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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

# Morbidity and psychological impact of prostate biopsy: the future calls for a change

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**Currently transrectal ultrasound-guided prostate biopsy (TRUS-Bx) is one of the most common urological procedures, with more than 1 million performed per year in Europe and the United States.[1] Among patients undergoing TRUS-Bx, approximately one-third will receive a diagnosis of prostate cancer (PCa), while two-thirds receive a negative result on initial biopsy. Negative biopsy patients maintain an estimated risk of repeated biopsy of 12% at 1 year and 38% at 5 years.[2] Standard TRUS-Bx is likely to systematically miss significant tumors, particularly in the anterior and apical parts of the gland.[3] A crucial aim of urologists in the next decade is to increase the accuracy of the procedure and avoid the use of inappropriate biopsies.**

## MORBIDITY OF PROSTATIC BIOPSY

Transperineal and transrectal TRUS-Bx are associated with a significant morbidity with a not negligible risk of hospitalization. Visible hematuria following TRUS-Bx is reported in a significant number of patients ranging between 10% and 84%, according to different definitions.[4-7] The majority of men have mild hematuria, while severe bleeding requiring hospitalization occurs in <1% of cases.[6] In a recent randomized European Randomized Study of Screening for Prostate Cancer (ERSPC) study, hematuria lasting >3 days was seen in 22.6% of men and was correlated with increased prostate volume.[7] The rate of rectal bleeding varies between 1.3% and 45%; whereas, severe rectal bleeding was reported in 1.3% of patients in ERSPC study.[7] Many authors found that nearly all men reported hemoejaculate after TRUS-Bx. About 25% of men perceived this as a concern, while hematuria and rectal bleeding are usually perceived as minor discomfort and of little consequence by appropriately counseled men.[8] Moreover, hemoejaculate declines over time from 84% in week 1 to 32% after 1 month and is resolved after a mean of eight ejaculations.[9]

Due to antimicrobial-resistance, particularly fluoroquinolones, the risk of infectious complications is increasing over time. This represents the most dangerous complication after TRUS-Bx, ranging from asymptomatic bacteriuria, urinary tract infections and epididymitis to more severe ones as sepsis and meningitis.[10] The frequency of infections requiring hospitalization varies between 0.6% and 6.3%.[10-12] In the Global Prevalence Study of Infections in Urology, 3.1% required hospitalization after biopsy due to febrile-urinary tract infection.[10]

Many patients experience a worsening of lower urinary tract symptoms after TRUS-Bx. Urinary retention is usually transient ranging from 0.2% to 1.7%.[6]

TRUS-Bx is associated with significant pain and discomfort in a proportion of men. Most studies evaluated pain using the visual analog scale (0 = none to 10 = worst pain), and in a recent study mean score resulted 1.4 (range 0–5) and 18% of patients would not accept a repeat biopsy.[13] Predictors of pain include young age, anxiety level, anorectal compliance, prostate volume and number of biopsy cores; while pain seems not affected by using 16- versus 18-gauge needles.

## PSYCHOLOGICAL IMPACT OF PROSTATE BIOPSY

Some studies have explored the psychological impact, including anxiety and depression, of TRUS-Bx.[14-16] Zisman and coworkers in a prospective study on 211 men, found a significant reduction in patients well-being, both prebiopsy within 30 days, including anxiety in 64% of patients.[14] Fowler *et al.*[15] showed that concerns about diagnosis may contribute to anxiety, but that it may occur also in patients with negative histology and persist up to 12 months. More recently, a prospective observational study of 1144 men undergoing standard TRUS-Bx (as part of more than 100 000 men invited for prostate-specific antigen (PSA) screening) investigated the psychological impact of TRUS-Bx, including relationships between physical biopsy-related symptoms and anxiety/depression using the Hospital Anxiety and Depression Scale (HADS).[16] Overall, depression and anxiety levels were relatively low and stable across all time points (approximately 3%–7% of men had HADS scores indicating anxiety) and confirmed that within 7 days of the biopsy, many men reported symptomatic adverse effects of the procedure (as pain, shivers, hematuria, hematochezia and hemoejaculate). At this time point, before the biopsy result was known, men who reported biopsy symptoms as a moderate/major problem had markedly higher levels of anxiety compared with those reporting biopsy symptoms as not a problem/a minor problem.[16]

Interestingly, 35 days after TRUS-Bx anxiety was reduced also in patients still experiencing adverse events, except for men who had received a cancer diagnosis. This suggests that better information provision in preparation for biopsy may reduce unnecessary anxiety and excess healthcare contact associated with postbiopsy symptoms.

This study deserves commendation for some unique aspects of methodology. First, a very high response rate to the questionnaires (95% at 7 days) in such a large population ($n$ = 1144) testifies the accuracy of data collection. Second, the

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inclusion of the questionnaire score at the time of PSA screening, before biopsy was indicated, provides the 'emotional baseline' of patients. Finally, anxiety and depression were measured using the HADS that is a simple, understandable tool focused on the reduction of hedonic capacity, considered to be the most sensitive indicators of anxiety and depression, regardless of their somatic symptoms (as fatigue and loss of libido) that can be caused also by organic diseases.[17] The HADS separately analyze the items for anxiety and for depression, and has identified the psychological impact of TRUS-Bx primarily as a problem of anxiety. However, the HADS also has some limitations as it evaluates the presence and the amount of anxiety without differentiating between trait anxiety (chronic, rooted in the behavioral style of the subject) and state anxiety (transient anxious state, e.g. due to TRUS-Bx). A more specific questionnaire for the distinction between the two types of anxiety, potentially useful for future evaluations, is the 'State and Trait Anxiety Inventory' (STAY).[18]

The psychological impact of TRUS-Bx along with its morbidity represents a further limitation and acts against its wide use as a main diagnostic tools and even more during active surveillance protocols, where rebiopsy is contemplated as in the Prostate Cancer Research International: active Surveillance (PRIAS) study where repeat biopsies are scheduled after 1, 4 and 7 years.[19]

## STRATEGIES TO IMPROVE TRUS-BX IMPACT

Various strategies have been proposed to reduce physical and psychological consequences of TRUS-Bx. Infectious complications can be reduced by switching/expanding the antimicrobial regimen, with rectal cleansing with povidone-iodine prior to procedures or with targeted prophylaxis after rectal swab cultures.[20-22] A case-control retrospective analysis compared a group of patients treated with standard prophylaxis consisting of 3 days of ciprofloxacin or trimethoprim/sulfamethoxazole to another 'augmented' with one dose of intramuscular gentamicin before biopsy, and found a decrease in hospitalization from 3.8% to 0.6%.[20] The efficacy of prophylaxis with double antibiotic was also confirmed in other studies, in which amoxicillin-clavulanate or cefoxitin, or aminoglycosides were added to the standard quinolone.[21] Potential drawback of augmented prophylaxis includes increased costs, side effects and the risk for future antimicrobial resistances. Nevertheless, it resulted as cost-effective in preliminary analysis.[20] A Cochrane review showed that enema plus antibiotics can reduce the risk of bacteremia compared with antibiotics alone, although there were no differences in febrile-urinary tract infection.[22] Some studies assessed whether the biopsy approach (transperineal *vs* transrectal) could influence the infection rate. Shen *et al*. did not find any qualitative difference in the infection rate between the two different approaches.[4] Another common post TRUS-Bx complication is pain. Strategies to reduce pain include intrarectal creams, periprostatic nerve blockade (PPNB), lidocaine suppositories and sedoanalgesia, and should be chosen according to patient's tolerance to pain, anxiety and sociocultural factors.[23] Some authors have proposed anxiety-reducing instruments such as music or distraction, which seems to reduce psychological perception of pain.[24] An accurate pre-TRUS-Bx counseling and reassurance about the normality of certain side effects, such as hemoejaculate, hematuria and fever, have proved to reduce the psychological impact (anxiety) caused by these side effects.[16]

## REDUCING THE NEED FOR TRUS-BX

Some new laboratory and imaging instruments may help to reduce the use of diagnostic biopsy and rebiopsy. Several studies demonstrated that multiparametric prostate MRI (MP-MRI) is sensitive and specific for PCa detection, with an accuracy that increases with tumor grade and size.[25,26] Kirkham *et al*. reported a >80% sensitivity in detection of a Gleason 4 + 3 tumor sized ≥0.2 $cm^3$ (equivalent to a 7 mm sphere) or a Gleason 3 + 4 tumor sized ≥0.5 $cm^3$ (equivalent to a 10 mm sphere).[25] Whereas, sensitivity resulted significantly lower for Gleason 3 + 3 tumors and the majority of small, low-grade PCas can be missed by MP-MRI, but these tumors are supposed to be clinically insignificant.[26] Moreover, in patients with previously negative biopsies and clinical progression, MP-MRI may detect missed tumors (often anterior) in up to 40% of cases.[3]

As a consequence, many authors believe that, in the future, the use of MP-MRI will avoid many unnecessary diagnostic biopsies, avoid false negative results, improve selection for surveillance, improve local staging and planning of therapy in men with intermediate-high risk PCa. To achieve these goals the definition of the correct detection protocol that can include diffusion-weighted and dynamic contrast-enhanced sequences as well as the definition of the scoring system to be used for the interpretation and reporting of MP-MRI needs to be clarified.

Several papers reported that serum isoforms of PSA and their derivatives, as p2PSA, %p2PSA and prostate health index may improve the clinical prediction of PCa, decrease the recourse to diagnostic biopsies and avoid unnecessary repeat biopsies.[27] Even more interestingly, Truong *et al*. showed that a novel combination of field defect DNA methylation markers could predict the presence of PCa in histologically normal TRUS-Bx cores (negative predictive value of 0.909).[28]

The role of TRUS-Bx has changed over time. Its importance has evolved from pure cancer detection to assisting clinical patient management; however, it is associated with significant morbidity and increased level of anxiety. Therefore, maximum efforts should be concentrated to reduce biopsy adverse effects, to improve selection for TRUS-Bx using novel cancer-specific biomarkers and imaging, and eventually to replace TRUS-Bx with promising noninvasive diagnostic tools such as MP-MRI, both for diagnosis and follow-up of patients under active surveillance.

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