

Results: A total of 252 (79%) and 68 (21%) men had primary Gleason pattern 3 and 4 identified on needle biopsy, respectively. Of the patients with Gleason pattern 3+4 tumors on biopsy, 24% were upgraded to primary pattern 4 or more on final pathologic analysis. Of the patients with Gleason pattern 4+3 tumors on biopsy, 47% were downgraded to primary pattern 3 or less on final pathologic analysis. The actuarial risk of biochemical prostate-specific antigen recurrence was significantly lower among patients with Gleason pattern 4+3 on biopsy, if the prostatectomy Gleason score was downgraded to 3+4 or less ( $p = 0.03$ ).

Conclusions: Approximately 47% of men with a diagnosis of Gleason pattern 4+3 on needle biopsy are downgraded at radical prostatectomy and will have biochemical prostate-specific antigen recurrence-free outcomes similar to patients originally diagnosed with Gleason pattern 3+4 adenocarcinoma. This group of patients may benefit from definitive treatment such as radical prostatectomy for management of their disease.

### Editorial Comment

Gleason score 7 may result from 3+4=7 or 4+3=7. Data regarding the importance of the percentage of Gleason 4 pattern in Gleason score 7 tumors are rapidly expanding but still controversial (1). In recently generated nomograms, patients with Gleason scores of 4+3 and 3+4 are stratified differently, underscoring the importance of the relative amount of pattern 4 (2). Whether or not the actual percentage of pattern 4 tumor should be included in the report is not clear based on the data published to date and, if this emerges as an important parameter, meaningful discriminatory cut-off points for the percentage of pattern 4 will need to be defined.

In the article surveyed, most frequently there is downgrading of patients originally graded as Gleason pattern 4+3=7. In 24% of the patients with Gleason pattern 3+4 tumors on biopsy were upgraded to primary pattern 4 or more on final pathologic analysis, and approximately 47% with a diagnosis of Gleason 4+3 on needle biopsy were downgraded at radical prostatectomy. The latter group had biochemical prostate-specific antigen recurrence-free outcomes similar to patients originally diagnosed with Gleason pattern 3+4 adenocarcinoma.

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**Dr. Athanase Billis**

*Full-Professor of Pathology  
State University of Campinas, Unicamp  
Campinas, São Paulo, Brazil*

## INVESTIGATIVE UROLOGY

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### **Urinary Hyaluronan as a Marker for the Presence of Residual Transitional Cell Carcinoma of the Urinary Bladder**

Passerotti CC, Bonfim A, Martins JR, Dall'Oglio MF, Sampaio LO, Mendes A, Ortiz V, Srougi M, Dietrich CP, Nader HB

*Disciplina de Urologia, Escola Paulista de Medicina, Universidade Federal de Sao Paulo, Brazil*

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**Objective:** The purpose of this report is to evaluate the value of urinary hyaluronan (HA) as a maker of residual transitional cell carcinoma (TCC).

**Patients and Methods:** Urine samples were collected from 83 patients hospitalized for transurethral resection (TUR). Patient ages ranged from 36 to 86 years. Samples were taken both before and after surgery. HA analysis was performed using an "ELISA-like" fluorometric assay.

**Results:** Patients were divided into two groups: a control group whose previous diagnosis was negative for tumors (n=22) and another with positive diagnosis for tumors (n=61) which was further sub-divided into with and without residual tumor. After the second procedure 47 individuals did not display residual tumor, whereas 14 (23%) did. The average HA in the control group was 8.3 microg/L pre- and 7.1 post-operatively, hence, no change occurred (p=0.471). In the group with TCC patients, the HA dropped from 885.5 microg/L to 215.3 microg/L with residual tumors and from 234.3 microg/L to 11.2 microg/L for those without residual tumor. Using a cut-off value of 20 microg/L, the sensitivity to detect residual tumor is 92.9% and specificity is 83%.

**Conclusion:** HA in addition to being one of the best markers for the initial evaluation of bladder carcinoma can be used to determine the presence of a residual tumor. This is associated with poor prognosis.

### Editorial Comment

This is a welcome from lab to bedside article demonstrating that the glycosaminoglycan (GAG) hyaluronan is a good marker for detecting the presence of residual transitional cell carcinoma of the bladder. In addition to traditional methods such as cystoscopy and urine cytology, hyaluronan detection is promise. Although the technique for hyaluronan analysis is being more widely used, unfortunately, it is not available yet in the majority of hospitals.

In every study concerning GAG urinary analysis it is important to take into account some variations that we have detect in our own laboratory. When investigating whether the menstrual cycle affects urinary GAG excretion in normal young women, we found a significant increase in total urinary GAG excretion in the first half of the cycle, which paralleled the normal increase in serum estrogen levels that occurs at this phase (1). In general, estrogen inhibits the synthesis of extracellular matrix molecules by many mesenchymal cell types, such as vascular smooth muscle cells. Such inhibition would shift normal proteoglycan turnover toward degradation, which could explain the increase in GAG urinary excretion that was found in the first half of the cycle. It was not observed significant variation in the relative concentration of sulfated GAG during the different phases of the cycle. On the other hand, our results indicate that heparan sulfate was the prevailing urinary GAG during the whole cycle. Because heparan sulfate is the most abundant GAG in the glomerulus, the present findings support the hypothesis that renal structures are one of the main sources of urinary GAG.

Since these previous results (1) indicate that urinary GAG excretion during the normal menstrual cycle has a significant and consistent variation, studies evaluating GAG excretion in women could lead to misleading or erroneous results if comparisons were made among samples taken from different phases of the cycle. This may be indeed the reason underlying the inconsistent results in previously published reports concerning GAG urinary excretion in various diseases, such as interstitial cystitis, lithiasis, genitourinary tumors, etc.

The authors should be commended for that important investigative work with immediate clinical application, and for such more than welcome integration between basic science and clinical urology.

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**Dr. Francisco Sampaio**  
*Full-Professor and Chair, Urogenital Research Unit  
State University of Rio de Janeiro  
Rio de Janeiro, Brazil*

## **Combination of Phosphodiesterase-5 Inhibitors and Alpha-Blockers in Patients with Benign Prostatic Hyperplasia: Treatments of Lower Urinary Tract Symptoms, Erectile Dysfunction, or Both?**

Carson CC

*University of North Carolina, Chapel Hill, North Carolina, USA*

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As the prevalence of both erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) increases with age, physicians could be in the position to manage these two conditions simultaneously. Moreover, medical therapies for either one of these conditions can affect the other and this should be carefully considered when making treatment decisions. Pharmacotherapy for benign prostatic hyperplasia (BPH)/LUTS can cause side-effects affecting sexual function. Hence, 5 $\alpha$ -reductase inhibitors such as finasteride and dutasteride are associated with a greater risk of ED, ejaculatory disorders (EjD) and decreased libido than is placebo. Among alpha (1)-adrenergic blockers, tamsulosin is associated with an increased risk of EjD. However, some alpha (1)-adrenergic blockers can also have a positive impact on erection. This is the case for alfuzosin, which has been shown to enhance erectile function in experimental models, probably by reducing the sympathetic tone and thus relaxing corpus cavernosum smooth muscle cells. Phosphodiesterase 5 (PDE-5) inhibitors are commonly used to treat ED. There is increasing evidence that they might also have a beneficial effect on LUTS, probably through the nitric-oxide pathway. Nitric oxide is an important mediator of the relaxation of isolated bladder and urethral smooth muscle, and could modulate prostatic smooth muscle tone. Alpha (1)-adrenergic blockers and PDE-5 inhibitors can therefore have a positive impact on both ED and LUTS. Although placebo-controlled studies are needed to confirm the impact of these drugs, alone or combined, on both ED and LUTS, this reinforces the need for a common approach to managing these two highly prevalent and bothersome conditions.

### **Editorial Comment**

Lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) association is a very much discussed theme in urology practice and many papers have been published during the last few years. Those involved with clinical practice have been learning from patients that when they take a phosphodiesterase-5 inhibitor they void better. Also, we learned from patients that when they are under treatment for LUTS with alpha-blockers, they void better and they improve their sexual function. Why this occur? Although it is hard to find placebo controlled studies in the literature on this topic, Doctor Carson provide us with a wonderful and thorough review on the current knowledge on combination of phosphodiesterase-5 inhibitors and alpha-blockers in patients with benign prostatic hyperplasia. Dr. Carson concluded that the concept of improving both lower urinary tract symptoms and erectile dysfunction with phosphodiesterase-5 inhibitors and alpha-blockers reinforces the need to have a common approach for managing this situation. I strongly recommend this paper for all urologists and other physicians dealing with LUTS and ED.

***Dr. Francisco Sampaio***

*Full-Professor and Chair, Urogenital Research Unit  
State University of Rio de Janeiro  
Rio de Janeiro, Brazil*