RESEARCH

Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study

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Derek J Rosario *senior lecturer in cancer studies*[1], J Athene Lane *senior research fellow*[2], Chris Metcalfe *senior lecturer in medical statistics*[2], Jenny L Donovan *professor of social medicine*[2], Andy Doble *consultant urological surgeon*[3], Louise Goodwin *research nurse and biobanker*[1], Michael Davis *research associate in health services research*[2], James W F Catto *reader in cancer studies*[1], Kerry Avery *research fellow and NIHR post-doctoral award holder*[2], David E Neal *professor of surgical oncology*[4], Freddie C Hamdy *professor of surgery*[5]

[1]Academic Urology Unit, Department of Oncology, Royal Hallamshire Hospital, University of Sheffield, Sheffield S10 2JF, UK; [2]School of Social and Community Medicine, University of Bristol, Bristol BS8 2PS, UK; [3]Department of Urology, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK; [4]Department of Oncology, University of Cambridge, Addenbrooke's Hospital; [5]Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK

Abstract

Objectives To measure the effect of the adverse events within 35 days of transrectal ultrasound guided biopsy from the perspective of asymptomatic men having prostate specific antigen (PSA) testing; to assess early attitude to re-biopsy; to estimate healthcare resource use associated with adverse events due to biopsy; and to develop a classification scheme for reporting adverse events after prostate biopsy.

Design Prospective cohort study (Prostate Biopsy Effects: ProBE) nested within Prostate Testing for Cancer and Treatment (ProtecT) study.

Participants Between 1999 and 2008, 227 000 community dwelling men aged 50 69 years were identified at 352 practices and invited to counselling about PSA testing. 111 148 attended a nurse led clinic in the community, and 10 297 with PSA concentrations of 3-20 ng/mL were offered biopsy within ProtecT. Between February 2006 and May 2008, 1147/1753 (65%) eligible men (mean age 62.1 years, mean PSA 5.4 ng/mL) having 10 core transrectal ultrasound guided biopsy under antibiotic cover in the context of ProtecT were recruited to the ProBE study.

Outcome measures Purpose designed questionnaire administered at biopsy and 7 and 35 days after the procedure to measure frequency and effect of symptoms related to pain, infection, and bleeding; patients' attitude to repeat biopsy assessed immediately after biopsy and 7 days later; participants' healthcare resource use within 35 days of biopsy evaluated by questionnaire, telephone follow-up, and medical note review; each man's adverse event profile graded according to symptoms and healthcare use.

Results Pain was reported by 429/984 (43.6%), fever by 172/985 (17.5%), haematuria by 642/976 (65.8%), haematochezia by 356/967 (36.8%), and haemoejaculate by 605/653 (92.6%) men during the 35 days after biopsy. Fewer men rated these symptoms as a major/moderate problem—71/977 (7.3%) for pain, 54/981 (5.5%) for fever, 59/958 (6.2%) for haematuria, 24/951 (2.5%) for haematochezia, and 172/646 (26.6%) for haemoejaculate. Immediately after biopsy, 124/1142 (10.9%, 95% confidence interval 9.2 to 12.8) men reported that they would consider further biopsy a major or moderate problem: seven days after biopsy, this proportion had increased to 213/1085 (19.6%, 17.4% to 22.1%). A negative attitude to repeat biopsy was associated with unfavourable experience after the first biopsy, particularly pain at biopsy (odds ratio 8.2, P<0.001) and symptoms related to infection (7.9, P<0.001) and bleeding (4.2, P<0.001); differences were evident between centres (P<0.001). 119/1147 (10.4%, 8.7% to 12.3%) men reported consultation with a healthcare professional (usually their general practitioner), most commonly for infective symptoms. Complete data for all index symptoms at all time points were available in 851 participants. Symptoms and healthcare use could be used to grade these men as follows: grade 0 (no symptoms/contact) 18 (2.1%, 1.3% to 3.3%); grade 1 (minor problem/no contact) 550 (64.6%, 61.4% to 67.8%); grade 2

Correspondence to: D J Rosario d.j.rosario@shef.ac.uk

(moderate/major problem or contact) 271 (31.8%, 28.8% to 35.1%); grade 3 (hospital admission) 12 (1.4%, 0.8% to 2.4%); and grade 4 (death) 0. Grade of adverse event was associated with an unfavourable attitude to repeat biopsy (Kendall's τ-b ordinal by ordinal 0.29, P<0.001).

Conclusion This study with a high response rate of 89% at 35 days in men undergoing biopsy in the context of a randomised controlled trial has shown that although prostate biopsy is well tolerated by most men, it is associated with significant symptoms in a minority and affects attitudes to repeat biopsy and primary care resource use. These findings will inform men who seek PSA testing for detection of prostate cancer and assist their physicians during counselling about the potential risks and effect of biopsy. Variability in the adverse event profile between centres suggests that patients' outcomes could be improved and healthcare use reduced with more effective administration of local anaesthetic and antibiotics.

Trial registration Current Controlled Trials ISRCTN20141297.

Introduction

Prostate cancer is a major health problem worldwide; 899 000 new cases were diagnosed in 2008 (13.6% of total incident cancers), and an estimated 258 000 deaths (6.1% of cancer deaths) from the disease occurred.[1] Recent evidence from large European randomised studies of screening suggests a reduction in disease specific mortality ranging between 20% and 44%,[2][3] but at the cost of over-detection and potential overtreatment,[4] which precludes the introduction of screening as public health policy. While the debate continues, men who seek early detection of prostate cancer by testing for prostate specific antigen (PSA) need accurate information on the consequences of the diagnostic process as well as the therapeutic dilemma. In men who have PSA testing, prostate biopsy is needed for a histological diagnosis of prostate cancer. Whereas considerable attention has been paid to PSA testing, relatively little is known about the effect of prostate biopsy in this group of otherwise healthy men. One of the criteria for suitability of a test for screening is that it is acceptable to the population being screened. In the context of prostate cancer, this criterion is often applied only to PSA testing but is also relevant in the context of subsequent prostate biopsy to provide the definitive diagnosis. Laboratories carrying out PSA testing for the National Health Service are subject to quality assurance under the United Kingdom National External Quality Assurance Service. Comparatively, transrectal ultrasound guided prostate biopsy (TRUS-Bx), the most commonly used technique for prostate biopsy in these asymptomatic men, has received little attention and is not subject to any similar external quality assurance.

TRUS-Bx was introduced more than two decades ago, initially without any form of analgesia, for the detection of prostate cancer.[5] The procedure has evolved, primarily to improve the rate of cancer detection by increasing the number of biopsy cores taken.[6] To reduce morbidity and improve tolerability of increasing the number of cores, the use of prophylactic antibiotics and analgesia in the form of intrarectal lidocaine gel or periprostatic infiltration of local anaesthetic have become commonplace, with considerable variability in practice and outcomes.[7][8][9] TRUS-Bx can be associated with appreciable morbidity, including sepsis, pain, bleeding, and even death on rare occasions. The true effect of biopsy is difficult to ascertain from the literature—the reported morbidity is highly variable, and although post-biopsy adverse events are often referred to as "major" or "minor," the basis of this classification is arbitrary and inconsistent. The incidence of major complications in the Rotterdam cohort of the European Randomized study of Screening for Prostate Cancer (ERSPC) was 12% (7.5% pain, 4% fever, 0.5% hospital admission for sepsis, 0.4% admission

for acute urinary retention),[10] in contrast with a reported incidence of "major" complications of 0.1% in an Austrian screened population (n=1051).[11] A systematic review of TRUS-Bx observed that only 41 of 87 studies made any mention of adverse events, and where mention was made no standardised approach to reporting was used.[12] Furthermore, the acceptability of re-biopsy is uncertain: in the era preceding widespread use of local anaesthetic, a British study reported that 19% of men refused re-biopsy without general anaesthesia,[13] and the Finnish study of screening for prostate cancer observed that 18% of screened men would not accept a repeat biopsy.[14] In contrast, Djavan et al reported that of 820 Austrian men previously biopsied, all re-attended for re-biopsy as an outpatient when invited.[11] The factors influencing this attitude towards repeat biopsy remain uncertain, but it is important as around two thirds of men initially have a negative biopsy and may need another.[15]

The wide variability in adverse events and acceptability probably reflects a combination of expertise, patients' expectations, and inconsistent reporting. Little evidence based information about the experience of TRUS-Bx is available to share with men having the procedure. Additionally, no systematic investigation of the acceptability of TRUS-Bx and association between adverse events after TRUS-Bx and attitude to re-biopsy in a PSA-tested population has been done. The aims of this study were to measure the effect of adverse events after a first prostate biopsy in asymptomatic men having PSA testing; to assess early attitudes to repeat biopsy; to estimate the effect of adverse events from TRUS-Bx on healthcare resource use; and to develop a simple classification system for consistent reporting of adverse events after prostate biopsy.

Methods

Design and sample size

A prospective cohort study (ProBE—Prostate Biopsy Effects) was embedded in the ongoing Prostate Testing for Cancer and Treatment (ProtecT) study, which is a large multicentre randomised controlled trial started some years previously to evaluate the effectiveness, cost effectiveness, and acceptability of treatments for men with localised prostate cancer.[15][16] General medical practices in and around nine cities throughout the United Kingdom recruited men to the ProtecT study. Lead partners of the practices received letters of invitation for their practice to participate in the study, detailing the rationale for a randomised controlled trial of treatment in clinically localised prostate cancer detected by PSA. Participating practices in turn sent letters inviting men aged 50-69 years registered at the practice to attend for PSA counselling. Nurse led clinics were held in a primary care setting, where participants with an estimated life expectancy of a minimum of 10 years and without important cardiorespiratory comorbidity were given detailed information about the implications of PSA testing, the uncertainties about treatments, and the need for a treatment trial; consent was sought thereafter for PSA testing. Biopsy was offered to all men with a PSA concentration of 3.0 ng/mL or above. The sample size calculation suggested that 880 participants would provide a precise estimate of an expected hospital admission rate of 1%,[10] with a 95% confidence interval of 0.4 to 2%. The target was to enrol 1200 men, allowing a priori for a 25% dropout rate.

Population and exposure

In February 2006, the ProBE study started recruitment in eight of the nine ProtecT centres. Men presenting with a PSA concentration of 3.0-19.9 ng/mL, with no previous experience of TRUS-Bx, were invited to participate in ProBE in addition

to their involvement in the ProtecT study. As many practices were part way through recruitment to ProtecT when ProBE started and stopped recruitment, not all practices nor all men at any given practice were offered the study.

The intention was for the ProBE study to recruit consecutive men attending for a prostate biopsy in ProtecT from February 2006 until the sample size of 1200 was reached (see above). Resource limitation at the height of recruitment to ProtecT meant that some biopsy sessions were not covered by research staff, so not all men attending biopsy sessions were offered participation in ProBE.

All men invited to join the ProBE study were given patients' information sheets on ProBE as well as ProtecT, in addition to local instructions related to the biopsy procedure. Baseline data including weight, height, drug history, comorbidity, Hospital Anxiety and Depression Scale (HADS) score, and urinary, bowel, and sexual symptoms were assessed by using the validated International Continence Society—male, International Consultation on Incontinence Modular Questionnaire—urinary incontinence, and University of California, Los Angeles Prostate Cancer Index questionnaires.[17 18 19] Outpatient TRUS-Bx was carried out in the left lateral decubitus position under antibiotic cover by using a 10 core lateral biopsy template.[20 21] In a pre-study questionnaire, seven of the eight centres reported using periprostatic infiltration of local anaesthetic (1% or 2% lidocaine) routinely before biopsy. All men received antibiotic prophylaxis according to contemporary practice; inter-centre variability existed, but each centre used a consistent schedule throughout the study period. A midstream specimen of urine was sent for culture immediately before antibiotic administration. Coumarin anticoagulant and clopidogrel treatment were discontinued up to 10 days before biopsy and advice sought as to appropriate substitutes if indicated. Aspirin was continued at the discretion of the physician doing the biopsy. Men were kept under observation after the biopsy until they voided. Urine was assessed for haematuria according to a four point colorimetric scale. Each centre provided its own post-biopsy written instructions and contact details.

Outcome measures

Symptoms

Men self reported pain and discomfort (referred to as pain hereafter) immediately after and seven days after TRUS-Bx on a four point Likert-type scale as none, mild, moderate, or severe. Specific related complications such as fever, flu-like shivers, pain, haematuria, haematochezia, and haemoejaculate were self reported at seven and 35 days after TRUS-Bx as absent or present following biopsy on a purpose designed questionnaire (TRUS-BxQ; see appendix 1). This included the validated International Continence Society—male, International Consultation on Incontinence Modular Questionnaire—urinary incontinence, and University of California, Los Angeles Prostate Cancer Index questionnaires.[17 18 19] For each reported symptom, participants were asked to grade the degree of "problem" associated with its presence as none, minor, moderate, or major. We used this information to derive a binary outcome for each symptom, as present with moderate/severe problem versus not present/minor problem. During the pilot phase (February 2006 to April 2006), an expert committee (appendix 2) reviewed the initial data from the TRUS-BxQ to optimise face validity and content validity.

Attitude to re-biopsy

To assess attitudes to possible further biopsies immediately after the biopsy and seven days later, men were asked to record on a four point Likert-type scale (no problem, minor, moderate, major problem) "how much of a problem would you find having another biopsy in the future?" Analyses explored the relations between men's reports of pain and symptoms and their attitude to re-biopsy.

Healthcare resource use

Men reported any contact with healthcare services in the TRUS-BxQ at seven and 35 days after biopsy. A non-clinical research assistant did semi-structured telephone interviews with men between seven and 10 days after biopsy. When self reported data were unclear or missing, we searched medical records (written and electronic) for any episode of contact with any provider in primary or secondary care occurring within 35 days of the date of biopsy. We used data from the participants' interviews, TRUS-BxQ, and the review of hospital records to ascertain the reason for any hospital admission. When contact with primary care was detected or reported, we made an assessment of its relevance to the biopsy procedure, on the basis of a free text description provided by participants in the self completed TRUS-BxQ and review of the clinical records where necessary.

Adverse event classification

We grouped adverse events of fever, flu-like shivers, haematuria, haematochezia, and haemoejaculate together as "infective," "haemorrhagic," and combined "infective/haemorrhagic" symptoms. We classified adverse events in a manner consistent with the National Cancer Institute's common toxicity criteria version 3.0 as grade 0 = no adverse event reported and no biopsy related healthcare contact, grade 1 = symptoms reported but causing no/minor problem and no biopsy related healthcare contact, grade 2 = symptom reported causing major/moderate problem or biopsy related healthcare contact without hospital admission, grade 3 = hospital admission within 35 days of biopsy, and grade 4 = death within 35 days of biopsy.[22] This analysis included only men with a complete dataset of symptoms at both assessments.

Data analysis

We used SPSS statistical software version 18.0 to do data analyses using the available data; we did not impute any missing data. We present the proportion of men who experienced each outcome, with 95% confidence intervals calculated by using Wilson's method (CIA software, version 2.2.0, www.som. southampton.ac.uk/cia). We estimated associations between risk factors and binary outcome measures (for example, moderate/major problem with re-biopsy, healthcare contact, hospital admission) as odds ratios by using logistic regression with adjustment for age and centre. For clarity, where the symptom scale is reduced to a binary distinction, this distinguishes men reporting a moderate/major problem from those reporting a mild/no problem. We used the logistic regression models as the basis of likelihood ratio tests to calculate P values. We adjusted for age and recruitment centre by adding dummy variables to the regression models—three dummy variables distinguishing four age groups (50-54, 55-59, 60-64, and 65-69 years) and seven dummy variables distinguishing eight study centres.

Results

In the ProtecT study overall, of the 227 000 men aged 5069 years who were identified at 352 practices and invited to nurse led clinics in the community for counselling about PSA testing, 111 148 attended. Of the 10 297 men offered TRUS-Bx within ProtecT, 1753 attended for biopsy between February 2006 and May 2008 and were eligible to enter the ProBE study; 1147 (65%) consented to participation. Table 1⇓ summarises baseline data.

Of the 1147 men who had TRUS-Bx within ProBE, TRUS-BxQ data were available for 1144 (99.7%) at baseline, 1090 (95.0%) at seven days, and 1018 (88.8%) at 35 days post-biopsy. Telephone follow-up, primary care, and hospital record data were available for all 1147 participants. We found no difference between the men recruited in the eight centres with regard to age (P=0.086), PSA concentration (P=0.51), body mass index (P=0.54), or HADS anxiety (P= 0.83) or depression scores (P=0.2). A difference in mean prostate volume existed (P<0.001).

Symptoms, degree of associated problem, and duration

Immediately after biopsy, 37/1134 (3.3%, 95% confidence interval 2.4% to 4.5%) men reported light-headedness and three (0.3%, 0.1% to 0.8%) experienced a short period of syncope. All men voided after the procedure. Moderate or severe haematuria was present in 78/1055 (7.4%, 6.0% to 9.1%) post-biopsy urine samples and was associated with large blood clots in 27 (2.6%, 1.8% to 3.8%). Three additional men passed clots without moderate or severe haematuria.

Table 2⇓ shows the number of men who reported pain, fever, flu-like shivers, haematuria, haematochezia, and haemoejaculate within seven and 35 days of biopsy and the proportion who reported a moderate/major problem associated with each symptom. Approximately one third of men (n=340/1147) reported no sexual activity within 35 days after biopsy, and the prevalence of haemoejaculate is therefore limited to those who were sexually active during the study period. Although the prevalence of each symptom and combination of symptoms was relatively high, most men reported the presence of a symptom as being no problem or a minor problem (table 2⇓ and box).

Attitude to repeat biopsy

Immediately after the procedure, 124/1142 (10.9%, 9.2% to 12.8%) men reported that having a repeat biopsy would represent a moderate/major problem. This rose to 213/1085 (19.6%, 17.4% to 22.1%) when the question was repeated seven days later (P=0.001, McNemar's test for a null hypothesis of no difference in the proportion finding re-biopsy a moderate/major problem). The proportion of men considering repeat biopsy to be a moderate/major problem differed by centre at both time points (P<0.001) (table 3⇓). These differences persisted following the exclusion of centre 3 (P=0.004), where local anaesthetic was not administered routinely.

A strong association existed between an unfavourable attitude to repeat biopsy at seven days and pain reported at both time points (immediately post-biopsy: odds ratio 12.1, P<0.001; at seven days: odds ratio 8.2, P<0.001) as well as symptoms within seven days related to infection (odds ratio 7.89, P<0.001) and bleeding (4.24, P<0.001) (table 4⇓).

Healthcare contact

No deaths occurred in this cohort within 35 days of biopsy (95% confidence interval 0 to 0.4%). In that period, 15/1147 (1.3%, 0.8% to 2.1%) men needed hospital admission for sepsis (n=7), urinary retention (n=3), haematuria (n=2), rectal bleeding (n=1), or other diagnoses (n=2). All admissions due to sepsis occurred within three days of biopsy, whereas one man with retention was admitted three weeks after biopsy. A further 119 (10.4%, 8.7% to 12.3%) men initiated a biopsy related consultation with their general practitioner (n=92), urology department nurse (14), or other source of medical advice (13) such as NHS Direct. The predominant reasons for seeking healthcare advice in primary care were infective symptoms (n=38), urinary symptoms including haematuria (34), haemoejaculate (14), possibility of antibiotic related adverse events such as diarrhoea or a skin rash (14), and discomfort/bleeding on defecation (10). We found no evidence that such contacts varied across centres (P=0.73).

Table 4⇓ lists selected variables examined for associations with healthcare contact within 35 days. Biopsy related healthcare contact within 35 days was more likely in men with a previous history of urinary tract infection (P=0.036) compared with others, and in men who reported moderate/severe pain immediately after the procedure (P=0.017). Cross sectional analysis showed a strong association between healthcare contact and symptoms of infection, bleeding, or both at seven days (P<0.001).

Owing to the low number of events, we could investigate only crude associations with hospital admissions. We found evidence of a higher risk of hospital admission in men treated with non-steroidal agents (3/58 (5%) *v* 11/1035 (1.1%), P=0.037) and those reporting a moderate/severe problem with symptoms of infection (7/47 (15%) *v* 7/1036 (0.7%), P<0.001) or bleeding (6/179 (3%) *v* 9/843 (1.1%), P=0.039) at 7 days. None of the men with a history of prostatitis (n=18) or warfarin treatment (n=14) or who had an infected midstream urine sample before biopsy (n=18) were admitted to hospital within 35 days of the procedure.

Adverse event classification

Complete data on the five index symptoms at seven and 35 days were available for 851/1147 (74.2%) men. We classified adverse events as grade 0 (no symptoms/contact) in 18 (2.1%, 1.3% to 3.3%), grade 1 (minor) in 550 (64.6%, 61.4% to 67.8%), grade 2 (moderate/major) in 271 (31.8%, 28.8% to 35.1%), and grade 3 (inpatient/hospital admission) in 12 (1.4%, 0.8% to 2.4%); no participants had a grade 4 event (death). We found strong evidence of an association between the grade of adverse event at 35 days and an unfavourable attitude to repeat biopsy at seven days (Kendall's τ-b ordinal by ordinal 0.29, P<0.001).

Exploratory analyses

Prostate volume, age, and attitude to repeat biopsy

We found weak evidence that older men were more likely to report a favourable attitude to repeat biopsy than were younger participants (odds ratio per 5 year increase in age between 50 and 69 years: 0.86, 0.75 to 1.00, P=0.056) (table 4[4]). Men who considered repeat biopsy to be a moderate/major problem were more likely to have a smaller prostate volume (P=0.027) (table 4⇓).

Box 1. Summary of adverse effects reported during 35 day follow-up period

Using a structured questionnaire, we asked more than 1000 men to record what their experience of a prostate biopsy had been both immediately and up to 35 days after biopsy. This box summarises their responses.

Immediate effects

- 85% of men described no pain or mild pain associated with the biopsy procedure itself
- 3% of men felt "lightheaded" or dizzy after the biopsy
- 7% passed blood in their urine immediately after biopsy
- 3% passed "clots"' in their urine immediately after biopsy

Delayed effects (in 35 days after biopsy)

- 44% of men had pain; 7% found this a moderate or serious problem
- 20% had a fever; 5% found this a moderate or serious problem
- 66% had blood in the urine; 6% found this a moderate or serious problem
- 37% had blood in the motions; 2% found this a moderate or serious problem
- 90% had blood in the semen; 25% found this a moderate or serious problem

Prolonged symptoms (two weeks or more after biopsy)

- 15% of men had some pain
- 3% had a fever
- 20% had blood in their urine
- 5% had blood in their motions
- 60% had blood in their semen

Prostate cancer diagnosis and healthcare contact

Prostate cancer was diagnosed on biopsy in 406/1147 (35.4%, 32.6% to 38.2%) men. We found a difference in cancer detection rates ranging between 23% (14% to 36%) and 53% (40% to 65%) across the eight centres (P=0.008). We found no convincing evidence that men subsequently diagnosed as having cancer were more likely to come into contact with healthcare services for a biopsy related adverse event within 35 days of the procedure compared with men in whom cancer was not diagnosed (48/406 (11.8%) v 87/741 (11.6%); odds ratio 1.03, 0.70 to 1.50, P=0.89, adjusted for age and study centre). The risk of hospital admission was 1.7% in men subsequently diagnosed as having cancer and 1.1% in those without cancer (P=0.84).

Discussion

This multicentre prospective study with a high response rate of 89% at 35 days provides generalisable quantitative data about the events occurring in the 35 days after a first prostate biopsy. The findings are based on patient reported outcomes and verifiable criteria, including healthcare resource use. Whereas prostate biopsy was reasonably well tolerated in most men, a few men rated post-biopsy pain and infective/haemorrhagic symptoms as a major/moderate problem—7.3% for pain, 5.5% for fever, 6.2% for haematuria, 2.5% for haematochezia, and 26.6% for haemoejaculate. Immediately after biopsy, 10.9% reported that they would consider further biopsy a major or moderate problem; seven days after biopsy, this proportion had increased to 19.6%. A negative attitude to repeat biopsy was associated with unfavourable experience after the first biopsy, particularly pain at biopsy; differences were evident between centres carrying out the biopsies. Consultation with a healthcare professional (usually their general practitioner) was reported by 10.4%, most commonly for infective symptoms.

Transrectal ultrasound guided biopsy of the prostate is an ambulatory procedure commonly carried out in consulting rooms and outpatient and radiology departments in small and large hospitals. Although accurate figures for the number of procedures carried out in the UK each year are difficult to elicit, approximately 37 000 new cases of prostate cancer are diagnosed annually (http://info.cancerresearchuk.org/cancerstats/types/prostate), with a cancer detection rate at biopsy of around 35%.[17] Assuming that around 100 000 procedures are carried out every year in the UK alone would thus be reasonable.

The results of this study are particularly relevant to screening for prostate cancer rather than the performance of prostate biopsy for confirmation of a diagnosis in clinically evident disease. The cohort is drawn from asymptomatic men, invited for PSA testing in the context of a large randomised controlled trial (ProtecT), with a first biopsy at a PSA concentration of 3.0-19.9 ng/mL, a range commonly held to be appropriate for detection of localised prostate cancer suitable for treatment with curative intent. None of the men had repeat biopsy during the timeframe specified. Particular emphasis was placed on the perception of the man having the biopsy, as well as the identification of adverse events. This emphasis allowed the study to measure how a man perceives the degree of "problem" associated with individual symptoms resulting from a first prostate biopsy. Cross referencing these perceptions with healthcare resource use provided useful triangulation. Maintaining a high response rate of 95% at seven days and 89% at 35 days is a particular strength of the study.

A significant number of men experienced difficulties during or after the biopsy, primarily associated with pain, sepsis, or bleeding. Very few men experienced no symptoms at all (2.1%, grade 0) in the five weeks after biopsy. Of those who did experience one or more symptoms, most considered them to be of little consequence (64.6%, grade 1). The remaining third experienced adverse events that they considered to be a moderate or severe problem. Of interest, the presence of blood in a man's ejaculate (haemoejaculate) after biopsy is seldom reported in the literature and is often labelled as a "minor" adverse event. In this study, haemoejaculate was perceived as a moderate to severe problem for around one quarter of sexually active men (table 2⇓). Further investigation of the problems generated by this symptom is warranted, and information about its duration and persistence should be given to all men having biopsies.

During initial counselling before PSA testing, men are informed of the possible requirement for repeat biopsies beyond the first procedure, in the event of equivocal results or a benign biopsy

with persistent risk factors such as a persistently raised serum PSA concentration. A recent study from the United States reported that 38% of men having a first biopsy will have a repeat procedure within five years of the initial biopsy; the proportion reaches 44% in men under the age of 70 years.[23] Several studies have shown that repeat biopsy leads to a detection rate for prostate cancer of 19-59%,[24 25 26] so understanding how a first biopsy affects a man's attitude to additional procedures if needed is essential. In this study, 11% and 20% of men reported an unfavourable attitude to repeat biopsy immediately after biopsy and seven days later; pain experienced at biopsy and infective symptoms in the week after biopsy were strongly associated with this response. Systematic TRUS-Bx was introduced initially without local anaesthetic, although this has been adopted in clinical practice more recently.[5 8 9 27] Meta-analyses have described a significant reduction in pain scores with periprostatic nerve blocks[28 29]; doubt remains, however, as to whether the reduction in pain scores translates to clinically meaningful changes, particularly as infiltration of local anaesthetic itself has been shown to be associated with pain.[30] The association between levels of pain experienced and attitude to having repeat biopsy described in this study is an important observation that supports the mandatory use of periprostatic nerve blockade with local anaesthetic. Even among centres where local anaesthetic was routinely administered, inter-centre variability in its effect existed. This suggests that the technique of administration may need to be standardised to ensure effectiveness of local anaesthesia.

As well as resulting in a negative attitude to re-biopsy, infective complications were the most common reason for seeking medical advice or primary care intervention (10.4%). Most symptoms were evident within seven days of biopsy, with a small proportion of men continuing to report symptoms for up to five weeks after biopsy (box). This information is particularly valuable for general practitioners when counselling patients before PSA testing. The American Urological Association's best practice policy statement recommends administration of a fluoroquinolone as uniform antimicrobial prophylaxis in all men having TRUS-Bx.[31] Current practice, however, has been influenced predominantly by randomised controlled trials indicating the efficacy of a single dose of ciprofloxacin in reducing the incidence of infective complications after TRUS-Bx[32 33]; subsequent studies have suggested that prolonging treatment to three days results in superior clinical effectiveness.[34] A recent report has identified an increasing rate of sepsis related admission to hospital after prostate biopsy in the decade between 1996 (0.6%) and 2005 (3.6%).[35] This may be related to a general reduction in peri-biopsy antibiotic use,[36] but the development of quinolone resistance may also be implicated.[37 38 39 40] Against this backdrop, antibiotic prophylaxis for TRUS-Bx is universally used, but without consensus on best practice.[41] We have shown some evidence of differences in infective complications between centres, but our study was not specifically designed to evaluate the effectiveness of antibiotic prophylaxis; this warrants further prospective investigation.

The classification of adverse events described in this study is similar to that described after systemic chemotherapy. It is based on a combination of reported events and their effect from a patient's perspective. Its wider use needs further validation and is likely to show the need to standardise and refine the technique of prostate biopsy to minimise its adverse events. No fatal events occurred in our cohort. This is not surprising, as our participants were relatively healthy with an upper age limit of 69 years and no symptoms. Mortality after prostate biopsy has been reported

as ranging between 0.09% and 1.3% at 120 days,[35 42] and it is associated with older, less healthy men.

In contrast with a large retrospective Canadian study referred to earlier,[35] we found no difference in our prospective study in hospital admission rate (grade 3 adverse event) between participants with cancer and those without (1.7% v 1.1%). The findings of the Canadian study may result from the investigation of a population at different risk or, as acknowledged by the authors, from inaccuracy in coding associated with its retrospective nature.

Limitations of study

The ProBE study cohort included asymptomatic men aged between 50 and 69 years presenting for a first prostate biopsy after a PSA test, received through the ProtecT study during the period February 2006 to May 2008. The ProBE study was carried out over this limited period, sampling approximately 11% of the ProtecT participants. The cohort did not include men seen in routine UK clinical practice with urinary symptoms or clinically suspected prostate cancer. Of the men eligible for inclusion, 65% were recruited and thus are likely to be representative of the men who attended for PSA testing within the ProtecT study. Embedding the ProBE study in the ProtecT trial was beneficial, providing a standardised biopsy template and recruitment from a wide range of practices across the UK and improving compliance with follow-up. However, participants had responded to a single written invitation to attend for PSA testing sent out via general practices, so non-responders may not be represented in this study. The observations are likely to remain valid in the context of men seeking PSA testing for detection of prostate cancer.

In the absence of nationally agreed, evidence based patient information leaflets, each centre delivered its own information about the biopsy process, which may have influenced men's views. Recall bias may also have occurred for recording the duration of symptoms, as men were asked to summarise their experience over the previous four weeks in the 35 day questionnaire. For the main analyses, we required data with evaluable responses from both the seven day and 35 day questionnaire assessments. This reduced the numbers and may have led to some degree of underestimation of the prevalence of adverse events. Although relevant to the overall outcome, some of the reported symptoms (such as fever/shivers) may not have been related to the biopsy itself and may have inadvertently influenced a negative attitude to repeat biopsy.

Additional items

Administration of local anaesthesia is important in determining pain experienced, but other factors, such as environment, training, education, and nursing care, will clearly affect anxiety and pain. We have explored some of these factors in a linked qualitative study (data not included). Similarly, although we have sought men's initial and early views on the acceptability of repeat biopsy, attitudes may change with time; we shall therefore follow up this cohort carefully to analyse the re-biopsy rate and assess patients' subsequent views.

While healthcare providers await further evidence to decide whether screening for prostate cancer should become public health policy, primary care physicians need to be well informed of the risks and adverse events related to TRUS-Bx as well as PSA before testing. The findings of this study contribute further generalisable quantitative data about the potential harms associated with making a diagnosis of prostate cancer in asymptomatic men.

Generalisability

The ProBE study investigated a large cohort of men aged between 50 and 69 years who had TRUS-Bx for the first time as a result of a PSA concentration between 3.0 and 20 ng/mL. The cohort comprised 65% of eligible men biopsied within a trial population. The results are likely to be generalisable to all asymptomatic men in this age group who seek diagnosis of prostate cancer through PSA testing and in the context of screening. They may, however, not be applicable to younger or older men, those with clinical evidence of prostate cancer, or men who have previously had prostate biopsy.

Conclusions

After prostate biopsy, one third of men having first time TRUS-Bx for a high PSA reported moderate to severe biopsy related symptoms. Immediately after TRUS-Bx, one in 10 men had an unfavourable attitude to repeat biopsy, rising to one in five later. This was associated with adverse events in the seven days after biopsy and seemed to affect younger men more; as these men are most likely to benefit from early diagnosis of prostate cancer as well as require re-biopsy, this requires further investigation. Within 35 days of biopsy, 1.3% of men required admission to hospital and a further 119 (10.4%) men initiated a biopsy related consultation with their general practitioner (n=92), urology department nurse (n=14), or other source of medical advice (n=13) such as NHS Direct, most commonly for infective symptoms. The adverse event classification scheme described may help to show variation in rates of adverse events across centres that arise from differences in information and biopsy technique. Training, protocols, and consistent reporting methods should be considered to achieve excellence in practice. Information for patients about biopsy should be standardised and include the findings of this study, so that men and physicians are fully informed about the risks and benefits of the diagnostic process before they embark on prostate cancer detection.

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What is already known on this topic

Prostate biopsy is essential for diagnosis of prostate cancer, but its acceptability and effects have rarely been investigated prospectively

Prostate biopsy is thought to be well tolerated, but little is known about the effect of adverse events on men, their attitude to re-biopsy, or their subsequent use of healthcare resources

Prostate biopsy can be associated with considerable morbidity, including sepsis, pain, bleeding, and even mortality, but at unknown rates owing to variable reporting

What this study adds

At seven days after biopsy, 39% of men had pain, 12% had fever, 64% had haematuria, 33% had rectal bleeding, and 94% of those who were sexually active had haemoejaculate; all symptoms were less prevalent at 35 days

Men rated only a small proportion of these events as serious, with the exception of haemoejaculate in those who were sexually active, with one in four describing this as a moderate/major problem

Immediately after a first biopsy, one in 10 men had an unfavourable attitude to a repeat procedure, increasing to one in five at seven days

After a first biopsy, one in 10 men sought help from primary care, and one in 100 needed hospital admission within 35 days of the procedure

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Tables

Table 1| Summary statistics for baseline measures overall and at each centre

Characteristics	Total cohort	Centre number								P value for between centre differences
		1	2	3	4	5	6	7	8	
No of biopsies	1147	282	206	176	149	115	102	56	61	
Mean (SD) age (years)	62.1 (5.1)	62.0 (5.0)	62.8 (4.6)	61.2 (5.4)	61.8 (5.1)	61.9 (4.9)	62.5 (5.1)	62.2 (5.7)	62.9 (5.1)	0.09*
Median (interquartile range) PSA (ng/mL)	4.2 (3.5 to 5.8)	4.3 (3.5 to 5.8)	4.3 (3.5 to 6.1)	4.2 (3.4 to 5.4)	4.2 (3.5 to 5.8)	4.1 (3.5 to 5.8)	4.3 (3.5 to 5.6)	4.8 (3.6 to 6.9)	4.1 (3.4 to 5.3)	0.69†
Mean (SD) body mass index (kg/m^2)	27.4 (3.6)	27.3 (3.8)	27.1 (3.3)	27.9 (3.4)	27.1 (3.6)	27.8 (3.8)	27.7 (3.7)	28.1 (4.4)	27.5 (3.2)	0.54*
Mean (SD) HADS (anxiety)	4.9 (3.3)	4.8 (3.2)	5.0 (3.4)	5.2 (3.3)	4.8 (3.6)	4.6 (2.7)	4.9 (3.2)	4.5 (2.9)	4.9 (3.5)	0.83*
Mean (SD) HADS (depression)	3.1 (2.7)	3.2 (2.5)	3.3 (2.7)	3.4 (2.8)	3.0 (2.8)	2.7 (2.5)	3.1 (2.4)	2.4 (2.2)	3.3 (2.9)	0.2*
Median (interquartile range) prostate volume (mL)	38 (28 to 52)	38 (30 to 53)	47 (34 to 66)	31 (24 to 43)	44 (32 to 65)	32 (27 to 39)	31 (24 to 41)	42 (35 to 57)	46 (36 to 55)	<0.001†

HADS=Hospital Anxiety and Depression Scale; PSA=prostate specific antigen.

*From ordinary least squares regression.

†From non-parametric comparison of medians.

Table 2| Specific symptoms—prevalence and association with moderate or severe problem within 7 days and within 35 days

Symptom reported	Symptom present		Moderate/serious problem (MS)*	
	Reporting/respondents	% (95% CI)	MS/respondents	% (95% CI)
Within 7 days				
Pain	425/1089	39.0 (36.2 to 42.4)	62/1085	5.7 (4.4 to 7.3)
Fever	128/1090	11.7 (10.0 to 13.8)	44/1088	4.0 (3.0 to 5.4)
Shivers	135/1089	12.4 (10.6 to 14.5)	35/1086	3.2 (2.3 to 4.5)
Haematuria	693/1085	63.9 (61.0 to 66.7)	52/1074	4.8 (3.6 to 6.3)
Haematochezia	354/1076	32.9 (30.0 to 35.8)	18/1061	1.7 (1.0 to 2.7)
Haemoejaculate†	645/747	86.3 (83.7 to 88.6)	148/740	20.0 (17.2 to 23.1)
Any infective/haemorrhagic symptom‡	691/735	94.0 (92.1 to 95.5)	160/714	22.4 (19.5 to 25.6)
Any infective/haemorrhagic symptom§	936/1047	89.4 (87.4 to 91.1)	196/1013	19.3 (17.0 to 21.9)
Within 35 days¶				
Pain	429/984	43.6 (40.5 to 46.7)	71/977	7.3 (5.7 to 9.1)
Fever	172/985	17.5 (15.2 to 20.0)	54/981	5.5 (4.2 to 7.1)
Shivers	185/985	18.8 (16.5 to 21.3)	49/979	5.0 (3.7 to 6.6)
Haematuria	642/976	65.8 (62.7 to 68.7)	59/958	6.2 (4.7 to 7.9)
Haematochezia	356/967	36.8 (33.8 to 39.9)	24/951	2.5 (1.6 to 3.7)
Haemoejaculate†	605/653	92.6 (90.4 to 94.4)	172/646	26.6 (23.3 to 30.2)
Any infective/haemorrhagic symptom‡	622/642	96.9 (95.2 to 98.0)	181/610	29.7 (26.2 to 33.4)
Any infective/haemorrhagic symptom§	881/937	94.0 (92.3 to 95.4)	240/887	27.1 (24.2 to 30.1)

*Presence of symptom causing moderate or severe problem.

†Excludes 339 men reporting no sexual activity at either 7 or 35 day assessment.

‡One or more of fever, shivers, haematuria, haematochezia, and haemoejaculate, excluding men reporting no sexual activity at either 7 or 35 day assessment.

§One or more of fever, shivers, haematuria, haematochezia, and haemoejaculate, including men reporting no sexual activity at either 7 or 35 day assessment.

¶Includes only men with evaluable data for both 7 day and 35 day assessments.

Table 3| Pain and report of attitude to re-biopsy across eight study centres

| Centre | No of biopsies | Immediate report | | | | 7 day report: problem with re-biopsy | |
| | | Pain | | Problem with re-biopsy | | | |
		MS/response*	% (95% CI)	MS/response*	% (95% CI)	MS/response*	% (95% CI)
1	282	21/282	7 (5 to 11)	23/281	8 (6 to 12	30/270	11 (8 to 15)
2	206	37/205	18 (13 to 24)	22/206	11 (7 to 16)	38/192	20 (15 to 26)
3	176	63/174	36 (30 to 44)	37/176	21 (16 to 28)	50/168	30 (23 to 37)
4	149	9/147	6 (3 to 11)	9/147	6 (3 to 11)	21/136	15 (10 to 23)
5	115	16/113	14 (9 to 22)	9/113	8 (4 to 14)	23/109	21 (15 to 30)
6	102	11/102	11 (6 to 18)	9/102	9 (5 to 16)	17/96	18 (11 to 27)
7	56	8/56	14 (7 to 26)	8/56	14 (7 to 26)	19/55	35 (23 to 48)
8	61	7/61	11 (6 to 22)	7/61	11 (6 to 22)	15/59	25 (16 to 38)
Total	1147	172/1140	15.1 (13.1 to 17.3)	124/1142	10.9 (9.2 to 12.8)	213/1085	19.6 (17.4 to 22.1)
P value†		<0.001		<0.001		<0.001	

*Number of men reporting moderate or severe problem/number responding.

†Age adjusted test of null hypothesis (no between centre difference).

Table 4| Associations between factors assessed at time of biopsy or at 7 day assessment (cross sectional analysis) and reporting moderate or major problem with re-biopsy 7 days after biopsy and contact with health services for biopsy related problem within 35 days of biopsy

Factors	Summary statistics in predictors for overall cohort	Problem with re-biopsy		Healthcare contact	
		Odds ratio (95% CI)	P value*	Odds ratio (95% CI)	P value*
Pain of biopsy	172/1140 (15.1%)	8.20 (5.54 to 12.13)	<0.001	1.81 (1.13 to 2.90)	0.017
Infective symptoms at 7 days	47/1083 (4.3%)	7.89 (4.16 to 14.94)	<0.001	16.78 (8.73 to 32.27)	<0.001
Haemorrhagic symptoms at 7 days	179/1022 (17.5%)	4.24 (2.92 to 6.15)	<0.001	2.89 (1.88 to 4.44)	<0.001
Age (odds ratio per 5 years)	Mean 62.1 (SD 5.1) years (n=1147)	0.86 (0.75 to 1.00)	0.056	1.11 (0.93 to 1.34)	0.25
Prostate volume (odds ratio per 20 mL)	Mean 43.5 (SD 22.8) mL (n=1062)	0.82 (0.69 to 0.99)	0.027	1.16 (0.99 to 1.37)	0.072
History of urinary tract infection	81/1097 (7.4%)	0.96 (0.52 to 1.79)	0.91	1.99 (1.08 to 3.65)	0.036
History of prostatitis	18/1094 (1.6%)	1.41 (0.47 to 4.18)	0.55	2.99 (1.02 to 8.76)	0.065
Positive midstream urine at biopsy	18/1078 (1.7%)	1.15 (0.32 to 4.15)	0.84	2.69 (0.93 to 7.80)	0.091
Warfarin treatment	14/1091 (1.3%)	0.38 (0.05 to 3.00)	0.30	2.99 (0.91 to 9.85)	0.097
Haematuria/clots in first voided urine	81/1055 (7.7%)	1.04 (0.59 to 1.85)	0.89	1.12 (0.56 to 2.22)	0.75
Aspirin treatment	244/1096 (22.3%)	0.87 (0.58 to 1.29)	0.48	0.87 (0.54 to 1.39)	0.55
NSAID treatment	58/1093 (5.3%)	0.68 (0.32 to 1.43)	0.29	0.85 (0.35 to 2.04)	0.71

Odds ratios and P values are adjusted for age and centre.

NSAID=non-steroidal anti-inflammatory drug.

*Calculated with likelihood ratio tests.