial gene DapB). The determination of the maximum number of red dots in a single high-power field (HPF) per core was conducted for the purpose of analyzing the expression of UCA1., and the results of two high-power fields were collected for each case. The number of dots was quantified using ImageJ (National Institutes of Health, Bethesda, MD, USA). UCA1 expression was divided into low- and high-expression groups, with the cutoff value determined using a receiver operating characteristic (ROC) curve.

Statistical analyses. Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Chi-square test was used for correlational analysis of UCA1 expression and clinicopathological features. Cox proportional hazard regression models were used to analyse the clinicopathological significance of UCA1 expression. Statistical significance was set at $p<0.05$.

Results

qPCR and UCA1 expression. We performed qPCR using 10 paired malignant and normal tissue specimens to determine the expression levels of 90 human lncRNAs. However, 41 of 90 lncRNAs were unavailable for lncRNA expression analysis in one paired sample because of the low quality of that sample. One paired sample failed to analyse the expression level of six lncRNAs, one failed to analyse three lncRNAs, two failed to identify two lncRNAs, four failed to identify one lncRNA, and one analysed all ninety lncRNAs. We calculated the average of $2^{-\Delta\Delta CT}$ for each lncRNA and found that 12 lncRNAs were expressed 10 times more or highly expressed in prostate cancer tissue compared with normal tissue.

We focused on UCA1 expression. When considering seven specimens, UCA1 expression was significantly increased, with a comparative ΔCT value ranging between 1.50 to 49.58 (average 18.90) in malignant tissues when compared with normal tissues. In the context of one specimen, the malignant tissue exhibited lower UCA1 expression than the normal tissue ($2^{-\Delta\Delta CT}$ value=0.02). The other two specimens were not available for UCA1 expression analysis. Nine patients exhibited a high Gleason score of >7. One patient had a Gleason score of 6 and showed increased UCA1 expression ($2^{-\Delta\Delta CT}$=1.50).

Clinicopathologic features of TMA samples. Seventy FFPE tissue specimens were collected to investigate the clinicopathological significance of UCA1. The clinicopathological characteristics of the 70 TMA samples were retrospectively reviewed and are summarized in Table I. When classified according to the 2023 NCCN guidelines, 37 (52.9%) patients belonged to either the high- or very-high-risk group, while 33 (47.1%) belonged to the low-risk group.

Table I. *Correlation between urothelial cancer-associated 1 (UCA1) expression and clinicopathologic features of the tissue microarray samples*.

	N	UCA1 expression		
		Low	High	*p*-Value
2023 NCCN risk group				
Low-risk group	33 (47.1%)	33	0	<0.001
High or very-high-risk group	37 (52.9%)	21	16	
Pathologic staging				
T2	48 (68.6%)	43	5	<0.001
T3	22 (31.4%)	11	11	
2014 ISUP Grade group				
Group 1	18 (25.7%)	15	3	0.095
Group 2	37 (52.9%)	28	9	
Group 3	9 (12.9%)	8	1	
Group 4	4 (5.7%)	3	1	
Group 5	2 (2.9%)	0	2	
Extraprostatic extension				
Present	17 (24.3%)	9	8	0.006
Absent	53 (75.7%)	45	8	
Seminal vesicle invasion				
Present	12 (17.1%)	7	5	0.088
Absent	58 (82.9%)	47	11	
Lymphatic invasion				
Present	4 (5.7%)	3	1	0.916
Absent	66 (94.3%)	51	15	
Venous invasion				
Present	0 (0%)	0	0	N/A
Absent	70 (100%)	54	16	
Perineural invasion				
Present	37 (52.9%)	27	10	0.379
Absent	33 (47.1%)	27	6	
Resection margin				
Involvement	41 (58.6%)	28	13	0.036
Free	29 (41.4%)	26	3	
Gleason's score 5				
Present	17 (24.3%)	10	7	0.045
Absent	53 (75.7%)	44	9	
Serum PSA level				
Increased (>4 ng/ml)	63 (90%)	50	13	0.184
Normal (≤4 ng/ml)	7 (10%)	4	3	
Age				
>60 years	49 (70%)	38	11	0.901
≤60 years	21 (30%)	16	5	
Recurrence				
Recurred	21 (30.0%)	17	4	0.619
No recurrence	49 (70.0%)	37	12	

NCCN: The National Comprehensive Cancer Network; ISUP: The International Society of Urological Pathology; PSA: prostate-specific antigen.

The average interval from the date of diagnosis to that of the last follow-up was 3,741.3 (range=805-5,178) days. Although no prostate cancer-related deaths were recorded, disease recurrence was documented in 21 (30.0%) patients during the follow-up period. Therefore, we defined disease-

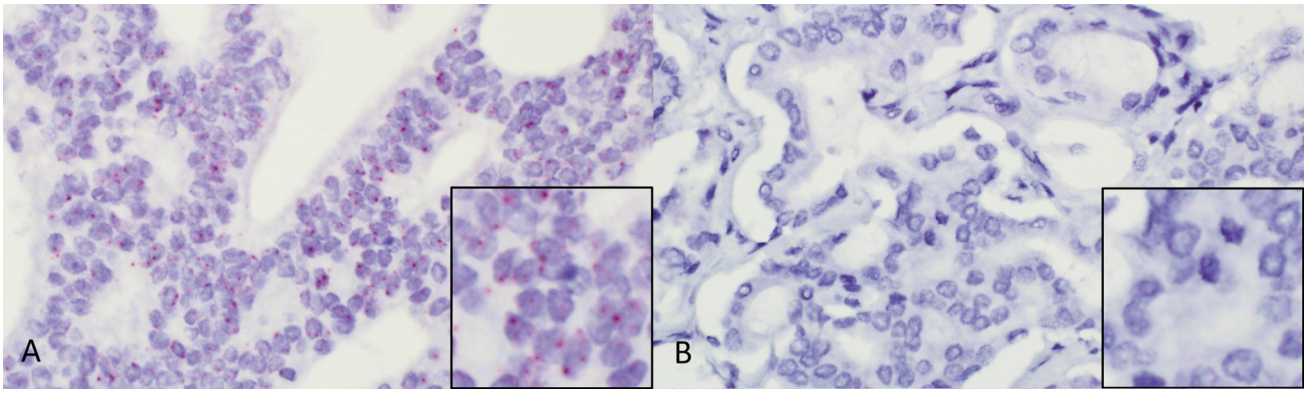

Figure 1. *RNA in situ hybridization analysis of samples with high (A) and low Urothelial cancer-associated 1 expression (B).*

free survival as the interval from the date of diagnosis to that of the last follow-up or recurrence, with an average duration of 2904.1 (range=40-5,072) days.

UCA1 expression using RNA ISH. ISH was performed to determine UCA1 expression of FFPE specimens. The calculated number of UCA1 dots ranged between 36 to 727 per sample, with an average of 219.5 dots (Figure 1). After drawing the ROC curve, the cut-off value was determined as the UCA1 expression value with the greatest sum of sensitivity and specificity. Notably, 16 (22.9%) and 54 (77.1%) patients exhibited high and low UCA1 expression, respectively.

Clinicopathologic significance of increased UCA1 expression. Increased UCA1 expression in prostate cancer was found to correlate significantly with high-risk clinicopathological features, including high pathologic T stage ($p<0.001$), presence of extra prostatic extension ($p=0.006$), presence of Gleason pattern 5 ($p=0.039$), and involvement of the resected margin ($p=0.036$). When grouped according to the 2023 NCCN guidelines, increased UCA1 expression markedly correlated with specimens derived from patients in the high- or very-high-risk group ($p<0.001$). Other factors, including 2014 ISUP grade group, seminal vesicle invasion, perineural invasion, serum PSA level, age, and recurrence, showed no significant correlation. The results are presented in Table I.

Discussion

Several studies have examined the roles of various proteins in cancer development. However, tumorigenesis cannot be comprehensively clarified using proteomic studies alone. Therefore, the function of non-coding RNAs, such as lncRNAs, has been examined in tumour pathogenesis (6). Short non-coding RNAs, such as microRNAs, have relatively well-described roles in human cancers. However, the involvement of lncRNAs in cancer remains poorly elucidated, as they are less conserved at the sequence level (8). Recently, some lncRNAs were found to significantly contribute to cancer development in humans and were considered potential oncogenes or tumour suppressors (25, 26). According to their location in the genome in comparison to protein coding genes, lncRNAs have been classified as intergenic and intragenic, and intragenic lncRNAs can be subdivided into exonic, intronic, and overlapping lncRNAs (2).

Moreover, lncRNAs exhibit aberrant expression in prostate cancer (7, 8). Metastasis associated lung adenocarcinoma transcript 1 (MALAT1), SWItch/Sucrose Non-Fermentable complex antagonist associated with prostate cancer 1 (SChLAP1), prostate cancer associated transcript 1, and focally amplified long non-coding RNA in epithelial cancer (FALEC) have been reported as prostate cancer-associated lncRNAs and proven to have oncogenic role (7). Additionally, various lncRNAs, including prostate cancer associated transcript 29 (PCAT29) downregulated RNA in cancer, inhibitor of cell invasion and migration, and imprinted maternally expressed transcript have been reported to be downregulated in prostate cancer and have tumour suppressor roles (7). Among these, several lncRNAs have clinical implications; for example, MALAT1 is a diagnostic biomarker, SchLAP1 is a risk predictive marker, FALEC is a prognostic biomarker, and PCAT29 is a recurrence risk prediction marker (7). Besides, many studies have attempted to identify the role and clinical significance of several prostate cancer-associated lncRNAs (7, 8).

UCA1, one of the lncRNAs associated with prostate cancer, is upregulated during the gestational period but is downregulated in most adult tissues (10, 11). Several studies have revealed that UCA1 is a proto-oncogene that plays a critical role in the pathogenesis of several cancers, including oesophageal squamous cell carcinoma (13), colorectal (14, 15), and ovarian cancers (16). UCA1 over-expression has been strongly associated with poor prognosis in several cancers, especially

bladder, pancreatic, and ovarian cancers (11, 17-20). Based on these findings, its oncogenic function has been suggested. UCA1 over-expression not only enhances cancer cell proliferation, migration, and invasion, but also inhibits apoptosis, thereby promoting tumour growth (11, 18, 20). Recent studies have shown that UCA1 regulates chemoresistance in bladder, gastric, and ovarian cancers (11, 16, 27, 28).

It is also considered that UCA1 plays an important role in prostate cancer. Hu *et al*. suggested a potential role of UCA1 in prostate cancer (29). The authors observed that UCA1 expression was markedly increased in prostate cancer tissues. Furthermore, the expression and clinicopathological significance of the UCA1 gene have been reported previously. Zhang *et al*. (21) reported that high UCA1 expression correlated with advanced TNM stages and high Gleason scores in 47 patients with prostate cancer. Furthermore, He *et al*. (22) reported correlations between high UCA1 levels and high Gleason scores. Yu *et al*. revealed that UCA1 expression was significantly associated with advanced stage and metastasis in 86 pairs of prostate cancer tissues (23). In contrast, Zhao *et al*. suggested the opposite biological function for lncRNA UCA1 in prostate epithelial cancer cells (24). The authors revealed that UCA1 perpetuated the low tumorigenic and non-metastatic status of primary prostate cancer cells by maintaining high levels of E-cadherin. Given these conflicting results, the biological significance of UCA1 in prostate cancer development warrants further clarification.

In the present study, using qPCR, we demonstrated that UCA1 expression was higher in most prostate cancer tissues from high-risk patients compared to paired normal tissues, implying that UCA1 is a promising diagnostic marker for prostate cancer. Since UCA1 is significantly downregulated in most adult tissues, increased UCA1 expression can be utilized as a diagnostic and therapeutic marker. Using RNA ISH, we revealed that increased UCA1 expression could be correlated with poor clinicopathological features, including high pathologic T stage, extra prostatic extension, presence of Gleason pattern 5, and involvement of resection margins. Notably, given that increased UCA1 expression significantly correlated with extra prostatic extension and Gleason pattern 5, this elevated expression was also significantly correlated with high- or very-high-risk groups of patients with prostate cancer, as defined by the 2023 NCCN guidelines.

The risk stratification of prostate cancer is of substantial clinical importance. Depending on the risk level, certain patients can undergo a prostatectomy, additional lymph node dissection, radiotherapy, chemotherapy, or hormonal therapy, whereas others may opt for active surveillance (30). However, a simple biopsy fails to precisely assess the risk classification criteria, including grade group, Gleason patterns of whole prostate cancer, and extra prostatic extension. The overtreatment of patients with indolent prostate cancer in the clinical setting occurs due to the lack of sensitive and specific biomarkers. Furthermore, serum PSA level measurement is the only prostate cancer screening test available, which results in overdiagnosis. Therefore, there is an urgent need to identify novel diagnostic and prognostic prostate cancer biomarkers, and lncRNAs as novel markers are promising.

UCA1 is a promising lncRNA that has the potential to act as a biomarker. Since UCA1 is normally downregulated in most adult tissues, its presence in urine could be considered an abnormal feature and a promising biomarker for various cancers. Moreover, UCA1 can be identified in easily obtained patient samples, allowing non-invasive detection, indicating that it may be a valuable lncRNA biomarker. The potential of urine UCA1 as a biomarker was suggested previously for the diagnosis of bladder cancer (10). Wang *et al*. documented extremely low UCA1 expression in normal bladder, leukocytes, and the prostate. Thus, urinary UCA1 expression may be a specific biomarker for diagnosing transitional cell carcinoma (10). As urine anatomically passes through the prostate, the clinical utility of urine lncRNA detection has been suggested for diagnosing prostate and bladder cancers. Evaluation of the clinical significance of urine UCA1 in prostate cancer suggests that urine UCA1 could be a potential biomarker for predicting the risk of prostate cancer (5).

As demonstrated in this study, increased UCA1 expression can be significantly associated with poor prognostic factors in prostate cancer. This finding suggests that UCA1 could be a valuable prognostic biomarker to help overcome the limited information acquired from small-needle biopsies. By assessing the level of UCA1 expression, it may be possible to establish proper treatment strategies more accurately, even in cases where the entire prostate cancer specimen has not been evaluated.

We used RNA ISH to detect lncRNAs in FFPE samples, while qPCR targeted only fresh tissue. Even though qPCR can also be used to detect lncRNAs in FFPE tissue, it may not be as effective as RNA ISH due to the potential degradation of RNA during the fixation process (31). Therefore, RNA ISH may be a more reliable and sensitive method for detecting lncRNAs in FFPE tissue.

This study has a few limitations. First, the small sample size of patients with cancer recurrence may have contributed to the lack of statistical significance of the findings. Future studies including larger number of patients with cancer recurrence should be conducted to verify our results. Second, no prostate cancer-related deaths were recorded. Therefore, larger patient groups may afford improved accuracy regarding UCA1 measurements, including data regarding patient deaths or presence of disease recurrence and metastasis. Third, since this study was performed retrospectively, the functional role of UCA1 was verified through cell culture or animal experiments. Finally, the total number of cases included in this study was small to evaluate the clinical significance of UCA1 as a biomarker. Further studies including larger number of cases will be needed to overcome this limitation.

In conclusion, UCA1 expression was elevated in prostate cancer tissues when compared with paired benign tissues. A correlation was observed between increased UCA1 expression and poor clinicopathological features. These findings suggest that UCA1 could be used as a novel diagnostic and prognostic biomarker that may help establish an effective treatment plan.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, C.H.K., S.G.K., and Y.J.L.; methodology, S.G.K., and Y.J.L; validation, C.H.K., and Y.J.L.; formal analysis, C.H.K., and Y.J.L.; investigation, Y.J.L.; data curation, S.G.K., Y.J.L.; writing—original draft preparation, Y.J.L.; writing—review and editing, C.H.K.; visualization, Y.J.L.; funding acquisition, Y.J.L. All Authors have read and agreed to the published version of the manuscript.

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