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ARTICLE

Assessment of complications after transperineal and transrectal prostate biopsy using a risk-stratified pathway identifying patients at risk for post-biopsy infections

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ABSTRACT

Introduction: Evidence of transperineal (TP) superiority over transrectal (TR) biopsy is growing due to lower infectious complication rates. However, TR biopsy is the most common procedure, and it seems that a cross-over to TP is delayed by logistical challenges such as costs, complexity, and lack of experience. We investigate whether well-selected patients without any risk factors may further undergo TR biopsy if all precautions to avoid infections are warranted.

Materials and methods: Data were collected in our academic institution between August 2021 and March 2022 and after clinical implementation of the currently updated European Association of Urology guideline recommendations on the performance of prostate biopsy. Patients underwent either TP or TR biopsy according to a riskstratification based on risk factors of infectious complications. Follow-up asked for post-biopsy complications. Inverse Probability of Treatment Weighting (IPTW) propensity score was used to balance baseline characteristics. Complications were subdivided into infectious and non-infectious complications.

Results: In total, 294 patients were included with 161 patients undergoing TR vs. 133 patients undergoing TP biopsy. Complication rates were 2.2% for TP vs. 5.5% for TR biopsy concerning all complications. Infectious complication rates only were 0.7% for TP vs. 1.8% for TR biopsy. After IPTW adjustment, differences were statistically significant different ($p = 0.01$).

Conclusion: Our study revealed that even in a well-selected patient cohort with presumably lower risk of infectious complications, TR biopsy leads to more post-biopsy complications than TP biopsy. This conclusion should motivate the urological community to switch to TP biopsy.

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Introduction

Histological confirmation by prostate biopsy is still the gold standard for the detection of prostate cancer (PCa). However, biopsies' role and performance have changed tremendously over the last decade. Driven by the increasing use of multiparametric magnetic resonance imaging (MRI), MRI-fusion targeted biopsies have become the current state of the art. Besides the need for MRI-fusion targeted biopsies, there is an ongoing debate on how to perform prostate biopsies. Transrectal (TR) and transperineal (TP) biopsies both have advocates and opponents in the current literature, with some authors recently demanding to abandon the TR approach at all [1]. Advocates of the TP biopsy underline the significant reduction of infectious complications. In contrast, opponents of this technique criticize the more complex and time-consuming procedure and assume the need for general anesthesia.

In 2021, the European Association of Urology (EAU) focused on this subject in their updated guideline. The current EAU guideline gives explicit recommendations on how to reduce infectious complications after TR prostate biopsy with a general preference of the TP approach as compared to the TR [2]. This new recommendation is based on evidence from several studies showing a significant reduction of infectious complications and fewer readmission rates after TP biopsies compared to TR biopsies [3–8]. With regard to infectious complications after prostate biopsy, several risk factors have been described by former studies – such as previous antimicrobial use, recent hospitalization, diabetes, or history of urinary infection. In 2021, Ding et al. could further demonstrate an association of higher infectious complication rates with an increasing number of biopsy cores as well as a history of urinary retention [9–13]. That said, an immediate switch to offer TP biopsies to every patient may be challenging for many institutions and physicians due to logistical difficulties, costs, and lack of experience. Therefore, we referred patients with known risk factors for infectious complications to undergo TP biopsies, whereas patients without those factors underwent the alternative TR approach. We

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hypothesized that implementing this risk-stratified pathway into daily clinical practice may be an option to identify those men who still may undergo TR biopsy with comparable infectious complication rates. This would be an adequate and equal alternative – at least for the interim period until TP biopsies have been established for most patients in the near future.

Materials and methods

Study population

Data were collected on 336 men who underwent prostate biopsies between August 2021 and March 2022 in our academic institution in Germany. The decision on whether to perform a prostate biopsy was based on a shared decision-making process with the patient. For the individual patient's risk calculation of being diagnosed with PCa, we used the validated Rotterdam Prostate Cancer Risk Calculator as stratification tool to support patient counseling [14–16]. All patients underwent an MRI of the prostate beforehand, and suspicious lesions as characterized by the Prostate Imaging – Reporting and Data System (PI-RADS) were outlined and marked by two dedicated uro-radiologists. Three physicians conducted all prostate biopsies with an experience of more than 200 TR biopsy sessions performed. Enrolled patients underwent an informed written consent process. Institutional review board approval was obtained according to institutional regulation (22-7658).

Data collection and exclusion criteria

A retrospective analysis was performed. Information on covariables such as age, Charlson Comorbidity Index (CCI), prostate-specific antigen level (PSA), digital rectal examination (DRE) findings, previous history of prostate biopsies, prostate volume, PI-RADS score, PI-RADS lesion size, number of biopsy cores taken and histology findings (Gleason Score) were collected.

Post-biopsy complications were collected between 12 and 14 days after the given procedure. Patients were contacted by phone or seen in the outpatient clinic and asked for post-biopsy complications such as 'fever' ($\geq$38.5 °C), 'prolonged gross hematuria' (more than 72 h and/or need for catheterization), 'prolonged rectal bleeding' (more than 72 h), 'urinary retention' (with the need for catheterization), 'further antibiotic treatment', 'suprapubic catheterization', 'readmission' (explicitly due to post-biopsy complications), and 'others'. For the final analysis, 'fever', 'antibiotic treatment', and 'suprapubic catheter' were defined as infectious complications. Patients with missing information on the above-mentioned covariables, missing consent as well as lost to follow-up were excluded from further analyses.

Risk-stratified pathway for the performance of transperineal prostate biopsy

Patients presenting in our institution with suspicion of PCa were advised to undergo or omit prostate biopsy based on their risk estimated by the Rotterdam Prostate Cancer Risk Calculator. In a second step, men were screened for known risk factors of infectious complications [9–11]. According to the current evidence of known risk factors for infectious complications after prostate biopsy, we referred men with *recent history/recurrent urinary tract infections, history of urinary retention, multiple previous antimicrobial use* or a *history of postinterventional complications after prior TR biopsy sessions such as sepsis* to undergo TP. Furthermore, patients with abnormal anatomical characteristics such as *rectal stenosis/fistula* or patients with *severe immunodeficiency* were referred to undergo TP biopsy. We aimed to select those men with the lowest risk for infectious complications to undergo TR biopsy. In this case, the performance of TR biopsy was adapted to the current recommendations of the EAU as described below. Our risk-stratified pathway and algorithm are demonstrated in Figure 1.

Adaption of the European Association of Urology recommendations on the performance of transperineal or transrectal prostate biopsy

Transperineal prostate biopsy

TP biopsy was performed as an outpatient procedure under local anesthesia (with/without sedation) and prior aseptic perineal cleansing. All patients underwent pre-biopsy rectal swab testing. This was done routinely as a precaution, whereas no antibiotic propyhlaxis was given at all. Biopsies were performed using the Artemis® system (Eigen, Grass Valley, CA, USA) combined with an Ultrasound unit (Noblus) by Hitachi (Hitachi Medical Systems Europe, Steinhausen, Germany) using a specific transrectal biplanar probe (C41L47RP).

Transrectal prostate biopsy

TR biopsy was performed as an outpatient procedure under local anesthesia. As recommended by the currently updated EAU guideline, we have adapted our clinical standards to reduce infectious complications in TR biopsies. Therefore, all patients underwent pre-biopsy rectal swab testing. Based on this rectal swab, patients received targeted prophylaxis. In most cases, cefpodoxime was tested susceptible and could be used as oral prophylaxis (200 mg). Furthermore, we always performed a rectal preparation/cleansing for several minutes before the TR biopsy was started. Biopsies were performed using the Artemis® system (Eigen, Grass Valley, CA, USA) combined with an Ultrasound unit (Noblus) by Hitachi (Hitachi Medical Systems Europe, Steinhausen, Germany) using a transrectal endfire probe (V53V).

Outcome

Our study's primary outcome was the event of any infectious complication after prostate biopsy within 12 up to 14 days. Two different biopsy approaches – TP and TR – were compared regarding infectious complication rates.

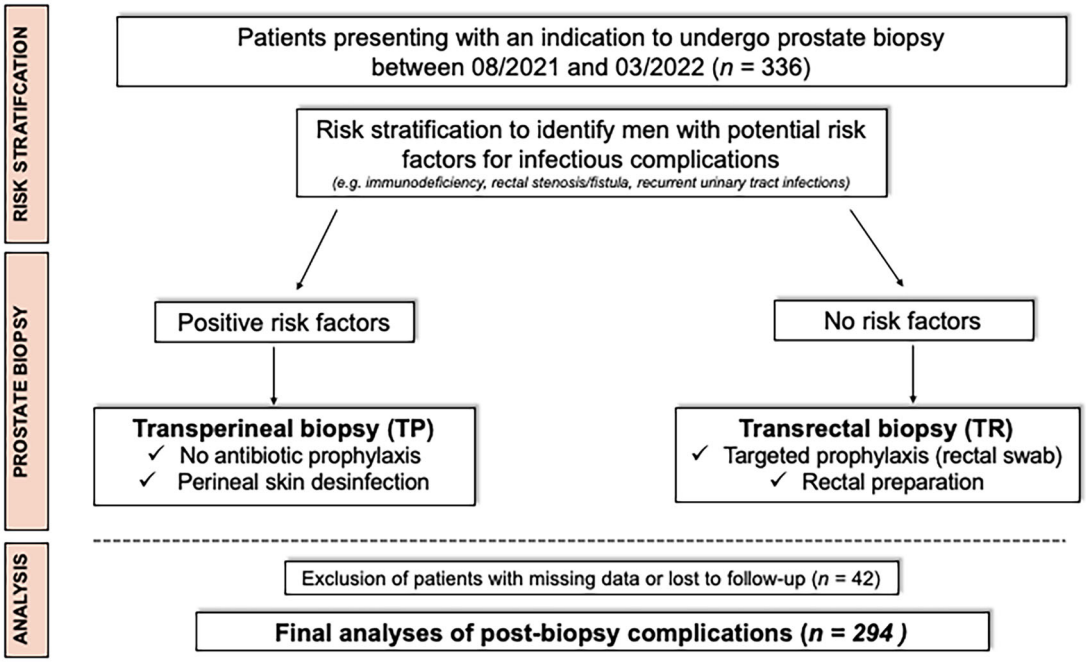

Figure 1. Study design and patient selection.

Furthermore, we analyzed the rates of any non-infectious complication after TP and TR biopsies as a secondary outcome.

Statistical analyses

We report frequencies and percentages for categorical variables and means for continuous variables.

Additionally, Inverse Probability of Treatment Weighting (IPTW) propensity score analysis was conducted to balance some of the patients' characteristics in our two study groups. This was done to simulate the effects of random allocation between the two study groups – apart from the identification of risk factors for infectious complications. The balance between patients' characteristics in pre- and post-weighted groups was evaluated using standardized differences and comparing their distribution with the original unweighted data. After propensity score weighting, variables of clinical interest were equally and well distributed with a standardized difference of $<10\%$. Chi-squared testing was used to investigate statistically significant differences between complication rates after TR and TP biopsies. All statistical analyses were performed using Stata version 14. A two-sided statistical significance level was set at p-value <0.05.

Results

Study groups and clinical baseline characteristics

The final study population comprised 294 patients (Figure 1). In the study cohort, the median age was 71 years, with 76 patients (25.8%) who underwent a previous biopsy. The median prostate volume was 42 ml, with a median PSA of 6.8 ng/ml. In patients with lesions on MRI, PI-RADS 4 was the most frequent score. Overall, PCa was detected in 204 patients (69.3%), with a median number of 15 biopsy cores taken (systematical and targeted biopsies). Further patients' characteristics are demonstrated in Table 1.

Infectious and non-infectious complications after transperineal and transrectal biopsy

In total, 12 (4%) patients suffered from any post-biopsy complication. In the TP biopsy group, one man needed (0.7%) further antibiotic treatment, whereas three men had (1.8%) an infectious complication in the TR biopsy group. According to non-infectious complications, two men (1.5%) reported prolonged gross hematuria along with rectal bleeding and urinary retention in the TP biopsy group vs. six men (3.7%) suffering from non-infectious events in the TR biopsy group, respectively. Two men (1.2%) undergoing TR biopsy needed rectal endoscopic clipping due to severe hematochezia. Chi-squared test of the unweighted cohorts revealed no statistically significant differences for the different biopsy approaches. Table 2 demonstrates infectious and non-infectious complications and their distribution after TP and TR biopsy.

Comparison of post-biopsy complication rates after inverse probability of treatment weighting adjustment

As demonstrated in Table 3, clinical variables such as age, CCI, PSA, prostate volume, and the number of biopsy cores taken were equally and well distributed with a standardized difference of $<10\%$. After IPTW adjustment, differences in post-biopsy complications rates after TP and TR reached statistical significance. Concerning infectious complications, TP biopsy revealed a lower complication rate than TR biopsy, 0.7% for TP vs. 1.8% for TR, $p = 0.01$. This tendency towards a lower complication rate for TP biopsy compared to TR

Table 1. Clinical baseline characteristics of 294 patients undergoing transperineal and transrectal prostate biopsy between August 2021 and March 2022.

Study group	Transperineal ($n = 133$)	Transrectal ($n = 161$)
Age (in years; median)	72	67
CCI (median)	3	3
PSA (in ng/ml; IQR)	6.8 (5.4–9.3)	6.8 (5.0–9.9)
DRE (*n*; %)		
Suspicious	42 (31.5)	47 (35.3)
Unsuspicious	91 (68.5)	114 (70.8)
History of previous biopsy		
Yes	39 (29)	37 (23)
No	94 (71)	124 (77)
Prostate volume (in ml; median; IQR)	42.5 (32–56)	42 (30.6–57.6)
PI-RADS score distribution (*n*)		
PI-RADS 3	14	23
PI-RADS 4	71	78
PI-RADS 5	40	29
PI-RADS lesion size (in mm; median)	11.5	12.8
Biopsy cores taken (median)	15	14
Histology (*n*; %)		
T0	35 (26.3)	42 (26)
ASAP	3 (2.2)	10 (6.2)
PCa ISUP 1	25 (18.7)	37 (22.9)
PCa ISUP 2	41 (30.8)	44 (27.3)
PCa ISUP 3	17 (12.7)	16 (9.9)
PCa ISUP 4	6 (4.5)	6 (3.7)
PCa ISUP 5	6 (4.5)	6 (3.7)

Abbreviations: CCI: Charlson Comorbidity Index; IQR: interquartile range; DRE: digital rectal examination; PI-RADS: prostate imaging reporting and data system; PCa: prostate cancer; ISUP: International Society of Urological Pathology; percentages may not add up to 100% because they are rounded.

Table 2. Infectious and non-infectious post-biopsy complications.

Post-biopsy complications	Transperineal biopsy	Transrectal biopsy
All complications	**3**	**9**
Infectious complications		
Total number of patients	**1**	**3**
Fever		3
Further antibiotic treatment	1	3
Suprapubic catheterization		1
Non-infectious complications		
Total number of patients	**2**	**6**
Prolonged gross hematuria	2	4
Prolonged rectal bleeding	1	2
Urinary retention	1	2
Re-admission		5
Others		
TUR coagulation		1
Rectal endoscopic clipping		2

Abbreviations: TP: transperineal; TR: transrectal; TUR: transurethral.

Table 3. Balance between the two weighted study groups after IPTW-adjustment.

Variable (mean)	Transperineal biopsy	Transrectal biopsy	SD
Age (years)	68.37	68.70	−0.05
CCI	2.81	2.84	−0.02
PSA (ng/ml)	8.68	8.66	0.002
Prostate volume (ml)	46.27	46.96	−0.025
Biopsy cores (*n*)	13.58	13.65	−0.026

Abbreviations: IPTW: inverse probability of treatment weighting; SD: standardized difference; CCI: Charlson Comorbidity Index; PSA: prostate-specific antigen.

biopsy could also be demonstrated for all complications (non-infectious and infectious), 2.2% for TP vs. 5.5% for TR, $p = 0.01$.

With regard to the detection rate of PCa, there was no statistically significant difference, with 71% in the TP biopsy group vs. 67% in the TR biopsy group, $p = 0.2$.

Discussion

Our study focused on complication rates after TP and TR biopsy in a risk-stratified pathway. After IPTW adjustment, complication rates of all complications, and infectious complications only, were significantly lower in the TP biopsy group compared to the TR biopsy group. Thus, our findings are in line with the currently growing evidence for the superiority of TP biopsy considering post-biopsy complications. However, it seems that this debate takes on an almost political or philosophical aspect. While some authors demand an immediate 'TREXIT' mainly based on lower complication rates, supporters of the TR biopsy approach underline the feasibility and cost-effectiveness and criticize the more complex and time-consuming TP biopsy approach [1,17–19].

Indeed, it has not been long that TP biopsy was seen as a complex procedure using a grid-stepper that was only tolerated in general anesthesia. Due to the development of free-hand techniques and modern software-based fusion equipment, TP biopsy has become feasible under local anesthesia [20–22]. Last year, the updated EAU guideline was issued on the biopsy approach and now recommends the performance of TP rather than TR despite any possible logistical challenges [2]. In our institution, biopsy routes were changed to TP biopsy based on the profound evidence of reduced infectious complications. Facing actual logistical challenges and a potential learning curve, we knew that a complete and immediate conversion to offer TP biopsy to every man was not realistic. Thus, we established our risk-stratified pathway by trying to select those men in whom a TR biopsy (according to the EAU recommendations with targeted prophylaxis and rectal preparation) revealed comparable complication rates to TP biopsy. Although we referred patients with potential risk factors of infectious complications to undergo TP biopsy, this technique still showed lower complication rates compared to the presumably healthy men in the TR biopsy group. More than six months after changing to TP at our institution, we can confirm not only low complication rates but also good feasibility and comparable detection rates of PCa. Nevertheless, in patients with an enlarged prostate or in patients where lithotomy position cannot be acquired, a TR biopsy should rather be performed so that this reliable approach will not completely disappear. Aside from clinical benefits, a TP biopsy may also reduce costs in the long term. Studies have shown that post-biopsy complications also lead to a financial burden due to high readmission costs and loss of productivity of affected patients [21,23,24]. This financial aspect should also be taken into account. Apart from this, the TP biopsy approach leads to a reduction of peri-interventional administration of antibiotics. On the one hand, this is a result of the lower number of post-biopsy sepsis. On the other hand, antimicrobial prophylaxis can usually be omitted, thereby avoiding unnecessary antibiotic overuse and reducing the risk of future antibiotic resistance. This is another crucial aspect in terms of modern antibiotic stewardship. Recently, a large meta-analysis did not find statistically significant differences comparing TP biopsy with and without periprocedural antibiotics [25].

This valuable effect may further underline the advantages of TP biopsy.

To our knowledge, this is the first study of a risk-stratified pathway investigating complications after TP and TR biopsy. This study was driven by the assumption that a TR biopsy may still be an acceptable option in patients with a low risk of infectious complications. A strength of our study is the direct comparison of both approaches after the exact transfer of the EAU guideline recommendations on how to perform a prostate biopsy. Another strength of our study is that the investigators performed both approaches, thus reducing a potential selection bias between the two study groups. Furthermore, we conducted IPTW-adjusted analyses to balance some clinical characteristics, thereby reducing another potential bias.

However, we also acknowledge the retrospective design as a major limitation of our study. In addition, we are aware that the individual patient's referral to one biopsy group or another based on our definition of 'risk factors of infectious complications' may add a certain selection bias influencing the final results of this study.

In summary, our study revealed that even in a well-selected patient cohort with presumably healthy men, the TR biopsy approach leads to more post-biopsy complications than the TP biopsy. This conclusion adds to the current evidence and should further motivate the urological community to cross over to TP biopsy.

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Conception and design: Sebastian Berg, Karl Tully, Vincent Hoffmann, Florian Roghmann, Guido Müller, Joachim Noldus, Moritz Reike. Administrative support: Sebastian Berg, Henning Bahlburg, Moritz Reike. Collection and assembly of data: Sebastian Berg, Karl Tully, Vincent Hoffmann, Nicolas von Landenberg, Henning Bahlburg. Data analysis and interpretation: Sebastian Berg, Vincent Hoffmann, Florian Roghmann, Joachim Noldus, Guido Müller, Moritz Reike. Manuscript writing: Sebastian Berg, Henning Bahlburg, Guido Müller. Revision of the draft and supervision: Sebastian Berg, Joachim Noldus, Moritz Reike. Final approval of manuscript: All authors.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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