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Systematic Review of Complications of Prostate Biopsy

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Abstract

Context: Prostate biopsy is commonly performed for cancer detection and management. The benefits and risks of prostate biopsy are germane to ongoing debates about prostate cancer screening and treatment.
Objective: To perform a systematic review of complications from prostate biopsy.
Evidence acquisition: A literature search was performed using PubMed and Embase, supplemented with additional references. Articles were reviewed for data on the following complications: hematuria, rectal bleeding, hematospermia, infection, pain, lower urinary tract symptoms (LUTS), urinary retention, erectile dysfunction, and mortality.
Evidence synthesis: After biopsy, hematuria and hematospermia are common but typically mild and self-limiting. Severe rectal bleeding is uncommon. Despite antimicrobial prophylaxis, infectious complications are increasing over time and are the most common reason for hospitalization after biopsy. Pain may occur at several stages of prostate biopsy and can be mitigated by anesthetic agents and anxiety-reduction techniques. Up to 25% of men have transient LUTS after biopsy, and <2% have frank urinary retention, with slightly higher rates reported after transperineal template biopsy. Biopsy-related mortality is rare.
Conclusions: Preparation for biopsy should include antimicrobial prophylaxis and pain management. Prostate biopsy is frequently associated with minor bleeding and urinary symptoms that usually do not require intervention. Infectious complications can be serious, requiring prompt management and continued work into preventative strategies.
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1. Introduction

Transrectal ultrasound–guided prostate biopsy (TRUS-Bx) is one of the most common urological procedures, with >1 million procedures performed per year in Europe and the United States. The indications for prostate biopsy include a suspicious digital rectal examination and elevated prostate-specific antigen (PSA) level, often considered in the context of other risk factors such as age, race, PSA velocity, and comorbidities [1]. Biopsy is typically well tolerated, with a low risk of major complications. However, minor complications such as pain and bleeding are frequent [2], and infectious complications have increased over time [3,4]. Our objective was to perform a systematic review of TRUS-Bx

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complications, including bleeding, infection, pain, lower urinary tract symptoms (LUTS), urinary retention, erectile dysfunction (ED), and mortality. In addition, we reviewed the complications of transperineal biopsies.

2. Evidence acquisition

First, we performed PubMed and Embase searches for all English-language publications from 2002 to January 2013 with the search terms *prostate biopsy AND complications*. This search identified 4818 records, which were reviewed by title or abstract. An additional 40 unique records were identified through hand searches, discussion with experts, and secondary searches, including the Web of Science, using the search terms *erections OR erectile function* or *erectile dysfunction AND prostate biopsy* as well as *transperineal AND prostate biopsy*. Figure 1 shows a flowchart of the search process. A total of 213 unique references from this search were included in the qualitative synthesis.

3. Evidence synthesis

3.1. Bleeding

One of the most frequent and bothersome complications of TRUS-Bx is bleeding [5], such as hematuria, hematospermia or hemoejaculate, and hematochezia, or rectal bleeding. In patients without coagulopathy, the incidence of these complications varies with patient factors such as prostate size, anticoagulative medication, and procedural factors such as the number of biopsy cores taken.

3.1.1. Hematuria

Visible hematuria following TRUS-Bx is common, with reported rates of 10–84% [2,4,6–14]. This wide range can be explained by different definitions for *hematuria* (visible blood, need for catheterization or hospital admission), duration, and method of data collection. In addition, higher rates are seen in prospective studies using patient–clinician interviews, and lower rates are seen in retrospective postal questionnaires [15]. In a recent nested cohort study [2], patient-reported questionnaires identified hematuria in 65.8% of patients, although it usually did not bother men (6.2% rated it as a major or moderate problem). Within the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC), hematuria lasting >3 d was seen in 22.6% of men and correlated with prostate (r = 0.096; $p < 0.001$) and transition zone volumes (r = −0.076; $p < 0.001$) [16]. Others have also found increased hematuria with larger prostate volume [17].

The influence of the number of biopsy cores on bleeding is controversial. In 760 men, Ghani et al. found that the prevalence of hematuria did not vary with core number (44% with 6 cores, 41% with 8 cores, and 39% with 12 cores, respectively) [18], while others have reported more

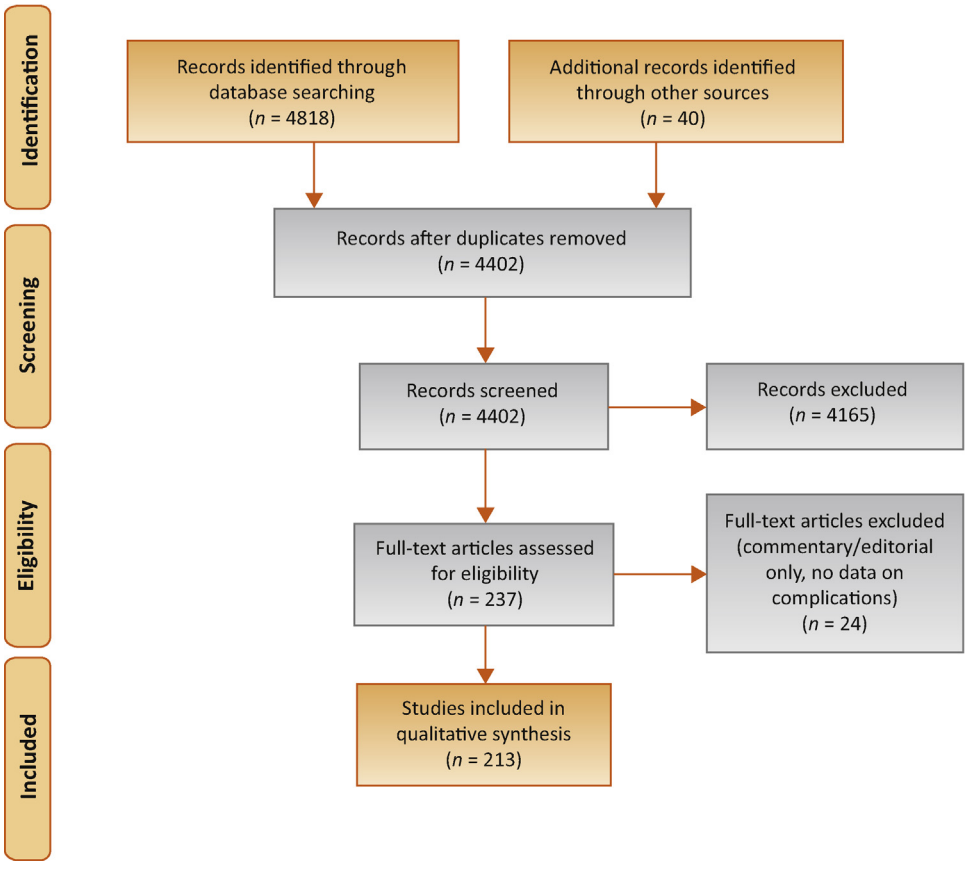

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the search process.

bleeding with increased sampling [19]. Several authors have reported that needle size (18 gauge vs 16 gauge) does not affect bleeding rates [20–22]. Interestingly, prebiopsy enemas were found to increase hematuria and hemoejaculate rates (2.5% [no enema] vs 7.9% [enema]; $p < 0.001$) [17].

Although the majority of men have minor hematuria without complications, a few develop severe hematuria [23]. Nam et al. reported that 1.4% of 75 190 men undergoing biopsy were readmitted within 30 d—20% for bleeding-related diagnoses (0.3% of the entire cohort). In contrast with infective biopsy-related complications, the rates of bleeding problems did not change between 1996 and 2005, despite the increasing number of cores obtained during this period. Similarly, in US Surveillance Epidemiology and End Results (SEER)–Medicare data, admissions for noninfectious urologic complications such as bleeding did not increase over time [3] and were similar between initial and repeat biopsy sessions [24]. These findings are supported by Pinkhasov et al., who identified gross hematuria requiring catheterization in 4 of 1000 patients (0.4%) [6]. Dodds et al. reported admission for bleeding in 3 of 2080 patients (0.14%) [21,25]. In summary, minor hematuria is common after prostate biopsy, while significant bleeding requiring hospitalization occurs in <1% of cases.

3.1.2. Rectal bleeding

As shown in Table 1, the rate of rectal bleeding varies between 1.3% and 45% [13,14]. McCormack et al. reported that this rate is affected by the number of biopsy cores and use of anticoagulation but not needle size [22]. Ghani et al. found significantly higher rates but not duration of rectal bleeding with 8- to 10-core biopsy (26–27%) compared to 6 cores (17%) [18]. Less rectal bleeding was reported within the ERSPC study (1.3%), and there was no correlation with other recorded parameters [16]. Rosario et al. suggested that rectal bleeding was more common than previously reported (36.8%), but only 2.5% found it a major or moderate problem [2]. As with hematuria, rectal bleeding is usually perceived as minor and of little consequence by appropriately counseled men. Massive rectal bleeding is uncommon but can be life threatening. Treatment options include rectal balloon tamponade, endoscopic adrenaline injection or sclerotherapy, or direct vessel clipping [25–28].

3.1.3. Hematospermia

The reported rate of hematospermia varies widely among studies (1.1–93%) [8]. This variation may reflect cultural issues, social stigma, or different perceptions of importance as well as differences in data collection among studies (timing and method of assessment). Rosario et al. found that nearly all men reported hematospermia (92.6%) during the 35 d after biopsy. Unlike other hemorrhagic problems, around one in four men perceived this as concerning or alarming [2].

Manoharan showed the decline in hematospermia over time from 84% in week 1 to 66% in week 2 and 32% after 4 wk [29]. Hematospermia was associated with anxiety and a reduction in sexual activity and resolved after a mean of eight ejaculations. Lee et al. reported hematospermia in 21%, with a median duration of 20 d [30], while others reported a higher frequency (60%) but shorter average duration (12.8 d) [31]. In the ERSPC study, hematospermia was reported by 50.4% and was correlated with age ($r = -0.228$; $p < 0.001$), prostate volume ($r = -0.058$; $p < 0.001$), and previous transurethral resection of the prostate (TURP; $r = -0.109$; $p < 0.001$) [16]. The number of biopsy cores is also associated with hematospermia. For example, one study of Berger et al. reported hematospermia in 31.8% of cases of 6-core biopsies, 37.4% of 10-core biopsies, and 38.4% of 15-core biopsies ($p < 0.001$) [32].

3.1.4. Anticoagulation

One contentious area is the discontinuation of anticoagulation before biopsy (Table 1), which involves a balance of risks between cardiovascular or thromboembolic events when stopping anticoagulation versus the risk for bleeding and associated complications with continuation. Patient factors modify the precise balance of risks and benefits. For example, men using warfarin anticoagulation for metal heart valves are at high risk of thromboembolic events compared with those taking preventative low-dose aspirin.

Various reports have described bleeding complications in men with warfarin and aspirin (Table 1). For example, two series from the same institution in which full anticoagulation was continued during biopsy did not show a higher rate of self-reported bleeding complications in men receiving anticoagulation. Giannarini et al. prospectively assigned 196 men to continue aspirin, replace it with low-molecular-weight heparin or discontinue aspirin without

Table 1 – Selected studies of bleeding complications after prostate biopsy

First author	Intervention	Design	Men, no.	Hematuria, %	Hemoejaculate, %	Rectal bleeding, %
Chowdhury [19]	No anticoagulation	Prospective questionnaire	617	37.0	13.8	11.5
Ihezue [40]	No anticoagulation	Prospective questionnaire	902	60.2	21.0	13.0
Kariotis [36]	No anticoagulation	Retrospective	282	60.6	86.9	25.9
Raheem [72]	No anticoagulation	Retrospective	98	63.0	10.0	39.0
Chowdhury [19]	LDA	Prospective questionnaire	217	33.8	12.0	14.4
Kariotis [36]	LDA	Retrospective	152	64.5	90.1	33.6
Raheem [72]	LDA, warfarin, clopidogrel, LMWH	Retrospective	91	46.0	6.0	40.0
Chowdhury [19]	Warfarin	Prospective questionnaire	69	27.9	7.4	13.2
Ihezue [40]	Warfarin	Prospective questionnaire	49	36.7	8.2	14.3

LDA = low-dose aspirin; LMWH = low-molecular-weight heparin.

replacement for TRUS-Bx. There was no difference in the overall bleeding rate (including hematuria, rectal bleeding, and hemoejaculate) among groups (78.5%, 69.7%, and 81.5%, respectively; $p = 0.26$). Although no severe bleeding complications occurred, men on anticoagulation reported bleeding for a longer duration. The authors concluded that aspirin did not increase mild bleeding but did prolong its duration [33], as found in other reports [34–36]. Interestingly, prostate biopsies have even been reported in a small series of hemophiliacs with proactive hemostatic management, with no major bleeding complications or clot retention during overnight observation [37].

A systematic review and meta-analysis of aspirin use and bleeding following TRUS-Bx found higher rates of hematuria with anticoagulation. In total, 3218 men were identified in reports from 1990–2011, and the risk of hematuria increased 1.36-fold with aspirin use (95% confidence interval [CI], 1.13–1.64; $p = 0.001$) [38]. This increased risk was caused by minor bleeding, although it should be noted that most studies were not powered to assess the rare event of severe hemorrhage. Rectal bleeding (1.24, 95% CI 0.80–1.93) and hemoejaculate (odds ratio [OR]: 1.52; 95% CI, 0.75–3.08) were not statistically increased. The authors concluded that continuing aspirin did not increase the risk of moderate and severe hematuria after TRUS-Bx, so stopping aspirin was unnecessary. Another recent review reported a pooled OR of 0.89 (95% CI, 0.45–1.76; $p = 0.73$) for bleeding complications with antiplatelet withdrawal versus continuation [39]. Thus, it is likely that TRUS-Bx is safe without stopping aspirin, because the frequency of bleeding complications is low [40,41]; however, the data on warfarin and clopidogrel are more limited for drawing conclusions [13,42]. With warfarin, an additional consideration is its interaction with antimicrobials frequently used for biopsy prophylaxis, necessitating careful monitoring of the international normalized ratio or substitution of an alternate antibiotic [43].

3.1.5. Reducing bleeding rates

Few authors have evaluated methods to reduce bleeding after TRUS-Bx, including the use of pressure [44]. Kilciler et al. reported that routine rectal balloon catheter tamponade did not alter hematuria or hemoejaculate rates but did reduce rectal bleeding from 17.7% to 1.5% [45]. Park and Kim evaluated ultrasound-guided pressure (mean duration: 3 min) upon the needle tracts immediately after biopsy [6]. No comparison arm was available, and bleeding rates appeared similar to those reported elsewhere without this intervention. When severe bleeding does occur, bed rest, fluids, and blood products may be required [13].

3.2. Infection

Infection is a well-established risk of TRUS-Bx [46], which is among the urologic procedures with the best evidence supporting antimicrobial prophylaxis [47]. A Cochrane review showed that antibiotic prophylaxis significantly reduces bacteriuria, bacteremia, fever, urinary tract infection (UTI), and hospitalization [48]. A separate meta-analysis similarly concluded that antimicrobial prophylaxis decreases bacteriuria [49]. Professional organizations recommend routine antimicrobial prophylaxis for TRUS-Bx [50]. A recent international survey reported that 98.2% of men undergoing biopsy in 84 countries received antimicrobial prophylaxis, with fluoroquinolones most commonly prescribed (92.5%) [51]. Although the reported duration of use varies widely [52], most show no significant benefit from durations $\geq$24 h [53–57]. Many additional studies support that a single dose of antibiotics may be sufficient [58–61].

Despite these efforts, a risk of infectious complications after biopsy remains. These complications range from asymptomatic bacteriuria, UTI, and epididymitis to more severe infections like meningitis [62], vertebral osteomyelitis [63], sepsis [6,23], and septic shock [64,65].

3.2.1. Incidence of infectious complications

The frequency of infection varies among studies, with most studies reporting hospitalization in 0–6.3% [13,66,67]. Among 72 500 biopsies in the United Kingdom, 2.15–3.6% were readmitted with infectious complications [68]. In the Global Prevalence Study of Infections in Urology, 3.5% had febrile UTI, and 3.1% required hospitalization after biopsy [51], similar to the 3.06% frequency of sepsis reported by Simsir et al. [69]. However, other series from North America and Brazil reported lower rates of sepsis (0.6% and 1.7%, respectively) [12,70]. One Asian study reported fever in 0.5% of cases but no increase in C-reactive protein or white blood cell count after biopsy [71], while another Asian study reported no septic complications [72]. Studies from Turkey [60] and Italy [64] reported approximately 2% hospitalizations after biopsy. In the United Kingdom, Rosario et al. reported a higher rate of 17.5% fever based on questionnaires, with 5.5% considered a major or moderate problem [2].

Recent studies have suggested an increase in antimicrobial and particularly fluoroquinolone resistance [66]. Correspondingly, most studies have shown an increase in infectious complications after prostate biopsy over time [3,4,25,66]. A large series from US SEER–Medicare reported that men undergoing biopsy were 2.26 times more likely to be hospitalized for infectious complications within 30 d compared with randomly selected controls [3]. There was a significant increase in hospitalizations for infection from 1991 to 2007. A follow-up study from the same group showed that the risk of infectious complications was similar between the initial and repeat biopsy sessions; however, the cumulative risk of experiencing an infection increases with a greater number of procedures [24]. Simsir et al. similarly found no difference in sepsis risk between the initial and repeat biopsies [69].

Nam et al. reported a rise in urologic complication rates amongst 75 190 men undergoing TRUS-Bx in Canada between 1996 and 2005 [4]. The 30-d hospitalization rate rose from 1.0% in 1996 to 4.1% in 2005 ($p < 0.0001$), and 72% were for sepsis. A more recent study from Canada reported an increase from 0.52 infections per 100 biopsies in 2002–2009 to 2.15 per 100 biopsies in 2010–2011 ($p < 0.001$) [73].

Table 2 – Studies on risk factors for fluoroquinolone resistance or infectious complications after prostate biopsy

Risk factor	Reference
Patient-related:	
Comorbidities	[3]
COPD	[73]
Heart valve	[78]
Diabetes	[69,73,74,76,184]
Benign prostate enlargement	[69,74]
Nonwhite race, Asian	[3,95]
Foreign travel	[185]
Recent urogenital infection	[186]
Recent antibiotics, particularly fluoroquinolones	[75,81,185,187]
Recent hospitalization	[73]
Physician/hospital employee	[188,189]
Presence of a catheter	[69]
Positive prebiopsy urine culture	[158]
Procedure-related:	
More biopsy cores	[69,83,158,173]
Repeat biopsy	[4,24,69]
Contaminated ultrasound gel	[190,191]

COPD = chronic obstructive pulmonary disease.

In the ERSPC Rotterdam section, Loeb et al. reported fever after 4.2% of prostate biopsies, although only 0.8% were hospitalized [74]. As in the United States and Canada, there was a significant increase in hospitalizations from 1993 to 2010. Most reported infectious complications result from *Escherichia coli*, with high rates of resistance to fluoroquinolones as well as ampicillin and sulfamethoxazole-trimethoprim [1,74–76]. Interestingly, bacteremia following prostate biopsy was more likely to require admission to the intensive care unit compared with other inciting reasons [1].

Fluoroquinolone resistance has increased globally [77], and the presence of fluoroquinolone-resistant organisms on rectal swab culture is a significant predictor of infection after prostate biopsy [78]. Other studies on patient-specific and procedural risk factors for fluoroquinolone-resistant organisms or infectious complications are summarized in Table 2.

3.2.2. *Reducing infectious complications*

Various strategies to reduce infectious complications have been explored, as were recently reviewed [13,79]. One strategy is rectal cleansing with povidone-iodine prior to TRUS-Bx. Gil-Vernet reported 0.2% *E. coli* epididymitis using this approach, which was lower than many other series in the literature [80]. Abughosh et al. randomized men to povidone-iodine cleanse versus no cleanse, with similar rates of infection (2.6% vs 4.5%; $p = 0.15$) [81]. Zaytoun et al. also found no difference in complications with enemas [17], while Park reported a lower frequency of infectious complications with rectal prep than without it (0.3% vs 6%) [82], as did Jeon (OR: 0.143; $p < 0.001$) [83]. Overall, a Cochrane review concluded that enema plus antibiotics reduced the risk of bacteremia (relative risk [RR]: 0.25; 95% CI, 0.08–0.75) compared with antibiotics alone, although there were no differences in fever or infection [48].

Many studies have investigated switching or expanding the antimicrobial regimen, performing rectal swab cultures, and using different techniques for biopsy. For example, several centers using amoxicillin-clavulanate reported a reduction in infections by adding ciprofloxacin [84] or switching to ciprofloxacin plus or minus cefoxitin [85,86]. Conversely, switching from ciprofloxacin to coamoxiclav and gentamicin was actually associated with increasing infections, highlighting the importance of monitoring patient outcomes following changes in protocol [87]. Adibi et al. compared 290 men undergoing biopsy with 3 d of trimethoprim-sulfamethoxazole or ciprofloxacin to 310 later TRUS-Bx with the addition of gentamicin and found a decreased frequency of hospitalization in the later group (from 3.8% to 0.6%) [88]. Others have reported good results adding gentamicin [89], amikacin [90], or isepamicin [71]. Yamamoto reported a similar frequency of infections using tosufloxacin (4.8%) compared to levofloxacin prophylaxis (5%) [91]. Another study reported that mixing 1 gram of ceftriaxone into the periprostatic lidocaine injection was associated with less sepsis [92].

Disadvantages of augmented prophylaxis include possible increases in side effects or cost. However, Adibi et al. showed that as the cost of hospital admission increases, using more intensive prophylaxis becomes more cost-effective [93]. However, a drawback is potentially increasing future antimicrobial resistance.

Alternatively, investigation is ongoing into the use of targeted prophylaxis. A rectal swab is performed at the visit preceding prostate biopsy and is plated on MacConkey agar containing ciprofloxacin. Patients with ciprofloxacin-sensitive bacteria can then receive ciprofloxacin prophylaxis, while culture results can guide an alternative selection for those with resistance. Although a positive rectal swab culture is a risk factor for TRUS-Bx infection [81,94], the presence of resistant organisms does not necessarily translate into clinical infection [95]. In fact, prevalence studies from several countries have shown fluoroquinolone-resistant organisms in 14–25% of rectal swab cultures, but only a small proportion of these patients actually develop clinical infection [76,78,94–98].

A few nonrandomized studies have examined the results of targeted prophylaxis. Duplessis et al. gave ciprofloxacin prophylaxis to all men except those with positive rectal swab cultures, who instead received targeted prophylaxis, and there were no infectious complications [97]. Taylor et al. reported a nonsignificant decrease in the frequency of sepsis using a targeted approach, compared with other patients receiving standard prophylaxis (0% vs 2.6%; $p = 0.12$) [96]. To date, there are no randomized studies showing that targeted prophylaxis using rectal swabs results reduces infection and cost compared with standard or expanded prophylaxis.

Finally, several studies have assessed whether technical modifications influence infection rates. For instance, transperineal biopsy has been suggested as a possible alternative way to perform the technique, although Shen et al. did not find any qualitative difference in infection rates in a secondary analysis of studies on transrectal versus transperineal biopsy [5]. Some technical aspects were not associated with infectious risk, such as needle size [22] or

washing the needle with povidone-iodine between samples [11]. Tuncel et al. reported fewer infectious complications with a disposable needle guide ($p < 0.0001$) [99], while others found no difference in bacteriologic or symptomatic UTIs with disposable versus reusable needle guides [100]. However, adequate reprocessing/disinfection of reusable needle guides and biopsy probes is critical [101–103].

Infectious complications after biopsy are an increasing issue, and numerous strategies are being evaluated to reduce this risk. As investigation in this area evolves rapidly, general recommendations include a thorough history and physical examination, including assessment of risk factors for resistant bacteria and infection (see Table 2). In the future, improved markers and imaging may reduce invasive biopsy procedures for many patients [104]. For men with signs or symptoms of infection after biopsy, prompt evaluation, including cultures, is recommended. Broad-spectrum antibiotics should be given (eg, Amikacin or carbapenems), and later tailored based on culture data [13,105].

3.3. Pain

Prebiopsy analgesia was not always routinely used for sextant TRUS-Bx [106,107]. However, TRUS-Bx is associated with significant pain, discomfort, and anxiety in a proportion of men [108], which is associated with an unfavorable attitude to rebiopsy [2]. For example, a Finnish study reported that 18% of men would not accept a repeat biopsy [109]. With many men ultimately requiring rebiopsy and greater sampling performed, effective pain management for TRUS-Bx is paramount [110,111].

3.3.1. Measures of pain

Most studies assessed pain using the visual analog scale (VAS; 0 = none to 10 = worst pain) or a five-point scale during different steps (probe insertion, periprostatic infiltration, and biopsy sampling) and less commonly after biopsy [31,112,113]. When evaluating studies using the VAS, it is important to consider whether the change is clinically meaningful (eg, >2 points). Other instruments used to evaluate biopsy pain include the verbal response scale; the Multidimensional Personality Questionnaire; the State-Trait Anxiety Inventory; and physiologic parameters such as blood pressure, heart rate, respiratory rate, or serum cortisol levels [114,115]. Patients with higher levels of anxiety based on these evaluations may require a higher level of anesthesia.

3.3.2. Managing pain

Numerous factors contribute to pain at biopsy, including anxiety [115,116], which may be greater in young patients but was unrelated to other prostate cancer (PCa) risk factors (such as PSA and positive family history) [117]. Some authors have therefore proposed anxiety-reducing instruments (eg, music) to mitigate perceived pain [118].

More pain was reported when a periprostatic injection of ceftriaxone was included [92]. However, it does not appear that using 16- versus 18-gauge needles affects pain [21,22]. Other predictors of pain include anorectal compliance, prostate volume, number of biopsy cores, and younger age [115,119–122]. As such, several studies have reported greater added value for anesthetic agents in younger men [120,121]. Kilciler et al. evaluated patient positioning and found slightly less pain in left lateral decubitus than lithotomy, although the difference may not be clinically meaningful (score 2.72 vs 4.02) [123]. In summary, selection of anesthesia for biopsy should take into consideration the patient's tolerance to pain, anxiety, and sociocultural factors [107,124,125].

With respect to the type of anesthetic agent, nitrous oxide has been shown to be effective [126]; however, in an underpowered comparison with periprostatic lidocaine injection, no significant difference was found [127]. Although the precise mechanism of pain reduction is uncertain, action on opiate receptors in the spinal cord and muscle relaxation may contribute to its effect.

The use of sedoanalgesia has also been described by several groups and was recently reviewed [128]. Although highly effective [129,130], its use remains somewhat cumbersome for outpatient practice and requires monitoring, which increases cost [131]. Nevertheless, for selected patients, including those with excessive anxiety or local anorectal conditions, it remains a viable option.

The use of saddle analgesia has been shown to be effective in reducing pain associated with biopsy and improving acceptability [132,133]. Several studies have compared this technique with periprostatic nerve blockade with variable findings, precluding definitive conclusions.

Periprostatic nerve blockade (PPNB) itself appears to be safe [134], and 10–20 cm^3 of lidocaine significantly reduces pain compared to no anesthetic agent [135–138]. Several technical modifications of PPNB have also been described, including apical infiltration, basal infiltration, and combination techniques [139–142]. A recent study found no significant difference in surgical complexity among men who received PPNB [143]. Numerous studies have examined intrarectal creams, gels, and lidocaine suppositories. A Spanish study reported that biopsies performed with rectal only lidocaine gel were generally well tolerated [119]. Although these agents in some studies were more effective than placebo, most studies have shown that local gels achieve inferior analgesia compared with PPNB [130,144–147]. That finding notwithstanding, numerous studies have demonstrated the efficacy of combining intrarectal local anesthetic agents or analgesics with PPNB, particularly to reduce the pain resulting from probe insertion and the periprostatic infiltration itself [122,148–150]. Strong evidence exists for employing some form of anesthetic agent to reduce pain at biopsy, but most of the comparative studies have been underpowered. The precise combination of techniques can be tailored to the individual patient, local circumstances, and individual expertise.

3.4. Lower urinary tract symptoms and urinary retention

A low risk of acute urinary retention exists after standard TRUS-BX, ranging from 0.2% to 1.7% [6,8,12,17,31,32,61,151–156]. Retention is usually transient, and most patients

do not require surgical intervention [6,151]. There is also a risk of short-term worsening of voiding complaints after TRUS-Bx [157]. Reported rates of dysuria typically range from 6% to 25% [15,30,109,158].

No convincing evidence exists that the number of biopsy cores affects risk of urinary retention [32]. The impact of serial biopsies has not been well studied. A cohort of 333 men undergoing active surveillance found no correlation between the number of biopsies and International Prostate Symptom Score (IPSS) [159]. However, Raaijmakers et al. reported that prostate volume, ratio of transition zone volume to total prostate volume, and a higher IPSS are associated with risk of urinary retention after prostate biopsy [16]. Similarly, Zaytoun et al. showed that increasing prostate size predicted retention after biopsy (OR: 4.45; 95% CI, 2.01–9.84; $p < 0.001$) [17].

There has also been investigation of α-blockers to prevent urinary problems following biopsy. A prospective study randomized 66 consecutive patients undergoing 12-core TRUS-Bx to 30 d of tamsulosin versus no tamsulosin [160]. Compared to baseline, tamsulosin was associated with a significant reduction in IPSS and increase in maximum flow rate as compared to worse voiding parameters at day 7 in controls.

In summary, the data suggest a low (<2%) overall risk of urinary retention, although ≤25% of patients experience transient worsening of LUTS after TRUS-Bx. Although premedication is not necessary for the majority, periprocedural α-blockers could be considered for patients with severe symptoms or large prostates to reduce the risk of urinary retention.

3.5. *Erectile dysfunction*

There is concern that prostate biopsy, especially if repeated or extensive, may lead to ED. However, the data on this are sparse and heterogeneous, with significant confounders. Reasons for heterogeneity among studies include intermixing initial with repeat TRUS-Bx and lack of adjustment for prebiopsy potency. Most studies on biopsy and erectile function included 62–100 patients followed for 1 wk to 1 yr (Table 3a) [161]. In general, there seemed to be a trend toward increasing ED at 1 mo, with five studies demonstrating statistically significant changes in rates of mild to severe ED. Longer follow-up showed that these changes resolved back to baseline. One study demonstrated a trend toward higher ED rates when using periprostatic local anesthetic nerve blocks ($p = 0.055$) [162]. One study demonstrated that sexual dysfunction can also occur in female partners of men undergoing TRUS-Bx at 1 and 6 mo, despite male function improving at 6 mo [163].

Three studies evaluated ED with repeat biopsies during active surveillance (Table 3b) [159,164,165]. One prospective study using the International Index of Erectile Function (IIEF-5) in 427 active surveillance patients reported changes in sexual activity level for >20% of respondents during 3.2-yr median follow-up [165]. Adjusted erectile function scores were not associated with biopsy exposure cross-sectionally or longitudinally.

Conversely, a different cohort of 333 men undergoing active surveillance found a correlation between increasing biopsy number and decreases in IIEF-5 score ($p = 0.04$) [159]. Multivariable analysis for biopsy number, age, prostate volume, and PSA showed that only biopsy number was associated with decreasing Sexual Health Inventory for Men score ($p = 0.02$). A limitation of studies performed in active surveillance populations is potential selection bias resulting from progression or reclassification, with subsequent treatment in some men.

It is also noteworthy that there is a strong psychogenic impact of knowing one has PCa that can also contribute to ED. A prospective study of 85 men who underwent a single 12-core TRUS-Bx found no significant differences in pre- and postbiopsy IIEF-15 scores (57.8 [SD 12.9] vs 54.3 [SD 17.2]), but men with biopsy-proven cancer had significantly greater changes in postbiopsy IIEF compared to men without cancer (−10.1 vs 1.0; $p < 0.001$) [161], including deteriorations in sexual desire, orgasmic function, intercourse satisfaction, and overall satisfaction.

One prospective evaluation attempted to reduce the confounder of PCa as a cause of ED by examining baseline, 1-, and 6-mo IIEF questionnaires for 88 patients who had negative saturation biopsies (median 22 cores) [166]. Patient age, serum PSA levels, prostate volumes, and number of cores showed no significant correlation with changes in IIEF scores. According to the IIEF-5, for previously potent cancer-free patients, 11.6% reported mild to moderate ED at the first month, which decreased to 0% at 6 mo. Thus, although IIEF-5 and IIEF-Erectile Function domain scores significantly declined from baseline to the first month, there was no difference by 6 mo.

Another prospective single-center study of 46 men who underwent a median of nine biopsy cores found that 6.52% and 4.34% reported biopsy-attributable ED 1 and 3 mo later, respectively [167]. In this study, 61% of men had a prior biopsy, and 30.4% had PCa detected. PCa diagnosis, prostate size, and number of cores were not significantly associated with ED. Rarely, more severe complications have been reported, including a case of Mondor's disease and high-flow priapism [168].

It appears that even the evaluation for PCa and concerns about elevated PSA may affect sexual function. A cross-sectional telephone survey showed that 109 men with negative biopsy were more worried about PCa, and 19% had moderate to big problems with sexual bother compared to 10% of age-matched primary care patients with a PSA <4 ng/ml [169].

Overall, the exact etiology of erectile problems following prostate biopsy is unknown. Temporary inflammatory and neurovascular damage are likely important, possibly combined with the impact of PPNB. Furthermore, the impact of anxiety and psychological factors is relevant, with some studies showing increased anxiety at the time of screening, biopsy, and immediately following biopsy [170].

In summary, if there is an impact of biopsy on erectile function, it appears to be relatively minimal and often transient [157]. The data on ED from multiple biopsies during active surveillance are more difficult to interpret,

Table 3 – Erectile dysfunction rates in men undergoing (a) transrectal biopsies and (b) active surveillance

(a)

First author	No. biopsied (evaluated/ total biopsied)	Type of biopsy	No. of biopsy cores (range)	Follow- up	Instrument	Definition of ED	ED rate	PDE5-I use
Chrisofos [167]	46	TRUS-Bx	Median: 9 (6–12)	1–3 mo	IIEF-5	Mild to severe	0: 82.6% 1 mo: 91.3% ($p = 0.216$) 3 mo: 89.1% ($p = 0.726$)	NR
Stravodimos [192]	62 RCT: 1. Without nerve block 2. With lidocaine PPNB	TRUS-Bx	NR	10 d and 20 d	IIEF-15-EF	Mild to severe (EF domain)	0: 6.6% vs 6.2% 10 d: 21.4% vs 16.6% 20 d: 7.1% vs 3.3% (not statistically significant; p value: NR)	NR
Akbal [166]	74/150 (75/150 had previous biopsy)	Saturation transrectal	Median 22 (20–30)	1 mo and 6 mo	IIEF-5	Mild to severe	0: 42% 1 mo: 49% ($p = 0.04$) 6 mo: 41% ($p = 0.14$)	NR
Aktoz [193]	62/90 RCT: 1. Diclofenac suppository 2. Levobupivacaine 3. Diclofenac suppository plus levobupivacaine	TRUS-Bx	10	1 mo and 3 mo	IIEF-5	Mild to severe	0: 85.5% 1 mo: 88.7% 3 mo: 88.7% ($p = 0.82$)	NR
Akyol [194]	136	TRUS-Bx	NR	6–12 mo	None	NR	1 mo: 2.2% (3/136) 6–12 mo: 0% (p value NR)	NR
Tuncel [163]	97 (and female partners)	TRUS-Bx	NR	1 mo and 6 mo	IIEF-5 Female Sexual Function Index for female partners	Mild to severe	0: 52.6% 1 mo: 72.2% 6 mo: 59.8% ($p < 0.001$) Female Sexual Function Index scores: significantly lower at 1 mo and 6 mo ($p < 0.001$)	NR
Turgut [195]	200	TRUS-Bx	NR	1 mo	Physician reported	ED	1 mo: 0%	NR
Klein [162]	198 RCT: 1. Without PPNB 2. With PPNB	TRUS-Bx	10 in biopsy naïve; 20 in previous negative biopsy	1 wk, 4 wk, 12 wk	IIEF-5	Mild to severe	Group 1 0: 70.5% 1 wk: 86.4% ($p = 0.119$) 4 wk: 86.4% ($p = 0.119$) 12 wk: 77.3% ($p = 0.628$) Group 2 0: 63.9% 1 wk: 86.1% ($p = 0.055$) 4 wk: 66.7% ($p = 0.811$) 12 wk: 63.9% ($p = 1.00$)	NR
Helfand [161]	85/134	TRUS-Bx	12	1–48 wk	IIEF-15	Change in IIEF-15 score	−3.5 (SD: 11.8) Positive biopsy best predictor of ED (OR: 9.16) on multivariate analyses	NR

(b)

First author	No. biopsied (evaluated/total biopsied)	No. of biopsy cores	Follow-up	Instrument	Definition of ED	ED rate	PDE5-I use
Fujita [159]	231/333	10–12	Mean: 3.2 yr (±2.3 yr)	IIEF-5	Mild to severe	0 mo: 56.6% At last follow-up: 65.1% ($p = 0.13$)	–
Braun (abstract) [164]	352 (on active surveillance)	NR	Median: 2.4 yr	NR (patient- and physician-reported scales)	NR	0.8-point-per-year decrease	NR
Hilton [165]	427/501	12	Median: 3.2 yr	IIEF-5	Change in adjusted IIEF-5 scores	No significant change related to biopsy exposure (after adjusting for age, sexual status, clinical stage, and diagnosis period [multivariate model])	NR

ED = erectile dysfunction; PDE5-I = phosphodiesterase type 5 inhibitor; TRUS-Bx = transrectal ultrasound–guided biopsy; IIEF = International Index of Erectile Dysfunction; NR = no result; RCT = randomized controlled trial; PPNB = periprostatic nerve block; EF = erectile function; SD = standard deviation; OR = odds ratio.

given that all of these men have PCa and that aging during the years between biopsies may have independently led to worsening ED.

3.6. Morbidity following transperineal prostate biopsy

Transperineal biopsy is increasingly popular as a means for accurate diagnosis and risk stratification. It is often used in men with a prior negative TRUS-Bx and persistent risk for PCa or those with low- to intermediate-risk disease electing active surveillance or focal therapy. Burden to the patient and health care system has been raised as a concern affecting the dissemination and diffusion of this technique. Some groups are also using transperineal template mapping biopsies, which fixes the systematic error of standard TRUS-Bx to a 5-mm sampling frame [171] as a tool to validate novel imaging techniques such as multiparametric magnetic resonance imaging, as it can be applied to all men at risk and thus minimizes selection bias [172].

Reports on the role of transperineal biopsies have varied in the technique used. Some have used sector biopsies, in which a full 5-mm sampling is not conducted but 1–2 biopsies are taken from predefined sectors. Others have limited the total number of transperineal biopsies to 14, 22, or 36 regardless of prostate size [173–175]. Two reports from the same group used a combination of TRUS biopsy and template mapping 5-mm sampling in men who were suitable for active surveillance [176,177].

Table 4 shows the results of identified studies on the complications of transperineal biopsy. UTI varied between 0% and 1.6% in the 12 of 24 series reporting on this outcome, with no instances of sepsis. Prolonged or severe hematuria requiring admission or catheterization was reported in 12 series and varied between 0% and 5.2%, with most showing no significant hematuria. Transient and mild hematuria was reported in three series in between 36.7% and 100%. Acute urinary retention was reported in 1.6–8.8% of cases. One outlier reported 20.6% urinary retention (7 of 34 men) but did not routinely use perioperative α-blockers, as was standard in all other series [178]. Overall, comparative studies have failed to demonstrate any significant differences in the rate of complications between transrectal and transperineal biopsies [5,179].

3.7. Mortality

Mortality after prostate biopsy is extremely rare, and most reported deaths are the result of septic shock [180]. Lethal Fournier's gangrene has also been reported [64,69,181]. Bleeding postprocedure is usually self-limiting and rarely life threatening (see previous section).

A few larger studies have attempted to examine mortality rates associated with prostate biopsy. One population-based study compared mortality between 22 175 patients who underwent prostate biopsy with 1778 age-matched controls [182]. Overall 120-d mortality after biopsy was 1.3% versus 0.3% ($p < 0.001$) in controls. Of men $\leq$60 yr of age, 0.2% died within 120 d versus 2.5% of men 76–80 yr of age. A higher Charlson Comorbidity Index

Table 4 – Morbidity following transperineal prostate biopsies

First author	Sample, *n*	No. of biopsy cores	Infection, no. (%)	Acute urinary retention, no. (%)	Significant hematuria, no. (%)	Other, no. (%)
Pinkstaff [196]	210	Mean: 21.2 (12–41)	0 (0)	24 (11)	11 (5.2)	–
Satoh [175]	128	22	1 (0.8)	2 (1.6)	NR	"Difficult urination": 2 (1.6)
Demura [197]	371	Mean: 20 ± 4	0 (0)	6 (1.6)	1 (0.3)	Hematospermia >1 mo: 1 (0.3)
Bott [198]	60	Median: 24 (18–36)	0 (0)	2 (3.3)	1 (1.7)	NR
Moran [199]	180	Mean: 41.3 (13–117)	NR	10 (4.5)	12 (5)	NR
Barzell [176]	80 (66 combined with repeat systematic TRUS-Bx)	Mean: 66 (20–138)	1 (1.3)	5 (6.3)	1 (1.3)	Perineal ecchymoses: 2 (2.6) Scrotal hematoma: 1 (1.3)
Li [152]	303	Mean; 23.7 (11–44)	0 (0)	7 (2.3)	0 (0)	Hematuria (mild and transient): 107 (45.3)
Merrick [200]	102	Median: 50	NR	9 (8.8)	1 (1.0)	NR
Merrick [201]	129	Median: 56	NR	11 (8.7)	1 (0.8)	IPSS deterioration: resolution by 30 d No rectal problems EF (IIEF-6): 3 (4.6); IIEF-5: ≤12 (in those with score ≥13)
Taira [202]	373	Mean: 54	0 (0)	NR	NR	IPSS: Baseline 10.4 7 d: 4.6 30 d: 3.8 No ED (physician reported)
Yan [203]	656	Median: 22	0 (0)	13 (2.0)	0 (0)	Hematuria mild and transient: 241 (36.7)
Galfano (abstract) [174]	126/378 biopsied	14	NR	NR	NR	ED (IIEF-5) at 1 mo: no statistically significant change in scores 17.6% without ED reported mild ED at 1 mo
Ayres [204]	101	Mean: 47 ± 14.5	NR	NR	NR	NR
Pal [173]	40	36	0 (0)	1 (2.5)	0 (0)	Hematospermia common
Patel [205]	539	Mean: 55.1 ± 11.8	NR	NR	NR	NR
Barqawi [206]	180	Median: 56 (8–124)	0 (0)	9 (4.2)	0 (0)	Hematuria (mild transient): all Transient orthostatic hypotension: 11 (5.1)
Taira [207]	64	Mean: 58.5 ± 6.3	0 (0)	3 (4.7)	NR	NR
Gershman [178]	34	Mean: 24.8 ± 7.8	NR	7 (20.6) (no perioperative α-blockers)	NR	NR
Hossack [208]	1132 (correlation with prostatectomy)	Mean: 23 (13–43)	NR	NR	NR	NR
Huo [209]	414 (correlation with prostatectomy)	Median: 22 ± 5.7	NR	(4.5)	NR	NR
Mabjeesh [210]	92	Mean: 30 (24–54)	NR	NR	NR	NR
Barzell [177]	124	Mean: 90	1 (0.8)	4 (3.2)	2 (1.6)	LUTS: 2 (1.6) Scrotal hematoma: 1 (0.8)
Kasivisvanathan [211]	182 (correlated with multiparametric MRI)	Mean: 44.6	Sepsis: 0 (0) UTI: 3 (1.6)	5 (2.7)	2 (1)	Perineal ecchymoses: all (self-resolving) Transient ED: 0 (0)
Crawford [212]	25 (correlation with prostatectomy)	Median: 49 (27–110)	NR	NR	NR	NR
Arumainayagam [213]	64 (correlation with multiparametric MRI)	34.0 (IQR: 29.0–40.8)	NR	NR	NR	NR

NR = no result; TRUS-Bx = transrectal ultrasound–guided biopsy; IPSS = International Prostate Symptom Score; EF = erectile function; IIEF = International Index of Erectile Function; ED = erectile dysfunction; LUTS = lower urinary tract symptoms; MRI = magnetic resonance imaging; UTI = urinary tract infection; IQR = interquartile range.

(CCI) score was also associated with increasing mortality, with 0.7%, 1.2%, and 2.2% mortality for scores 0, 1–2, and ≥3, respectively. Perhaps unexpectedly, initial biopsy procedures carried a higher mortality risk than subsequent procedures (1.4% vs 0.8% vs 0.6% for first biopsy, second biopsy, and three or more biopsies). On multivariable analysis, age, CCI score, and total number of biopsy procedures represented independent predictors of mortality. Although this study did not explain the cause of death, it does suggest that careful consideration of life expectancy should be factored into biopsy decisions.

In Canada, Nam et al. reported a 0.09% 30-d mortality rate after biopsy [4]. In the ERSPC, 11 721 men who underwent TRUS-Bx had a significantly lower risk of 120-d

age-adjusted other-cause mortality (RR: 0.41; 95% CI, 0.23–0.73; p = 0.002) compared to screen-negative men [183]. A later study about infectious complications in the ERSPC Rotterdam section reported no biopsy-related deaths [74], as is the case in other major biopsy series [134]. Similarly, in US SEER–Medicare data, 55 men (0.31%) who underwent biopsy died within 30 d compared with 1474 controls (1.09%) [3]. On multivariable analysis adjusting for age, race, SEER region, year, and CCI score, biopsied men had a markedly lower 30-d mortality rate compared with controls (OR: 0.29; 95% CI, 0.22–0.38; $p < 0.0001$). However, men who were hospitalized with an infectious complication had a 12-fold greater 30-d mortality rate compared with those who were not (95% CI, 8.59–16.80; $p < 0.0001$).

Overall, this suggests that men being selected for biopsy are generally healthier than the general population, and biopsy itself has an exceedingly low risk of fatal complications. However, patients should be counseled to seek immediate attention for signs of postbiopsy infection to initiate prompt management.

4. Conclusions

Bleeding is the most frequently reported complication after biopsy, but it is usually minor and resolves spontaneously. All men undergoing TRUS-Bx should receive antimicrobial prophylaxis for ≤24 h, should be warned about the increasing risk of infection, and told to seek prompt medical care. The increase in fluoroquinolone-resistant organisms is a trend that must be monitored, and tailored antibiotic regimens may be necessary in the future. The use of anesthetic agents can reduce the pain associated with prostate biopsy. An exacerbation of LUTS may also occur after biopsy, particularly in men with an enlarged prostate, but urinary retention is infrequent. Overall, men undergoing biopsy are generally healthier than the general population, and biopsy-related mortality is extremely rare.

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