Am J Clin Exp Urol 2013;1(1):66-71
www.ajceu.us /ISSN:2330-1910/AJCEU1311001

Original Article

Complications of initial prostate biopsy in a European randomized screening trial

Suzanne van den Heuvel[1], Stacy Loeb[2], Xiaoye Zhu[1], Paul CMS Verhagen[1], Fritz H Schröder[1], Chris H Bangma[1], Monique J Roobol[1]

[1]Department of Urology, Erasmus University Medical Centre, Rotterdam, The Netherlands; [2]Department of Urology, New York University School of Medicine, New York, United States

Received November 11, 2013; Accepted December 15, 2013; Epub December 25, 2013; Published December 30, 2013

Abstract: Background: Transrectal prostate needle biopsy (PNB) is a standard procedure for the diagnosis of prostate cancer. We recently found an increasing frequency of hospitalization with infectious complications associated with PNB over time. Objective: To perform an updated analysis of overall complication rates in a large screening population over the past 18 years and to examine possible predictors of complications on initial PNB. Design, Setting and Participants: From 1993-2011, 7216 men underwent initial lateralized sextant PNB in European Randomized Study of Screening for Prostate Cancer (ERSPC) Rotterdam. After 2 weeks a questionnaire was administered to 6962 men regarding PNB-related complications. Outcome Measurements & Statistical Analysis: Overall complication rates as well as specific complications (hematuria for >3 days, hematospermia, significant pain after biopsy, fever, and hospitalizations) were prospectively recorded. Multivariable logistic regression models were performed to assess the relationship between age, comorbidities, and prostate volume with specific complications. Results and Limitations: A total of 4674 (67.1%) men reported any sequelae after initial PNB, with hematospermia as the most frequent (53.8%), followed by hematuria (24.3%). Significant pain (4.8%), fever (4.1%), and hospital admission (0.7%) were reported less frequently. Hematospermia was significantly more likely in younger men with fewer comorbidities and smaller prostate volume; whereas hematuria was significantly more frequent among men with increasing comorbidities and prostate volume. In addition, pain was inversely associated with age and was also reported less frequently during later years of biopsy. Limitations of our study include the use of sextant biopsies and a relatively healthy population, while strengths include the large sample size and data on patient-specific covariates. Conclusion: Many men experience minor complications after initial PNB, although the frequency of specific complications such as hematospermia and hematuria differed based upon factors such as prostate volume and comorbidities. Overall, these data are useful to counsel patients who are undergoing their first PNB on the frequency of complications in a screening population.

Keywords: Complications, prostate biopsy

Introduction

Prostate cancer is the second most frequently diagnosed cancer of men and represents a significant health problem. Worldwide, more than 900,000 men are diagnosed with prostate cancer every year, with an estimated 258,000 deaths in 2008. Nearly three-quarters of the diagnosed cases occur in developed countries (658,000), largely because of widespread PSA testing and subsequent prostate needle biopsy (PNB) in those regions [1].

Transrectal PNB is a well established procedure used for the histological diagnosis of prostate cancer [2]. Despite the fact that PNB is considered a generally safe and well-tolerated outpatient procedure, it is associated in some series with a complication rate up to 64-78% [3].

Fortunately, complications encountered after transrectal biopsy are commonly minor and self limiting, including mild hematuria, hematospermia and transient rectal bleeding. Nonetheless patients need to be prepared for these sequelae. More serious complications are urinary retention, urinary tract infection, transitory bacteremia, fever episodes, and sepsis.

Alarmingly there are recent international reports of an increasing frequency of complications associated with PNB over time [4, 5]. Also in our population, we recently found an increasing frequency of hospitalization for infectious complications [6]. Based on these findings, the goal of the current study was to assess the overall complication rate in men undergoing initial PNB in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC), which was last reported by Raaijmakers et al. in 2002 [7]. Indeed, as PNB is widespread, it is essential for clinicians and patients to understand the full spectrum of potential associated morbidity. Another goal of the study was to identify patient-specific risk factors predisposing to complications, which might be useful for clinical decision making and may be used to increase the safety of biopsy in the future.

Patients and methods

The ERSPC was initiated in the early 1990s to study the effect of screening on prostate cancer specific mortality [8]. Between December 1993 and December 1999, in the section Rotterdam, 42,376 men aged 55-74 years were randomized after providing written consent. In all, 21,210 men were randomized into the screening arm and 21,166 into the control arm. In the screening arm men were screened at 4-year intervals. The indication for biopsy was originally set at a PSA cutoff of ≥4.0 ng/mL and/or suspicious findings on digital rectal examination (DRE) and/or transrectal ultrasound (TRUS). Since May 1997, a PSA threshold of ≥3.0 ng/mL has been used as the sole screening test. In screen positive men, we performed sextant transrectal biopsies of the prostate which were lateralized from June 1996. An additional biopsy was taken from any suspicious area seen on TRUS.

From 1993-2010, a total of 7216 initial biopsies were performed. No prebiopsy cleansing enemas were used, and the procedure was performed without anesthesia. Aspirin or anticoagulant agents were stopped 7 to 10 days before biopsy. Prophylaxis consisted of 160 mg trimethoprim/800 mg sulfamethoxazole until 2008 after which it was switched to 500 mg Ciprofloxacin 2 hours before and 4 hours after biopsy. If men had insulin-dependent diabetes, recently used prednisone, or had a prosthetic device, a more extended duration of antibiotic prophylaxis was given (5 additional days). Finally, for patients with a history of endocarditis or artificial cardiac valves, intravenous amoxicillin was given 1 hour prior to the biopsy in addition to the standard prophylaxis.

Two weeks after biopsy, participants returned to the screening office to discuss their pathology results. At this visit, a urologist administered a questionnaire regarding biopsy-related complications: hematuria for >3 days, hematospermia, pain after biopsy requiring medication, fever and hospitalization. These data were prospectively recorded in the study database, along with other demographic and clinical characteristics, e.g. age and comorbidities (diabetes, heart disease and/or hypertension).

During the starting phase of the ERSPC data on complications was not collected uniformly (n=244); therefore the data presented here are from 1995-2010. First, descriptive statistics were reported for individual complications after initial PNB as a proportion of the total number of men completing that item on the questionnaire. The median ages were 66.8 and 66.9 years, PSA levels were 3.7 and 4.0 ng/ml, and prostate volumes were 40.9 and 39.3 cc for men with and without completed questionnaires.

Our group previously examined the frequency of febrile complications and admissions over time [9]; however, it is unknown whether the frequency of other biopsy-related complications have changed since the prior report by Raaijmakers et al. [7] The chi-square test was therefore used to compare the proportion of initial PNB with hematuria, hematospermia and pain before and after 2001 (end of the Raaijmakers study period).

Next, multivariable logistic regression models were performed to assess the relationship between age, comorbidities, and prostate volume with specific complications. $P<0.05$ was considered statistically significant. SPSS 17 and STATA 11 were used for statistical analysis.

Results

Among the 7,216 men who underwent initial PNB, 1,899 (26.3%) were diagnosed with pros-

Table 1. Comparison of clinical characteristics between participants with and without any complication after initial prostate biopsy

	No Complication	Complication	*p*-value
Median age, yr (range)	68.1 (54.95-7.56)	66.1 (54.6-75.4)	<0.001
Median PSA, ng/mL (range)	3.8 (0.1-315.7)	3.7 (0.2-259.8)	0.0021
Median TRUS volume, mL (range)	40.4 (4.7-239.4)	41.2 (5.8-186.1)	0.086
Comorbidity*, n (%)	841 (37.0)	1563 (33.6)	0.0049

*Comorbidity: diabetes, heart disease and/or hypertension.

Table 2. Summary of comparisons between prior study by Raaijmakers et al. and current study

	Raaijmakers (2002)	Current Study (2010)
Hematospermia, %	50.4	53.8
Hematuria, %	22.6	24.3
Pain, %	7.5	4.8
Fever, %	3.5	4.1
Hospital Admission, %	0.5	0.7

tate cancer. **Table 1** shows the demographics of the study population.

Overall, 6962 of 7216 men returned a questionnaire (96.5%), and 4674 (67.1%) reported any sequelae after initial PNB. Hematospermia (3553/6602, 53.8%) was the most frequent, followed by hematuria (1586/6525, 24.3%). Significant pain (307/6379, 4.8%) and fever (263/6358, 4.1%) were reported less frequently. The hospital admission rate due to a PNB complication was 44/6324 (0.72%).

Compared to the prior study by Raaijmakers et al. [7], i.e. after 2001 vs. before 2001 (**Table 2**), we observed no significant difference in hematuria (OR 1.0, 95% CI 0.90-1.16, p=0.718) or hematospermia (OR 1.0, 95% CI 0.90-1.11, p=0.991) after PNB. By contrast, pain (OR=0.62, 95% CI 0.46-0.82, p=0.0007) was reported less frequently in the interval after 2001.

Multivariable logistic regression analysis was performed to identify patient-specific risk factors of different complications (**Table 3**). Hematospermia was significantly more likely in younger men, with fewer comorbidities, and smaller prostate volume. Hematuria was significantly more frequent among men with increasing comorbidities and larger prostate volume. In addition, pain was inversely associated with age. None of the patient-specific risk factors studied were significantly associated with fever or admission in this initial biopsy population.

Discussion

In 2002, Raaijmakers et al. reported on complications after all 5676 initial PNB in the Rotterdam ERSPC through 2001 [7]. A summary of comparisons between the prior study by Raaijmakers et al. and this updated analysis including initial biopsies through 2010 is shown in **Table 2**. We have recently reported an increase in hospitalizations with infectious complications over time [9]. In the current study, we found no significant differences in hematuria or hematospermia since the Raaijmakers study [7]. However, there were significantly fewer men with persistent pain after biopsy, possibly reflecting differences in perceptions of pain or improvement of patient counseling and urologist experience with the procedure over time [10].

Overall, our data from ERSPC Rotterdam are similar to prior studies, demonstrating that major complications are infrequent, but minor complications are frequent. For example, in one early series, Rodriguez and Terris conducted telephone interviews of 128 patients who had prostate biopsy from 1995-1996 [11]. Overall, 63.6% of the study population had at least one complication, with hematuria as the most common (47.1%). As in our study, persistent pain was significantly more likely in younger men (p=0.005). Hematospermia reported by 53% of the men in our study was also more frequent in young men, although this was not reported in other studies, both findings are useful for patient counseling.

In a larger series of 1051 men from the European Prostate Cancer Detection Study, 69.7% of patients had at least 1 minor complication, while only two major complications (urosepsis and rectal bleeding that required intervention) were reported. In that study, mild persistent hematuria was the most common complication overall [12]. More recently, Ecke et al. studied biopsy complications using a questionnaire in 336 patients [13]. Forty eight

Table 3. Multivariable models to predict complications on initial prostate biopsy including patient-specific covariates

	OR (95% CI), *p*-value		
	Age	Comorbidities*	Prostate Volume
Hematuria	0.99 (0.98-1.00), p=0.196	1.21 (1.07-1.36), p=0.002	1.01 (1.01-1.01), p<0.001
Hematospermia	0.92 (0.91-0.93), p<0.001	0.83 (0.75-0.92), p=0.001	0.99 (0.99-0.99), p=0.013
Pain	0.96 (0.94-0.98), p=0.001	1.06 (0.83-1.35), p=0.639	1.00 (0.99-1.01), p=0.154
Fever	1.01 (0.95-1.08), p=0.142	1.07 (0.82-1.39), p=0.627	1.00 (0.99-1.01), p=0.146
Hospitalization	1.01 (0.95-1.08), p=0.735	1.58 (0.86-2.89), p=0.142	1.01 (0.99-1.02), p=0.399

*Comorbidities: diabetes, heart disease and/or hypertension.

patients had minor complications, while there were only two major complications (0.6%). Although persistent hematuria was again the most common complication, only 6.5% lasted for more than 2 weeks. Many men experience complications after initial PNB, which should be considered as part of the informed consent process for patients. These issues should also be considered in the larger context of decisions regarding the benefits and harms of prostate cancer screening. The positive predictive value of the applied PSA threshold in the ERSPC is approximately 25% in the first screening round [14]. This means that about 75% of the biopsies were unnecessary; this number increases even further in subsequent screening rounds.

Limitations of our study include the use of a sextant biopsy strategy, which does not reflect current routine practice. In this regard, Naughton et al. randomized 179 men to undergo 6 or 12 core transrectal ultrasound guided biopsy. They found no significant difference in pain, fever or hospitalization in both groups. In the 12-core group there was a significant increase in hematospermia, but no significant difference between groups reporting morbidity as a moderate or major problem [15]. Berger et al. found similar results, they compared three biopsy regimens used in Tyrol, Austria during different time periods: 6-core, 10-core, and 15-core [16]. They found no difference between these protocols in the frequency of hematuria, rectal bleeding or major complications. However, hematospermia was significantly more common with >6 cores. We found an increase in hematospermia over time, the underlying reason for this finding (increased number of cores versus era) is unknown. For example, a possible explanation is changes in the patient-physician interaction over time, leading to increased comfort in discussing these issues nowadays. It is unclear whether our results would differ with a more extended biopsy scheme.

The psychological effect of minor complications on patients is still difficult to determine. The patients' acceptance and how they would rate the severity of the complication was not taken into account in our study. This issue was previously reported by Rosario et al. in a series of 984 men. For example, they reported that hematospermia was the most common complication (92.6%), but only 25% of the patients rated this as a moderate or serious problem. Hematuria was reported by 65.8%, of whom 6.2% found it moderate/serious. Similarly, pain was reported by 43.6% but was only moderate/serious for 7% [17]. These results highlight the discrepancy between the overall frequency of these issues and the proportion that substantially affect the patient experience.

It is also noteworthy that our center does not use local anesthetic during prostate biopsy. However, the rapid half-life of lidocaine suggests that this may be unlikely to have a significant impact on persistent pain experienced several days after biopsy. Additionally, cultural perceptions and management of pain may differ [18, 19], so our findings are not directly applicable in another population. Finally, men participating in ERSPC Rotterdam may be healthier than men in the general population [20], such that the complication rates might be underestimated.

Nevertheless, strengths of our study include the prospective design and large sample size. Additionally, the use of a standardized questionnaire and high overall response rates make these data useful for counseling similar patients undergoing initial PNB.

Conclusions

Although minor complications are often reported after initial PNB, the frequency of specific complications such as hematospermia and hematuria depends on patient-specific factors such as prostate volume and comorbidities. Our group recently reported an increase in hospitalizations after prostate biopsy over time, primarily due to febrile complications. Since the previous report by Raaijmakers, we also observed more reports of hematospermia and fewer reports of persistent pain from PNB. Overall, these data are useful to counsel patients prior to initial PNB on the frequency and risk factors for complications in a screening population.

Acknowledgements

The ERSPC Rotterdam is supported by: The Dutch Cancer Society (KWF 94-869, 98-1657, 2002-277, 2006-3518, 2010-4800) The Netherlands Organisation for Health Research and Development (ZonMW-002822820, 22-000106, 50-50110-98-311, 62300035). SL was supported by the Elisabeth Pickett Award, Society of Women in Urology.

Address correspondence to: Dr. Suzanne van den Heuvel, Department of Urology, Erasmus University Medical Centre, Gravendijkwal 230, room Na-1719, 3015 CE Rotterdam, The Netherlands. Tel: +3124856170; Fax: +31107033968; E-mail: s.vandenheuvel.1@erasmusmc.nl

References

[1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-917.

[2] Hodge KK, McNeal JE, Stamey TA. Stamey, Ultrasound guided transrectal core biopsies of the palpably abnormal prostate. J Urol 1989; 142: 66-70.

[3] Rodríguez LV, Terris MK. Risks and complications of transrectal ultrasound. Curr Opin Urol 2000; 10: 111-6.

[4] Nam RK, Saskin R, Lee Y, Liu Y, Law C, Klotz LH, Loblaw DA, Trachtenberg J, Stanimirovic A, Simor AE, Seth A, Urbach DR, Narod SA. Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. J Urol 2010; 183: 963-8.

[5] Loeb S, Carter HB, Berndt SI, Ricker W, Schaeffer EM. Complications After Prostate Biopsy: Data From SEER-Medicare. J Urol 2011; 186: 1830-4.

[6] Loeb S, van den Heuvel S, Zhu X, Bangma CH, Schröder FH, Roobol MJ. Infectious complications and hospital admissions after prostate biopsy in a European randomized trial. Eur Urol 2012; 61: 1110-4.

[7] Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schrder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. Urology 2002; 60: 826-30.

[8] Schröder FH, Denis LJ, Roobol M, Nelen V, Auvinen A, Tammela T, Villers A, Rebillard X, Ciatto S, Zappa M, Berenguer A, Paez A, Hugosson J, Lodding P, Recker F, Kwiatkowski M, Kirkels WJ; ERSPC. The story of the European Randomized Study of Screening for Prostate Cancer. BJU Int 2003; 92 Suppl 2: 1-13.

[9] Loeb S, van den Heuvel S, Zhu X, Bangma CH, Schröder FH, Roobol MJ. Infectious Complications and Hospital Admissions After Prostate Biopsy in a European Randomized Trial. Eur Urol 2012; 61: 1110-4.

[10] Chapple AB, Ziebland S, Brewster S, McPherson A. Patients' perceptions of transrectal prostate biopsy: a qualitative study. Eur J Cancer Care (Engl) 2007; 16: 215-21.

[11] Rodríguez LV, Terris MK. Risks and complications of transrectal ultrasound guided prostate needle biopsy: a prospective study and review of the literature. J Urol 1998; 160: 2115-20.

[12] Djavan B, Waldert M, Zlotta A, Dobronski P, Seitz C, Remzi M, Borkowski A, Schulman C, Marberger M. Safety and morbidity of first and repeat transrectal ultrasound guided prostate needle biopsies: results of a prospective European prostate cancer detection study. J Urol 2001; 166: 856-60.

[13] Ecke TH, Gunia S, Bartel P, Hallmann S, Koch S, Ruttloff J. Complications and risk factors of transrectal ultrasound guided needle biopsies of the prostate evaluated by questionnaire. Urol Oncol 2008; 26: 474-8.

[14] Bokhorst LP, Zhu X, Bul M, Bangma CH, Schröder FH, Roobol MJ. Positive predictive value of prostate biopsy indicated by prostate-specific-antigen-based prostate cancer screening: trends over time in a European randomized trial*. BJU Int 2012; 110: 1654-60.

[15] Naughton CK, Ornstein DK, Smith DS, Catalona WJ. Pain and morbidity of transrectal ultrasound guided prostate biopsy: a prospective randomized trial of 6 versus 12 cores. J Urol 2000; 163: 168-71.

[16] Berger AP, Gozzi C, Steiner H, Frauscher F, Varkarakis J, Rogatsch H, Bartsch G, Horninger W. Complication rate of transrectal ultrasound

guided prostate biopsy: a comparison among 3 protocols with 6, 10 and 15 cores. J Urol 2004; 171: 1478-80; discussion 1480-1.

[17] Rosario DJ, Lane JA, Metcalfe C, Donovan JL, Doble A, Goodwin L, Davis M, Catto JW, Avery K, Neal DE, Hamdy FC. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. BMJ 2012; 344: d7894.

[18] Ulmert D, Cronin AM, Björk T, O'Brien MF, Scardino PT, Eastham JA, Becker C, Berglund G, Vickers AJ, Lilja H. Prostate-specific antigen at or before age 50 as a predictor of advanced prostate cancer diagnosed up to 25 years later: a case-control study. BMC Med 2008; 6: 6.

[19] Zborowski M. Cultural Components in Responses to Pain. Journal of Social Issues 1952; 8: 16-30.

[20] Otto SJ, Schröder FH, de Koning HJ. Low all-cause mortality in the volunteer-based Rotterdam section of the European randomised study of screening for prostate cancer: self-selection bias? J Med Screen 2004; 11: 89-92.