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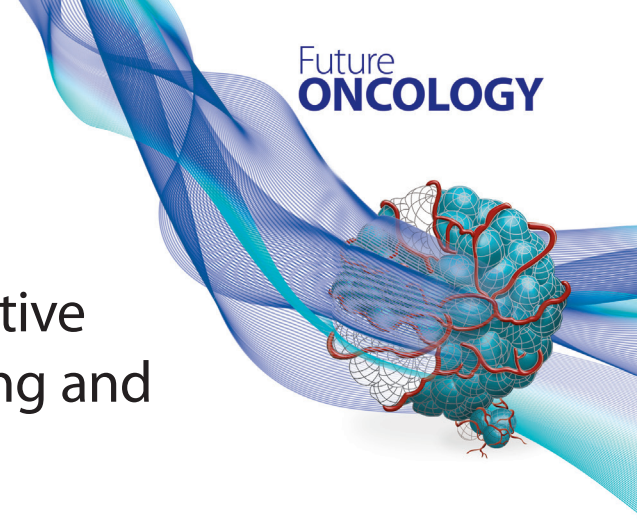

Urotensin II receptor on preoperative biopsy is associated with upstaging and upgrading in prostate cancer

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Aim: A higher Gleason score was associated with a lower tumor urotensin II receptor (UTII-R) expression in prostate cancer patients. **Methods:** A retrospective review of formalin-fixed paraffin-embedded tumor tissue derived from those who had prostatectomy and matching biopsy specimens was conducted at six Institutions. UTII-R expression was evaluated on biopsy by immunohistochemistry. **Results:** A total of 58 subjects undergoing radical prostatectomy were included. At multivariate analysis, low UTII-R expression was a significant predictor of Gleason upgrading, with an odds ratio of 10.3 (95% CI: 1.55–68.4), and of pathology upstaging, with an odds ratio of 11.1 (95% CI: 1.23–100.48). **Conclusions:** UTII-R expression on biopsy was associated with Gleason upgrading and pathology upstaging in prostate cancer patients.

KEYWORDS
• Gleason score • prostate cancer • urotensin II receptor

Prostate cancer is the most prevalent malignant tumor in men, with varying incidences among different geographical areas and populations because of a complex interplay of genetic and socioeconomic factors [1]. The highly heterogeneous prognosis of localized disease poses a great challenge for clinicians and investigators, since prognostic assessment is essential to assess the balance of benefits and harms of treatment [2–5]. While a subset of patients can be safely actively monitored avoiding sexual, urinary and bowel toxicity associated with local treatments [2], patients with aggressive disease require a multimodality approach that includes surgery [3] and/or radiation therapy plus adjuvant hormonal treatment [4]. The clinical stage, prostate-specific antigen (PSA) levels and the biopsy Gleason score have been incorporated in an extensively employed risk classification model originally

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developed by D'Amico *et^al.* [5]. The biopsy Gleason score has also been included in models predicting organ-confined disease [6] as well as lymph node involvement [7], and it is associated with outcome even in patients with advanced disease receiving systemic treatment [8,9].

Preoperative staging underestimates pathologic stage and prostate biopsies underestimate the Gleason score compared with prostatectomy specimens in up to 66% of patients, depending on PSA levels, biopsy Gleason score and clinical stage [10]. Apart from these variables, which have been incorporated in a validated predictive model to predict Gleason upgrading [11], a number of biomolecular markers were associated with Gleason upgrading [12,13]. Upgrading and upstaging have important therapeutic implications, as biopsy Gleason score and clinical stage along with PSA levels are the mainstay of the treatment-decision algorithm for localized prostate cancer [2–5]. Notably, baseline radiographic clinical staging has serious limitations.

Urotensin II (UTII) is a vasoconstrictive agent that binds to UTII receptor (UTII-R) and is able to stimulate human corticoadrenal carcinoma proliferation [14]. In three different prostate cancer cell lines, UTII-R was highly expressed in the LNCaP androgen-dependent prostate cancer cells, while a low expression was reported in PC3 and DU145 androgen-independent prostate cancer cell lines [15]. Furthermore, a higher Gleason score and a more advanced stage were associated with a lower UTII-R expression on both biopsy and radical prostatectomy specimens [15]. On the basis of these findings, we evaluated UTII-R expression in a retrospective case series of patients with prostatectomy and matching biopsy specimens in order to assess the association of UTII-R expression with upstaging and upgrading in Gleason score in prostate cancer patients following radical prostatectomy. The ability to better predict true pathologic stage and Gleason score at baseline can be anticipated to have implications for therapy. A multivariable logistic regression model including known clinical predictors was constructed by using a stepwise forward strategy.

Patients & methods

• Inclusion criteria

A retrospective review of medical records of prostate cancer patients undergoing radical prostatectomy since January 2013 to January 2015 was conducted at six participating Institutions (European Institute of Oncology, University of Bari, Tor Vergata University of Rome, University of Salerno, National Cancer Institute of Naples, University Federico II of Naples). Patients were included if prostatectomy and matching biopsy specimens were available for pathology review. Prostatectomy was required to be performed not later than 6 months following the biopsy. Patients who had either received neoadjuvant androgen therapy, or who had less than ten cores taken at biopsy or with a biopsy Gleason score >7 were excluded. The following data were required for inclusion in this retrospective study: clinical stage assigned according to the 2002 TNM system, PSA levels, total prostate volume on transrectal ultrasound, the biopsy Gleason score, total number of biopsy cores, number of positive biopsy cores, maximum cancer length in the positive cores, total length of positive cores and Gleason score on the prostatectomy specimen. The protocol was approved by the Internal Institutional Review Board of the participating Institutions and an informed written consent was obtained from each patient before the initiation of the study. This study was undertaken in accordance with principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

• Histology analysis

Haematoxylin–eosin slides of biopsy and prostatectomy specimens for each case were reviewed by an expert uropathologist (R Franco), in order to confirm the stage, the diagnosis and the Gleason grading score according to the 2005 ISUP-modified Gleason System. Significant Gleason score upgrading was defined as a Gleason sum increase between biopsy and radical prostatectomy either from 6 to >6 or from 7 to >7. Upstaging was defined as pathological tumor stage ≥pT3 (nonorgan confined disease) or pN1. The percentage of cancer involvement in positive cores was calculated by dividing the cumulative cancer length to the cumulative length of positive cores. Cumulative cancer length was defined as the sum of the length of all cancerous lesions of the in millimeter, whereas cumulative length of positive cores was defined as the sum of the length of all positive cores in millimeter. Formalin fixed, and paraffin-embedded prostate core biopsies were independently and blindly evaluated by C Manini for UTII-R expression by immunohistochemistry (IHC) using the Urotensin II Receptor Detection System Kit (Pharmabullett), with the automated staining

system bond (Leica). UTII-R was evaluated on biopsy specimens only. UTII-R expression was 'low' if weak or no staining was reported, while UTII-R expression was 'high' in case of intense staining, independently of the percentage number of stained cells. In case of coexisting weak and intense staining, the score was assigned according to the most predominant pattern.

• Data analysis & statistics

Data for continuous variables are summarized as median with interquartile range. Data for categorical variables are presented as frequencies and percentages. Univariate analysis to test the association of was based on the nonparametric Mann–Whitney U-test for quantitative variables. Chi-square test or Fisher exact test was used in case of categorical variables. Given the limited number of expected events of upgrading and upstaging, a maximum of three variables among those that were associated with upgrading and upstaging with a $p < 0.1$ at univariate analysis were entered in the multivariate analysis. Statistical significance was achieved with $p < 0.05$. All statistical analyses were performed by using the R statistical computing environment (version 3.2.1).

Results

A total of 58 subjects undergoing radical prostatectomy using open or laparoscopic techniques with matching biopsy information were included in this retrospective study. Digital rectal examination, serum PSA-level assessment and transrectal ultrasound were performed in all patients before undergoing transperineal prostatic biopsies and radical prostatectomy procedures. Prostate biopsies were performed with the same technique and by the use of a 18 G needle (cutting length: 23 mm). All of the clinical and pathological characteristics of the patients are detailed in **Table 1**. Significant Gleason score upgrading was observed in 17 patients (29.3%): 9 patients had their Gleason score upgrading from 6 to 7 and 8 patients had their Gleason score upgrading from 7 to 8. These data suggest that our study population is a representative sample for Gleason score upgrading studies. The transition matrix of Gleason score from biopsy to prostatectomy is shown in **Table 2**. UTII-R score was low in 38 patients and high in 20 patients. Univariate analysis testing the association of upstaging and Gleason score upgrading with continuous and categorical variables is reported in **Tables 3 & 4**, respectively. The biopsy Gleason score, clinical T-stage and the UTII-R expression, which were significant at univariate analysis, showed a significant odds ratio for Gleason upgrading of 6.46 (95% CI: 1.41–29.52), 5.41 (95% CI:

Table 1. Characteristics of the patients' population (n = 58).

Variable	Median (IQ range)
Total PSA	5.46 (4.56–7.8)
PSA density	0.19 (0.13–0.26)
Number of biopsy cores taken	12.0 (10.0–12.0)
Age (years)	65.0 (61.0–68.0)
Percentage of cancer involvement in positive cores	33.5 (22.0–59.0)
Positive biopsy cores (%)	30 (20–40)
Variable	Patients (n)
Clinical stage:	
– T1	38
– T2	20
Pathologic stage:	
– Pt2a	13
– Pt2b	9
– Pt2c	23
– Pt3a	9
– Pt3b	4
Lymphnode status:	
– Unknown	12
– N^-	38
– N^+	8
Margin status:	
– Positive	6
– Negative	52
Biopsy Gleason score:	
– Gleason 6	15
– Gleason 3 + 4	12
– Gleason 4 + 3	31
PSA:	
– <4	11
– 4–10	40
– >10	7
Gleason score on prostatectomy:	
– Gleason 6	7
– Gleason 7	42
– Gleason 8–10	9
UTII-R score:	
– 0	2
– 1	36
– 2	20
Gleason upgrading:	
– Yes	17
– No	41
Upstaging:	
– Yes	13
– No	45

Table 2. Transition matrix of Gleason score from biopsy to radical prostatectomy.

	Upgrading to 7 on prostatectomy	Upgrading to 8–10 on prostatectomy
Gleason 6 at biopsy	9	0
Gleason 7 at biopsy	-	8

1.29–22.53) and 10.3 (95% CI: 1.55–68.4), respectively, at the multivariate analysis including these three variables. The clinical T-stage and the UTII-R expression, which were respectively borderline significant and significant at univariate analysis, showed a significant odds ratio for upstaging of 5.05 (95% CI: 1.22–20.81) and 11.1 (95% CI: 1.23–100.48), respectively, at the multivariate analysis including these two variables. Multivariate analysis of predictors of Gleason upgrading and pathology upstaging is reported in **Tables 5** and **6**, respectively.

Discussion

Pathologic upstaging and Gleason upgrading before radical treatment for prostate cancer have important therapeutic implications. As an example, biopsy Gleason grade is a criterion for initiation and also interruption of active surveillance [2]. In a cohort of 993 men with Gleason 6 or 3 + 4 prostate cancer who were enrolled in an active surveillance protocol, 267 patients received radical treatment and biopsy grade progression was the cause of intervention in 94 (35%) of patients [2]. Furthermore, in patients undergoing radiotherapy, biopsy Gleason score is essential for optimal dosing and duration of androgen deprivation treatment [4]. Finally, patients with clinical T2 disease but pathologic T3 disease who undergo radical prostatectomy also have to receive subsequent radiotherapy in addition to surgery, with increased morbidity and decreased quality of life [3]. The importance of upstaging and upgrading is also underlined by their independent prognostic value.

In a large retrospective study, Gleason upgrading was reported in 466 of 1629 prostatectomized men, with a risk of biochemical recurrence of patients upgrading from Gleason score 6 (3 + 3) to Gleason 7 (4 + 3) and of patients upgrading from Gleason 7 to Gleason >7 that was intermediate between that of concordant tumors of the lower and higher grade [16]. Another retrospective study of 60,165 men with prostate cancer treated with radical prostatectomy showed that the prognosis of patients with cT1/T2 but pathologic T3a disease was better with respect to patients with clinical T3 disease, but it was worse with respect to men with pathologic T2 disease [17]. In our limited study group of 58 prostatectomized patients with Gleason 6–7, cT1–2 prostate cancer, we found that the biopsy Gleason score (7 vs 6), clinical T-stage (T2 vs T1) and the UTII-R expression (absence vs presence) showed a significant odds ratio for Gleason upgrading of 6.46 (95% CI: 1.41–29.52), 5.41 (95% CI: 1.29–22,53) and 10.3 (95% CI: 1.55–68.4), respectively. While UTII-R expression has not been previously evaluated in this setting, biopsy Gleason score and clinical stage were predictive of Gleason upgrading in several different studies and patient populations [18,19]. A SEER (Surveillance, Epidemiology, and End Results)-based registry study conducted in a selected cohort of 25,858 prostatectomized patients (biopsy Gleason score of 6 or 7, clinical T1 or T2 disease and PSA levels <30 ng/ml) reported Gleason upgrading in the subset of men with Gleason 6 prostate cancer in 43% of patients with PSA levels <10 ng/ml, in 56% of patients with PSA levels in the range of 10–19.9 ng/ml and in 61% of patients with PSA levels in the range of 20–29.9 ng/ml [18]. Conversely, in the subset of men with a biopsy Gleason score

Table 3. Univariate analysis of continuous variables.

Variable	No upgrading median (IQ range)	Upgrading median (IQ range)	p-value	No upstaging median (IQ range)	Upstaging median (IQ range)	p-value
PSA	5 (3–7.8)	6 (4.94–8.1)	0.16	5.6 (4.5–7.8)	5.0 (4.1–7.1)	0.6
Age	65 (62–67)	66 (60–69.50)	0.52	65 (60–67)	66 (63–68)	0.66
Positive biopsy cores (%)	28 (23–41)	30 (20–40)	0.82	28 (23–40)	30 (20–41)	0.75
PSA density	0.19 (0.12–0.26)	0.21 (0.14–0.26)	0.31	0.19 (0.13–0.26)	0.20 (0.12–0.24)	0.53
Percentage of cancer involvement in positive cores	36 (27–45)	25 (18–65)	0.25	29 (24–55)	36 (22–87)	0.35

IQ: Interquartile; PSA: Prostate-specific antigen.

of 7, Gleason upgrading was reported in only 3–7% of cases with a biopsy Gleason of 3 + 4 and in only 11–19% of cases with a biopsy Gleason of 4 + 3. In patients with biopsy Gleason 7, but not in those with biopsy Gleason 6, clinical T2 disease was associated with Gleason upgrading [18]. Similarly, in another retrospective study conducted in 862 prostate cancer patients managed with active surveillance, Gleason upgrading was reported in 31.3% of cases and was associated with clinical stage T2, higher prostate specific antigen and higher percentage of positive cores [19]. We also found that the clinical T-stage (T2 vs T1) and the UTII-R expression showed a significant odds ratio for upstaging of 5.05 (95% CI: 1.22–20.81) and 11.1 (95% CI: 1.23–100.48), respectively, at multivariate analysis. The association of upstaging with clinical stage is consistent with previous findings. In a retrospective cohort of 324 patients undergoing prostatectomy for low-risk prostate cancer, clinical stage (T2 vs T1) was associated with an odds ratio for upstaging of 2.4 (0.95–6.24), after adjusting for age, % positive biopsy cores, PSA and prostate volume [20]. The Partin tables that predict extraprostatic extension, seminal vesicle positivity and lymphnode positivity also include clinical stage, along with biopsy Gleason score and serum PSA [6]. The clinical stage was included in our multivariable model to predict upstaging, so we suggest that UTII-R should be further explored in order to improve the accuracy of the Partin tables. The exact biological role of UTII-R, which is overexpressed in a number of solid malignancies, such as breast, prostate and bladder cancer [15,21,22], is yet to be fully elucidated. Higher expression of UTII-R has been associated with improved prognosis in bladder cancer. In a series of 130 bladder cancer tissue samples, UTII-R expression was able to discriminate between nonmuscle invasive and muscle invasive bladder cancer, while among nonmuscle invasive tumor samples, higher UTII-R expression was associated with both lower grade and longer time to progression [22]. In a retrospective cohort of 184 prostate

Table 4. Univariate analysis of categorical variables.

Variable	No upgrading	Upgrading	p-value
Clinical stage:			0.043
– T1	27	6	
– T2	14	11	
PSA:			
– <4	11	0	0.053
– 4–10	25	15	
– >10	5	2	
Biopsy Gleason score:			0.02
– 6	7	8	
– 7	34	9	
UTII-R:			0.03
– 0–1	23	15	
– 2	18	2	
	No upstaging	**Upstaging**	
Clinical stage:			0.054
– T1	29	4	
– T2	16	9	
PSA:			0.30
– <4	8	3	
– 4–10	33	7	
– >10	4	3	
Biopsy Gleason score:			0.47
– 6	13	2	
– 7	32	11	
UTII-R:			0.02
– 0–1	26	12	
– 2	19	1	

Table 5. Multivariate logistic regression model coefficients for Gleason upgrading.

	Odds ratio	p-value
Clinical stage (T2 vs T1)	5.41 (1.29–22.53)	0.02
Biopsy score (6 vs 7)	6.46 (1.41–29.52)	0.01
UTII-R (0–1 vs 2)	10.3 (1.55–68.4)	0.01

cancer patients with available follow-up data [15], 83 (45%) and 101 (55%) patients, respectively showed high and low UTR expression. Survival was improved in patients with high UTR expression versus those with low UTR expression, with approximately 65 versus 40% of patients, respectively, alive 8 years after diagnosis. In this series, if tumors were stratified in low (Gleason score <7), medium (7) and high (>7) grade according to Gleason score, the high-UTR staining rate was recorded in 34 (68%) of the 50 low grade, 36 (52%) of the 70 medium, but only in 19 (25%) of the 75 high-grade tumors. These differences were statistically meaningful. Similarly, UTII-R expression was reported in 57, 42 and 38% of II-, III- and IV-stage tumors, respectively, although these differences were only borderline significant.

These findings provided the rationale for the assessment of UTII-R expression as a predictor of upstaging and Gleason upgrading in this study. As far as the biological role of UTII-R is concerned, it must be noted that both in bladder and prostate cancer cell lines, downregulation of UTII-R decreased motility and invasion, which may be related to its role in the regulation of intracellular Ca^{++} levels, cell contraction and cytoskeleton changes [15,22]. In prostate cancer cell lines, downregulation of UTII-R was also associated with increased activity of RhoA [15], a small guanosine triphosphate hydrolase with important tumorigenic and angiogenic activity in prostate cancer [23]. Further studies are required to confirm the prognostic value of UTII-R expression and to explore the underlying biological mechanisms of such an association.

Our study must be considered hypothesis generating and all of the findings reported require external validation. The limited number of the patients included, the lack of a sample size calculation, the assessment of the specimens 'per patient' and not 'per core,' along the retrospective nature of the study are some of the limitations of our study. Nevertheless, the evaluation of UTII-R expression and of Gleason upgrading and pathology upstaging by two independent blinded uropathologists as well as the inclusion in the multivariate model of a few factors of established predictive value strengthen the results obtain here and warrant further studies exploring the role of UTII-R as a predictor of Gleason upgrading and pathology.

Future perspective

Certain molecular tumor tissue-derived panels are commercially available to assist in selecting surveillance versus intervention (Prostate Oncotype DX and Prolaris assays), as well as risk stratifying patients following radical prostatectomy (Decipher assay). Our study shows that biopsy UTII-R may serve as an affordable and readily performed predictive factor of upstaging and Gleason upgrading, with diagnostic and therapeutic implications. In order to build more accurate models, expression of UTII-R on biopsy could be combined with other markers of upstaging and Gleason upgrading. These include soluble serum biomarkers, such as insulin-like growth factor-binding protein-3 [12], genetic polymorphism, such as rs33999879 [13], as well as radiological findings on MRI [24]. Simultaneous assessment of these markers in an appropriately large cohort is required to explore their independent predictive value and the possibility to combine them in a single model.

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Financial & competing interests disclosure

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Table 6. Multivariate logistic regression model coefficients for upstaging.

	Odds ratio	p-value
Clinical stage (T2 vs T1)	5.05 (1.22–20.81)	0.02
UTII-R (0–1 vs 2)	11.1 (1.23–100.48)	0.03

other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

EXECUTIVE SUMMARY

Background

- Upstaging and upgrading in Gleason score in prostate cancer patients following radical prostatectomy are frequent and have important clinical implications.

Discussion

- In a retrospective series of prostate tumors that were stratified in low (Gleason score <7), medium (7) and high (>7) grade according to Gleason score, the high urotensin II receptor (UTII-R) staining rate was recorded in 34 (68%) of the 50 low-grade, 36 (52%) of the 70 medium, but only in 19 (25%) of the 75 high-grade tumors. Similarly, UTII-R expression was reported 57, 42 and 38% of II-, III- and IV-stage tumors, respectively, although these differences were only borderline significant.

Conclusion

- We showed that Gleason upgrading was associated with low UTII-R expression after adjusting for Gleason biopsy and clinical stage, while upstaging was associated with low UTII-R expression after adjusting for clinical stage.
- Limitations of retrospective studies apply. Our results must be considered hypothesis generating and require external validation.

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