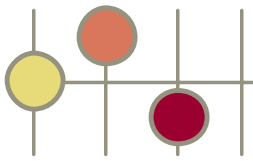

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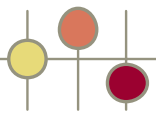
Diagnostic Value of Systematic Prostate Biopsy Methods in the Investigation for Prostate Cancer

A Systematic Review



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REPORT 29

DIAGNOSTIC VALUE OF SYSTEMATIC PROSTATE BIOPSY METHODS IN THE INVESTIGATION FOR PROSTATE CANCER

A SYSTEMATIC REVIEW

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CONTENTS

LIST OF TABLES AND FIGURES

ABBREVIATIONS

CDR.....cancer detection rate

Ca.....cancer

DRE.....digital rectal examination

HGPIN.....high grade prostatic intraepithelial neoplasia

LD..... lesion directed (prostate biopsies)

LPZ.....lateral peripheral zone

MPZ..... mid-lobar peripheral zone

MLiPZ.....mid-line peripheral zone

n.a. .....not available, not applicable

NNB.....Number needed to biopsy

NNT .....number needed to treat

PrCa .....prostate cancer

PSA ..... prostate specific antigen

PZ.....peripheral zone

RCT .....randomised controlled trial

RPR.....relative positivity rate

TRNB..... transrectal needle biopsy

TRUS.....transrectal ultrasound

TZ .....transition zone

US .....ultrasound

ABSTRACT

Objective To compare the diagnostic performance of systematic prostate biopsy schemes in men scheduled for biopsy due to suspected prostate cancer.

Design Systematic review

Data sources Electronic databases, reference lists of included studies, relevant urological journals, and experts.

Review methods We included studies that compared the cancer yield of a systematic prostate biopsy scheme (index test) with any systematic reference scheme in the same population of men. We excluded studies that did not compare the tests in the same population, non-systematic biopsies, and computer simulation studies. The primary measure of comparison between index test (in general the standard sextant scheme) and reference test was the relative positivity rate (RPR) of the index test. We pooled data using a random effects model, where appropriate.

Results Eighty-seven studies with 20,698 patients were analysed. The standard sextant scheme had a significantly lower cancer yield than most of the more extensive biopsy schemes. Adding laterally directed cores increased the yield significantly, whereas additional transition zone cores did not. Schemes with 18 and more cores of the 5-region pattern showed the highest cancer yield (RPR 1.48; 95%-CI 1.32-1.66). However, the difference in the cancer yield of this scheme to the yield of the 12-core scheme from pattern ‘mid-lobar peripheral zone + lateral peripheral zone’ (RPR 1.31; 95%-CI 1.25-1.37) and the 10-core scheme of the 5-region pattern (RPR 1.38; 95%-CI 1.08-1.76) was not statistically significant. While some evidence suggests that adverse events for schemes up to 12 cores are similar to those of the sextant pattern, this remains unclear for more extended schemes.

Conclusions Schemes, which apply additional laterally directed cores, showed a higher cancer yield. It still has to be demonstrated that extended biopsy schemes with a higher cancer yield do lead to a survival benefit due to early cancer detection.

EXECUTIVE SUMMARY

Background

Prostate cancer is the second leading cause of male cancer death in Europe and North America. Opportunistic or population screening programmes using the prostate specific antigen (PSA) test have been introduced to detect localized cancer stages that may progress to advanced disease. Generally, patients with raised PSA levels or abnormal rectal digital examination undergo ultrasound guided transrectal needle biopsy (TRNB) to gain specimens of the prostate for a histopathological diagnosis. This diagnostic procedure has considerable public health implications due to its widespread use.

For many years, the systematic sextant biopsy protocol (i.e. a fixed pattern with three cores from the apex, the middle and base of the prostate bilaterally in the mid-lobar peripheral zone) has been the standard procedure. Recently studies with more extended schemes have shown that the standard sextant protocol leaves between 10% and 30% of cancers undetected. Consequently, many new biopsy protocols have been proposed with respect to their main features 'number of biopsy cores' (from 6 cores up to 32 in some studies) and 'biopsy pattern' (i.e. the anatomical prostate areas where the cores are taken). Some guidelines recommend laterally directed cores. Some experts propose biopsy schemes with up to 12 cores. Evidence from computer simulation studies suggests that laterally placed biopsies or multi site-directed schemes might be the most efficient patterns. Recent surveys showed that the traditional sextant biopsy was still applied by about 20% of US community urologists and by about 70% of the surveyed centres in the UK reflecting the ongoing debate about the optimal biopsy scheme.

Objectives of this systematic review

i) To carry out a systematic review to compare the diagnostic value of various systematic prostate biopsy methods in the diagnostic work up of men scheduled for biopsy for the evaluation of possible prostate cancer.

ii) To formulate recommendations for application of optimal biopsy schemes in clinical practice.

Methods

Study selection

Prospective studies were included that compared the cancer yield of a systematic prostate biopsy scheme (index test) with a systematic reference test. Sufficient information had to be available to construct a 2 x 2 table. Excluded were studies that did not compare the index test with the reference test in the same population, non-systematic biopsy schemes (e.g. lesion directed biopsies), and computer simulation studies. Included participants were men of all age groups with suspected prostate cancer scheduled for a prostate biopsy. Men with already proven prostate cancer were excluded.

Test accuracy studies that use an accepted gold standard to calculate classical diagnostic test parameters (e.g. sensitivity, positive predictive value) were not available for this clinical situation. Patients with a negative biopsy do not undergo prostatectomy nor do all patients with a positive biopsy undergo surgery in the presence of alternative treatments like radical radiation. Studies were therefore selected comparing different systematic prostate biopsy methods with each other in the same population. These studies use either a sequential sampling design or a randomised design.

Data sources

Electronic databases were searched without language restriction from 1980 onwards (MEDLINE, PREMEDLINE, Cochrane Library, EMBASE, BIOSIS, Pascal, LILACS, Science Citation Index, Current Contents, Inside Conferences, Dissertation Abstracts, SIGLE, and NTIS; last search May 2004). We screened reference lists of included papers, contacted experts and manufacturers and relevant urological journals were hand searched. (Detailed inclusion criteria and search strategy in the appendix.)

Anatomic model

An advisory board was established including clinical experts and methodologists (see acknowledgements). The widely established '5-region anatomic model' of the prostate introduced by Eskew was chosen to describe different biopsy patterns Biopsies in region 1 and 5 sample tissue from the lateral peripheral zone (LPZ), in region 2 and 4 from the mid-lobar peripheral zone (MPZ; the area of the standard sextant pattern) and in region 3 from the transition zone (TZ) and possibly of the mid-line peripheral zone (MLiPZ).

This model was used to describe seven different biopsy patterns as combinations of those regions. A matrix was then constructed that combined the main features of the biopsy schemes 'pattern' and 'number of cores'. Thus, similar biopsy methods could be clustered in the same cell of the matrix according to their two main features pattern and number of cores.

Data extraction

The systematic review was undertaken in accordance with current guidelines. Teams of two reviewers independently screened titles and abstracts, assessed studies for inclusion by full text, and extracted data. Disagreements between reviewers were resolved by consensus. Data were extracted on study population, test details, methodological characteristics and aspects relevant for implementation into daily routine. If a study provided several index tests it could be categorized to several cells of the matrix. In theory, most of the studies with extended biopsy methods could have provided many comparisons. Sometimes up to 10 schemes were reported whereas most of the authors focussed on two or three schemes. In order to prevent over-weighting of studies and to assure that each study contributed to a cell only once a maximum four biopsy schemes per study were extracted (the most extensive scheme and additional pivotal schemes that represented the main results of the study). Data for studies with transrectal and transperineal biopsy approach were extracted using the same procedure relying on the authors' information in the methods section. In studies with sequential sampling, adverse events were counted for the most extensive scheme. In studies with randomised design we were able to count adverse events for each scheme separately. For quality assessment we used selected criteria from QUADAS (e.g. spectrum bias, patient selection, review bias) and additional clinical quality items (e.g. length of follow up to detect adverse effects like infection; details see appendix). We chose no pre-specified quality categorisation as weighting of items is problematic. In randomised diagnostic studies, we additionally assessed the generation of random sequence and concealment of allocation.

Analyses

We calculated the cancer detection rate (CDR number of cancers detected / number of persons biopsied) for each biopsy method. Our primary measure of comparison between index test and reference test was the relative positivity rate (RPR cancer detection rate of index test/cancer detection rate of reference test). An RPR of 1.33 for example means that the index test (e.g. a 12-core scheme) will discover 33% more cancers in comparison to the reference test (e.g. a 6-core scheme). A value of 1.0 means, that the index test will discover as many cancers as the reference test. A risk ratio, like the RPR, better accounts for variable cancer prevalences between study populations and cancer distributions within the prostate than the crude CDR.

We pooled the RPR of all schemes with the same 'pattern', the same 'number of cores' (and the standard sextant pattern as reference test) using a random effects model to account for unexplained clinical and methodological heterogeneity. We did not pool data that were derived from different study designs like sequential sampling design and randomised design. Thus we derived a summary estimate for the RPR of each cell of the matrix. We tested for heterogeneity within each cell using the I2 test for heterogeneity and Cochran's Q (defining heterogeneity as absent at a p-value >0.1). We tried to explain heterogeneity by stratification for methodological characteristics, mean patients' age, mean PSA levels, mean prostate volumes, and first or repeat biopsy population.

Using univariable models, we investigated the effect on the cancer yield of adding a specific anatomical prostate region to a given pattern. We also investigated the effect of the number of cores on the cancer yield.

With a multivariable model we analysed the combined effect of adding a specific region and of the number of cores on the cancer yield. For the pooled results we evaluated if study characteristics had

a systematic impact on study results. We summarized data for adverse events in tabulated form. Analyses were performed using the STATA 8.2 software package (StataCorp. 2004. Stata Statistical Software, College Station, Texas, USA).

Results

Eighty-seven studies with 20,698 patients met the inclusion criteria (study details see appendix). Eighty studies used a sequential sampling (n=19,307) and seven studies (n=1391) a randomised design.

In 66 of 70 studies the mean age of participants lay between 60 and 70 years (17 studies without age information). Mean PSA values ranged from 4.8 to 52.5 ng/ml.

Most of the included studies (68/87; i.e. 78.2%) used the standard sextant scheme as the reference test. We extracted data of 94 comparisons from these 68 studies. Additionally, 23 comparisons from 19 studies with a different reference test were extracted. Therefore, a total of 117 comparisons from 87 studies were analysed.

Methodological quality

Forty-five of 87 studies (52%) provided sufficient information to conclude that the spectrum of the patients was representative for patients who will receive the test in practice (8 of the 45 studies involved a screening population). Only 28 studies (32%) clearly described selection criteria. Eighteen studies (21%) described the index test and the reference test in sufficient detail according to our predefined criteria. Only one study reported that the pathologist was blinded for test sequence. Information about skills of examiners, length of follow up, and method of histological work up was scarce.

Of the seven randomised studies, only three studies reported a suitable method for generation of the random sequence and only two studies reported that the allocation to the groups was concealed (details see full report http//www.york.ac.uk/inst/crd/).

Cancer yield

Schemes with 18 to 22 cores of the 5-region pattern showed the highest cancer yield of all clusters compared to the standard sextant scheme (3 studies; RPR 1.48; 95%-CI 1.32-1.66).

Schemes with 12 cores from biopsy pattern ‘MPZ+LPZ’ showed a RPR of 1.31 (95%-CI 1.25-1.37) compared to the standard sextant scheme (16 studies). Ten-core schemes from this ‘MPZ+LPZ’-pattern had a RPR of 1.25 (95%-CI 1.19-1.33; 13 studies; evidence for heterogeneity).

Cancer yields of pattern ‘MPZ+TZ (+MiLPZ)’ and of pattern ‘LPZ’ were lower (RPR ranged from 1.04 to 1.23 and from 0.86 to 1.15, respectively).

(Result of randomised studies see appendix; studies with different reference test see full report http//www.york.ac.uk/inst/crd/).

The number of cores was significantly associated with the cancer yield. The addition of laterally directed cores from the lateral peripheral zone to a mid-lobar peripheral zone pattern (‘MPZ+LPZ’) enhanced the cancer yield significantly (p=0.003). If transition zone biopsies (‘TZ’) are added to obtain a 5-region biopsy (‘MPZ+LPZ+TZ’) the additional cancer yield was no longer statistically significant (p=0.62).

Analysis of the combined effect of the biopsy pattern and the number of cores with a multivariable model showed that the cluster with the highest RPR (18-22 cores of the 5-region pattern) had a significantly higher yield than most of the clusters. However, there was no statistically significant difference between this scheme and the 12-core scheme from pattern ‘MPZ+LPZ’ or the 10-core scheme from the 5-region pattern.

Adverse events

As reporting of adverse events was poor and methods of data collection for this outcome varied between studies, we did not perform a statistical analysis based on the overall data. Results were summarized in a tabulated form grouped for the number of cores taken. Minor adverse events (minor haematuria, minor haematospermia, minor rectal bleeding, pain/discomfort) were common and reported over a wide range of frequencies. major complications were less frequent Major infections (e.g. bacteraemia, urosepsis, abscess) with 0.0% to 1.8%, and major bleeding with 0.0% to 0.6%. No death due to a prostate biopsy was reported.

We could not discover a systematic pattern of increase of adverse events when more cores were taken. However, studies with more extended schemes sometimes used more invasive strategies to achieve patient tolerance or to avoid adverse events (e.g. intravenous sedation or general anaesthesia; extended antibiotic regimens; urinary catheter).

For our quantitative analysis of adverse events we relied on randomised studies only as they reported adverse events for the reference test and the index test group separately and used identical methods of data collection. Four of seven randomised studies reported numerical results for adverse events. In 2 studies a 12-core scheme and in one study a 10-core scheme from ‘MPZ+LPZ’ was compared with a 6-core scheme. None of these studies reported about major adverse events (like death, major bleeding or major infection). There was no statistical significant difference between the rates of minor adverse events of the schemes up to 12-cores and the 6-core schemes (data of three studies for minor infection, haematuria, and haematospermia). Schemes up to 12 cores tended to result in higher rates of minor rectal bleeding (absolute risk difference 0.08; 95%-CI 0.00-0.16; p=0.037; data of two studies).

In one study the rate of patients with moderate or severe pain was not different between a 10-core scheme and a 6-core scheme (33% vs. 32%) and in another study more patients with a 14-core scheme reported ‘discomfort’ than those with a 10-core scheme (65% vs. 28%).

Discussion of the results

This systematic review showed that most of the more extensive biopsy schemes have a significantly higher cancer yield than the standard sextant scheme. The addition of laterally directed cores from the lateral peripheral zone (LPZ) to the mid-lobar peripheral zone (MPZ) increased the yield significantly. Biopsy schemes with 18-22 cores from the 5-region pattern showed the highest RPR. The difference in the cancer yield of this scheme and the yield of 12 cores from pattern ‘MPZ+LPZ’ and the yield of 10 cores from the 5-region pattern was not significant however. While some evidence suggests that adverse events for schemes up to 12 cores are similar to those of the sextant pattern, this remains unclear for more extended schemes.

Validity of the findings

Eighty-seven studies including more than 20,000 patients were analysed. Most of the studies used a valid sequential sampling design in which each patient acted as his own control.

The following limitations have to be discussed. First, the quality of reporting in the primary studies was often poor. The influence of different patient profiles (i.e. selection criteria, PSA levels, prostate volume or first vs. repeated biopsies) on the pooled results could not be assessed systematically. Lack of data comparing test details, biopsy equipment, skills of the operators, and work up of specimens was an additional shortcoming. As a consequence, the external validity of the results of this review is limited. Secondly, the chosen anatomic model with five biopsy regions may have some limitations. Core length and angle of the needle can sometimes be modifying factors. Thirdly, the biopsy schemes clustered in one cell of the matrix may not be exactly identical. We are convinced, however, that the anatomic model, which was derived in cooperation with the expert panel, provides a reasonable compromise of accuracy and practicability for the research question.

Clinical interpretation

The standard sextant scheme has a significantly lower cancer yield than most of the more extensive biopsy schemes.

As the number of cores increases, the yield improves for most of the schemes. Addition of laterally directed cores from the lateral peripheral zone (LPZ) to the mid-lobar peripheral zone (MPZ) increases the yield significantly, whereas additional transition zone (TZ) cores did not.

Data on adverse events are scarce. While some evidence suggests that adverse events for schemes up to 12 cores are similar to those of the sextant pattern, this remains unclear for more extended schemes.

Applying more complex biopsy schemes to clinical practice will need special training for less experienced examiners and measures for quality control. Patient tolerance, which can be improved by proper local anaesthesia, is another important point that has to be taken into consideration for applicability of the extended schemes.

Whether the results of the analysed studies translate directly into clinical routine is not clear as populations may differ from those in clinical practice.

Recommendations

For recommendations of a biopsy scheme in clinical practice some priorities have to be defined in advance (highest possible cancer yield vs. efficient cancer detection with a balanced rate of adverse events).

The 5-region biopsy schemes with 18 and more cores are an option, if the highest possible cancer yield is the first aim. This aim has been questioned, however, as PSA screening may lead to over-diagnosis rather than under-diagnosis. False positive results (i.e. no diagnosis of cancer in the prostatectomy specimen after a ‘positive’ biopsy), that might result in psychological or physical harm, have so far been scarce but might increase if a maximum of cores is taken. Cost issues have to be considered as well. In addition, there is insufficient evidence in our data to determine whether extended biopsy schemes do increase the rate of major adverse events.

Some evidence from randomised studies suggests that adverse events for schemes up to 12 cores are similar to those of the sextant pattern. If a maximum of 12 cores are taken the pattern ‘MPZ+LPZ’ may be chosen. If a maximum of 10 cores is aimed at, either 10 cores from pattern ‘MPZ+LPZ’ or alternatively 10 cores of the 5-region pattern may be appropriate. However, the pooled results of both 10-core schemes have to be interpreted with caution, as there was evidence for heterogeneity. Based on our findings that additional TZ-cores had a low additional value the 10-core schemes from pattern ‘MPZ+LPZ’ may be preferable.

These recommendations are in line with biopsy patterns applied in current large-scale studies. This systematic review gives empiric foundation for this decision. The European Randomised Study of Screening for Prostate Cancer (ERSPC) decided in their initial protocol to apply sextant biopsies. In many centres, however, it has become common practice to take 10 to 12 cores for this study. In the British ProtecT-study the biopsy protocol has been recently modified to a 10-core pattern.

Implications for future research

i) A standardised nomenclature of anatomical regions has to be applied in future studies for a better comparison of different prostate biopsy schemes.

ii) Future studies should report better about patient characteristics and consider restriction to prognostically homogeneous subgroups.

iii) There should be a standardised reporting of patient preparation, biopsy procedure and the method of histological work-up to enable a better comparison of the diagnostic performance of different biopsy schemes.

iiii) Striking the balance between cancer yield and adverse events is the challenge that could not be assessed satisfactorily in this report. Future studies should focus on this issue.

iiiii) It has to be demonstrated that more extensive biopsy schemes with a higher cancer yield do lead to reduced cancer mortality due to early detection of prostate cancer.

CHAPTER 1 BACKGROUND

1.1 Burden of disease

In Europe and North America, prostate cancer is the most common non-skin malignancy and second leading cause of male cancer death. The reported incidence of this malignancy rose steadily since the late 1980s and has only recently declined. The age adjusted death rates of prostate cancer (per 100,000 population) in the period 1995 to1997 range from 29.7 in Norway, 27.7 in Sweden, 20.5 in the UK, 16.7 in US (14.7 in white and 35.5 in non-white), to 18.2 in Spain, 12.2 in Greece, 9.4 in Russian Federation and 6.7 in Japan.[1]

In 1998 the new cases of prostate cancer in Wales represented 18% of new male cancer cases. This made it - just - the most common cancer in men in Wales.[2] In May 2002, the Institute of Cancer Research predicted that prostate cancer would soon overtake lung cancer to become the most common cancer in men in the UK.

The disease is uncommon in younger men, with incidence increasing with age. For instance, for the period 1989 to 1998, less than 5% of cases in Wales were in men under 60, and over half of all new cases were in men aged 75 and more.[2]

There is considerable uncertainty about the natural history of prostate cancer. Autopsy studies show that 30% to 40% of men over 50, who had no symptoms of prostate cancer whilst alive, have histological evidence of prostate cancer at the time of death.[3,4] This percentage rises to 60% to 70% in men over 80 years of age.[5]

This is because most prostate cancers in the population are slow growing and unlikely to cause clinically important symptoms during a man's life. Obviously, prostate cancer in younger men has a greater chance of clinically progressing because of their longer remaining life span.[3]

1.2 Detection of prostate cancer

As the first non-invasive steps in the chain of measures to detect prostate cancer the digital rectal examination (DRE) and a prostate-specific antigen testing (PSA testing) are used. It is more difficult to detect cancer with DRE than with PSA.[6]

In the case of a raised PSA-test result a prostate biopsy is performed to gain specimens for the diagnostic workup for prostate cancer. A prostate biopsy is an invasive diagnostic procedure, which can be used to confirm or to rule out the diagnosis of prostate cancer. The biopsy is most often conducted as a transrectal needle biopsy (TRNB) under transrectal ultrasound (TRUS) guidance and antibiotic prophylaxis to gain specimens of the organ for a histopathological diagnosis. In some centres a transperineal technique is applied. The prostate biopsy is embedded in a chain of several diagnostic procedures, which are described below (see figure 1.1). If a carcinoma is confirmed by the pathologist, several therapeutic options can be discussed which range from ‘active monitoring’ to radical prostatectomy.[7] Management of men who have demonstrated a raised PSA level but whose biopsy was negative is subject to individual patient and clinician discussion. If a carcinoma is not confirmed and there is a high index of suspicion of a false negative biopsy results repeat prostate biopsies can be performed.[8]

Prostate biopsy methods

Various systematic prostate biopsy methods and strategies are established in daily work. Systematic biopsy means that biopsy taking follows a well defined pattern. These procedures are discussed in the literature with respect to their respective diagnostic accuracy to detect prostate cancer. The differences between these systematic methods and strategies refer to the following points:

Number of biopsy cores to be taken

For many years, the sextant biopsy protocol (i.e. 3 cores from the apex, the middle and base of the prostate bilaterally in the mid-lobar peripheral zone) has been the standard procedure.[8,10]

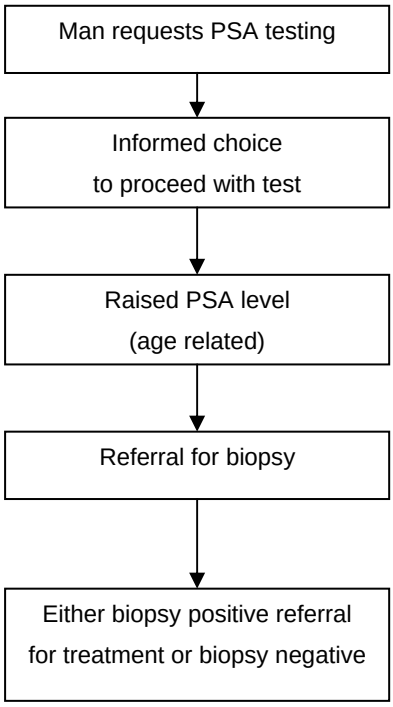


Figure 1.1 Flow chart to illustrate the position of prostate biopsies in the diagnostic work up for prostate cancer
(adopted from NHS Prostate Cancer Risk Management Programme[9]).
The NHS Prostate Cancer Risk Management Programme permits PSA testing on request for asymptomatic men providing the man has made an 'informed choice' to be tested.)

Some studies have shown that the standard sextant protocol leaves about 20% to 30% of cancers undetected and that the detection rate can be enhanced by taking 8 or 10 biopsies depending on the size of the gland.[11,12] Recent publications recommend up to 14 to 18 biopsies as a function of prostate gland size and age to ensure 90% certainty of cancer detection.[8] In patients with a high suspicion of prostate cancer sometimes protocols with up to 32 cores ('saturation biopsies') during repeat biopsies are performed.[13] The more biopsies performed, the greater will be the chance of sampling cancers. To set the absolute number of detected cancers as the first aim may be questionable however. On the other hand, there is no test yet to detect whether a small cancer is clinically insignificant. For some authors the relevant question is whether maximising the detection rate of cancer is really worthwhile and resulting in a decreased prostate cancer mortality.[14,15]

Anatomical prostate areas where cores are taken

With the sextant protocol, tissue cores are obtained bilaterally in the parasaggital plane of the prostate sampling the apex, the mid region and the base of the prostate (at intervals of approximately 1cm). Systematic analyses of radical prostatectomies have shown that prostate cancer expands mostly in the transversal direction of the peripheral zone. The addition of biopsies at different locations in the lateral peripheral zone enhanced the sensitivity for cancer detection.[16,17] As some cancers arise in the transition zone, also transition zone biopsies can be part of recommended systematic biopsy patterns.[18]

Definition of patients who should undergo repeat biopsies after a negative previous biopsy

A negative (previous) biopsy in patients with a high index of suspicion for prostate cancer is a well known clinical situation. At least 10% of patients with a negative first time biopsy were diagnosed with prostate cancer in the repeat biopsy of the European Prostate Cancer detection (EPCD) study.[8] In some studies the cancer detection rate for repeat biopsies was up to 30%.[18] Some predictors of cancer in men who had undergone previous negative prostate biopsies have been defined.[8,19] The indications for repeat biopsy are, however, not clearly defined.

Maximal number of sets of repeat biopsies

The indications for the optimal number of sets of repeat biopsy are not clearly defined. In the EPCD-study the cancer detection rates from biopsy 1 (first time biopsy), to biopsy 2 (first repeat biopsy), biopsy 3 and biopsy 4 decreased in the respective biopsy set from 22% to 4%[8].

Lesion directed biopsies

In the same session so-called additional lesion directed biopsies are sometimes taken out of suspicious prostate regions (suspicious due to palpation or ultrasound). These cores are taken in addition to the systematically taken cores. Thus additional lesion directed biopsies are not part of the systematic biopsy methods, do not follow a well-defined pattern and enhance the number of cores taken.

If lesions are located within the systematic pattern some authors incorporate them into their systematic approach by directing the needle to those lesions without enhancing the total number of cores taken.

1.3 NHS Prostate Cancer Risk Management Programme

There is increasing pressure on doctors to test men for the early detection of prostate cancer.[3] However, there is currently no evidence that population-wide screening will reduce mortality from prostate cancer [3,6,20] and therefore screening has not been introduced in the NHS. In a recent study, the five-year probability of death (all causes) after diagnosis of early prostate cancer for men in their mid-sixties is about 10% for radical prostatectomy and for watchful waiting.[7]

PSA testing on the other hand is often used opportunistically for testing for prostate cancer (testing of individual patients driven following consultation between patients and physicians). Different cut-off values (thresholds) and different PSA-ratios (e.g. free to bound PSA) are used to define a raised test result, which then may lead to biopsy. In this context the NHS Prostate Cancer Risk Management Programme[9] was first introduced in July 2001 by Ministers, with a detailed pack for General Practitioners and leaflets for men introduced in September 2002. The NHS Prostate Cancer Risk Management Programme permits PSA testing on request for asymptomatic men provided the man has made an 'informed choice' to be tested (see figure 1.1).

In this investigation, commissioned in the context of the Prostate Cancer Risk Management Programme, the diagnostic value and possible adverse effects of recommended biopsy methods were systematically compared as a rational base for future recommendations. Our study will not focus on the screening topics mentioned above or on the value of PSA testing and the different definitions of a raised test result. The research objective is the diagnostic work up, which is done with prostate needle biopsy after a raised PSA test result that is defined in different ways.

Several points have to be addressed to choose the best possible prostate biopsy method. The primary determinant of the benefit of a prostate biopsy method is the test's sensitivity for detecting prostate cancer. Biopsy regimens with a reduced diagnostic accuracy (enhanced rate of false negative results) would lead to a delayed diagnosis. This could be of importance if rapidly growing tumours are not detected. False positive results (the histological diagnosis of carcinoma based on the biopsy specimens without carcinoma in the gland) leading to an unnecessary operation are scarce.[21] The question of how to avoid the detection of so called 'minimal' cancers, which will not be of clinical significance for men during their life span remains an important question, too.[22]

Different prostate biopsy methods may cause a variable degree of discomfort and pain. Some of the possible complications of the invasive biopsy are bleeding, localized infection, abscesses and, very, rarely death. This might be particularly important for patients with a relatively low risk of prostate cancer, e.g. young patients who wish to be PSA tested.

1.4 Existing knowledge and recommendations

Various computer simulation studies[23-26] have been conducted in the past to analyse the distribution of prostate cancer in the gland and to give recommendations for optimal biopsy schemes. The main findings were that laterally placed biopsies with 10 to 12 cores [23] or multisite-directed schemes with 11 cores[24] (at a maximum of 18 tested cores in each study) may be the most efficient schemes. A recent

computer simulation study[25] which developed a cancer distribution map of the prostate suggested that cancer may be most prevalent in the mid and apex zones however. One study recommended a gland volume-based biopsy algorithm setting the emphasis on the number of cores (up to 12) with even distribution over the gland.[26]

Current recommendations of experts often conclude that the optimal biopsy scheme still has to be defined[27-29] or recommendations for a state of the art biopsy scheme are not explicit.[29-32] For some experts sextant biopsies remain the gold standard for the detection of prostate cancer[22] even though they point at the limitations of this method. Some authors provide decision aids for taking more than 6 cores.[15,33] Ten or twelve multiple core biopsies have been adopted in many academic centres.[27] Laterally directed and extended biopsy schemes (with 8 to 12 cores)[34 35] or age and prostate volume adjusted schemes (with 8 to 14 cores)[8] are recommended. However, recent surveys[36,37] among academic centres and community urologists, evaluating the current state of prostate biopsy taking in clinical practice, showed considerable disagreement reflecting an ongoing debate about the optimal biopsy scheme. A study from the United States[36] showed a high variability among urologists in their applied biopsy procedures. Twenty-three percent of the responding American urologists each applied an 8-core or a 10-core scheme (most frequently from midline and lateral zones), whereas 17% used a sextant scheme and 13% a 5-region biopsy with 13 cores. A telephone survey from the UK and the Republic of Ireland[37] involved 60 centres across 12 regions. Most centres (78%) performed sextant biopsies. Some centres took 10 or more cores (21%).

The current European Randomised Study of Screening for Prostate Cancer (ERSPC), a big-scale multinational study to evaluate the efficacy of prostate cancer screening, decided in their initial protocol to apply sextant biopsies. In many centres, however, it has become common practice to take 10 to 12 cores for this study.[38] In the British ProtecT-study[39] the biopsy protocol has been recently enhanced to a 10-core scheme (personal communication).

Some guidelines based on consensus do not address the biopsy procedure specifically and make no recommendations for a special biopsy scheme.[6] The EAU (European Association of Urology) Guidelines on Prostate Cancer[40] (last online access on www.uroweb.org 12th August 2004) emphasize laterally directed sextant biopsies to optimise the cancer detection rate by including posterolateral aspects of the gland.

A systematic review about the diagnostic value of different systematic prostate biopsy methods is lacking. As a rational base for future recommendations the diagnostic value and possible adverse effects of recommended biopsy methods were systematically compared together with consideration of their widespread applicability in routine practice.

CHAPTER 2 OBJECTIVES OF THIS SYSTEMATIC REVIEW

i) To carry out a systematic review to compare the diagnostic value of various systematic prostate biopsy methods in the diagnostic work up of men scheduled for biopsy for the evaluation of possible prostate cancer.

ii) To formulate recommendations for application of optimal biopsy schemes in clinical practice.

CHAPTER 3 METHODS

A systematic review of the literature was undertaken to determine the diagnostic value of various systematic prostate biopsy methods in the diagnostic work up of men scheduled for biopsy for the evaluation of possible prostate cancer. The systematic review was undertaken in accordance with the Centre for Reviews and Dissemination (CRD) guidelines for undertaking systematic reviews[41] and published guidelines on the meta-analysis of diagnostic tests.[42-44]

An advisory panel was established and invited to offer comment on the protocol and draft report. The panel consisted of a urologist, a radiologist, a pathologist and experts on the methodological aspects of diagnostic tests. Members of the advisory panel and other experts in relevant areas (e.g. a statistician with special expertise in diagnostic tests) were contacted to help identify further information and theoretical perspectives relevant to the review.

3.1 Methodological considerations

Some methodological aspects had to be taken into consideration for a suitable approach.

Analysis of test accuracy studies

The preferred approach would have been an analysis of test accuracy studies of different systematic prostate biopsy methods. Diagnostic accuracy studies follow a similar basic structure. They aim to determine how good a particular test, known as the 'index' test, is at detecting the target condition. A series of patients receive the test (or tests) of interest, known as the 'index test(s)' and also a reference standard. The results of the index test(s) or interpretations thereof are then compared to the results of the reference standard, i.e. the degree of association between an index test (diagnostic indicator) and the definitive diagnosis is investigated. The reference standard should be the best available method to determine whether or not the patient has the condition being tested for.[45] In the context of prostate biopsies the index test under evaluation is the respective diagnostic biopsy method and the reference standard is the complete histological workup of the removed prostate gland after surgery.

In a typical test accuracy study, all the participants receive both the index test and the reference standard to evaluate positive and negative test results of the index test, e.g. colonoscopy irrespective of positive or negative test results for FOBT (faecal occult blood testing) in screening for colorectal carcinoma. In the context of diagnosing prostate carcinoma this is normally not the case patients with a negative prostate biopsy (i.e. no carcinoma cells found) will not undergo surgery. That means that it is not possible to construct a complete 2 x 2 table (index test vs. gold standard) because the results of the gold standard (histological workup after surgery) are lacking for negative results of the index test (prostate biopsy).

As expected, our literature search did not retrieve diagnostic studies with surgery after a negative biopsy (two studies were retrieved that reported about surgery after negative biopsy but only in patients with already known prostate cancer or bladder cancer who are not representative for our study population.[46,47]) Thus it was not possible in this context to count on classical test accuracy studies.

Additionally, there are alternative forms of cancer treatment – like radical radiotherapy, brachytherapy and cryotherapy, for whom there is no histological 'radical prostatectomy specimen'. If one would only look at studies with patients who have had subsequent radical prostatectomy - this would cause bias as it potentially favours men with lower stage and lower grade disease.

The solution of this problem could have been that a 'gold standard' less invasive than surgery had to be chosen. But this could have introduced bias (disease progression bias for long term follow up and possible necropsy of index test negative persons) or was hardly feasible (e.g. confirmation biopsy for all patients with a 18 G diameter needle in anaesthesia; no studies found).

Analysis of concordance studies

Thus the second best way for analysis was to rely on studies that are comparing different systematic prostate biopsy methods with each other (concordance studies). One approach for those concordance studies is to randomise the study population to either the standard method (e.g. the systematic sextant prostate biopsies as the reference test) or to a more extensive systematic sample strategy (the respective index test under evaluation). An alternative and more efficient study design is a sequential sampling for all patients starting with the standard sextant method and then extending to the more extensive index test in the same session. This approach requires separately labelled biopsy cores out of clearly defined anatomical prostate regions and a pathological diagnosis according to these well defined gland regions. With this approach it is possible to define the diagnostic value of the specimens taken additionally to a reference method (e.g. the standard sextant technique).

Given that more than 80 different methods have been reported in the literature, clinically meaningful patterns of distinct sampling methods had to be defined in consultation with the review advisory panel. After grouping studies (or different systematic sampling methods described within studies) which have used similar systematic sample strategies we calculated summary estimates for their additional diagnostic value (see 3.6. Analysis).

Additional study designs used in the literature

Prostate biopsy studies sometimes use several repeat biopsies using the same biopsy pattern within the same collective to get an impression of the maximal possible number of cancers detectable by this method. With this approach some authors calculate a so called ‘cancer detection rate’ for the respective method. This ‘cancer detection rate’ is then compared with the ‘cancer detection rate’ of alternative methods of former studies. Those comparisons do not solve the gold standard problem (they do not use a gold standard) and can be influenced by bias The spectrum of patients with repeat biopsies differs from patients with a first biopsy. In addition those ‘cancer detection rates’ are often derived from different collectives, are susceptible to disease progression bias, and their value for defining the diagnostic value of the respective systematic biopsy method remains unclear. Studies that used the design described above were not included in our review.

3.2 Grouping of biopsy methods

Selection of an existing anatomic prostate model

As a first step we selected an existing anatomic prostate model from the literature. This model was used to define clinically meaningful groups (patterns) of sampling methods, which applied similar sampling strategies. The model served also as a reference for communication and stringent wording within the review team.

The ‘5-region anatomic model’ of the prostate, described by Eskew,[48] is used by several authors for description of biopsy regions and was seen as suitable for the review (see figure 3.1 below).

Grouping of biopsy methods to patterns

In a second step we grouped the biopsy methods to patterns. The grouping of biopsy methods to patterns had to be a reasonable, pragmatic compromise based on the above defined regions, on already used biopsy methods and on computer simulation studies.[23, 24]

Firstly, each pattern had to be as homogenous as possible according to clinical judgement (i.e. grouped biopsy methods were expected to provide a similar diagnostic value and to be applied in technically similar ways). In the second place, different patterns had to be distinct from each other (i.e. each group was expected to provide a different diagnostic value and be technically distinct enough from other groups to be reliably applied as a distinct group of methods in clinical practice).

The following table shows the seven different patterns of how the 5 anatomical regions are included in biopsy schemes in clinical practice. For further details see Appendix 6 ‘Applied anatomic model of prostate regions and grouping of prostate biopsy methods’.

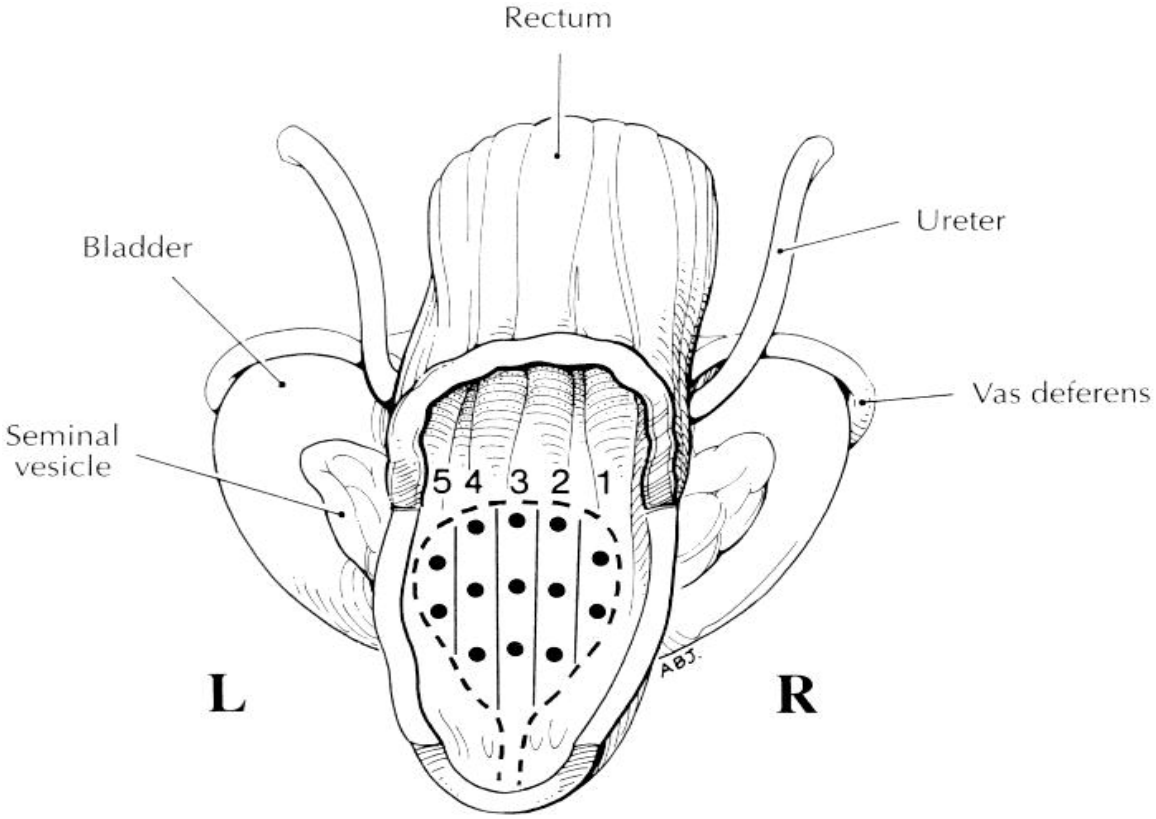


Figure 3.1 '5-region anatomic model' of the prostate in longitudinal plane (figure from Eskew[48]; with permission of the publisher).

In this model biopsies taken out of defined symmetric regions sample different histological zones:
Region 1 Tissue is sampled of the lateral peripheral zone (LPZ)
Region 2 Tissue is sampled of the mid-lobar peripheral zone (MPZ)
Region 3 Tissue is sampled of the transition zone (TZ) and possibly of the mid-line peripheral zone (MLiPZ)
Region 4 Tissue is sampled of the mid-lobar peripheral zone (MPZ)
Region 5 Tissue is sampled of the lateral peripheral zone (LPZ)
For pragmatic reasons we chose this simplified model. Core length and angle of the needle can sometimes be modifying factors. Thus in clinical practice it may happen that biopsies of one region sample tissue out of the transition zone and the peripheral zone as well (e.g. in region 3).

During data extraction, each included primary study was categorized to one of these predefined seven patterns. Additionally the number of cores taken with the respective biopsy pattern was documented. If a study was providing several biopsy patterns under evaluation it could be categorized to several of these predefined seven patterns. We extracted data for studies with transrectal and transperineal biopsy approach using the same procedure and relying on the authors information in the methods section. Cores taken from the left and right anterior horn of the peripheral zone were grouped to the lateral peripheral zone (LPZ) as they represent extreme lateral and anterior peripheral zone tissue.[49] Where the location of the biopsy cores seemed not clear to us we tried to receive further information from the author.

In a next step we constructed a matrix that combined the features 'pattern' and 'number of cores' (table 3.2). Thus it was possible to group similar tests in the same cell of this matrix. Grouping for cores was done in pairs by two (i.e., 8 and 9 cores were grouped together, 10 and 11 cores were grouped together, etc.).

Table 3.1 Grouping of prostate biopsy methods to patterns according to included anatomical regions

Pattern	1	2	3	4	5	6	7
sampled region	MPZ	TZ	LPZ	MPZ+ TZ (+MLiPZ)	LPZ+ TZ (+MLiPZ)	MPZ+LPZ	5-region MPZ+ LPZ+TZ (+MLiPZ)
Region1			**X**		**X**	**X**	**X**
Region2	**X**			**X**		**X**	**X**
Region3		**X**		**X**	**X**		**X**
Region4	**X**			**X**		**X**	**X**
Region5			**X**		**X**	**X**	**X**

(MPZ mid-lobar peripheral zone; LPZ lateral peripheral zone; MLiPZ midline peripheral zone TZ transition zone)

Table 3.2 Matrix for grouping of tests under evaluation to predefined patterns.
Tests under evaluation with the standard sextant test as reference test were grouped according to pattern and number of cores taken.

	Pattern MPZ	Pattern 2	Pattern LPZ	Pattern MPZ+TZ(+ MLiPZ)	Pattern 5	Pattern MPZ+LPZ	The 5-region pattern	
	MPZ	TZ	LPZ	MPZ+TZ (+MLiPZ)	LPZ+TZ	MPZ+LPZ	'5-region' MPZ+LPZ+ TZ (+MLiPZ)	
cores	2 to 12	2 to 6	4 to 6	8 to 10	8	6 to 12	6 to >=24	cores
2								2
4								4
6	*							6
8/9								8/9
10/11								10/11
12/13								12/13
14/15								14/15
16/17								16/17
18/19								18/19
20/21								20/21
22/23								22/23
>=24								>=24

MPZ mid-lobar peripheral zone; LPZ lateral peripheral zone; MLiPZ midline peripheral zone TZ transition zone
*The 6-core scheme of pattern MPZ is the cell of the standard sextant reference test and by definition no study was expected for this cell

3.3 Search strategy

A database of published and unpublished literature was assembled from systematic searches of electronic sources (last search May 2004), hand searching and consultation with experts in the field. The database was built using the Endnote software package.

Diagnostic studies were identified by searching major medical databases including the following MEDLINE, PREMEDLINE, Cochrane Library, EMBASE, BIOSIS, Pascal, LILACS, Science Citation Index, Current Contents, Inside Conferences, Dissertation Abstracts, SIGLE, and NTIS. These databases index both the journal literature and other forms of publication such as conference abstracts, dissertations and reports.

Relevant urological journals, supplements and conference proceedings were hand searched for studies (Journals: Prostate, Journal of Urology, Urology, European Urology, BJU International from

1998 to June 2004 each; forthcoming papers were included where accessible). Relevant authors and manufacturers of biopsy equipment were contacted for unpublished, additional and linked studies.

In addition we undertook Internet searches using Google (http//www.google.co.uk/) and scanned the reference lists of identified included papers from all the searches. Citation searches of key authors were undertaken, too, using key references to search forward in the literature to locate further articles which cite that reference in their bibliographies.

The search strategy is presented in Appendix 1.

3.4 Inclusion/exclusion criteria

The inclusion criteria for the review are summarised below in table 3.3.
We included studies with publication date from 1980 onwards because of the introduction of PSA-tests into clinical routine after this time point.
We searched without language restriction.

The exclusion criteria for the review (with respect to study design and interventions) are summarised below in table 3.4.

Systematic reviews that were relevant to the planned review were eligible as reviews if they met defined inclusion criteria. However, no relevant systematic reviews were retrieved.

Table 3.3 Inclusion criteria for the systematic review of the diagnostic value of various prostate biopsy methods in the diagnostic work up for prostate cancer

Inclusion criteria	
Study design	Any study design* (*After inclusion assessment by full text we had retrieved a large number of prospective studies. To avoid potential bias we decided to exclude studies with a retrospective design.)
Population	Men of all age groups scheduled for a prostate biopsy in the diagnostic investigation for possible prostate cancer
Gold standard	Any reported gold standard (in test accuracy studies) orany reference test in concordance studies
Intervention/tests	a) Any systematic prostate biopsy method used in the diagnosis of prostate cancer as *first* time biopsy b) Any systematic prostate biopsy method used in the diagnosis of prostate cancer as *repeat* biopsy
Results	For test accuracy studies sufficient information to construct a 2 x 2 table For concordance studies sufficient information to construct a 2 x 2 table for paired data to calculate the additional diagnostic value of the index test compared with the reference test in detecting prostate cancer Adverse effects

Table 3.4 Exclusion criteria for the systematic review of the diagnostic value of various prostate biopsy methods in the diagnostic work up for prostate cancer

Exclusion criteria	
Study design	Retrospective study design* (*After inclusion assessment by full text we had retrieved a large number of prospective studies. To avoid potential bias we decided to exclude studies with a retrospective design.)
Intervention/tests	Studies of a single prostate biopsy method without comparison to another method in that population Transperineal prostate biopsy in patients with colitis or anus praeter naturalis (transperineal biopsies in patients with normal intestinum were included) Studies with the *main* topic • Digital rectal examination (DRE) • Prostate specific antigen (PSA) testing • Prostate imaging techniques as main topic (e.g. ultrasound, MRI) • Fine needle aspiration of prostate tissue or comparison of fine needle aspiration vs. core biopsies • Comparison of lesion directed biopsies vs. lesion directed biopsies or vs. random systematic biopsy patterns • Biopsy taking in the assessment of the response to therapy or for cancer staging • Computer simulation models for prostate biopsy taking or ex vivo (in vitro) biopsies of reshaped prostatectomy specimens • Comparison of different methods of anaesthesia or of prophylactic antibiotic regimens for prostate biopsies, studies examining enema application or prophylactic medical regimens for voiding problems after biopsy • Histological workup of specimens

3.5 Assessing relevance and inclusion

Teams of two reviewers independently screened titles and abstracts for each study on Endnote for relevance using a form with the defined study selection criteria. Disagreements between reviewers were resolved by consensus.

Potentially relevant studies were ordered and two reviewers independently assessed for inclusion from the full text. For this step a predefined checklist was constructed, pilot tested and adapted where necessary to enable the best possible consistency for inclusion among the reviewers. Disagreements between reviewers were resolved by consensus.

The form with the study selection criteria (for relevance screening of titles and abstracts) and the checklist (for inclusion of retrieved full text papers) are presented in Appendices 2 and 3. (As it was unclear in advance how many studies with a relevant topic could be retrieved, the study selection criteria and the checklist also covered the issue of adverse events of prostate biopsies as an additional issue.)

3.6 Data extraction

Data extraction forms were developed using Microsoft Access and piloted independently on a small selection of studies. We checked for completeness of items for the intended analysis and for unnecessary items without any additional value for analysis. Data extraction forms were adjusted as necessary. Data were then extracted by one reviewer and checked independently by a second reviewer. Disagreements between reviewers were resolved by consensus.

If a study provided several index tests it could be categorized to several cells of the matrix. In theory, most of the studies with extended biopsy methods could have provided many comparisons. Sometimes up to 10 schemes were reported whereas most of the authors focussed on two or three

schemes. In order to prevent over-weighting of studies and to assure that each study contributed to a cell only once we extracted at maximum four biopsy schemes per study (the most extensive scheme and additional pivotal schemes that represented the main results of the study). We extracted data for studies with transrectal and transperineal biopsy approach using the same procedure relying on the authors' information in the methods section. In studies with sequential sampling we counted adverse events for the most extensive scheme. In studies with randomised design we were able to count adverse events for each scheme separately.

Data were extracted on:

(1) general information study identifier (study number), related studies, author, year, aim of the study, study design, number of participants per study, location (country), and setting.
(2) participant details complete propensity and preceding diagnostic profile of the study population age (mean, range), recruitment (screening, transferral due to symptoms, mixed population), biopsy indication (abnormal DRE and/or raised PSA; abnormal DRE only, raised PSA only); first time biopsy/repeat biopsy/mixed study population; prostate volume of patients (mean, min, max, threshold); PSA-values (thresholds used for PSA; PSA mean and ranges of included patients).
(3) test details for reference test and index test each applicable biopsy pattern, number of biopsy cores taken, biopsy access, needle angulation, additional lesion directed biopsies (if any).
(4) results details of test performance (data to construct a 2 x 2 table; amount of cancers detected in the studied population by the reference test and by the index test; amount of cancers uniquely detected by additional lesion directed biopsies (if any), adverse effects.
(5) practical aspects for implementation in daily routine education level/skills of the examiner (urologist, radiologist, nurses, allied health professionals),[50] number of examiners, training of the examiner (case load biopsies taken per year); technical equipment like ultrasound equipment (ultrasound probe, scan frequency, ultrasound brand), biopsy gun or biopsy needle brand, needle thickness, length of sample or needle throw; patient preparation (anaesthesia method, antibiotic prophylaxis, enema application).[51 52]
Items and detailed answer categories of the data extraction form are presented in the Appendix 4.

3.7 Quality assessment

Quality assessment forms were also developed on Microsoft Access using QUADAS.[45]

The sources of bias that are assessed using the QUADAS instrument are spectrum bias, patient selection, appropriateness of reference standard, verification bias, review bias, and clinical review bias.

As it was not possible to rely on classical test accuracy studies but on concordance studies it was necessary to modify or to remove some of the QUADAS criteria for quality assessment. Most of the QUADAS criteria, however, were applicable for concordance studies

QUADAS criterion 1 Was the spectrum of patients representative?
QUADAS criterion 2 Were selection criteria clearly described?
QUADAS criterion 8 Was the index test (test2) described in sufficient detail to permit replication?
QUADAS criterion 9 Was the reference test described in sufficient detail to permit replication?
QUADAS criterion 10 Were the index test results interpreted without knowledge of results of reference test?
QUADAS criterion 11 Were the reference test results interpreted without knowledge of results of index test?
QUADAS criterion 12 Were the same clinical data available for test interpretation as in clinical practice?
QUADAS criterion 13 Were uninterpretable/intermediate test results reported?
QUADAS criterion 14 Were study withdrawals explained?

Additional clinical quality items were applied to assess the study quality (Follow up long enough for important events to occur? Specific labelling of each core for histological work up reported? Method of histologic work up specified?)[53]

Additional quality items for randomised diagnostic studies referred to the generation of random sequence and the concealment of allocation (Was the method used to assign patients to the group really random? Was the allocation to the groups concealed?).

Quality assessment was carried out by one reviewer and checked independently by a second reviewer. Disagreements between reviewers were resolved by consensus.

Quality assessment was used for descriptive purposes to provide an evaluation of the overall quality of the included studies. We chose no pre-specified quality categorisation as weighing of items is problematic. Based on the findings of the quality assessment, recommendations were made for the conduct of future studies evaluating prostate biopsies for the diagnosis of prostate cancer.

Quality assessment criteria of the data extraction form and explicit definitions for answer categories are presented in the Appendix 5.

3.8 Analysis

3.8.1 Measures of diagnostic performance

As no test accuracy studies were retrieved the classical test parameters like sensitivity, specificity, likelihood ratios, positive and negative predictive values were not calculated.

For the included concordance studies (with sequential sampling or randomised design) we alternatively compared the cancer detection rates of the index test with a reference test.

Most of the included studies (68/87; 78.2%) referred to the standard sextant method[10] as the reference test. Due to pragmatic reasons we also related to this reference test whenever possible to have a standardised reference base for this systematic review.

Data of trials with sequential sampling were tabulated in a 2x2 table for paired data (see figure 3.2) . An example is given for 100 patients and a total cancer detection rate of 40%.

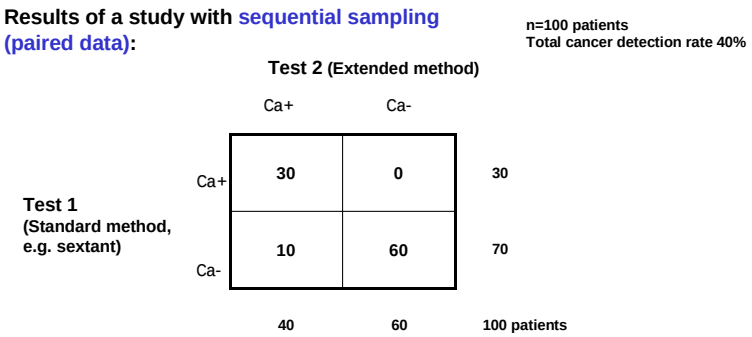


Figure 3.2 2x2 table for paired data

Data of trials with randomised design were tabulated in a 2x2 table for unpaired data (parallel trial design) (see figure 3.3). An example is given for 100 patients with a cancer detection rate of 50% for test 2 and 30% for test 1

Results of a randomised study (parallel trial design)

n= 100 patients
Total cancer detection rate 40%

	Ca+	Ca-	
Test 2 (intervention group)	25	25	50
Test 1 (control group, e.g. Sextant)	15	35	50
	(40)	(60)	N=100 patients

Figure 3.3 2x2 table for unpaired data

As a measure of diagnostic performance we calculated the cancer detection rate for each biopsy method (i.e. for the reference test and for the index test). Our primary measure of comparison for two biopsy methods was the relative positivity rate (RPR). The RPR is defined as Cancer detection rate of index test / Cancer detection rate of reference test. The RPR can be seen as a risk ratio for cancer detection. For each index test we calculated the RPR and its variance.

The absolute cancer detection rate (CDR) of a test depends on the prevalence of the target disease in the studied population resulting in a variation of the event rates across trials.[54] Thus the absolute CDR of a test under evaluation or differences in the CDR between two biopsy schemes seemed not appropriate for our research question. A risk ratio, like the RPR, takes the different study populations with their different prostate cancer prevalences into account and provides a better comparison between primary studies with different populations.[54] We calculated the RPR of each index test using a stepwise approach:

(1) Cancer detection rate of the reference test
Number of cancers detected by the reference test / number of persons biopsied with the reference test

(2) Cancer detection rate of the index test
Number of cancers detected by the index test / number of persons biopsied with the index test

(3) Relative positivity rate of the index test
Cancer detection rate of the index test / Cancer detection rate of the reference test
This analysis for a risk ratio was calculated in a separate way for paired data (sequential sampling) or for unpaired data (randomised studies) depending on the design of the primary study[55]
paired data (sequential sampling) $RPR_{paired}=(a+c)/(a+b)$; 95%CI; SE
unpaired data (randomised studies) $RPR_{un\text{-}paired}=(a/(a+b))/(c/c+d)$; 95%CI; SE

We calculated the following measures additionally:
(4) Unique cancer detection rate of additional lesion directed biopsies (LD)
number of cancers uniquely detected by LD / number of all biopsied persons

(5) Total cancer detection rate
Number of all cancers detected (all methods) / number of all biopsied persons

Additional calculations for studies with sequential sampling:
(6) Concordance rate of the reference test with the index test
(a+d)/(a+b+c+d)

(7) Dis-Concordance rate of the reference test with the index test
(b+c)/(a+b+c+d)

Description of results

For each cell of our matrix we printed the raw data and the respective calculated data (like RPR with 95%-CI) of their primary studies in a tabulated form. This allowed us to get an overview of variation in study results, patient characteristics and study quality for each cell.

We then evaluated the applicability of a statistical meta-analysis of the RPR of the primary studies of each cell. We graphically presented the RPR of each primary study for each cell as a forest plot. We stratified this forest plot according to publication year, study size, study design and patient variables (age groups; PSA-values; prostate volume; first vs. repeat biopsy) to detect visually if the results differed systematically between stratified groups.

Judgements for heterogeneity

As a first step we made judgements from these findings for possible clinical and methodological heterogeneity of the results. Secondly we evaluated heterogeneity statistically using the I^2 Test for heterogeneity.[56] In advance we defined heterogeneity as present at an I^2 value of above 50% (i.e. moderate to high heterogeneity). Thirdly we also evaluated heterogeneity statistically using Cochran's Q. We defined heterogeneity as absent at a p-value > 0.1.

We pooled the RPR of all schemes with the same 'pattern'and the same 'number of cores' (and the standard sextant scheme as reference test) using a random effects model to account for unexplained heterogeneity. We tested for heterogeneity within each cell and tried to explain heterogeneity by methodological characteristics, mean patients' age, mean PSA levels, mean prostate volumes, and first or repeat biopsy population. To get an overview over the diagnostic yield of the analysed clusters we grouped the calculated RPR to the cells of the matrix introduced in chapter 3.2.

Using univariable models we investigated the effect on the cancer yield of adding a specific anatomical prostate region to a given pattern. We also investigated the effect of the number of cores on the cancer yield.

With a multivariable model we analysed the combined effect of adding a specific region and of the number of cores on the cancer yield. For the pooled results of all cells we evaluated if study characteristics had a systematic impact on study results.

We summarized the extracted information for adverse events in a tabulated form and calculated risk differences for adverse events in randomised studies that reported this outcome for both groups (index test and reference test) separately.

Analyses were performed using the STATA 8.2 software package (StataCorp. 2004. Stata Statistical Software, College Station, Texas, USA).

To translate the findings of the systematic review into absolute figures for clinicians and their patients we calculated the NNB (the number needed to biopsy with a defined biopsy scheme for one additional cancer to be discovered in a defined population group with known prevalence of prostate cancer).
We also provided examples for the increased cancer detection rate per 10'000 persons of a hypothetical population scheduled for biopsy. This is an alternative approach to define the absolute diagnostic value of the cores taken additionally to a reference method (e.g. the standard sextant technique).

3.8.2 Adverse events

We have summarized the extracted information for adverse events in a tabulated form. Quantitative analyses were not possible due to inconsistent reporting and different methods of data generation in the primary studies.

We provide an overview for the range of adverse events over all studies that were included. Additionally we have grouped the available adverse events data according to the number of cores taken for biopsy.

For studies with sequential sampling it was not possible to attribute adverse events specifically to one of the reported biopsy schemes. Thus we grouped adverse events to the most extensive scheme. For studies with randomised design we extracted and grouped adverse event data for each study arm (i.e. biopsy scheme) separately.

Detailed information regarding adverse events for each study is provided in Appendix 7.

CHAPTER 4 RESULTS OF THE REVIEW

4.1 Identification of eligible studies

Our searches retrieved 9941 potentially relevant studies. After relevance screening by title and abstracts 823 studies were retrieved for inclusion assessment by full text. 736 studies were excluded (most frequent reasons no comparison of systematic biopsy methods, only background information, case reports, retrospective studies, clinical reviews). 87 studies met the inclusion criteria for the systematic review. From these 87 studies data were extracted and analysed (study flow see figure 4.1).

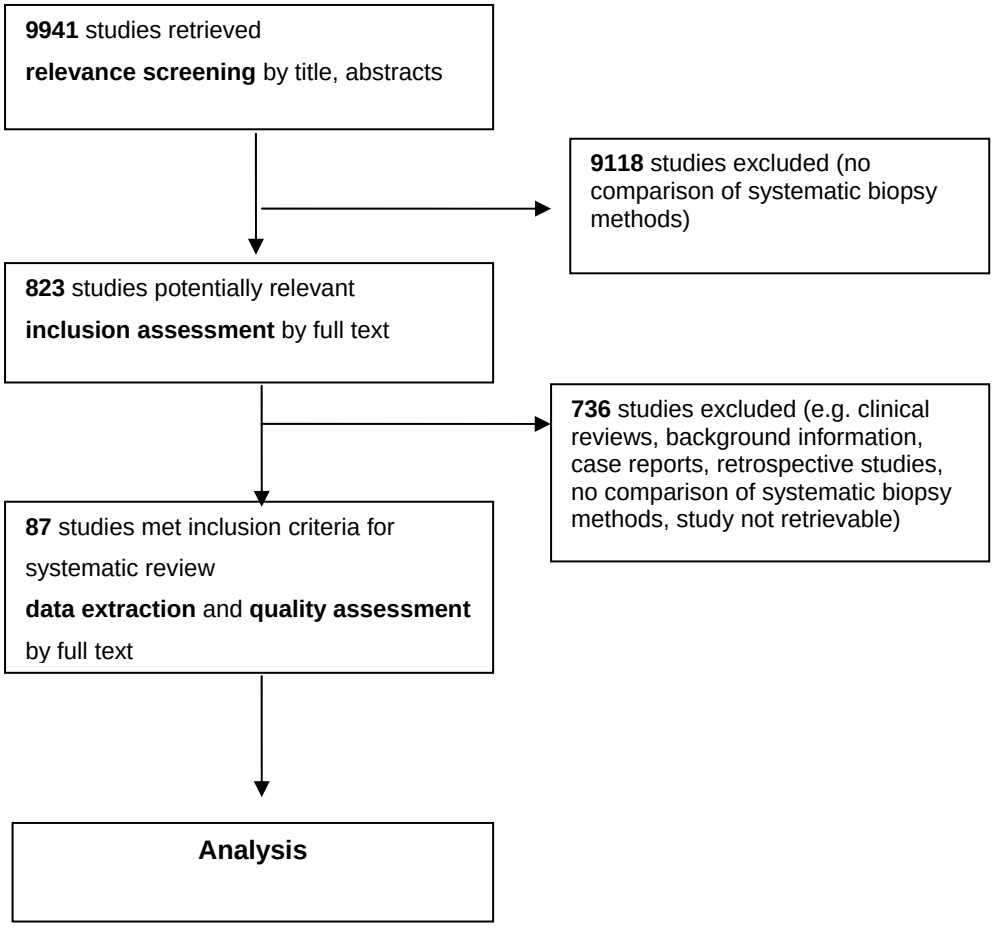


Figure 4.1 Study flow of the systematic review.

The 87 studies were conducted in the following countries USA n=27, Canada n=7, Europe n=35, Japan n=11, other countries n=7. Most of the studies (86%) were published in English.

4.2 Study design of eligible studies

Test accuracy studies

As expected none of the studies was conducted as a classical test accuracy study where all the biopsy participants, regardless of the biopsy findings, were examined with the gold standard prostatectomy and complete histological exam of the gland. (Two retrieved studies with the above mentioned design were excluded as they did not represent the predefined population One study reported on sextant prostate biopsies before prostatectomy due to bladder pathologic findings[47] and in one abstract lateral and standard sextant biopsies in patients with already diagnosed prostate cancer were applied before therapeutic prostatectomy.[46])

Concordance studies

All included studies were prospectively conducted as concordance studies and compared two systematic biopsy schemes with each other. (After inclusion assessment we had decided to exclude studies with a retrospective design to avoid potential bias.) 80 studies used a sequential sampling design starting with the reference method and then extending to the more extensive method under evaluation (index test) in the same session. Seven trials used the alternative approach of randomising the study population to either the reference method or to the alternative systematic sample strategy with the index test.

4.3 Characteristics of study participants

Study participants were men scheduled for prostate biopsy with mean ages between 57.7 and 70.9 years (17 studies did not report any age information of participants).

Biopsy indication was mostly abnormal DRE and/or raised PSA (70.1%). A biopsy indication due to abnormal PSA values only was explicitly reported for 16 studies (18.4%). Procedures nearly always took place in a secondary care setting (hospital; university hospital). Only one study reported about patients of a urological primary care practice.[57] Information on whether men were scheduled for first or repeat biopsy was only partly provided (10 studies with first time biopsy population, 11 studies with repeat biopsy population, 13 studies with mixed population, for 53 studies no information available). Reporting of recruitment of participants was poor. Eight studies reported about screening as recruitment method, in two studies men were transferred due to symptoms solely, six studies reported about a mixed recruitment and for 71 studies no information was available.

Mean PSA values of participants ranged from 4.8ng/ml to 52.5ng/ml (22 studies reported no PSA values at all). For the 72% of studies that reported a PSA threshold for biopsy indication the threshold was mostly 4ng/ml, for nine studies it was between 2ng/ml and 4ng/ml, and in one study it was 1.25ng/ml.[58] Four out of 87 studies explicitly reported about age standardisation of PSA values.

Mean prostate volume of participants ranged from 30.5 ml to 70ml in 35 studies (52 studies reported no prostate volume at all).

4.4 Technical aspects and the skills of the examiners

We tried to extract data directly related to the technical equipment and the skills of the examiners to enable us to discuss applicability of findings to clinical practice. In most studies information about technical equipment was more detailed than about the skills of the examiners.

Ultrasound equipment

Mostly biplanar, multi-plane or three dimensional ultrasound probes were used (53 studies without information). Reported scan frequencies lay between 5 and 10 MHz (34 studies without information). The ultrasound brand was provided in 50 studies, the needle brand in 33 trials. Needle thickness was standardised 18 gauge where reported, in one study 14 gauge needles were used for transperineal biopsies[59] (34 studies without information about needle thickness). Information about the sample length was provided in 11 studies only (range 10mm-23mm).

Anaesthesia method

57% of all studies did not mention anaesthesia at all. Eight studies with transrectal biopsies reported explicitly that no anaesthesia was used. Twelve trials reported about locally injected anaesthesia (for transrectal and transperineal approaches), six about local gel anaesthesia (for transrectal approach), four times spinal or peridural regional anaesthesia was used (mostly for the transperineal approach), and four times intravenous sedation was used (for transrectal biopsies). Two studies applied general anaesthesia for a combination of transrectal and transperineal biopsies[59] or for a saturation biopsy protocol.[13]

Antibiotic prophylaxis

Thirty-six studies (two of them with transperineal approach) explicitly reported about the applied antibiotic prophylaxis often with additional information for substances and dosages. Fifty-one trials did not mention antibiotic prophylaxis at all. Thirty-nine out of these 51 were studies of transrectal biopsies.

Biopsy approach

77% of the studies described the transrectal approach for biopsy taking (67 out of 87 studies). In seven studies a transperineal approach was chosen, six trials described a combination of both, and seven studies provided no information.

Skills and experience of examiner

For 26 studies information was available that biopsies were taken by urologists, in three trials it was a radiologist (56 studies without information). The number of examiners who took the biopsies in the study varied between 1 and 7 (43 studies without information). The case load of the examiners was not reported at all; only five studies described the training of the examiners (e.g. 'senior urologist' or '5 years experience in uroradiology').

4.5 Biopsy patterns and reference tests

Reference test

In 78.2% (68 of 87 studies) the standard systematic sextant biopsy scheme with three cores from the mid-lobar peripheral zone at the base, mid and apex of each prostate lobe was chosen as the reference test. This reference test is part of pattern MPZ. Six studies chose MPZ with 4 cores and two studies chose MPZ with 8 cores as the reference test.

Different reference tests were provided for the rest of the studies. Table 4.1 provides an overview of the reference tests that were used.

Table 4.1 Provided reference tests in the included studies

Pattern of reference test	Number of cores of reference test	Number of studies	% of studies
MPZ	6	68	78.2%
MPZ	4	6	7.0%
MPZ	8	2	2.3%
LPZ	6	5	5.8%
MPZ+TZ (+MLiPZ)	6	1	1.1%
MPZ+TZ (+MLiPZ)	10	1	1.1%
MPZ+LPZ	6	1	1.1%
MPZ+LPZ	10	2	2.3%
MPZ+LPZ	18	1	1.1%
		87	100%

(MPZ mid-lobar peripheral zone; LPZ lateral peripheral zone; MLiPZ midline peripheral zone TZ transition zone)

Index test

For each primary study with the standard sextant scheme as reference test we grouped the respective test under evaluation to the predefined patterns (for predefined patterns see section 3.2. Grouping of biopsy methods). Three patterns represented the majority of the comparisons (see table 4.1).

The most frequently used pattern was 'MPZ+LPZ' 39 biopsy schemes (with 6 to 12 biopsy cores) out of this pattern were compared to a reference test. The next most frequent pattern was 'MPZ+TZ (+MLiPZ)' where 24 schemes (with 8 to 12 biopsy cores) out of this pattern were evaluated against a reference test. Twenty comparisons were grouped to pattern 'MPZ+LPZ+TZ (+MLiPZ)', the 5-region biopsy pattern. Tests under evaluation consisted of 6 up to 22 cores out of this pattern (a 32-core scheme used a different reference test).

For the most extensive systematic sampling strategy (i.e. the sampling strategy described in the methods section of each report) the number of cores ranged from 6 to 32 cores among all extracted studies.

Authors also sometimes provided data for additional biopsy schemes that were derived from the prospectively taken schemes as cores were analysed separately. These additional schemes could be compared with the (same) reference test as the most extensive scheme of the respective study. Where authors discussed or recommended such additional schemes we extracted the data.

Finally we extracted data for 94 comparisons out of 68 studies with the standard sextant scheme as reference test (see table 4.2) and 23 comparisons out of 19 studies with a different reference test. Thus, 117 comparisons out of 87 studies were analysed for this systematic review.

For further details of the tests under evaluation and their respective additional diagnostic value and relative positivity rates (RPR) see 4.7 Diagnostic value of different biopsy schemes.

Table 4.2 Matrix with grouping of tests under evaluation to predefined patterns.

	Pattern MPZ	Pattern 2	Pattern LPZ	Pattern MPZ+TZ(+MLiPZ)	Pattern 5	Pattern MPZ+LPZ	The 5-region pattern	
	MPZ	TZ	LPZ	MPZ+TZ (+MLiPZ)	LPZ+TZ	MPZ+LPZ	'5-region' MPZ+LPZ+ TZ (+MLiPZ)	
cores	2 to 12	2 to 6	4 to 6	8 to 12	8	6 to 12	6 to >=18	cores
2	**0**	**0**						2
4	**2**	**0**	**1**					4
6	**----- (1*)**	**0**	**4**			**3**	**1**	6
8	**0**			**16**	**0**	**7**	**0**	8
10	**2**			**4**		**13**	**3**	10
12	**1**			**4**		**16**	**8**	12
14							**2**	14
16							**0**	16
18							**4**	18
20								20
22								22
>=24								>=24
Total	**6**	**0**	**5**	**24**	**0**	**39**	**20**	Total

Each of the 68 primary studies (sequential or randomised design), with the standard sextant scheme as reference test, contributes to at least one test under evaluation for this grouping. Tests under evaluation were grouped according to pattern and number of cores taken. Figures in cells of the matrix indicate the number of tests under evaluation that were extracted.

MPZ mid-lobar peripheral zone; LPZ lateral peripheral zone; MLiPZ midline peripheral zone TZ transition zone
*Pattern MPZ (with 6 cores) is the cell of the standard sextant reference test and by definition no study was expected (however, 1 study was retrieved that compared the transrectal with the transperineal approach for this scheme).

4.6 Quality assessment of eligible studies

We applied nine quality criteria of the QUADAS instrument[45] that were applicable for our review question and three additional clinical quality items. For randomised studies we additionally applied two methodological items evaluating the randomisation process (see methods section 3.5 Quality assessment).

The following figure provides an overview of the proportion of studies scoring 'yes', 'no' or 'not clear' for the different quality items

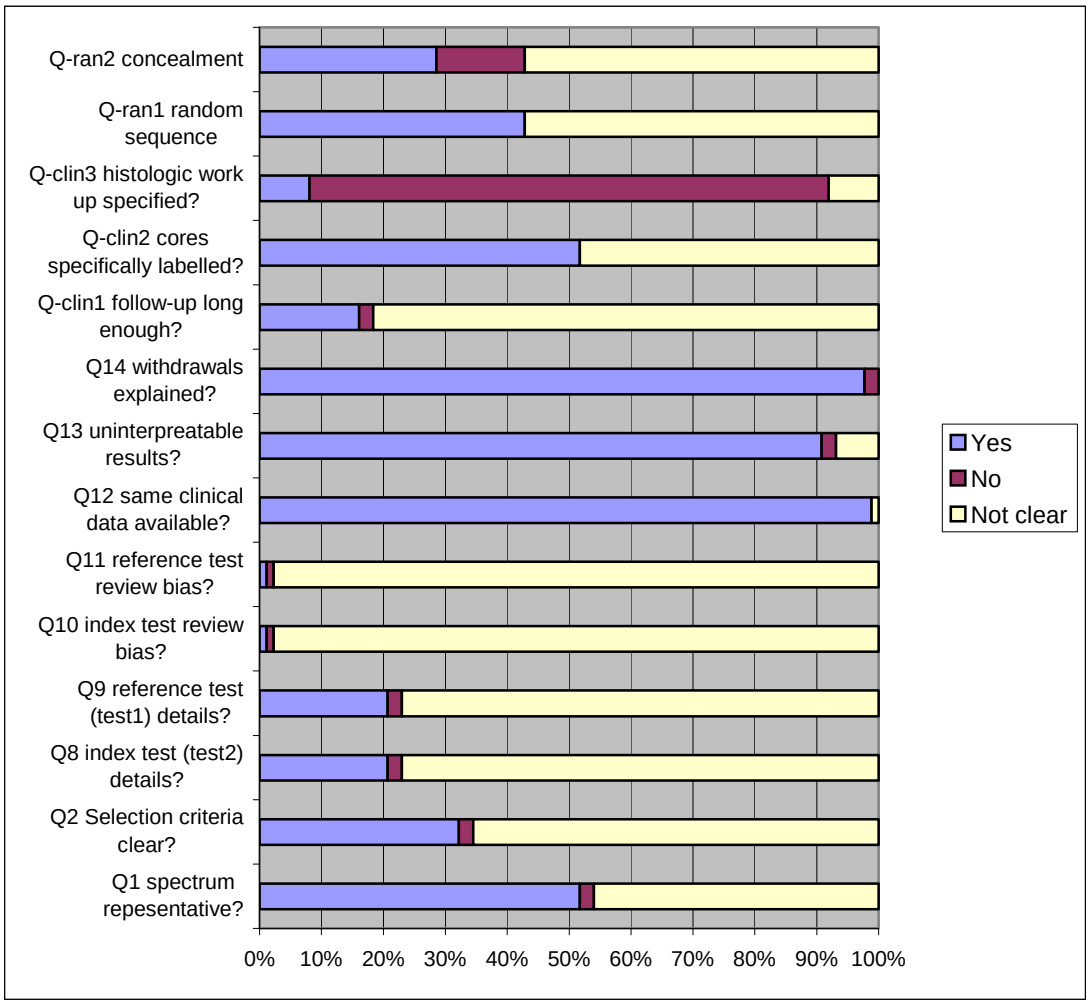


Figure 4.2 Proportion of studies scoring 'yes', 'no' or 'not clear' for the different quality items

QUADAS items

Forty-five of all 87 studies (52%) provided sufficient information to judge whether the spectrum of the patients was representative (predefined criteria 1. consecutive patients or random sample referred to biopsy due to abnormal PSA and/or abnormal DRE or 2. screening population). For 46% of the studies it was not clear if the spectrum of the patients was representative (no information or incomplete information). Two percent of all studies described a population that could be categorised as not representative according to the predefined criteria. In 32% of all studies (28 of 87) the selection criteria for the participants were clearly described, whereas they were only partly described (=not clear) for 46%, and not described at all (=no) for 2% of the studies.

A description of the index test and the reference test was given in sufficient detail in 21% of the studies (information for all predefined items patient preparation as anaesthesia method for any approach and antibiotic prophylaxis for transrectal approach; needle thickness; biopsy access; number of cores taken, detailed anatomical regions of cores; labelling cores specifically). 77% of the studies provided only some of those test details, 2% gave no such information.

Only one study reported, that the pathologist was blinded for test sequence (i.e. the index test results were interpreted without knowledge of the results of the reference test and vice versa). Eighty-five studies provided no information about a blinding for the histological examination (=not clear); one study reported explicitly that the pathologist was aware of the test sequence.

In most of the study reports the same clinical data were available for test interpretation as in clinical practice (99%), it was clear that all test results (e.g. including results of incomplete sampling) were reported (91%) and it was clear what happened to all the included patients (98%).

Clinical quality items

In 16% of all studies the described follow up was long enough (mailing of questionnaires or delayed patient examination) to discover delayed infectious complications (e.g. abscess). In 82% the follow up was not reported at all and in 2% the described follow up was too short to discover delayed infectious or other complications.

52% of all studies gave detailed information about the cores being specifically labelled for histological work up in order to calculate the additional diagnostic value of an extended sampling. In 48% the labelling of the cores was not reported at all.

The method of histological work up was specified in detail (i.e. description of embedding and staining; examined levels per tissue core) in 8% of all studies. Eight percent provided only some of those details, 84% did not report the histological work up at all.

Randomisation process

Of the seven randomised studies, three studies reported on a suitable method for generation of the random sequence. Two randomised studies reported that the allocation to the groups was concealed. In most of the randomised studies (four for each quality item) no description of generation of random sequence or concealment of allocation was provided.

We provide the information of the quality assessment for each study in the table with the general results in Appendix 7. (We use a code as follows 5/3/4 means 5 times ‘yes’, 3 times ‘no’; 4 times ‘not clear’ if 12 quality items have been evaluated.) In Appendix 8 we provide the detailed results for each study and each single quality item.

4.7 Diagnostic value of different biopsy schemes

In this chapter we provide the findings for each of the seven predefined patterns of biopsy schemes separately to enable a better orientation for the reader. Studies that have used the sextant method as reference test are presented first. Studies that have used a different reference test are presented thereafter.

Within each pattern we present the findings for different groups of biopsy schemes according to the number of cores that were taken. Each such group corresponds to one cell in the introduced matrix (see chapter 3.2).

For each included primary study we present the most important study characteristics and the relative positivity rate (RPR with 95% CI) in a tabulated form. For each group of studies the results of the RPR are given in a forest plot to enable a better visual orientation. A meta-analysis of the RPR of the primary studies for each cell was carried out where indicated using a random effects model to provide a summary estimate of the studies of one cell. Randomised studies, if any, are presented separately from studies with sequential sampling.

(For each included primary study the raw data and the respective calculated data are described in a tabulated form in more detail in Appendix 7.)

4.7.1. Pattern 1 Mid-lobar peripheral zone (MPZ)

MPZ 4 Cores

Two primary studies with sequential sampling[60 61] provided data for this biopsy pattern. In one study[60] different 4-sector biopsy solutions were simulated out of the in vivo taken 6-sector biopsies by computer simulation. Results in that study are based on the average of undetected cancers of 1000 simulations.

These two studies with 4 cores had a RPR of less than 1.0 in comparison to the sextant scheme. The pooled RPR of these two studies was 0.91 (95%-CI 0.86 to 0.95) as shown in the following forest plot (figure 4.3).

Table 4.3 Study characteristics and relative positivity rate (RPR) of studies with index test of pattern MPZ (4 cores).

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
Garber 1994[61], Canada	n=669	n.a. (n.a.-n.a.)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ 4 cores	**0.92** (0.89 to 0.96)	4/0/8
Karakiewicz 1996[60], Canada	n=749	n.a. (n.a.-n.a.)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ 4 cores	**0.88** (0.83 to 0.93)	3/1/8

(n.a. not available)

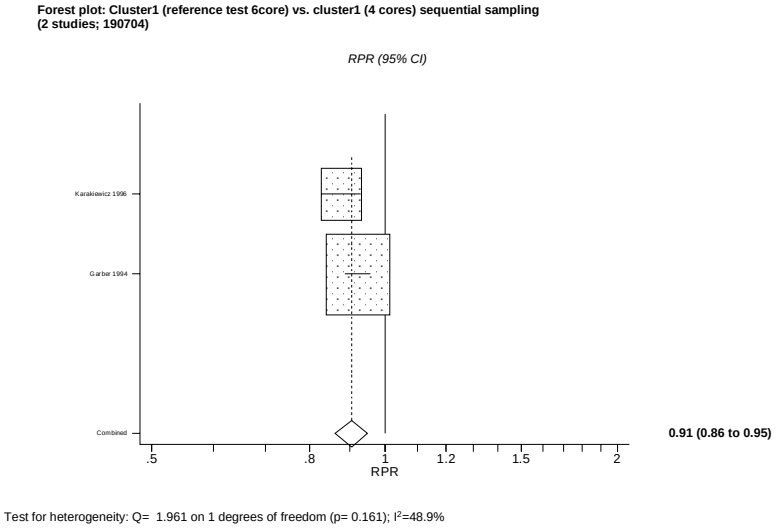


Figure 4.3 Forest plot of relative positivity rates (RPR) of studies with index test of pattern MPZ (4 cores taken).

Conclusion The pooled estimate shows a significantly lower yield than the sextant reference test but is based on two primary studies only.

MPZ 6 Cores

One primary study[59] with sequential sampling provided data that compared a sextant scheme by transrectal approach with a sextant scheme by transperineal approach. In this study 6 transperineal biopsies (with intrarectal guidance of the left forefinger) were taken before the TRUS guided 6 transrectal biopsies.

The RPR of the transperineal sextant scheme was not significantly different from the transrectal sextant scheme (RPR 1.18; 95%-CI 0.86 to 1.62) as shown in the following forest plot (figure 4.4).

Conclusion The data of one primary study with 51 patients show no significant difference in the diagnostic yield for a sextant scheme with transperineal approach vs. a transrectal approach.

Table 4.4 Study characteristics and relative positivity rate (RPR) of studies with index test of pattern MPZ (6 cores).

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
Garcia 2001[59], France	n=51	67 (53-79)	15.7 (4.6-63)	MPZ 6 cores (trans-rectal)	MPZ 6 cores (trans-perineal)	**1.18** (0.86 to 1.62)	3/1/8

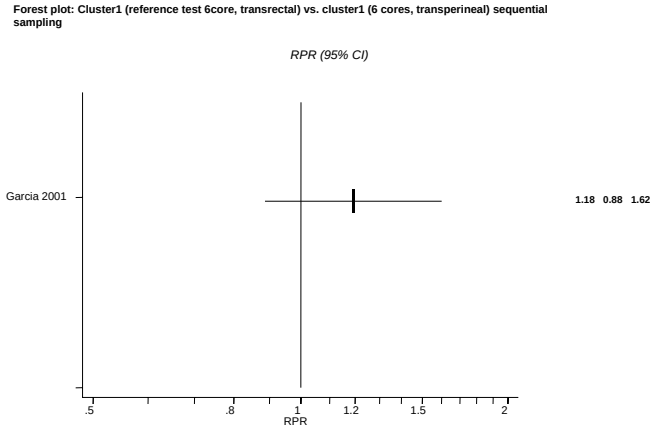


Figure 4.4 Forest plot of the relative positivity rate (RPR) of a study[59] with a transperineal sextant scheme of pattern MPZ(6 cores taken) compared to the reference test of a transrectal sextant scheme

MPZ 8 Cores

No primary study was retrieved that compared this scheme with the standard sextant scheme.

MPZ 10 Cores

Two primary studies with sequential sampling[62 63] provided data for this biopsy scheme. The studies were published by the same author and covered a different population over time (information retrieved from the author). An extensive biopsy protocol of the MPZ was used involving four additional transrectal biopsies to the standard sextant scheme.

Table 4.5 Study characteristics and relative positivity rate (RPR) of studies with index test of pattern MPZ (10 cores).

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
Ravery 1998[62], France	n=92	66.4 (n.a.-n.a.)	13.3 (n.a.-n.a.)	MPZ 6 cores	MPZ 10 cores	**1.13** (1.00 to 1.28)	3/3/6
Ravery 1999[63], France	n=162	66.2 (39-87)	16.8 (1-600)	MPZ 6 cores	MPZ 10 cores	**1.08** (1.01 1.16)	5/1/6

(n.a. not available)

The pooled RPR of these two studies with 10 cores was 1.09 (95%-CI 1.03 to 1.16) as shown in the following forest plot (figure 4.5).

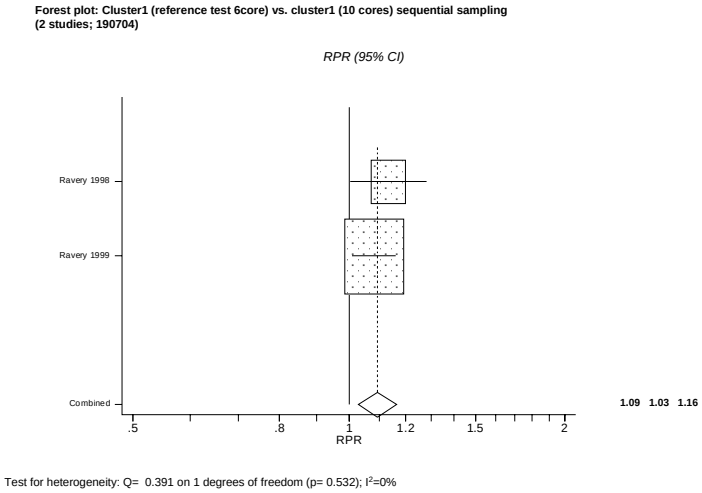


Figure 4.5 Forest plot of relative positivity rates (RPR) of studies with index test of pattern MPZ (10 cores taken).

Conclusion The pooled estimate shows a slight but significant higher cancer yield than the sextant reference test. The result is based on two primary studies only.

MPZ 12 Cores

One primary study[64] with sequential sampling provided data for this biopsy scheme. This study investigated the role of performing 2 consecutive sets of transrectal ultrasound guided sextant biopsies of the prostate in a single office visit as the protocol for detecting prostate cancer. We analysed this combination of 2 sextant tests as a 12-core protocol of the MPZ.

Table 4.6 Study characteristics and relative positivity rate (RPR) of studies with index test of pattern MPZ (12 cores).

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/not clear)
Levine 1998[64], USA	n=137	65 (n.a.-n.a.)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ 12 cores	1.43 (1.18 to 1.75)	8/1/3

(n.a. not available)

The RPR of 2 consecutive sextant schemes (analysed as a 12-core regimen) was significantly higher than the standard sextant scheme (RPR 1.43; 95%-CI 1.18 to 1.75) as shown in the following forest plot (figure 4.6).

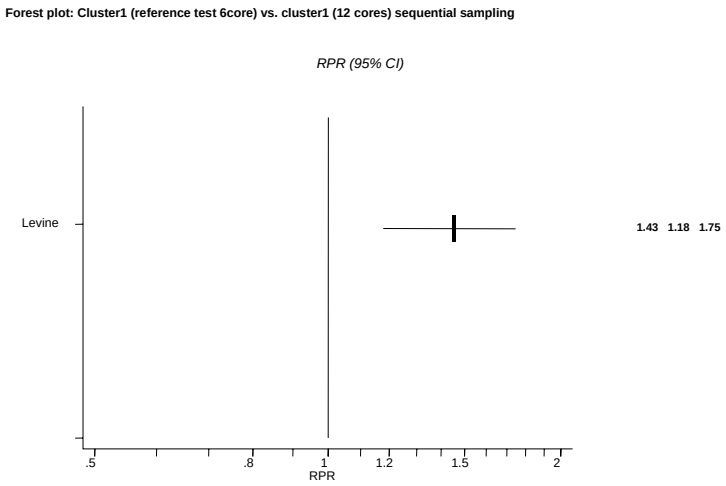


Figure 4.6 Forest plot of the relative positivity rate (RPR) of a study[64] with index test of pattern MPZ (12 cores taken).

Conclusion The data of one primary study show a significant difference in the diagnostic yield for a 12-core scheme of the MPZ vs. the sextant reference test.

4.7.2. Pattern 2 Transition zone (TZ)

No studies were retrieved that compared a biopsy scheme consisting solely of systematic transition zone (TZ) biopsies with a reference standard test.

Studies that evaluated the diagnostic value of biopsy schemes where TZ biopsies were included (i.e. TZ biopsies were part of biopsy schemes done in different anatomical regions) are reported in the chapters for pattern MPZ+TZ(+MLiPZ) (MPZ+TZ) and the 5-region pattern (MPZ+LPZ+TZ; '5-region biopsies').

4.7.3. Pattern 3 Lateral peripheral zone (LPZ)

LPZ 4 Cores

One primary study[16] with sequential sampling provided data for this biopsy scheme. Patients underwent a 10-core scheme (6 cores from MPZ and 4 from LPZ). Here data are provided for the diagnostic value of the 4 cores from the LPZ (i.e. as if they had been applied solely).

Table 4.7 Study characteristics and relative positivity rate (RPR) of studies with index test of pattern LPZ (4 cores).

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no /not clear)
Chang 1998[16], USA	n=273	70 (n.a.-n.a.)	6.6 (n.a.-n.a.)	MPZ 6 cores	LPZ 4 cores	0.86 (0.74 to 0.99)	5/1/6

(n.a. not available)

The data of this study with 4 cores from the LPZ result in a RPR of less than 1.0 in comparison to the sextant scheme. The RPR was 0.86 (95%-CI 0.74 to 0.99) as shown in the following forest plot (figure 4.7).

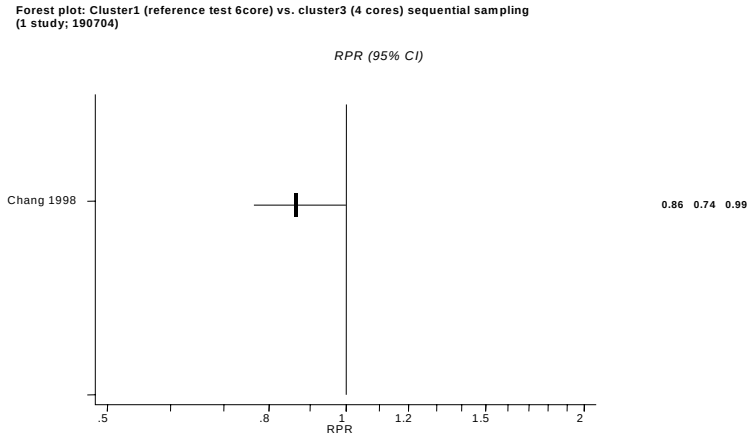


Figure 4.7 Forest plot of the relative positivity rate (RPR) of a study[16] with index test of pattern LPZ (4 cores).

Conclusion The data of one primary study with four cores from the LPZ show a significant lower yield than the sextant reference test. The difference is at borderline statistical significance.

LPZ 6 Cores

Three primary studies with sequential sampling[65-67] provided data for this biopsy scheme. Patients underwent a 12-core scheme (6 cores from MPZ and 6 from LPZ). Here data are provided for the diagnostic value of the 6 cores from the LPZ (i.e. as if they had been applied solely).

The 12-core arm of one primary study with a randomised design[68] was also analysed for this biopsy scheme. For this analysis patients of that 12-core study arm were analysed as patients with sequential sampling.

Table 4.8 Study characteristics and relative positivity rate (RPR) of studies with index test of pattern LPZ (6 cores).

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/not clear)
Kravchick 2004[66], Israel	n=120	65.1 (52-77)	7.3 (2.3-15)	MPZ 6 cores	LPZ 6 cores	**1.04** (0.74 to 1.47)	6/1/5
Naughton 2000[68], USA	n=122 (12 core arm of 244 pts totally)	65.5 (n.a.-n.a.)	5.9 (2.5-20)	MPZ 6 cores	LPZ 6 cores	**1.00** (0.75 to 1.33)	9/1/2
Slongo 2003[65], Brazil	n=54	57.7 (41-80)	6.5 (2.7-10)	MPZ 6 cores	LPZ 6 cores	**1.82** (1.13 to 2.93)	9/0/3
Terris 1997[67], USA	n=41	67.5 (49-79)	10.9 (0.3-37.4)	MPZ 6 cores	LPZ 6 cores	**1.14** (0.88 to 1.46)	6/0/6

(n.a. not available)

Three of the four studies with 6 cores from the LPZ had a RPR of more than 1.0 in comparison to the sextant scheme. The pooled RPR of these four studies was 1.15 (95%-CI 0.94 to 1.41) as shown in the following forest plot (figure 4.8).

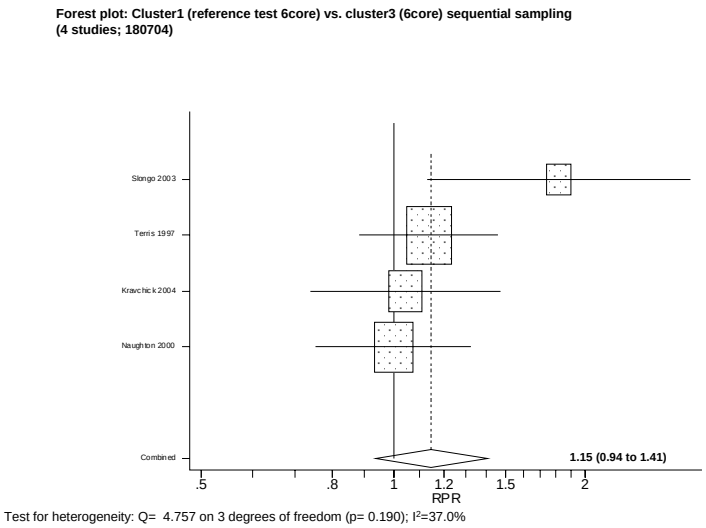


Figure 4.8 Forest plot of relative positivity rates (RPR) of studies with index test of pattern LPZ (6 cores).

Conclusion Based on the data of four included studies that compared a 6-core LPZ scheme with the standard sextant scheme the applied 6-core scheme showed a higher cancer yield than the reference test (pooled RPR 1.15; 95%-CI 0.94 to 1.41). However, the confidence interval is crossing the RPR of 1.0.

4.7.4. Pattern 4 Mid-lobar peripheral zone + transition zone (+midline peripheral zone)

MPZ + TZ (+MLiPZ) 8 Cores

Sixteen primary studies with sequential sampling[69-84] provided data for this biopsy scheme. Altogether 5013 men were included who underwent an 8-core scheme (6 cores from MPZ and 2 from TZ). Here data are provided for the diagnostic value of these 8 cores from the MPZ and the TZ together.

For details of sampling procedure and reporting within each single study see Appendix 7 (Results of data extraction) and Appendix 8 (Quality assessment Detailed results of for each single study and each single item).

The RPR ranged for all but one study between 1.00 and 1.11. One primary study[70] showed a relatively high point estimate (RPR 1.40; 95%-CI 1.24 to 1.59) in comparison to the rest of the group. Unfortunately this study did not provide data for mean-age, mean-PSA (PSA threshold for inclusion was 2.5ng/ml), prostate volume or if a first or repeat biopsy population was studied. Thus we could not examine if such factors could explain the study results.

The pooled RPR of the meta-analysis of these 16 studies (figure 4.9) was 1.04 (95%-CI 1.02 to 1.06) but there was significant statistical heterogeneity (p=0.000; I^2=71,4%). Excluding the study[70] with the high point estimate did not change the results and heterogeneity remained significant (p=0.009). We grouped the studies according to publication year, study size and patient variables (age groups; PSA-values; prostate volume; first vs. repeat biopsy). We could not detect visually that the results differed systematically between stratified groups.

Table 4.9 Study characteristics and relative positivity rate (RPR) of studies with index test of pattern MPZ+TZ(+MLiPZ) (8 cores)

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
Bazinet 1996[75], Canada	n=847	64 (38-83)	7.9 (n.a.-n.a.)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.03** (1.01 to 1.05)	4/1/7
Cam 2001[72], Turkey	n=271	n.a. (n.a.-n.a.)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.00** (0.98 to 1.02)	3/1/8
Deliveliotis 2002[77], Greece	n=420	64 (42-88)	10 (3.2-88)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.08** (1.03 to 1.14)	6/1/5
Egawa 1998[82], Japan	n=344	67.6 (32-89)	5.5 (1.0-20'100)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.04** (0.99 to 1.09)	4/2/6
Fowler 1996[69], USA	n=12	n.a. (n.a.-n.a.)	n.a. (10-50)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.00** (0.78 to 1.28)	4/1/7
Gómez Veiga 1999[74], Spain	n=238	66 (48-88)	n.a. (4-10)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.11** (1.01 to 1.21	4/1/7
Karakiewicz 1995[83], Canada	n=847	63.7 (38-83)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.03** (1.01 to 1.05)	3/1/8
Kitamura 2002[76], Japan	n=139	69 (50-88)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.00** (0.95 to 1.05)	4/1/7
Morote 1999[79], Spain	n=164	69 (48-89)	10.0 (0.4-574)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.03** (0.99 to 1.06)	5/1/6
Nakata 1998[80], Japan	n=83	70.0 (48-86)	14.2 (0.5-124.6)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.04** (0.96 to 1.13)	4/0/8
Onder 1998[81], Turkey	n=189	66.8 (40-87)	27.3 (0.3-495.6)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.02** (0.98 to 1.06)	6/2/4
Reissigl 1997[70], Austria	n=340	n.a. (n.a.-n.a.)	n.a. (2.5-n.a.)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.40** (1.24 to 1.59)	6/1/5
Robles 1999[78], Spain	n=164	69 (48-89)	10 (0.4-574)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.03** (0.99 to 1.06)	4/1/7
Tan 2001[84], Canada	n=126	n.a. (n.a.-n.a.)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.08** (1.00 to 1.17)	4/2/6
Terris 1997[71], USA	n=161	69.6 (51-82)	26.2 (1.2-225)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.02** (0.98 to 1.06)	6/0/6
Traverso 2001[73], Italy	n=668	68.9 (n.a.-n.a.)	10.3 (n.a.-n.a.)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 8 cores	**1.10** (1.06 to 1.14)	5/1/6

(n.a. not available**)**

TZ biopsies are more recommended for patients with repeat biopsies than for patients with a first time biopsy.[8] For 8 of the 16 studies we also had information available if a first or repeat or a mixed biopsy population was included. We stratified the primary studies according to these categories and conducted a meta-analysis for each subgroup (Figure 4.10). The results were similar for each subgroup. In the subgroup 'mixed population', statistical heterogeneity was present.

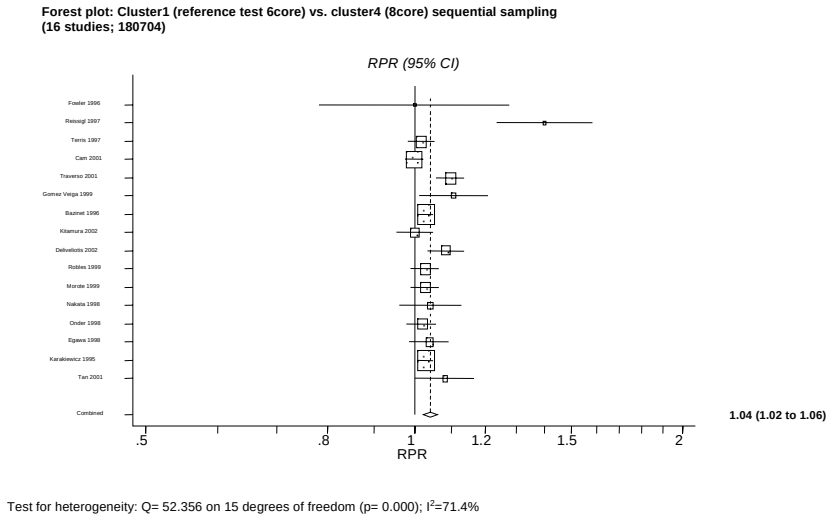


Figure 4.9 Forest plot of relative positivity rates (RPR) of 16 studies with index test of pattern MPZ+TZ(+MLiPZ) (8 cores).

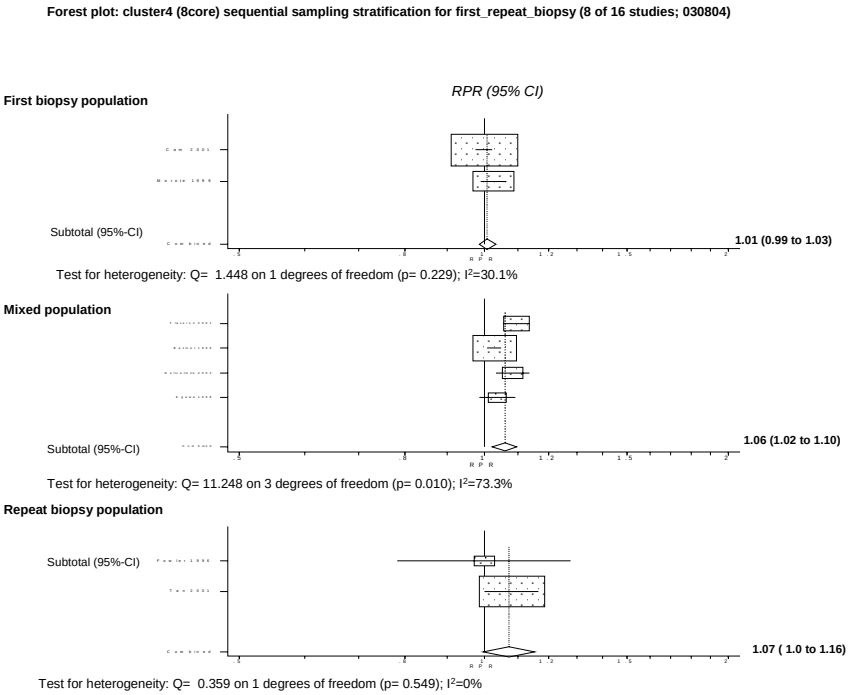


Figure 4.10 Forest plots of relative positivity rates (RPR) of studies with index test of pattern MPZ+TZ(+MLiPZ) (8 cores) stratified for first, repeat or mixed biopsy population. (Only 8 out of 16 studies where relevant information was available were included for this stratification.)

Conclusion Sixteen included studies compared an 8-core scheme (6 cores from MPZ and 2 from TZ) with the standard sextant scheme. Based on these data the applied 8-core scheme showed a slightly higher cancer yield than the reference test (pooled RPR 1.04; 95%-CI 1.02 to 1.06). However, there was significant statistical heterogeneity.Results for first, mixed and repeat biopsy populations were similar and showed only marginally higher RPR's for mixed and repeat populations (information available for 8 studies only).

MPZ + TZ (+MLiPZ) 10/11 Cores

Four primary studies with sequential sampling[85-88] provided data for this biopsy scheme. Data were analysed for the diagnostic value of the 10 to 11 cores from the MPZ and the TZ together.

Altogether 955 men were included who underwent a 10/11-core scheme (6 cores from MPZ and on average 4/5 cores from TZ). The number of TZ cores varied between studies and between participants depending on the size of the prostate.[85 86] We used the average number of cores from the TZ that was described in the publication as criterion for grouping these studies together. Although 90 patients were enrolled in one trial,[88] only 49 had received the 11-core biopsy and were suitable for data extraction.

For details of sampling procedure and reporting within each single study see Appendix 7 (Results of data extraction) and Appendix 8 (Quality assessment: Detailed results of each single study and each single item).

Table 4.10 Study characteristics and relative positivity rate (RPR) of studies with index test of pattern MPZ+TZ(+MLiPZ) (10 cores)

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
Arger 2002[88], USA	n=90 (n=49 analysed)	65 (53-85)	9.6 (n.a.-n.a.)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 10/11 core	**1.62** (1.15 to 2.26)	3/1/8
Ishizuka 2002[85], Japan	n=192	70 (39-90)	10.5 (0.7-6530)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 10/11 core	**1.04** (0.99 to 1.09)	5/1/6
Liu 2001[86], USA	n=390	65.1 (53-83)	12.4 (4.2-66.9)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 10/11 core	**1.21** (1.10 to 1.34)	4/0/8
Mansec k 2001[87], Germany	n=324	64.7 (37-88)	8.3 (0.4-3773)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 10/11 core	**1.10** (1.04 to 1.17)	5/1/6

(n.a. not available)

The pooled RPR of the meta-analysis of these four studies (figure 4.11) was 1.13 (95%-CI 1.04 to 1.24) but there was significant statistical heterogeneity (p=0.004; I^2=77,2%). We grouped the studies after publication year and patient variables (age groups; PSA-values; prostate volume; first vs. repeat biopsy). We could not detect visually that the results differed systematically between stratified groups.

One primary study[88]that had the lowest number of analysed participants (n=49) showed a relatively high point estimate (RPR 1.62; 95%-CI 1.15 to 2.26) in comparison to the rest of the group. Analysing only studies with more than 100 patients changed the pooled result only slightly (RPR 1.11; 95%-CI 1.03 to 1.19) and heterogeneity tests remained significant.

Conclusion Four included studies compared a 10/11-core scheme (6 cores from MPZ and on average 4/5 from TZ) with the standard sextant scheme. Based on these data the applied 10/11-core scheme showed a slightly higher cancer yield than the reference test (pooled RPR 1.13; 95%-CI 1.04 to 1.24). However, there was significant statistical heterogeneity.

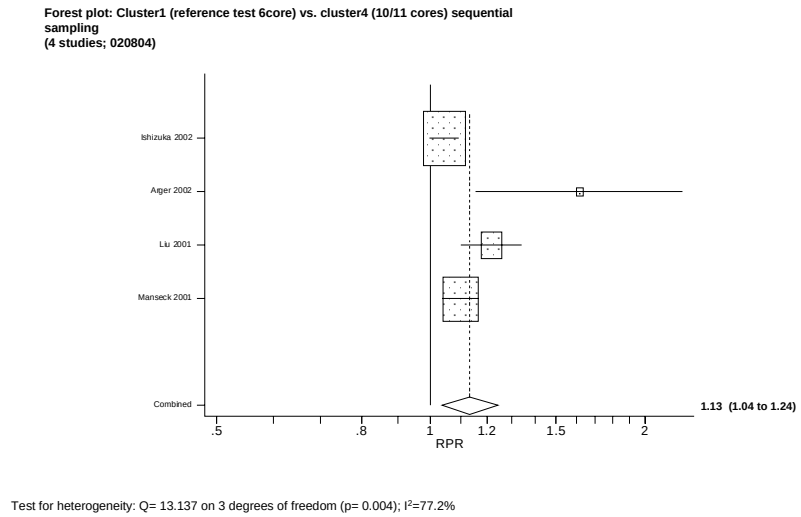


Figure 4.11 Forest plot of relative positivity rates (RPR) of studies with index test of pattern MPZ+TZ(+MLiPZ) (10/11 cores).

MPZ + TZ (+MLiPZ) 12/13 Cores

Three primary studies with sequential sampling[89-91] provided data for this biopsy scheme. Data were analysed for the diagnostic value of the 12 cores from the MPZ and the TZ together.
Altogether 512 men were included who underwent a 12-core scheme (6 cores from MPZ and 6 from TZ). In one study,[90] the origin of the samples from the peripheral zone was not specified in detail by the authors. Further information was not retrievable. For our analysis we grouped these cores to the mid-lobar peripheral zone (MPZ), i.e. the region of the standard sextant scheme.

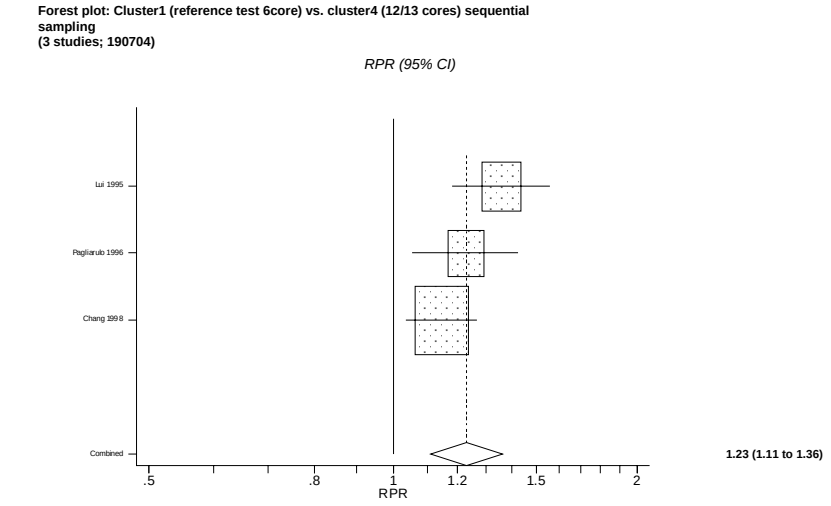
For details of sampling procedure and reporting within each single study see Appendix 7 (Results of data extraction) and Appendix 8 (Quality assessment Detailed results of for each single study and each single item).

Table 4.11 Study characteristics and relative positivity rate (RPR) of studies with index test of pattern MPZ+TZ(+MLiPZ) (12 cores)

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
Chang 1998[91], USA	n=213	70.8 (65-76)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 12 cores	**1.15** (1.04 to 1.27)	5/1/6
Lui 1995[89], USA	n=187	67.4 (52-86)	34.6 (0.8-457)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 12 cores	**1.36** (1.18 to 1.56)	4/0/8
Pagliarulo 1996[90], Italy	n=112	67.4 (56-84)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 12 cores	**1.23** (1.05 to 1.43)	5/0/7

(n.a. not available)

The pooled RPR of the meta-analysis of these three studies (figure 4.12) was 1.23 (95%-CI 1.11 to 1.36). There was low to moderate statistical heterogeneity (p=0.149; I^2=47,5%). Grouping the studies according to publication year appeared to show a pattern of decreasing RPR over time.



We grouped these three studies also for age groups (>=70yrs vs. <70yrs). Pooling only the two studies with patients <70yrs changed the pooled result slightly (RPR 1.30; 95%-CI 1.17 to 1.43).

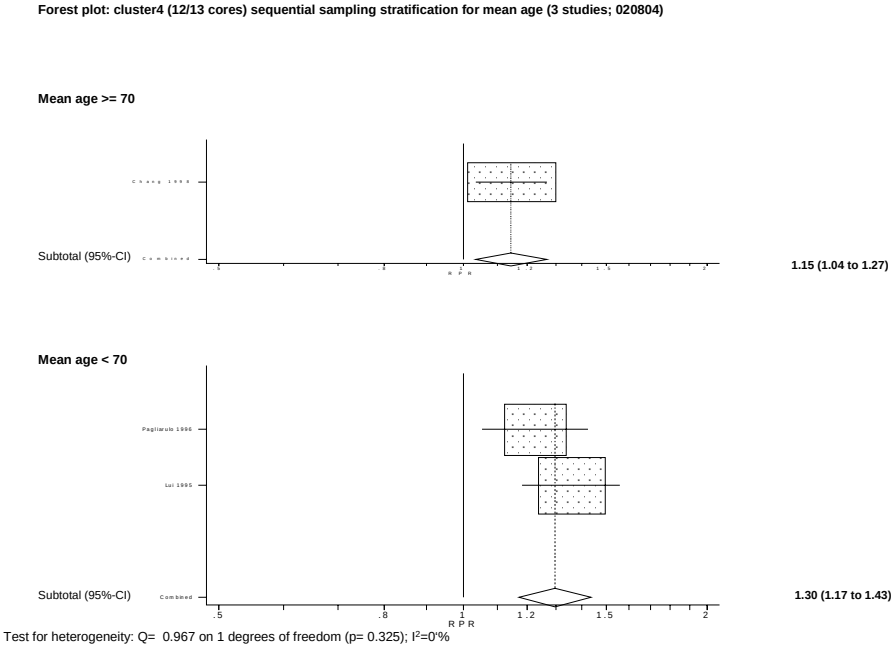


Figure 4.12 Forest plot of relative positivity rates (RPR) of studies with index test of pattern MPZ+TZ(+MLiPZ) (12 cores).

Studies with randomised design

One primary study[92] with randomised design and 120 included men provided data for this biopsy scheme. In this trial patients were randomised to three groups of 40 patients each. One group underwent a 12-core scheme (6 cores from MPZ and 6 from TZ). Seven cancers were detected in this group and six cancers were detected in the reference group (standard sextant scheme). The RPR of the 12-core group was slightly enhanced but the result reached no statistical significance (RPR 1.17; 95%-CI 0.43-3.17).

Table 4.12 Study characteristics and relative positivity rate (RPR) of randomised studies with index test of pattern MPZ+TZ(+MLiPZ) (12 cores)

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
Nava 1997[92], Italy	n=120	64 (n.a.-n.a.)	8.0 (4.1-9.9)	MPZ 6 cores	MPZ+TZ (+MLiPZ) 12 cores	**1.17** (0.43 to 3.17)	4/1/7 R 0/0/2

(n.a. not available)

Conclusion Three included studies with sequential sampling compared a 12-core scheme (6 cores from MPZ and 6 from TZ) with the standard sextant scheme. Based on these data the applied 12-core scheme showed a significantly higher cancer yield than the reference test (pooled RPR 1.23; 95%-CI 1.11 to 1.36). In studies with a mean age of less than 70 years the RPR tended to be slightly higher (pooled RPR 1.30; 95%-CI 1.17 to 1.43). The results are based on three studies only. One included study with randomised design compared the same 12-core scheme (6 cores from MPZ and 6 from TZ) with the standard sextant scheme. The RPR of the 12-core group was slightly enhanced but the result reached no statistical significance

4.7.5. Pattern 5 Lateral peripheral zone + transition zone

No studies were retrieved that compared a biopsy scheme consisting solely of systematic lateral peripheral zone (LPZ) biopsies and transition zone (TZ) biopsies with a reference standard test.

Studies that evaluated the diagnostic value of biopsy schemes where LPZ biopsies and TZ biopsies were included (i.e. both were part of a more complex biopsy scheme) are reported in the chapter for the 5-region pattern (MPZ+LPZ+TZ; '5-region biopsies').

4.7.6. Pattern 6 Mid-lobar peripheral zone + lateral peripheral zone (MPZ+LPZ)

MPZ + LPZ 6 Cores

For three primary studies,[16,93,94] in which men had undergone a 10 or 12-core scheme, the authors also provided data for a 6-core scheme consisting of cores from MPZ and LPZ. Altogether 565 men with data for a 6-core scheme from MPZ and LPZ were included in our analysis. Here data are provided for the diagnostic value of those six cores from the MPZ and LPZ solely.

Table 4.13 Study characteristics and relative positivity rate (RPR) of studies with index test of pattern MPZ+LPZ (6 cores)

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
Chang 1998[16], USA	n=273	70 (n.a.-n.a.)	6.6 (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 6 cores	**1.07** (0.97 to 1.18)	5/1/6
Chon 2002[94], USA	n=185	64 (n.a.-n.a.)	8.4 (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 6 cores	**1.16** (0.97 to 1.40)	8/1/3
Emiliozzi 2003[93], Italy	n=107	68 (52-88)	8.2 (4.1-240)	MPZ 6 cores	MPZ+LPZ 6 cores	**1.21** (1.01 to 1.44)	5/1/6

(n.a. not available)

The three studies provided data for a sextant scheme with four lateral and two apical cores[16], a sextant scheme that included the apex, lateral mid gland and lateral base[94] or six transperineal cores using a 'fan' scheme close to midline, mid-lobar, and lateral for each lobe.[93]

For details of sampling procedure and reporting within each single study see Appendix 7 (Results of data extraction) and Appendix 8 (Quality assessment Detailed results of for each single study and each single item).

The pooled RPR of the meta-analysis of these three studies was 1.11 (95%-CI 1.03 to 1.20). There was no evidence for statistical heterogeneity (p=0.44; I^2=0%).

We grouped the studies according to study size. Smaller studies tended to provide higher estimates for the RPR (figure 4.13).

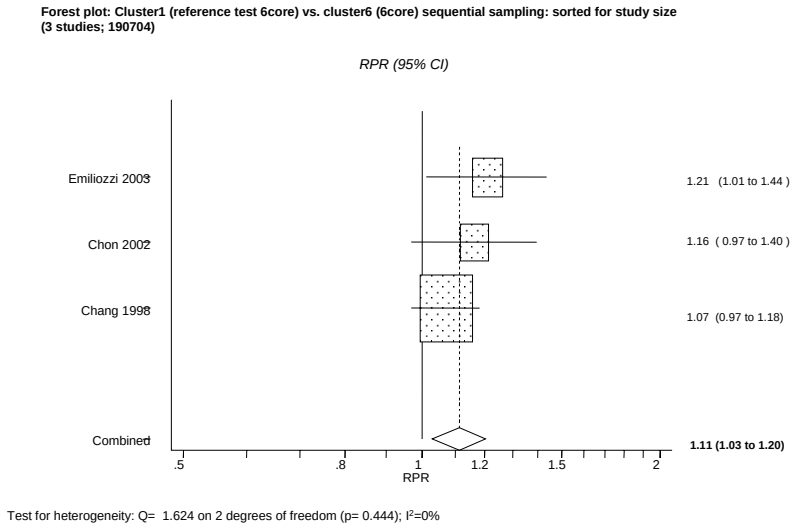


Figure 4.13 Forest plot of relative positivity rates (RPR) of studies with index test of pattern MPZ+LPZ (6 cores) sorted by study size.

When we sorted for publication year and patient variables (age groups; PSA-values; prostate volume; first vs. repeat biopsy) we could not detect visually that the results differed systematically between stratified groups.

Conclusion Three included studies compared a 6-core scheme (cores from MPZ and from LPZ) with the standard sextant scheme. Based on these data the applied 6-core schemes showed a higher cancer yield than the reference test (pooled RPR 1.11; 95%-CI 1.03 to 1.20). There was no evidence for statistical heterogeneity. Smaller studies tended to provide slightly higher estimates for the RPR.

MPZ + LPZ 8 Cores

For seven primary studies,[11,12,94-98] in which men had undergone prostate biopsy schemes between 10 and 22 cores, the authors also provided data for an 8-core scheme from MPZ and LPZ.

Altogether 2437 men with data for an 8-core scheme from MPZ and LPZ were included in our analysis. Here data are provided for the diagnostic value of those 8 cores from the MPZ and LPZ solely.

The analysed studies defined their respective 8-core schemes from MPZ and LPZ in a slightly different way. On average about the same number of cores from both zones was taken. For details of sampling procedure and reporting within each single study see Appendix 7 (Results of data extraction) and Appendix 8 (Quality assessment Detailed results of for each single study and each single item).

Table 4.14 Study characteristics and relative positivity rate (RPR) of studies with index test of pattern MPZ+LPZ (8 cores)

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/not clear)
Chon 2002[94], USA	n=185	64 (n.a.-n.a.)	8.4 (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 8 cores	**1.29** (1.11 to 1.49)	8/1/3
Eskicorapci 2004[95], Turkey	n=303	63 (43-80)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 8 cores	**1.26** (1.10 to 1.44)	6/1/5
Kawakami 2003[96], Japan	n=254	68 (n.a.-n.a.)	8.3 (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 8 cores	**1.29** (1.13 to 1.48)	4/1/7
Meng 2003[97], USA **(EN9770)**	n=255	67 (n.a.-n.a.)	6.0 (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 8 cores	**1.14** (1.04 to 1.25)	4/2/6
Norberg 1997[11], Sweden	n=512	65 (34-81)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 8 cores	**1.13** (1.08 to 1.18)	8/0/4
Philip 2004[98], UK	n=445	64.5 (43-84)	n.a. (2.6-10)	MPZ 6 cores	MPZ+LPZ 8 cores	**1.24** (1.13 to 1.34)	7/1/4
Presti 2000[12], USA	n=483	69.0 (n.a.-n.a.)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 8 cores	**1.19** (1.11 to 1.27)	6/1/5

(n.a. not available)

The pooled RPR of the meta-analysis of these seven studies was 1.19 (95%-CI 1.14 to 1.24). There was low to moderate statistical heterogeneity (p=0.19; I^2=31.8%). Smaller studies tended to provide higher estimates for the RPR (figure 4.14).

When we sorted for publication year and patient variables (age groups; PSA-values; prostate volume; first vs. repeat biopsy) we could not detect visually that the results differed systematically between stratified groups.

Conclusion Seven included studies compared an 8-core scheme (cores from MPZ and from LPZ) with the standard sextant scheme. Based on these data the applied 8-core schemes showed a higher cancer yield than the reference test (pooled RPR 1.19; 95%-CI 1.14 to 1.24). There was no evidence for statistical heterogeneity. Smaller studies tended to provide slightly higher estimates for the RPR.

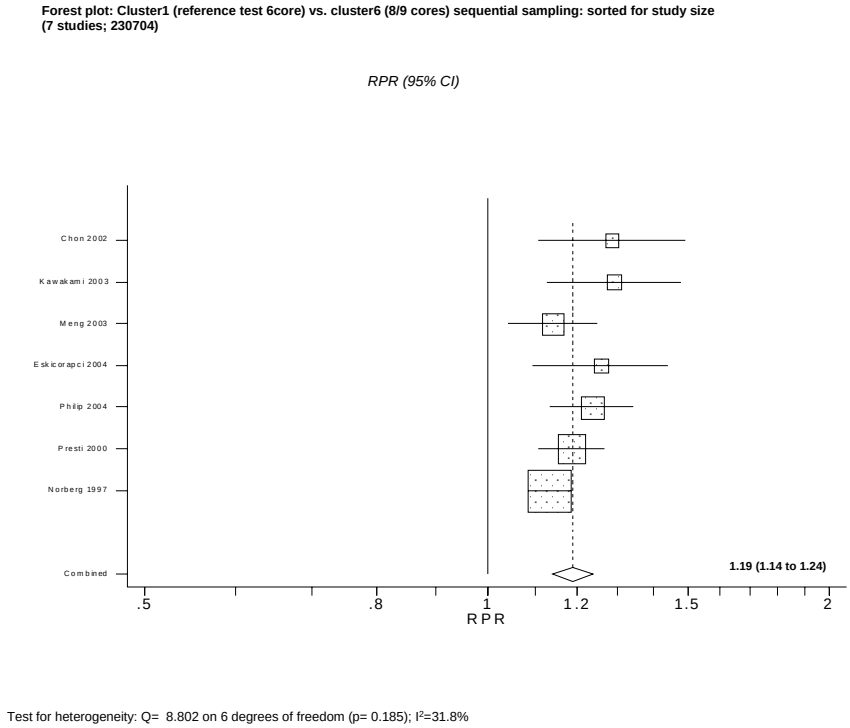


Figure 4.14 Forest plot of relative positivity rates (RPR) of studies with index test of pattern MPZ+LPZ (8 cores) sorted for study size

MPZ + LPZ 10 Cores

For 13 primary studies,[12,16,65,94,95,98-104] in which men had undergone prostate biopsy schemes between 10 and 22 cores, the authors also provided data for a 10-core scheme from MPZ and LPZ.

Altogether 3155 men with data for a 10-core scheme from MPZ and LPZ were included in our analysis. Here data are provided for the diagnostic value of those 10 cores from the MPZ and LPZ solely. The analysed studies defined their respective 10-core schemes from MPZ and LPZ in a slightly different way. For details of sampling procedure and reporting within each single study see Appendix 7 (Results of data extraction) and Appendix 8 (Quality assessment Detailed results of for each single study and each single item).

The pooled RPR of the meta-analysis of these 13 studies was 1.25 (95%-CI 1.19 to 1.33). There was evidence for high statistical heterogeneity (p=0.000; I^2=70.3%; figure 4.15).

Table 4.15 Study characteristics and relative positivity rate (RPR) of studies with index test of pattern MPZ+LPZ (10 cores)

Study	Patients	Mean age (range)	PSA mean (range)	Ref. test (pattern, cores)	Index test (pattern, cores)	RPR (95%-CI)	Q-items (yes/no/not clear)
Balaji 2003[99], USA	n=23	62.2 (41-74)	8.1 (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 10 cores	**1.33** (0.89 to 1.99)	4/0/8
Chang 1998[16], USA	n=273	70 (n.a.-n.a.)	6.6 (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 10 cores	**1.17** (1.09 to 1.26)	5/1/6
Chon 2002[94], USA	n=185	64 (n.a.-n.a.)	8.4 (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 10 cores	**1.33** (1.15 to 1.52)	8/1/3
Durkan 2002[101], UK	n=493	68.7 (44-89)	10.2 (0.5-901)	MPZ 6 cores	MPZ+LPZ 10 cores	**1.11** (1.05 to 1.16)	8/1/3
Eskicorapci 2004[95], Turkey	n=303	63 (43-80)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 10 cores	**1.34** (1.19 to 1.51)	6/1/5
Gore 2001, USA	n=104	n.a. (n.a.-n.a.)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 10 cores	**1.41** (1.17 to 1.69)	4/0/8
Ng 2002[100], Singapore	n=191	64.6 (38-85)	9.05 (0.7-19.6)	MPZ 6 cores	MPZ+LPZ 10 cores	**1.27** (1.09 to 1.47)	5/1/6
Leibovich 2000[103], USA	n=125	n.a. (n.a.-n.a.)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 10 cores	**1.87** (1.34 to 2.62)	2/1/9
Philip 2004[98], UK	n=445	64.5 (43-84)	n.a. (2.6-10)	MPZ 6 cores	MPZ+LPZ 10 cores	**1.37** (1.23 to 1.53)	7/1/4
Presti 2000[12], USA	n=483	69.0 (n.a.-n.a.)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 10 cores	**1.20** (1.13 to 1.28)	6/1/5
Ravery 2000[102], France	n=303	64.3 (43-86)	11.3 (0.4-138)	MPZ 6 cores	MPZ+LPZ 10 cores	**1.20** (1.11 to 1.31)	7/1/4
Slongo 2003[65], Brazil	n=54	57.7 (41-80)	6.5 (2.7-10)	MPZ 6 cores	MPZ+LPZ 10 cores	**2.00** (1.32 to 3.04)	9/0/3
Tsai 2000[104], USA	n=173	66 (n.a.-n.a.)	6.9 (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 10 cores	**1.12** (1.03 to 1.22)	4/1/7

(n.a. not available)

Smaller studies tended to provide higher estimates for the RPR

Excluding the studies with less than 100 participants changed the pooled estimate slightly (RPR 1.24; 95%-CI 1.17 to 1.31). When we sorted for publication year and patient variables (age groups; PSA-values; prostate volume; first vs. repeat biopsy) we could not detect visually that the results differed systematically between stratified groups.

Conclusion Thirteen included studies compared a 10-core scheme (cores from MPZ and from LPZ) with the standard sextant scheme. Based on these data the applied 10-core schemes showed a higher cancer yield than the reference test (pooled RPR 1.25; 95%-CI 1.19 to 1.33). However, there was evidence for high statistical heterogeneity. Smaller studies tended to provide slightly higher estimates for the RPR.

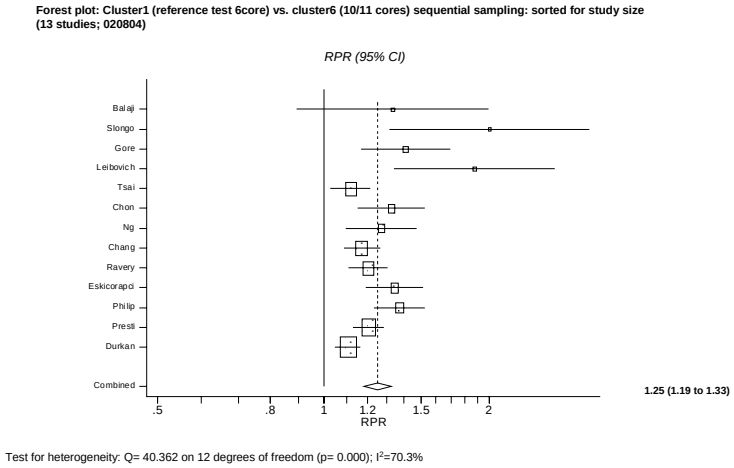


Figure 4.15 Forest plot of relative positivity rates (RPR) of studies with index test of pattern MPZ+LPZ (10 cores) sorted for study size

MPZ + LPZ 12 Cores

Thirteen studies provided data for this scheme In eleven studies men underwent a sequential sampling with 12 cores[65-67 93 97 98 105-109] and one study with a 21-core sequential sampling also provided data for this 12-core scheme from MPZ and LPZ[110].

The 12-core arm of one primary study with a randomised design[68] was also analysed for this biopsy scheme. For this analysis, patients of the 12-core study arm were analysed in the same way as patients with sequential sampling.

Altogether 2178 men with data for a 12-core scheme from MPZ and LPZ were included in our analysis. In general 6 cores were taken from MPZ and 6 cores from LPZ. For details of sampling procedure and reporting within each single study see Appendix 7 (Results of data extraction) and Appendix 8 (Quality assessment Detailed results of for each single study and each single item).

Table 4.16 Study characteristics and relative positivity rate (RPR) of studies with index test of pattern MPZ+LPZ (12 cores)

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
Balbontin 2000[106], Chile	n=49	63.7 (48-85)	10.7 (2.46-38.6)	MPZ 6 cores	MPZ+LPZ 12 cores	**1.59** (1.19 to)2.12	3/1/8
de la Taille 2003[110], France	n=303	65.6 (48-82)	9.2 (0.7-40)	MPZ 6 cores	MPZ+LPZ 12 cores	**1.25** (1.12 to 1.38)	9/1/2
Emiliozzi 2003[93], Italy	n=107	68 (52-88)	8.2 (4.1-240)	MPZ 6 cores	MPZ+LPZ 12 cores	**1.26** (1.08 to 1.47)	5/1/6
Gore 2001[107], USA	n=104	n.a. (n.a.-n.a.)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 12 cores	**1.41** (1.17 to 1.69)	4/0/8
Kravchick 2004[66], Israel	n=120	65.1 (52-77)	7.3 (2.3-15)	MPZ 6 cores	MPZ+LPZ 12 cores	**1.39** (1.12 to 1.73)	6/1/5
Meng 2003[97],	n=255	67 (n.a.-	6.0 (n.a.-	MPZ 6 cores	MPZ+LPZ 12 cores	**1.19** (1.10 to	4/2/6

USA		n.a.)	n.a.)			1.29)	
Naughton 2000[68], USA	n=122 (12 core arm of 244 pts totally)	65.5 (n.a.-n.a.)	5.9 (2.5-20)	MPZ 6 cores	MPZ+LPZ 12 cores	**1.27** (1.06 to 1.52)	9/1/2
Pepe 2002[105], Italy	n=190	n.a. (n.a.-n.a.)	n.a. (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 12 cores	**1.27** (1.14 to 1.42)	3/1/8
Philip 2004[98], UK	n=445	64.5 (43-84)	n.a. (2.6-10)	MPZ 6 cores	MPZ+LPZ 12 cores	**1.39** (1.26 to 1.54)	7/1/4
Rowe 2002[109], UK	n=52	n.a. (n.a.-n.a.)	n.a. (n.a.-<20 ng/ml)	MPZ 6 cores	MPZ+LPZ 12 cores	**1.54** (1.12 to 2.12)	4/1/7
Singh 2003[108], USA	n=336	n.a. (n.a.-n.a.)	n.a. (4-10)	MPZ 6 cores	MPZ+LPZ 12 cores	**1.34** (1.21 to 1.48)	4/1/7
Slongo 2003[65], Brazil	n=54	57.7 (41-80)	6.5 (2.7-10)	MPZ 6 cores	MPZ+LPZ 12 cores	**2.00** (1.32 to 3.04)	9/0/3
Terris 1997[67], USA	n=41	67.5 (49-79)	10.9 (0.3-37.4)	MPZ 6 cores	MPZ+LPZ 12 cores	**1.27** (1.05 to 1.54)	5/0/7

(n.a. not available)

The pooled RPR of the meta-analysis of these 13 studies was 1.31 (95%-CI 1.25 to 1.37). There was evidence for low statistical heterogeneity only (p=0.197; I^2=24.3%; figure 4.16).

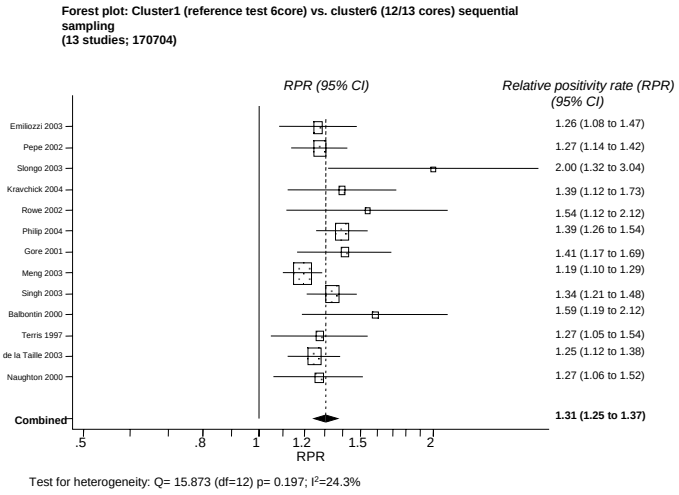


Figure 4.16 Forest plot of relative positivity rates (RPR) of studies with index test of pattern MPZ+LPZ (12 cores)

Smaller studies tended to provide higher estimates for the RPR. Excluding the studies with less than 100 participants changed the pooled estimate slightly (RPR 1.28; 95%-CI 1.23 to 1.34).

We sorted the studies for study size and patient variables (age groups; PSA-values; prostate volume; first vs. repeat biopsy). Stratification for age groups less or more than 65 years (nine studies with available information) seems to explain some of the heterogeneity. (see figure 4.17)

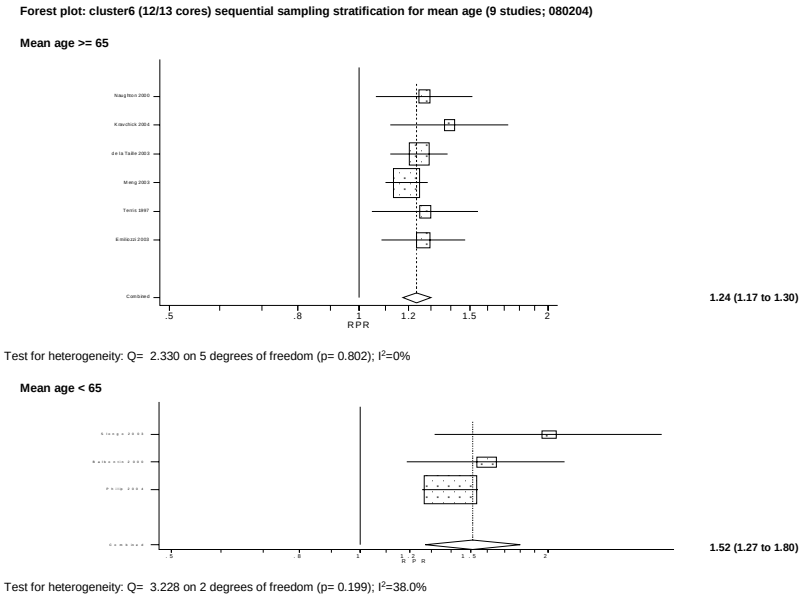


Figure 4.17 Forest plot of relative positivity rates (RPR) of studies with index test of pattern MPZ+LPZ (12 cores) stratified for age groups

When we sorted the studies for study design we could not detect visually for this 12-core scheme that the results differed systematically between studies with randomised or sequential sampling (see figure 4.18)

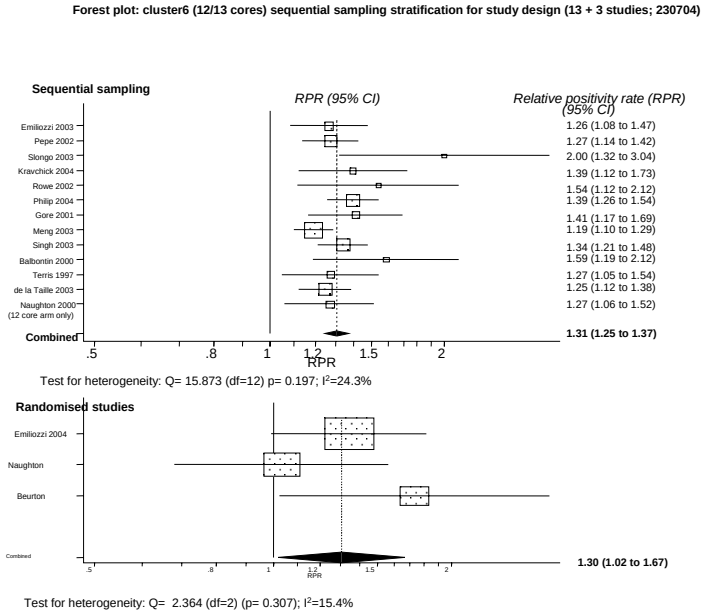


Figure 4.18 Forest plot of relative positivity rates (RPR) of studies with index test of pattern MPZ+LPZ (12 cores) stratified for study design

Studies with randomised design

Three primary studies with randomised design[68 111 112] and 652 included men in total provided data for this biopsy scheme.

The 12-core arm of one randomised study[68] was also analysed for sequential sampling in this chapter. Here we provide the data for the comparison of the 6-core arm vs. the 12-core arm of this study in the randomised design. Interestingly the difference between the RPR of the 12-core arm vs. the 6-core arm has nearly disappeared.

For details of sampling procedure and reporting within each single study see Appendix 7 (Results of data extraction) and Appendix 8 (Quality assessment Detailed results of for each single study and each single item).

Table 4.17 Study characteristics and relative positivity rate (RPR) of randomised studies with index test of pattern MPZ+LPZ (12 cores)

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
Beurton 2000[111], France	n=194	n.a. (n.a.-n.a.)	n.a. (4.0-< 20)	MPZ 6 cores	MPZ+LPZ 12 cores	**1.73** (1.02 to 2.92)	4/1/7 R 2/0/0
Emiliozzi 2004[112], Italy	n=214	67.5 (n.a.-n.a.)	8.1 (n.a.-n.a.)	MPZ 6 cores	MPZ+LPZ 12 cores	**1.34** (0.99 to 1.82)	7/1/4 R 0/0/2
Naughton 2000[68], USA	n=244	65.5 (n.a.-n.a.)	5.9 (2.5-20)	MPZ 6 cores	MPZ+LPZ 12 cores	**1.03** (0.68 to 1.56)	9/1/2 R 2/0/0

(n.a. not available)

The pooled RPR of these three studies was 1.30 (95%-CI 1.02 to 1.67). There was evidence for low statistical heterogeneity only (p=0.307; I^2=15.4%; figure 4.19).

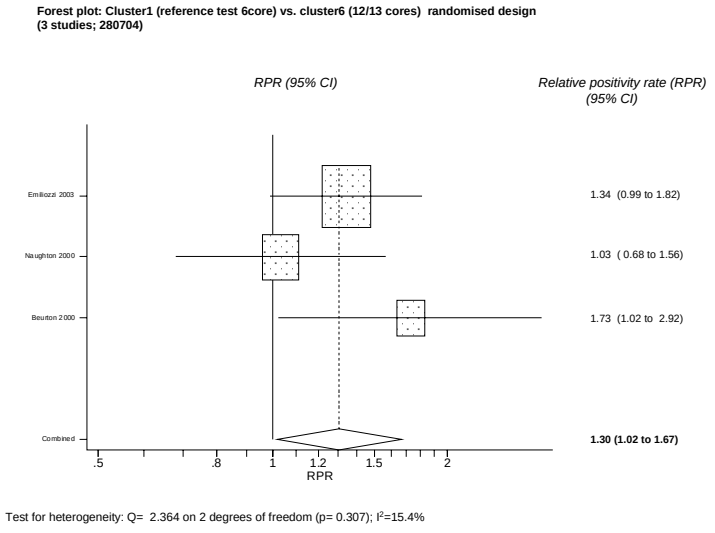


Figure 4.19 Forest plot of relative positivity rates (RPR) of randomised studies with index test of pattern MPZ+LPZ (12 cores)

Conclusion Thirteen included studies with sequential sampling compared a 12-core scheme (cores from MPZ and from LPZ) with the standard sextant scheme. Based on these data the applied 12-core schemes showed a significantly higher cancer yield than the reference test (pooled RPR 1.31; 95%-CI 1.25 to 1.37).

Three included studies with a randomised design compared the same 12-core scheme (cores from MPZ and from LPZ) with the standard sextant scheme. These 3 randomised studies showed a similar result (pooled RPR 1.30; 95%-CI 1.02 to 1.67).

For both met-analyses there was evidence for low statistical heterogeneity only.

4.7.7. Pattern 7 Mid-lobar peripheral zone + lateral peripheral zone + transition zone (+ midline peripheral zone) '5-region pattern'

5-region pattern 6 Cores
One primary study[113] with sequential sampling provided data for this biopsy scheme. Patients underwent a 12-core scheme. Beside 6 standard sextant cores 6 cores were taken in a fan-shaped technique (from the left to right lateral prostate margin always penetrating the apex in the same angle; so called *'fan shaped technique').*

Here data are provided for the diagnostic value of the six cores of the fan shaped technique (i.e. as if they had been applied solely). We grouped this scheme to the 5-region pattern as it samples tissue from the left to right lateral prostate margin through all five regions (LPZ+MPZ+TZ).

Table 4.18 Study characteristics and relative positivity rate (RPR) of studies with index test of the 5-region pattern (6 cores).

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
Broessner 1999[113], Austria	n=280	67 (40-87)	n.a. (n.a.-n.a.)	MPZ 6 cores	5-region 6 cores	1.00 (0.90 to 1.11)	7/0/5

(n.a. not available)

In this study the cancer yield of the 6 cores from the 5-region pattern (fan shaped technique) was exactly the same as the yield of the 6-core scheme in the standard sextant technique from MPZ. Thus the RPR was 1.00 (95%-CI 0.90 to 1.11) as shown in the following forest plot (figure 4.20).

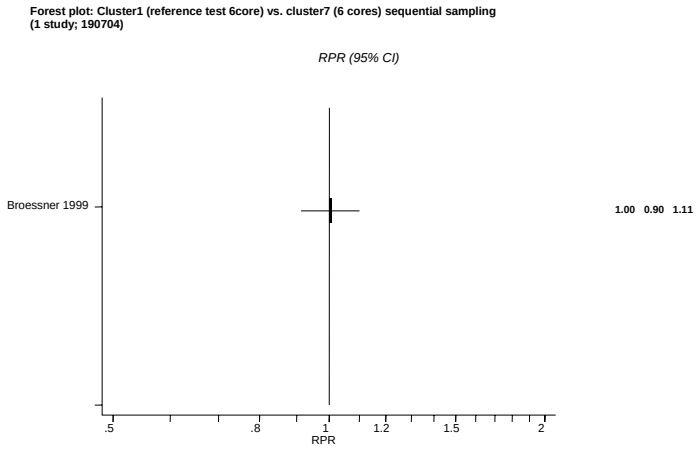


Figure 4.20 Forest plot of the relative positivity rate (RPR) of a study[16] with index test of the 5-region pattern (6 cores).

Conclusion The data of one primary study with a 6-core scheme from the 5-region pattern (LPZ+MPZ+TZ; fan shaped technique) show no difference in the cancer yield compared to the sextant reference test.

5-region pattern 8 Cores
No primary study was retrieved that compared this scheme with the standard sextant scheme.

5-region pattern 10/11 Cores
Three primary studies with sequential sampling[11 49 114] provided data for this biopsy scheme. Altogether 963 men were included who underwent a 10-core[11] or an 11-core[49 114] scheme of the 5-region pattern (MPZ+LPZ+TZ+ MLiPZ).

Generally 6 cores were taken from the standard MPZ, 2 cores from the LPZ and 2 cores from the TZ. The 11-core schemes took one additional core from the midline peripheral zone (MLiPZ). In one study[49] 2 cores resulted from the right and left anterior horn which represents extreme lateral and anterior peripheral zone tissue. We have grouped this location to LPZ.

Here data are provided for the diagnostic value of these 10/11 cores together. For details of sampling procedure and reporting within each single study see Appendix 7 (Results of data extraction) and Appendix 8 (Quality assessment Detailed results of for each single study and each single item).

Table 4.19 Study characteristics and relative positivity rate (RPR) of studies with index test of the 5-region pattern (10/11 cores)

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
Babaian 2000[49], Canada, USA	n=362	63.7 (39-80)	10.2 (0.5-49.5)	MPZ 6 cores	5-region 11 cores	**1.49** (1.30 to 1.69)	7/1/4
Norberg 1997[11], Sweden	n=512	65 (34-81)	n.a. (n.a.-n.a.)	MPZ 6 cores	5-region 10 cores	**1.15** (1.10 to 1.20)	8/0/4
Vakar-Lopez 2002[114], USA	n=89	60.4 (44-74)	7.9 (0.7-36.1)	MPZ 6 cores	5-region 11 cores	**1.88** (1.17 to 3.01)	3/1/8

(n.a. not available**)**

The pooled RPR of the meta-analysis of these three studies (figure 4.21) was 1.38 (95%-CI 1.08 to 1.76) but there was evidence for high statistical heterogeneity (p=0.000; I^2=88.1%).

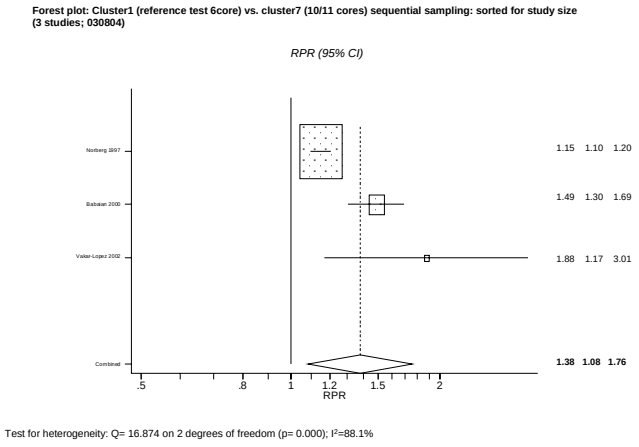


Figure 4.21 Forest plot of relative positivity rates (RPR) of studies with index test of the 5-region pattern (10/11 cores).

The smallest study,[114] that was available as an abstract publication only and had included patients with repeat biopsy after a prior negative extended biopsy only, showed the largest point estimate.

A systematic grouping of these three studies for additional patient variables (age groups; PSA-values; prostate volume) seemed not applicable due to the small number of studies and lacking data.

Conclusion Three included studies compared a 10/11-core scheme (5-region biopsies) with the standard sextant scheme. Based on these data the applied 10 or 11-core scheme showed significantly higher cancer yields than the reference test (pooled RPR 1.38; 95%-CI 1.08 to 1.76). However, there was evidence for high statistical heterogeneity between the studies. The smallest study showed the largest point estimate.

5-region pattern 12/13 Cores
Eight primary studies with sequential sampling provided data for this biopsy scheme.

Altogether data for 2111 men were available who underwent either a 12-core scheme[101,113,115-117] or a 13-core scheme.[48,118] In one study[119] patients underwent a 14 core biopsy and authors provided data for a 12-core scheme as well.

Generally 6 cores were taken from the standard MPZ, 2 to 4 cores from the LPZ and 2 to 4 cores from the TZ. Here data are provided for the diagnostic value of these 12 or 13 cores together.

For details of sampling procedure and reporting within each single study see Appendix 7 (Results of data extraction) and Appendix 8 (Quality assessment Detailed results of for each single study and each single item).

Table 4.20 Study characteristics and relative positivity rate (RPR) of studies with index test of the 5-region pattern (12/13 cores)

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	RPR (95%-CI)	**Q-items** (yes/no/ not clear)
Broessner 1999[113], Austria	n=280	67 (40-87)	n.a. (n.a.-n.a.)	MPZ 6 cores	5-region 12 cores	**1.09** 81.02 to 1.17)	7/0/5
Durkan 2002[101], UK	n=493	68.7 (44-89)	10.2 (0.5-901)	MPZ 6 cores	5-region 12 cores	**1.23** (1.15 to 1.33)	8/1/3
Eskew 1997[48], USA	n=256 (with 1999-update[120])	65.8 (45-82)	n.a. (4.0-n.a.)	MPZ 6 cores	5-region 13cores	**1.46** (1.30 to 1.64)	6/1/5
Fuganti 2002[115], Brazil	n=78	69 (n.a.-n.a.)	17.3 (n.a.-n.a.)	MPZ 6 cores	5-region 12 cores	**1.08** (0.97 to 1.19)	5/0/7
Kojima M. 2001[116], Japan	n=541	70.0 (n.a.-n.a.)	52.5 (n.a.-n.a.)	MPZ 6 cores	5-region 12 cores	**1.16** (1.08 to 1.24)	4/1/7
Perdona 2000[119], Italy	n=177	64.1 (n.a.-n.a.)	8.36 (4.0-13)	MPZ 6 cores	5-region 12 cores	**1.45** (1.23 to 1.72)	7/1/4
Tokumitsu 2000[117], Japan	n=73	70.9 (50-88)	n.a. (n.a.-n.a.)	MPZ 6 cores	5-region 12 cores	**1.11** (0.99 to 1.25)	4/1/7
Zhong 2003[118], China	n=213	n.a. (48-87)	n.a. (n.a.-n.a.)	MPZ 6 cores	5-region 13cores	**1.27** (1.12 to 1.44)	3/1/8

(n.a. not available)

The pooled RPR of the meta-analysis of these eight studies (figure 4.22) was 1.21 (95%-CI 1.13 to 1.30). There was evidence for high statistical heterogeneity (p=0.001; I^2=77.2%) between the studies.

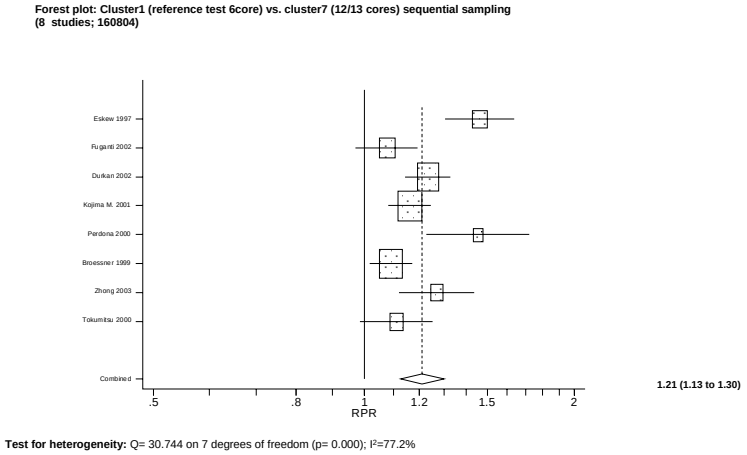


Figure 4.22 Forest plot of relative positivity rates (RPR) of studies with index test of the 5-region pattern (12/13 cores).

When we sorted for publication year, study size and patient variables (age groups; PSA-values; prostate volume) we could not detect visually that the results differed systematically between stratified groups. No data were available that allowed a stratification with regard to first or repeat biopsy schedules.

Conclusion

Eight included studies compared a 12/13-core scheme (5-region biopsies) with the standard sextant scheme. Based on these data the applied 12/13-core scheme showed in six of eight studies significant higher cancer yields than the reference test. The pooled RPR was 1.21 (95%-CI 1.13 to 1.30). However, there was evidence for high statistical heterogeneity between the eight studies.

5-region pattern 14/15 Cores

Two primary studies[119 121] with sequential sampling provided data for this biopsy scheme.
342 men were included who underwent a 14-core scheme in both studies (6 cores standard MPZ, 2 cores LPZ, 4 cores TZ, 2 cores mid zone).

Here data are provided for the diagnostic value of these 14 cores altogether. For details of the sampling procedure and reporting within each single study see Appendix 7 (Results of data extraction) and Appendix 8 (Quality assessment Detailed results of for each single study and each single item).

Table 4.21 Study characteristics and relative positivity rate (RPR) of studies with index test of the 5-region pattern (14/15 cores)

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
Damiano 2003[121], Italy	n=165	64.5 (n.a.-n.a.)	7.24 (n.a.-n.a.)	MPZ 6 cores	5-region 14 cores	**1.25** (1.11 to 1.42)	8/1/3
Perdona 2000[119], Italy	n=177	64.1 (n.a.-n.a.)	8.36 (4.0-13)	MPZ 6 cores	5-region 14 cores	**1.45** (1.23 to 1.72)	7/1/4

(n.a. not available)

The pooled RPR of the meta-analysis of these 2 studies was 1.33 (95%-CI 1.15 to 1.54). There was evidence for moderate statistical heterogeneity (p=0.17; I^2=46.6%) (see figure 4.23).

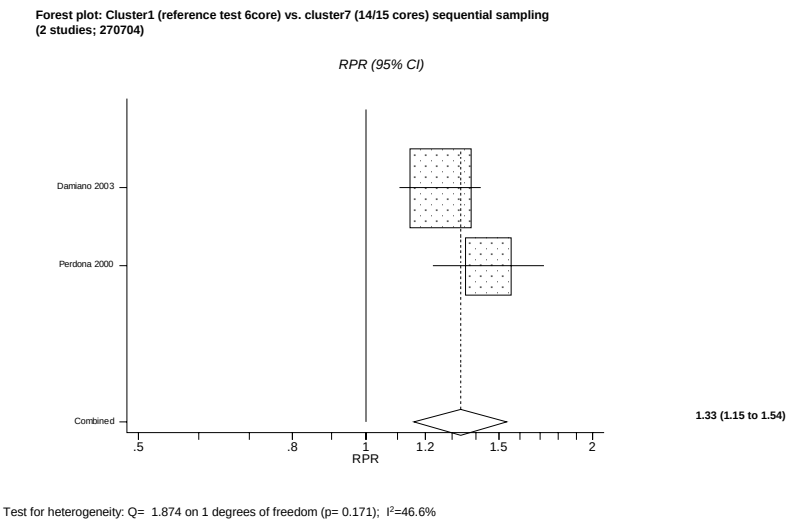


Figure 4.23 Forest plot of relative positivity rates (RPR) of studies with index test of the 5-region pattern (14/15 cores).

Conclusion Two included studies compared a 14-core scheme (5-region biopsies) with the standard sextant scheme. The applied 14-core scheme showed a significant higher cancer yield than the reference test. The pooled RPR was 1.33 (95%-CI 1.15 to 1.54). There was evidence for moderate statistical heterogeneity. The result is based on two primary studies only.

5-region pattern 16/17 Cores
No primary study was retrieved that compared this scheme with the standard sextant scheme.

5-region pattern >=18 Cores
Three primary studies with sequential sampling[110,122,96] and altogether 657 included men provided data for this biopsy scheme.

In two studies patients underwent a transrectal 21-core[110] or a transrectal/transperineal 22-core scheme[96] of the 5-region pattern (MPZ+LPZ+TZ+ MLiPZ).

In the third study[122] an age- and prostate volume-adjusted biopsy scheme was applied and 8 to 20 cores were taken. We grouped this method to the schemes of up to 18 cores as for instance for patients of the age group 55-59 yr. and prostate volume of up to 20 cc (and of age group 60 to 64 yr. and prostate volume of up to 30 cc, respectively) at least 18 cores were taken.

For details of sampling procedure and reporting within each single study see Appendix 7 (Results of data extraction) and Appendix 8 (Quality assessment Detailed results of for each single study and each single item).

Table 4.22 Study characteristics and relative positivity rate (RPR) of studies with index test of the 5-region pattern (>=18 cores)

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
de la Taille 2003[110], France	n=303	65.6 (48-82)	9.2 (0.7-40)	MPZ 6 cores	5-region 21 cores	**1.38** (1.22 to 1.56)	9/1/2
Ito 2002[122], Japan	n=100	68.2 (50-79)	n.a. (4.1-10)	MPZ 6 cores	5-region 8-20 cores (dynamic scheme)	**1.48** (1.21 to 1.81)	2/1/9
Kawakami 2003[96], Japan	n=254	68 (n.a.-n.a.)	8.3 (n.a.-n.a.)	MPZ 6 cores	5-region 22 cores	**1.67** (1.39 to 1.99)	4/1/7

(n.a. not available)

The pooled RPR of the meta-analysis of these three studies (figure 4.24) was 1.48 (95%-CI 1.32 to 1.66). There was evidence for low to moderate statistical heterogeneity (p=0.225; I^2=32.9%).

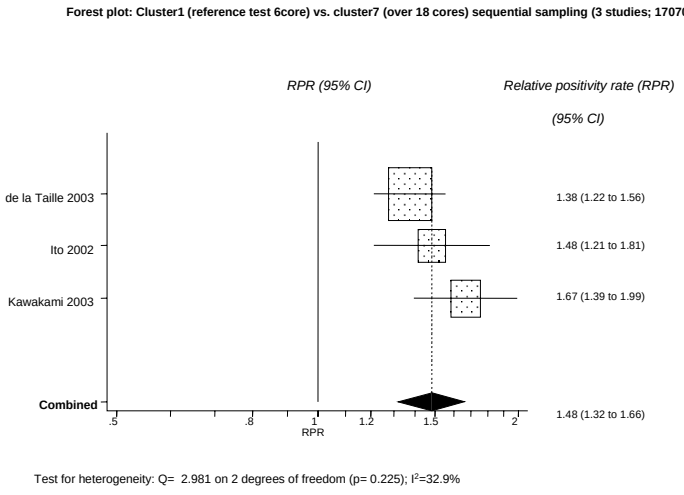


Figure 4.24 Forest plot of relative positivity rates (RPR) of studies with index test of the 5-region pattern (>=18 cores).

A systematic grouping of these three studies for patient variables (age groups; PSA-values; prostate volume; first vs. repeat biopsy population) was not applicable due to lacking data.

Studies with randomised design

One primary study[92] with randomised design and 120 included men provided data for this biopsy scheme. In this trial patients were randomised to three groups of 40 patients each. One group received an 18-core pattern scheme (7). Thirteen Cancers were detected in this group and six cancers were detected in the reference group (standard sextant scheme). The RPR of the 18-core group was enhanced but the result did not reach statistical significance (RPR 2.17; 95%-CI 0.91-5.13).

Table 4.23 Study characteristics and relative positivity rate (RPR) of randomised studies with index test of the 5-region pattern (>=18 cores)

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/ not clear)
Nava 1997[92], Italy	n=120	64 (n.a.-n.a.)	8.0 (4.1-9.9)	MPZ 6 cores	5-region 18 cores	**2.17** (0.91 to 5.13)	4/1/7 R 0/0/2

(n.a. not available)

Conclusion Three included studies with sequential sampling compared biopsy schemes with at least 18 cores (5-region biopsies) with the standard sextant scheme. Based on these data the applied schemes with at least 18 cores showed significant higher cancer yields than the reference test (pooled RPR 1.48; 95%-CI 1.32 to 1.66). There was evidence for only low to moderate statistical heterogeneity.

One included study with randomised design compared the same schemes. The RPR of the 18-core group was enhanced but the result did not reach statistical significance.

4.7.8. Comparisons with different reference tests

Studies with sequential sampling

The following sixteen studies with sequential sampling[13,8,57,123-135] have chosen a different reference test than the standard sextant scheme.

These studies cannot be pooled statistically due to variation in the reference test. The studies are grouped according to the chosen reference test in the following tables. Each study can contribute more than one comparison if authors have provided data accordingly.

For details of sampling procedure and reporting within each single study see Appendix 7 (Results of data extraction) and Appendix 8 (Quality assessment Detailed results of for each single study and each single item).

Reference test Pattern MPZ with 4 cores

Seven primary studies with sequential sampling and altogether 1482 included men provided data for this reference test.

In three data sets of two studies[123 124] a combination of MPZ+LPZ cores (4 to 8 cores totally) was evaluated against this reference test. The combinations of MPZ+LPZ cores showed a significant enhancement of the cancer yield.

Study	**Patients**	**Mean age** (range)	**PSA mean** (range)	**Ref. test** (pattern, cores)	**Index test** (pattern, cores)	**RPR** (95%-CI)	**Q-items** (yes/no/not clear)
Aus 2001[123], Sweden	n=692	n.a. (50-66)	7.4 (3-220)	MPZ 4cores	MPZ+LPZ (4) 4cores	**1.14** (1.06 to 1.22)	5/2/5
Aus 2001[123], Sweden	n=692	n.a. (50-66)	7.4 (3-220)	MPZ 4cores	MPZ+LPZ 6 cores	**1.18** (1.11 to 1.26)	5/2/5
Harewood 1996[124], Australia	n=124	65.7 (49-83)	8.7 (n.a.-n.a.)	MPZ 4cores	MPZ+LPZ 8 cores	**2.00** (1.46 to 2.75)	4/1/7

(n.a. not available)

In four studies[57,125-127] a combination of MPZ+TZ cores (6 to 8 cores totally) was evaluated against the same reference test. The combinations of MPZ+TZ cores showed no (or only a borderline) significant enhancement of the cancer yield.

Study	Patients	Mean age (range)	PSA mean (range)	Ref. test (pattern, cores)	Index test (pattern, cores)	RPR (95%-CI)	Q-items (yes/no/not clear)
Maeda 1997[57], Japan	n=217	70.8 (n.a.-n.a.)	9.4 (n.a.-n.a.)	MPZ 4cores	MPZ+TZ (+MLiPZ) 6 cores	**1.03** (0.99 to 1.07)	5/1/6
Soramoto 1999[127], Japan	n=56	n.a. (n.a.-n.a.)	n.a. (0.8-2360)	MPZ 4cores	MPZ+TZ (+MLiPZ) 6 cores	**1.08** (0.97 to 1.21)	3/1/8
Keetch 1995[125], USA	n=166	66 (50-87)	6.39 (4.1-n.a.)	MPZ 4cores	MPZ+TZ (+MLiPZ) 8 cores	**1.12** (0.96 to 1.30)	4/2/6
Keetch 1996[126], USA	n=227	n.a. (50-n.a.)	n.a. (4.1-n.a.)	MPZ 4cores	MPZ+TZ (+MLiPZ) 8 cores	**1.11** (1.01 to 1.21)	4/1/7

(n.a. not available)

Reference test Pattern MPZ with 8 cores

Two primary studies with sequential sampling and altogether 230 included men provided data for this reference test.

In one study,[129] 24 cores from MPZ+LPZ and 16 cores from LPZ, respectively, were evaluated against this reference test. Both scheme showed a significant enhancement of the cancer yield. The 16-core scheme from LPZ had the same performance as the 24-core scheme from MPZ+LPZ.

In one study,[128] 12 cores from MPZ+TZ were evaluated against this reference test. The combination of MPZ+TZ with 12 cores totally showed only a borderline significant enhancement of the cancer yield.

Study	Patients	Mean age (range)	PSA mean (range)	Ref. test (pattern, cores)	Index test (pattern, cores)	RPR (95%-CI)	Q-items (yes/no/not clear)
Patel 2004[129], USA	n=100	62.1 (n.a.-n.a.)	9.4 (n.a.-n.a.)	MPZ 8 cores	LPZ 16 cores	**2.78** (1.65 to 4.68)	3/1/8
Patel 2004[129], USA	n=100	62.1 (n.a.-n.a.)	9.4 (n.a.-n.a.)	MPZ 8 cores	MPZ+LPZ 24 cores	**2.78** (1.65 to 4.68)	3/1/8
Kojima 2000[128], Japan	n=130	70 (48.4-86.3)	13.8 (0.7-92.4)	MPZ 8 cores	MPZ+TZ (+MLiPZ) 12 cores	**1.11** (1.00 to 1.23)	3/1/8

(n.a. not available)

Reference test Pattern LPZ with 6 cores

Four primary studies with sequential sampling and altogether 447 included men provided data for this reference test.

12 cores from MPZ+LPZ were evaluated against this reference test.[130] The 12-core scheme from MPZ+LPZ pattern showed a significant enhancement of the cancer yield.

Three biopsy schemes[13 130 131] were evaluated with additional cores coming from the same LPZ as the reference test. The 8- and 12-core scheme showed a significantly enhanced cancer yield, the result of the 18-core scheme did not reach statistical significance.

Study	Patients	Mean age (range)	PSA mean (range)	Ref. test (pattern, cores)	Index test (pattern, cores)	RPR (95%-CI)	Q-items (yes/no/ not clear)
Ellis 2002[130], USA	n=164	n.a. (n.a.-n.a.)	n.a. (n.a.-n.a.)	LPZ 6 cores	MPZ+LPZ 12 cores	**1.34** (1.17 to 1.53)	4/1/7
Ellis 2002[130], USA	n=164	n.a. (n.a.-n.a.)	n.a. (n.a.-n.a.)	LPZ 6 cores	LPZ 8 cores	**1.26** (1.12 to 1.43)	4/1/7
O'Connell 2004[131], Ireland	n=202	62 (51-81)	9.91 (1.1-98.4)	LPZ 6 cores	LPZ 12 cores	**1.08** (1.02 to 1.16)	7/0/5
Fleshner 2002[13], Canada	n=37	62.4 (39-75)	22.4 (7.8-73.8)	LPZ 6 cores	LPZ 18 cores	**2.50** (0.85 to 7.31)	8/1/3

(n.a. not available)

In two studies[13 132] the combination of MPZ+TZ-cores (8 and 32 cores respectively) were evaluated against the same reference test. Both schemes did not show a significant enhancement of the cancer yield.

Study	Patients	Mean age (range)	PSA mean (range)	Ref. test (pattern, cores)	Index test (pattern, cores)	RPR (95%-CI)	Q-items (yes/no/ not clear)
Pasqualotto 2000[132], USA	n=44	66.7 (n.a.-n.a.)	7.0 (4.6-10.9)	LPZ 6 cores	LPZ+TZ (5) 8 cores	**1.00** (0.91 to 1.10)	3/1/8
Fleshner 2002[13], Canada	n=37	62.4 (39-75)	22.4 (7.8-73.8)	LPZ 6 cores	LPZ+TZ (5) 32 cores	**2.50** (0.85 to 7.31)	8/1/3

(n.a. not available)

Reference test Pattern MPZ+TZ with 6 cores

One primary study[135] with sequential sampling and 666 included men provided data for this reference test.

The diagnostic value of 8 cores from MPZ+LPZ+TZ was evaluated. The 2 additional cores from LPZ lead to a slightly enhanced cancer yield.

Study	Patients	Mean age (range)	PSA mean (range)	Ref. test (pattern, cores)	Index test (pattern, cores)	RPR (95%-CI)	Q-items (yes/no/ not clear)
Romagnoli 2002[135], Italy	n=666	n.a. (n.a.-n.a.)	n.a. (n.a.-n.a.)	MPZ+TZ (+MLiPZ) 6 cores	5-region 8 cores	**1.05** (1.03 to 1.08)	6/1/5

(n.a. not available)

Reference test Pattern MPZ+LPZ with 6, 10, 18 cores

Three primary studies with sequential sampling and 434 included men provided data for these reference tests from pattern MPZ+LPZ.

14 or 23 cores of a 5-region pattern were evaluated against a reference test from MPZ+LPZ (pattern MPZ+LPZ) with 6,[134] 10[133] or 18 cores,[18] respectively.
The additional diagnostic value was only slight[134] or did not reach statistical significance/.[18,133]

Study	Patients	Mean age (range)	PSA mean (range)	Ref. test (pattern, cores)	Index test (pattern, cores)	RPR (95%-CI)	Q-items (yes/no/ not clear)
Limitone 1998[134], Italy	n=247	63.4 (48-83)	23.5 (2.3-355)	MPZ+LPZ 6 cores	5-region 14 cores	**1.15** (1.07 to 1.24)	6/3/3
Eskicorapci 2004[133], Turkey	n=130	62 (46-78)	8.7 (1.28-30)	MPZ+LPZ 10 cores	5-region 14 cores	**1.03** (0.98 to 1.08)	2/1/9
Borboroglu 2000[18], USA	n=57	61.4 (47-72)	8.6 (n.a.-n.a.)	MPZ+LPZ 18 cores	5-region 23 cores	**1.06** (0.94 to 1.20)	8/2/2

(n.a. not available)

Studies with randomised design

The following three studies with randomised design[58,136,137] have chosen a different reference test than the standard sextant scheme.

The studies are grouped according to the chosen reference test in the following tables.

Reference test Pattern MPZ+TZ (+MLiPZ) with 10 cores

One primary study[58] with randomised design and 222 included men provided data for this reference test.

The diagnostic value of 14 cores from MPZ+TZ was evaluated versus 10 cores from MPZ+TZ. The 4 additional cores lead to no significant change of the cancer yield.

Study	Patients	Mean age (range)	PSA mean (range)	Ref. test (pattern, cores)	Index test (pattern, cores)	RPR (95%-CI)	Q-items (yes/no/ not clear)
Horninger 1999[58], Austria	n=222	n.a. (n.a.-n.a.)	4.8 (1.25-10)	MPZ+TZ (+MLiPZ) 10 cores	MPZ+TZ (+MLiPZ) 14 cores	**0.89** (0.55 to 1.44)	4/4/4 R 0/0/2

(n.a. not available)

Reference test Pattern LPZ with 6 cores

One primary study[136] with randomised design and 200 included men provided data for this reference test.

The diagnostic value of 10 cores from MPZ+LPZ was evaluated versus 6 cores from LPZ. The 4 additional cores from MPZ lead to no significant change of the cancer yield.

Study	Patients	Mean age (range)	PSA mean (range)	Ref. test (pattern, cores)	Index test (pattern, cores)	RPR (95%-CI)	Q-items (yes/no/ not clear)
Paul 2003[136], Germany	n=200	n.a. (n.a.-n.a.)	n.a. (n.a.-n.a.)	LPZ 6 cores	MPZ+LPZ 10 cores	**1.25** (0.86 to 1.82)	3/3/7 R 1/1/0

(n.a. not available)

Reference test Pattern MPZ+LPZ with 10 cores

One primary study[137] with randomised design and 197 included men provided data for this reference test.

A 10-core scheme from MPZ+LPZ was extended to a 5-region 24-core scheme. The 14 additional cores lead to no significant change of the cancer yield.

Study	Patients	Mean age (range)	PSA mean (range)	Ref. test (pattern, cores)	Index test (pattern, cores)	RPR (95%-CI)	Q-items (yes/no/ not clear)
Sur 2002[137], USA	n=197	n.a. (42-82)	n.a. (n.a.-n.a.)	MPZ+LPZ 10 cores	5-region 24 cores	**1.07** (0.75 to 1.53)	4/1/7 R 0/0/2

(n.a. not available)

4.7.9. Comparing patterns and number of cores

Relative positivity rates (RPR) of analysed clusters

To provide an overview over the diagnostic yield of the analysed clusters we grouped the pooled RPR to the cells of the matrix introduced in chapter 3.2. To enable a comparison between cells we have only used studies that applied the same standard reference test (sextant scheme from the mid-lobar peripheral zone, MPZ) and studies with sequential sampling as we did not want to blend studies with different study designs (see table 4.24).

Table 4.24 Matrix with relative positivity rates (RPR) of different biopsy clusters.

	Pattern MPZ	Pattern 2	Pattern LPZ	Pattern MPZ+TZ(+MLiPZ)	Pattern 5	Pattern MPZ+LPZ	The 5-region pattern	
	MPZ	TZ	LPZ	MPZ+TZ (+MLiPZ)	LPZ+TZ	MPZ+LPZ	'5-region' MPZ+LPZ+ TZ (+MLiPZ)	
Cores taken								Cores taken
2	No study	No study						2
4	**0.91** (0.86 - 0.95)	No study	0.86** (0.74 - 0.99)					4
6	1.00 (1.18; 0.88-1.62)	No study	**1.15** (0.94 - 1.41)			**1.11** (1.03 - 1.20)	1.00** (0.90 - 1.11)	6
8/9	No study			1.04[$] (1.02 - 1.06)	No study	**1.19** (1.14 - 1.24)	No study	8/9
10/11	**1.09** (1.03 - 1.16)			1.13[$] (1.04 - 1.23)		1.25[$] (1.19 - 1.33)	1.38[$] (1.08 - 1.76)	10/11
12/13	1.43** (1.18 - 1.75)			**1.23** (1.11 - 1.36)		**1.31** (1.25 - 1.37)	1.21[$] (1.13 - 1.30)	12/13
14/15							**1.33** (1.15 - 1.54)	14/15
16/17							No study	16/17
18/19							**1.48** (1.32 - 1.66)	18/19
20/21								20/21
22/23								22/23

The RPR are based on the data of 65 primary studies with sequential sampling and standard sextant scheme as reference test (64 studies with sequential sampling + 1 arm of a randomised study, analysed as sequential sampling). These studies contribute data for 90 comparisons. Studies with a different reference test or randomised studies are not included here.
Abbrevations MPZ mid-lobar peripheral zone; LPZ lateral peripheral zone; MLiPZ midline peripheral zone TZ transition zone
figures in bold type no statistical heterogeneity (Cochran's Q p > 0.1)
[$] means statistical heterogeneity (Cochran's Q p < 0.1)
** means result derived from 1 study only

Some of the cells do not contain data. We did not retrieve studies for those cells. The cell of the reference test (MPZ, pattern MPZ, 6 cores) is set as 1.0 per definition.

Some of the cells contain data from one primary study only. For some cells the pooling of the RPR of the primary studies showed statistical heterogeneity. Those RPR-values are not printed in bold type.
The RPR of 17 cells with data in most of the cases follow a general pattern The more cores per cluster are taken the higher the RPR. The more to the right side of the matrix a cell is located (i.e. the cluster includes more anatomical regions) the higher the RPR. For the 5-region pattern, specially, some of the cells with statistical heterogeneity between the primary studies do not follow the described pattern.

Comparing number of cores and different patterns
Using univariable models, we investigated the effect of the number of cores on the cancer yield. We also investigated the effect on the cancer yield of adding a specific anatomical prostate region to a given pattern.

The number of cores was significantly associated with the cancer yield. The addition of laterally directed cores from the lateral peripheral zone to a mid-lobar peripheral zone pattern ('MPZ+LPZ') enhanced the cancer yield significantly (p=0.003). If transition zone biopsies ('TZ') are added to obtain a 5-region biopsy ('MPZ+LPZ+TZ') the additional cancer yield was no longer statistically significant (p=0.62).

With a multivariable model we analysed the combined effect of adding a specific region and of the number of cores on the cancer yield.
Analysis of the combined effect of the biopsy pattern and the number of cores showed that the cluster with the highest RPR (18-22 cores of the 5-region pattern) had a significantly higher yield than most of the clusters. However, there was no statistically significant difference between this scheme and the 12-core scheme from pattern 'MPZ+LPZ' or the 10-core scheme from the 5-region pattern.

4.7.10. Additional lesion directed biopsies

Nineteen studies reported in their methods section that additional lesion-directed (LD) biopsies were taken out of suspicious prostate regions (suspicious due to palpation or ultrasound). Those LD cores were taken additionally to the systematically taken cores.

We tried to extract data for the unique cancer yield of those LD biopsies (i.e. cancers which were not detected by the systematic scheme but only by additional LD biopsies). We did not extract data for LD biopsies if authors incorporated them into their systematic approach by directing the needle to those lesions without enhancing the total number of cores taken.

We could not calculate a relative positivity rate (RPR) as LD biopsies are not applied for every patient and further details were often lacking in the studies. In addition, LD biopsies do not follow a well-defined pattern and the number of cores varies between patients. Thus we calculated the unique cancer detection rate of LD biopsies (number of cancers detected uniquely by LD / number of all study patients). The unique cancer detection rate of LD and the cancer detection rate (CDR) of the systematic scheme together add up to the total cancer detection rate in the studied population.

Six of the 19 studies[61,75,77,82,134,136] did not provide data for the unique cancer yield of the additional LD cores.

For six studies with information [84,91,95,99,107,128] the LD biopsies detected no additional cancer (i.e. CDR 0%).

For another six studies with information[11,12,16,72,97,121] the additional CDR of the LD biopsies varied between 0.4% and 1.4%.

One study[66] with 120 patients reported about 11 of 43 cancers, which were uniquely detected by colour Doppler directed biopsies (CDR total 38.8%; CDR-LD 9.2%).

4.8 Adverse events

Only 44 of 87 studies mentioned adverse events in their reporting and 36 out of those 44 studies provided data for adverse events.

The reporting of adverse events was generally not standardised and the length of follow up mostly not reported or not long enough to discover delayed events. Methods for data collection of this outcome varied (e.g. chart reports; questionnaires) or were sometimes not reported at all.

Some authors reported all complications. Some authors reported only 'serious complications'.

In studies with sequential sampling we counted adverse events for the most extensive scheme. In studies with randomised design we were able to count adverse events for each scheme separately.

When an author reported explicitly that a defined complication did not occur we extracted this information as 0.0%. When no information was available for a defined complication we extracted this information as 'not available'.

For data extraction of adverse events we have tried to count each patient only once (i.e. if a serious complication occurred that lead to a hospitalisation we have counted this event for the serious complication and not for hospitalisation). We were not able to extract reliable data for hospitalisation due to complications after biopsy as patients with serious complications were counted twice by some authors and counted only for serious complications by others.

Table 4.25 provides an overview over the range of reported adverse events of all 87 studies of this review. Minor adverse event were common and reported over a wide range of frequencies minor haematuria (0.8% to 95%), minor haematospermia (2.0% to 95%), minor rectal bleeding (0.7% to 95%), pain/discomfort (6% to 64.8%). Minor infections (e.g. fever as single symptom) were reported in 0.0% to 6.9% of the patients. Additional reported adverse events included prostatitis, urinary tract infection, voiding difficulties after biopsy, epididymitis, urethrorrhagia, vagal syndrome, dizziness. Major complications were less frequent: major infections (e.g. bacteraemia, urosepsis, abscess) with 0.0% to 1.8%, and major bleeding with 0.0% to 0.6%. No death due to a prostate biopsy was reported.

Table 4.25 Range of reported adverse events. 36 studies of sequential and randomised design contributed data for this table.

Adverse events	Min. (%)	Max. (%)	Number of studies with available information
Death due to complications	0.0	0.0	2
Infection major (e.g. bacteraemia, urosepsis, abscess)	0.0	1.8	11
Infection minor (e.g. fever as single symptom)	0.0	6.9	16
Prostatitis	0.0	1.25	7
Urinary tract infection	0.0	2.5	6
Voiding difficulties	0.0	10.5	16
Bleeding (major)	0.0	0.6	8
Haematuria (minor)	0.8	95	21
Haematospermia (minor)	2.0	95	10
Rectal bleeding (minor)	0.7	95	11
Pain (pain was reported from 'discomfort' over 'mild pain' to 'severe pain'; see details in the 'adverse event comment field' of each study')	6	64.8	6
Hospitalisation*	--	--	--
Other (e.g. epididymitis, urethrorrhagia, vagal syndrome, dizziness)	0.6	23.7	10
None (one author reported there were no complications)	--	100	1

(*Hospitalisation We have not extracted data for 'hospitalisation' as this item was reported in different ways by authors. Sometimes patients with serious complications were counted twice, sometimes patients were counted only for 'hospitalisation'.)

Either the number of cores[138] or the region where the biopsies are taken could be a predictor for complications. To get an overview visually whether the adverse events rate depended on the number of cores, we grouped the ranges of reported adverse events to the number of cores of our matrix. We did this irrespective of the pattern of the biopsy schemes (table 4.26). We did not have enough data to evaluate if biopsy schemes that include TZ-biopsies or midline biopsies result in higher complication rates (e.g. bleeding due to midline cores that go through the urethra).

We could not discover a systematic pattern of increasing adverse events with an increasing number of cores taken. A trend for increasing adverse events for more extended schemes may be visible for minor events like haematuria (minor), haematospermia (minor) or rectal bleeding (minor). However, we are not able to evaluate the impact of poor reporting in individual studies.

Additionally, studies with more extended schemes (e.g. a saturation biopsy with 32 cores[13]) sometimes used more invasive strategies to avoid adverse events (e.g. extended antibiotic prophylaxis with ciprofloxacin, ampicillin, gentamycin to avoid infections) or all patients were sent home with urinary catheter to avoid voiding problems and general or spinal anaesthesia was used to assure patient tolerance.

For our statistical analysis we relied on randomised studies as they reported adverse events for the reference test and the index test group separately and used identical methods of data collection. Four of seven randomised studies[58,68,112,136] reported numerical results for adverse events (table 4.26b). In 2 studies[68,112] a 12-core scheme and in one study[136] a 10-core scheme from 'MPZ+LPZ' was compared with a 6 core scheme. None of these studies reported on major adverse events (like death, major bleeding or major infection). There was no statistical significant difference between the rates of minor adverse events of the schemes up to 12-cores and the 6-core schemes (data of three studies for minor infection, haematuria, and haematospermia). Schemes up to 12 cores resulted in slightly higher rates of minor rectal bleeding (absolute risk difference 0.08; 95%-CI 0.00-0.16; p=0.037; data of two studies).

In one study[136] the rate of patients with moderate or severe pain was not different between a 10 core scheme and a 6 core scheme (33% vs. 32%), in one study[58] more patients with a 14-core scheme reported 'discomfort' than those with a 10-core scheme (65% vs. 28%).

Table 4.26 Reported adverse events grouped for number of cores taken. 36 studies of sequential and randomised design (with 40 schemes) contributed data for this table.

Adverse events	**6 cores** (Min.-Max; %)	**8 cores** (Min.-Max; %)	**10 cores** (Min.-Max; %)	**12/13 cores** (Min.-Max; %)	**14 cores** (Min.-Max; %)	**>=18 cores** (Min.-Max; %)
Number of schemes with reported AE	6	4	7	14	4	5
Death due to complications	0.0	---	---	0.0	---	---
Infection major (e.g. bacteraemia, urosepsis, abscess)	0.0	---	0.9	0.0– 0.7	1.8	0.0
Infection minor (e.g. fever as single symptom)	0.0–6.0	1.1–6.9	2.3–2.6	0.0–5.2	0.0–3.9	---
Prostatitis	0.0	---	0.7–1.25	0.2	---	1.0
Urinary tract infection	---	---	---	0.0–2.5	0.0	---
Voiding difficulties	0.0	0.5–1.9	0.8–2.6	0.0–7.2	4.9–5.4	2.0[+]
Bleeding (major)	0.0	0.6	0.3–0.6	0.0	---	0.0–0.3
Haematuria (minor)	17.6-50.0	5.0–71.4	1.6–72	0.8–80.0	5.3–95.0	84.0
Haematospermia (minor)	73.0; 79.0	2.0–27.8	75	6.2–82.0	24.7–95.0	60.0
Rectal bleeding (minor)	2.0–17.0	2.0–33.8	29	0.7–23.0	7.9–95.0	45.0
Pain[$]	---	---	27.9–33	6.0–33.3	6.9–64.8[++]	---
Hospitalisation*	---	---	---	---	---	---
Other (e.g. epididymitis, urethrorrhagia, vagal syndrome, dizziness)	---	1.1– 7.5	---	0.6–11.0	4.8–23.7	1.6
None**	---	---	---	100	---	---

--- means none of the studies of this group reported data for this item.

Pain[$] pain was reported from 'discomfort' over 'mild pain' to 'severe pain'; see details in the 'adverse event comment field' of each study'

*Hospitalisation We have not extracted data for 'hospitalisation' as this item was reported in different ways by authors Sometimes patients with serious complications were counted twice, sometimes patients were counted only once for 'hospitalisation'.

**None 100% means that one author reported there were no complications.

+Voiding difficulties All 37 patients after a 32-core saturation biopsy were sent home with urinary catheter (removal after week 1; in 4 patients the catheter was not removable before week 3).

[++]Pain 64.8% was reported as 'discomfort' in one study; abstract form only; no information available whether anaesthesia was used.

Table 4.**26b Adverse events in randomised studies. Four randomised studies contributed data for this table.**

	Paul 2003[136]		**Emiliozzi 2004**[112]		**Naughton 2000**[68]		**Horninger 1999**[58]	
Adverse events (in %)	**6* cores**	**10* cores**	**6**† **cores**	**12**† **cores**	**6**‡ **cores**	**12**‡ **cores**	**10**§ **cores**	**14**§ **cores**
Infection (minor)	2	2	0	0	6	4	---	---
Haematuria (minor)	58	72	45	43	50	55	---	---
Haematospermia (minor)	65	75	79	74	73	82	---	---
Rectal bleeding (minor)	18	29	---	---	17	23	---	---
Voiding difficulties	---	---	0	0	---	---	---	---
Pain	32	33	---	---	---	---	28	65

*Adverse events were collected up to 3 months
†Data extracted from additional publication.[138] Pain % of patients with moderate or severe pain during biopsy.
‡Author reports that no significant difference between groups was observed regarding impact of adverse events for patients[139] and quality of life (up to 4 weeks).[140]
§Pain was measured as % of patients with 'discomfort'.

CHAPTER 5 DISCUSSION OF RESULTS

5.1 Main findings

We analysed 87 primary studies with a total of 20,698 patients that evaluated a prostate biopsy procedure with a reference test. Some of the studies provided data for more than one biopsy scheme under evaluation. Most of the studies chose the standard sextant scheme of the mid-lobar peripheral zone as reference test. Eighty studies (n= 19,307) used a sequential sampling design. The more extensive biopsy protocol was applied after the reference test and each patient served as his own control (concordance studies). Only seven studies (n=1391) used a randomised parallel trial design. Of the seven randomised studies only three studies reported about a suitable method for generation of the random sequence and only two randomised studies reported that the allocation to the groups was concealed.

Studies were conducted in hospital settings. The studied population mainly consisted of men who were scheduled for biopsy due to abnormal DRE and/or raised PSA. Only in some studies men were explicitly recruited through screening. Mean ages of participants varied between 57.7 and 70.9 years. Information about technical equipment and patient preparation varied between studies. Reporting about skills of examiners was generally poor.

We extracted data for 94 comparisons out of 68 studies with the standard sextant scheme as reference test. The most frequent biopsy pattern of the analysed studies was ‘MPZ+LPZ’; 39 biopsy schemes (with 6 to 12 biopsy cores) out of this pattern were compared to the standard sextant reference test. The next frequent pattern was ‘MPZ+TZ (+MLiPZ) (4)’ where 24 schemes (with 8 to 12 biopsy cores) out of this pattern were evaluated. We grouped 20 comparisons to pattern ‘MPZ+LPZ+TZ (+MLiPZ)’, the 5-region biopsy pattern. Tests under evaluation consisted of 6 up to 22 cores out of this pattern.

Additional 23 comparisons out of 19 studies with a different reference test were extracted. Thus, 117 comparisons out of 87 studies were analysed for this systematic review.

Biopsy schemes of the 5-region biopsies with 18 and more cores showed the highest cancer yield, expressed as the relative positivity rate (RPR) in comparison to the standard sextant scheme (3 studies; RPR 1.48; 95%-CI 1.32-1.66). For studies with less cores of this pattern the cancer yield was lower (14 cores; 2 studies; RPR 1.33; 95%-CI 1.15-1.54).

In the most frequently analysed biopsy pattern ‘MPZ+LPZ’, the 12-core scheme (generally 6 cores from MPZ and 6 cores from LPZ) showed the highest cancer yield in comparison to the standard sextant scheme (13 studies with sequential sampling; RPR 1.31; 95%-CI 1.25-1.37; 3 randomised studies with almost identical result). For studies with less cores of this pattern the cancer yield was lower (8 cores; 7 studies; RPR 1.19; 95%-CI 1.14-1.24).

Cancer yields of pattern ‘MPZ+TZ (+MLiPZ)’ were lower than in the two patterns described above. The 12-core scheme of this pattern (6 cores from MPZ and 6 cores from TZ) showed a RPR of 1.23 (95%-CI 1.11-1.36) in comparison to the standard sextant scheme (3 studies with sequential sampling; 1 randomised study showed no significantly enhanced RPR). For studies with less cores of this pattern the cancer yield was still lower. For the most frequent analysed comparison in this review (an 8 core scheme with 6 cores from MPZ and 2 cores from TZ) the cancer yield was only slightly enhanced (16 studies provided data; RPR 1.04; 95%-CI 1.02-1.06; evidence for heterogeneity).

In pattern LPZ, studies were analysed which provided data for cores from the lateral peripheral zone (LPZ) only. The 6-core scheme of this pattern (data of 4 studies with sequential sampling) showed a RPR of 1.15 (95%-CI 0.94-1.41) indicating no significant difference in comparison to the standard sextant scheme.
For schemes of pattern MPZ (cores from the MPZ only) the information was scarce. Two studies provided data for an 8-core scheme (RPR 1.09; 95%-CI 1.03-1.16) and one primary study only was analysed for a 12-core scheme from MPZ (RPR 1.43; 95%-CI 1.18-1.75).

The number of cores was significantly correlated with the cancer yield.

Results from a regression analysis showed that the addition of laterally directed LPZ cores to a MPZ pattern ('MPZ+LPZ') enhanced the cancer yield significantly (p=0.003).

If transition zone biopsies are added to get a 5-region biopsy pattern ('MPZ+LPZ+TZ') the additional cancer yield is no longer statistically significant (p=0.624).

Transition zone cores are not routinely recommended for initial biopsies [8] as the additional yield is low. Our findings of the relatively low RPR of pattern 'MPZ+TZ' and the non-significant difference in the yield between the patterns 'MPZ+LPZ' and the 5-region pattern support this approach.

Analysing the combined effect of the biopsy pattern and the number of cores showed that the cluster with the highest RPR (18-22 cores from the 5-region pattern) has a significant higher cancer yield than most of the clusters. The difference to three of the other clusters is not significant, however 12 cores from pattern 'MPZ+LPZ', 10 cores from the 5-region pattern and 12 cores from pattern 'MPZ' (result based on one primary study only).

Studies that used a different reference test than the standard sextant scheme in general confirmed the findings as mentioned above The addition of LPZ cores to MPZ cores (or vice versa) lead to enhanced cancer yields. If a scheme from MPZ+LPZ (with already 10 or 18 cores) was extended to a 5-region pattern the additional yield was low. Finally, the addition of transition zone (TZ) cores did often not lead to significantly enhanced cancer yields.

The value of additional lesion directed (LD) biopsies seems to be marginal in the era of extended systematic biopsy schemes (12 studies with information showed a unique cancer detection rate of LD biopsies between 0% and 1.4%; one study with colour Doppler directed biopsies showed a unique cancer detection rate of 9.2%). The validity of those results is limited, however, as the cancer yield of LD biopsies was not in the focus of our review.

For all pooled results we suggest some caution in their interpretation because there was frequently heterogeneity between studies that we were unable to explain.

Adverse events

Minor adverse events (minor haematuria, minor haematospermia, minor rectal bleeding, pain/discomfort) were common and reported over a wide range of frequencies. Major complications were less frequent Major infections (e.g. bacteraemia, urosepsis, abscess) with 0.0% to 1.8%, and major bleeding with 0.0% to 0.6%. No death due to a prostate biopsy was reported. We could not discover a systematic pattern of increasing adverse events with an increasing number of cores taken. However, we are not able to evaluate the impact of poor reporting of adverse events. Additionally, studies with more extended schemes sometimes used more invasive strategies (e.g. intravenous sedation or general anaesthesia; extended antibiotic regimens; urinary catheter) to achieve patient tolerance or avoid adverse events.

Some evidence from randomised studies suggests that minor adverse events for schemes up to 12 cores are similar to those of the sextant pattern.

5.2 Validity of the findings

We have made considerable efforts to bring together all available primary studies that were relevant for our research question. Finally, 87 primary studies including more than 20,000 patients could be analysed.

Several methodological issues of this systematic review have to be critically discussed, however. First, the quality of reporting in the primary studies was often poor with lack of important information. Some studies were only retrievable as abstracts. Variability of test performance parameters for different patient profiles (i.e. PSA levels, prostate volume or first vs. repeated biopsies) could not be assessed properly. Thus, grouping of studies to detect influence of patient variables on the pooled results was only possible under the problematic assumption that test performance would not vary

across different clinical profiles. As a consequence, external validity of the results of this review has limitations because the results presented here cannot be adjusted according to variability in clinical findings. Secondly, the chosen anatomic model with five biopsy regions may have some limitations. The mid zone (region 3) may cover transitional tissue and peripheral zone tissue as well. Thirdly, the biopsy schemes clustered in one cell of the matrix may not be exactly identical, i.e. LPZ cores from different studies may not have been taken from exactly the same location within the LPZ. We are convinced, however, that the anatomic model, which was derived in cooperation with the expert panel, provides a reasonable compromise of accuracy and practicability for the research question.

Most of the studies used a robust design with sequential sampling in which each patient acted as their own control (paired data). Sampling error (i.e. some biopsies were taken from locations other than pre-specified in the study protocol) was possible in principle for all studies, specifically for those with a complex biopsy scheme, but it is presumably a scarce phenomenon in a well-defined study setting. Review bias could be a further possible source of bias. Only 1 study reported that the pathologist was blinded for the sequence of the tests when examining the tissues cores. This may lead to inflated measures of diagnostic accuracy of the index test in comparison to the reference test.[45] Non standardised core lengths and different methods of pathological examination can affect cancer detection rates[53,141-143] and systematically influence comparisons between different biopsy schemes. There is great variation in the processing of prostatic needle cores in clinical practice.[144] In the primary studies of our review the sample length was often not described and varied between 10mm and 23mm for 11 studies with information. The method of histological work-up was mostly not specified or unclear.

Additionally, the validity of data for adverse events has limitations. The reporting of adverse events was generally not standardised and the length of follow up mostly not reported or not long enough to discover delayed events. Methods for data collection of this outcome varied or were often not reported at all. The available data, however, were in general comparable to prospectively collected adverse event data of recent studies.[138,145]

Applying more complex biopsy schemes to clinical practice will need special training for less experienced examiners, measures for quality control, and application of proper local anaesthesia to improve patient tolerance.[52]

Anaesthesia methods, however, were not reported at all for 57% of the studies. Most of them were recent studies published from the year 2000 onwards. A biopsy procedure with an extended scheme may not be prolonged significantly in absolute terms. But patient tolerance may be an important factor, which limits applicability of extended schemes. Despite receiving adequate information about the procedure many patients remain anxious to a certain degree. Having a big probe inserted in the rectum is an invasive and uncomfortable procedure even if a well-placed local anaesthesia is applied.

Further questions arise regarding the skills of the examiners. Those skills are often not reported or only poorly reported. In general, experienced examiners, mostly from specialised centres, may have taken the cores resulting in a standardised biopsy procedure. In those circumstances the results reported here may not be directly applicable in clinical routine.

Furthermore, taking more cores results in higher costs as each examined core of a more extensive scheme will be charged additionally. Prostate biopsy is now a common biopsy procedure undertaken in all hospitals and small changes in resource usage in an individual patient have major consequences in a public health perspective.

5.3 Clinical interpretation

The standard sextant scheme has a significantly lower cancer yield than most of the more extensive biopsy schemes.

As the number of cores increases, the yield improves for most of the schemes.

Addition of laterally directed cores from the lateral peripheral zone (LPZ) to the mid-lobar peripheral zone (MPZ) increases the yield significantly, whereas additional transition zone (TZ) cores did not. Transition zone cores are not routinely recommended for initial biopsies[8] as the additional yield is

generally low. Our findings of the relatively low yield of pattern ‘MPZ+TZ’ in comparison to the standard sextant pattern and the non-significant difference in the yield between the patterns ‘MPZ+LPZ’ and the 5-region pattern support this approach.

Data on adverse events are scarce. While some evidence suggests that adverse events for schemes up to 12 cores are similar to those of the sextant pattern, this remains unclear for more extended schemes.

Applying more complex biopsy schemes to clinical practice will need special training for less experienced examiners and measures for quality control. Patient tolerance, which can be improved by proper local anaesthesia, is another important point that has to be taken into consideration for applicability of the extended schemes.

Whether the results of the analysed studies translate directly into clinical routine is not clear as populations may differ from those in clinical practice.

A relevant issue is how the findings of this systematic review translate into absolute figures for clinicians and their patients

A RPR of 1.33 means that a biopsy scheme under evaluation will discover 33% more cancers relative to the applied reference test. For translation of this relative measure into absolute figures the prevalence of cancer in the examined population of men scheduled for biopsy has to be taken into consideration. The higher the prevalence of cancer in the examined population the higher will be the absolute additional diagnostic value of the biopsy scheme under evaluation (see table 5.1).

The following example will illustrate the figures in table 5.1 We chose a biopsy scheme with a RPR of 1.31 (like the 12-core scheme of the pattern ‘MPL+LPZ’) in a hypothetical population of 100 men referred for biopsy (not a screening population), where the standard sextant scheme detects 30% of the scheduled patients with cancer. Thus a test with an RPR of 1.31 detects 39% (30% x 1.31) of the scheduled patients with cancer. 30 men are detected with the sextant test and 39 men are detected with the 12-core scheme. Nine out of 100 men are detected additionally because the 12-core scheme has been applied. The number of men needed to biopsy (NNB) with the 12-core scheme to detect one additional cancer patient (in comparison to the application of the sextant scheme) are 11 men (100/9) in this example.

Table 5.1 Number needed to biopsy (NNB) to detect one additional cancer patient. The table gives a hypothetical example for three populations of 100 men referred for biopsy (not a screening population) with different cancer prevalences. Calculations are based on an index test with a relative positivity rate (RPR) of 1.33 (example A) and on an index test with a relative positivity rate (RPR) of 1.50 (example B).

A) Population n=100 RPR of index test 1.33	low cancer prevalence	mid cancer prevalence	high cancer prevalence
Reference test Absolute number of men detected with cancer	20	30	50
CDR reference test	20%	30%	50%
Index test test Absolute number of men detected with cancer	27	40	67
CDR index test	27%	40%	67%
Absolute risk difference to be detected as a cancer patient	7%	10%	17%
Number needed to biopsy to detect 1 additional cancer patient	100/7=15	100/10=10	100/17=6
Rate of patients with diagnostic benefit	1/15=7%	1/10=10%	1/6=17%
Rate of patients without diagnostic benefit	14/15=93%	9/10=90%	5/6=83%

B) Population n=100 RPR of index test 1.50	low cancer prevalence	mid cancer prevalence	high cancer prevalence
Reference test Absolute number of men detected with cancer	20	30	50
CDR reference test	20%	30%	50%
Index test test Absolute number of men detected with cancer	30	45	75
CDR index test	30%	45%	75%
Absolute risk difference to be detected as a cancer patient	10%	15%	25%
Number needed to biopsy to detect 1 additional cancer patient	100/10=10	100/15=7	100/25=4
Rate of patients with diagnostic benefit	1/10=10%	1/7=14%	1/4=25%
Rate of patients without diagnostic benefit	9/10=90%	6/7=86%	3/4=75%

An alternative way to describe the absolute diagnostic value of the cores taken additionally to a reference method (e.g. the standard sextant technique) is to calculate the increased cancer detection rate of the index biopsy method (per 10,000 biopsied persons). An example is given below in table 5.2.

Table 5.2 Increased cancer detection rate of the index biopsy method (per 10,000 biopsied persons). The table gives a hypothetical example for a population referred for biopsy (not a screening population) of 10'000 men with three different cancer prevalences. Calculations are based on an index test with a relative positivity rate (RPR) of 1.33.

Population n=10'000 RPR of index test 1.33	low cancer prevalence	mid cancer prevalence	high cancer prevalence
Reference test Absolute number of men detected with cancer	2000	3000	5000
CDR reference test	20%	30%	50%
Index test test Absolute number of men detected with cancer	2700	4000	6700
CDR index test	27%	40%	67%
Absolute difference of detected cancer patients (per 10,000 biopsied persons)	700	1000	1700

The following example will illustrate the figures in table 5.2: we chose again a biopsy scheme with an RPR of 1.31 (like the 12-core scheme of the pattern 'MPL+LPZ') in a population of 10,000 men referred for biopsy (not a screening population), where the standard sextant scheme detects 30% of the scheduled patients with cancer (mid cancer prevalence of men scheduled for biopsy). Thus a test with a RPR of 1.33 detects 39% (30% x 1.31) of the scheduled patients with cancer. 3000 men are detected with the sextant test and 3930 men are detected with the 12-core scheme. 930 of 10,000 men are detected additionally because the 12-core scheme has been applied.

5.4 Recommendations

For recommendations of a biopsy scheme in clinical practice some priorities have to be defined in advance (highest possible cancer yield vs. efficient cancer detection with a balanced rate of adverse events).

The 5-region biopsy schemes with 18 and more cores are an option, if the highest possible cancer yield is the first aim (3 studies; RPR 1.48; 95%-CI 1.32-1.66). This aim has been questioned, however, as PSA screening may lead to over-diagnosis rather than under-diagnosis.[15,34] False positive results (i.e. no diagnosis of cancer in the prostatectomy specimen after a 'positive' biopsy), that might result in psychological or physical harm, have so far been scarce[21] but might increase if a maximum of cores is taken. Cost issues have to be considered as well. In addition, the reported data provide an insufficient body of evidence to determine whether extended biopsy schemes do increase the rate of major adverse events.

Some evidence from randomised studies suggests that adverse events for schemes up to 12 cores are similar to those of the sextant pattern.[68,112,138] If a maximum of 12 cores are to be taken the pattern 'MPZ+LPZ', i.e. adding lateral cores to the standard sextant pattern, may be chosen (13 studies with sequential sampling; RPR 1.31; 95%-CI 1.25-1.37; 3 randomised studies with almost identical result).

If a maximum of 10 cores is aimed at, either 10 cores from pattern 'MPZ+LPZ' or alternatively 10 cores of the 5-region pattern may be appropriate. However, the pooled results of both 10-core schemes have to be interpreted with caution, as there was evidence for heterogeneity. Based on our findings that additional TZ-cores had a low additional value, the 10-core schemes from pattern 'MPZ+LPZ' may be preferable.

These recommendations are in line with biopsy patterns applied in current large-scale studies. This review gives empiric foundation for this selection.

For example the European Randomised Study of Screening for Prostate Cancer (ERSPC), a big-scale multinational study to evaluate the efficacy of prostate cancer screening, decided in their initial protocol to apply sextant biopsies. In many centres, however, it has become common practice to take 10 to 12 cores for this study.

In the British ProtecT-study the biopsy protocol has been recently modified to a 10-core pattern (personal communication).

CHAPTER 6 IMPLICATIONS FOR FUTURE RESEARCH

i) A standardised nomenclature of anatomical regions has to be applied in future studies for a better comparison of different prostate biopsy schemes.

ii) Future studies should improve reporting on patient characteristics and consider restriction to prognostically homogeneous subgroups.

iii) A standardised reporting of patient preparation, biopsy procedure and the method of histological work-up to enable a better comparison of the diagnostic performance of different biopsy schemes.

iiii) Striking the balance between cancer yield and adverse events is the challenge that could not be addressed satisfactorily in this report. Future studies should focus on this issue.

iiiii) It has to be demonstrated that more extensive biopsy schemes with a higher cancer yield do lead to reduced cancer mortality due to early detection of prostate cancer.

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APPENDIX 1 SEARCH STRATEGY

An initial scoping search in MEDLINE identified appropriate terms for a draft search. The strategy was developed further by identifying thesaurus/keyword terms used to index articles deemed to be relevant. After taking the decision not to limit the search by study design nor by a diagnostic accuracy filter the following strategy was chosen as capturing relevant records whilst excluding large numbers of irrelevant records. This strategy is shown in a version that will run in the Ovid interfaces of MEDLINE. The strategy was appropriately adapted to run on other databases with different interfaces and search options.

Search strategy:

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1. exp Prostatic Neoplasms/
2. ((prostate or prostatic) adj4 (cancer$ or neoplas$ or oncology$ or malignan$ or tumour$ or tumor$ or carcinoma$ or adenocarcinoma$ or adenoma$ or sarcoma$)).ti,ab.
3. 1 or 2
4. exp Biopsy/
5. (transperineal adj4 biops$).ti,ab.
6. (transperineal ultraso$ or tpus).ti,ab. (93)
7. (peripheral adj3 biops$).ti,ab.
8. (transrectal adj4 biops$).ti,ab.
9. (transrectal ultraso$ or trus).ti,ab.
10. needle biops$.ti,ab.
11. (core biops$ or biopsy core$).ti,ab.
12. (sextant adj3 biops$).ti,ab.
13. or/4-12
14. 3 and 13
15. limit 14 to yr=1980-2003
16. limit 15 to human

A wide range of bibliographic sources were consulted in order to identify the studies used in this review:

- MEDLINE
- PREMEDLINE
- EMBASE
- SIGLE
- BIOSIS
- PASCAL
- Science Citation Index (SciSearch)
- Dissertation Abstracts Online
- National Technical Information Service (NTIS)
- Inside Conferences
- Current Contents Search
- LILACS

Update searches of all the above databases, from the date on which they had previously been searched, was carried out in April/May 2004.

A search of Internet sources was conducted on 18/12/2003 and a selection of the results was scanned for further studies.

The full strategies and descriptions of the searches undertaken are presented below.

In addition to these searches, hand searching of relevant urological journals (Prostate, Journal of Urology, Urology, European Urology and BJU International: from 1998 to 2004) for relevant studies, supplements and conference proceedings was carried out. Forthcoming papers were included in the hand search where journals provided pre view information.
Additionally, the bibliographies of retrieved articles were checked to find additional studies.
Finally a cited reference searching was undertaken on key references, tracking down further studies that cited key references
In all, over 20694 references were retrieved and scanned for relevance. The results of the searching, 9926 records (after deduplication), are in prostate-MASTER.enl.

Detailed searches carried out to inform the review

1. Databases

1a. MEDLINE

Draft search strategy from the initial scoping search on MEDLINE.

4 exp Prostatic Neoplasms/
5 (prostate or prostatic).ti,ab.
6 exp BIOPSY/
7 (transperineal adj4 biops$).ti,ab.
8 (peripheral adj3 biops$).ti,ab.
9 (transrectal adj4 biops$).ti,ab.
10 needle biops$.ti,ab.
11 (core biops$ or trus).ti,ab.
12 or/1-2
13 or/3-8
14 9 and 10
15 animal/ not (animal/ and human/)
16 11 not 12

This strategy was further developed to take account of additional keywords and phrases identified in relevant papers from the initial scoping search.

23/10/2003 first search – downloaded 4206 records from Ovid MEDLINE. Results in file prostate-medline.txt. Created new Endnote libraries: prostate-medline.enl and prostate-master.enl.

Database: MEDLINE <1966 to October Week 3 2003>

Search Strategy:
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1. exp Prostatic Neoplasms/ (40037)
2. ((prostate or prostatic) adj4 (cancer$ or neoplas$ or oncology$ or malignan$ or tumour$ or tumor$ or carcinoma$ or adenocarcinoma$ or adenoma$ or sarcoma$)).ti,ab. (37416)
3. 1 or 2 (46629)
4. exp Biopsy/ (120035)
5. (transperineal adj4 biops$).ti,ab. (138)
6. (transperineal ultraso$ or tpus).ti,ab. (93)
7. (peripheral adj3 biops$).ti,ab. (856)
8. (transrectal adj4 biops$).ti,ab. (1003)

9. (transrectal ultraso$ or trus).ti,ab. (2521)
10. needle biops$.ti,ab. (6923)
11. (core biops$ or biopsy core$).ti,ab. (1510)
12. (sextant adj3 biops$).ti,ab. (383)
13. or/4-12 (125147)
14. 3 and 13 (4691)
15. limit 14 to yr=1980-2003 (4230)
16. limit 15 to human (4206)

The search was re-run on MEDLINE on 27/04/2004 to capture recent studies. The dates searched, using the search field '*ed*: Entry Date', were 01/10/2003 to April Week 2 2004. 237 records were downloaded.

1b. EMBASE

EMBASE was searched via the Ovid interface on the web on 23/10/2003. The dates searched were 1980 to 2003 Week 42. 4517 records were downloaded.

Search Strategy:
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1 exp Prostatic Neoplasms/ (35291)
2 ((prostate or prostatic) adj4 (cancer$ or neoplas$ or oncology$ or malignan$ or tumour$ or tumor$ or carcinoma$ or adenocarcinoma$ or adenoma$ or sarcoma$)).ti,ab. (31755)
3 1 or 2 (39448)
4 exp Biopsy/ (122293)
5 (transperineal adj4 biops$).ti,ab. (116)
6 (transperineal ultraso$ or tpus).ti,ab. (88)
7 (peripheral adj3 biops$).ti,ab. (674)
8 (transrectal adj4 biops$).ti,ab. (837)
9 (transrectal ultraso$ or trus).ti,ab. (2215)
10 needle biops$.ti,ab. (5357)
11 (core biops$ or biopsy core$).ti,ab. (1417)
12 (sextant adj3 biops$).ti,ab. (372)
13 or/4-12 (125635)
14 3 and 13 (4687)
15 limit 14 to yr=1980-2003 (4671)
16 limit 15 to human (4517)

The search was re-run on EMBASE on 27/04/2004 to capture recent studies. The dates searched, using the search field '*em*: Entry Week', were 2003 Week 42 to 2004 Week 17. 359 records were downloaded.

1c. MEDLINE® In-Process & Other Non-Indexed Citations (PREMEDLINE)

PREMEDLINE was searched via the Ovid interface on 23/10/2003. The PREMEDLINE issue searched was dated 22 October 2003. The MEDLINE strategy was used with the subject headings removed. 80 records were identified and saved as prostate-premedline.txt.

Search Strategy:

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1. ((prostate or prostatic) adj4 (cancer$ or neoplas$ or oncology$ or malignan$ or tumour$ or tumor$ or carcinoma$ or adenocarcinoma$ or adenoma$ or sarcoma$)).ti,ab. (1414)
2. (transperineal adj4 biops$).ti,ab. (1)
3. (transperineal ultraso$ or tpus).ti,ab. (4)
4. (peripheral adj3 biops$).ti,ab. (9)
5. (transrectal adj4 biops$).ti,ab. (28)
6. (transrectal ultraso$ or trus).ti,ab. (93)
7. needle biops$.ti,ab. (126)
8. (core biops$ or biopsy core$).ti,ab. (62)
9. (sextant adj3 biops$).ti,ab. (21)
10. or/2-9 (275)
11. 1 and 10 (80)

The search was re-run on PREMEDLINE on 27/04/2004 to capture recent studies. The dates searched, using the search field '*up*: Update Code', were 01/10/2003 to 26/04/2004. 72 records were downloaded.

1d. SciSearch

The Science Citation Index was searched using the Dialog search interface on 30/10/2003. The search covered the period 1980 to 2003/Oct W3. 1962 records were downloaded and saved as files prostate-scisearch1.txt, prostate-scisearch2.txt and prostate-scisearch3.txt.

s ((prostate or prostatic)(w)(cancer? or neoplas?))/de (7753)

s ((prostate or prostatic)(2n)(cancer? or neoplas? or oncology? or malignan? or tumour? or tumor? or carcinoma? or adenocarcinoma? or adenoma? or sarcoma?))/ti,ab (32609)

s s1 or s2 (33262)

s (biopsy or biopsies)/de (8553)

s (transperineal(4n)biops?)/ti,ab (70)

s (transperineal(w)ultraso? or tpus)/ti,ab (128)

s (peripheral(3n)biops?)/ti,ab (450)

s (transrectal(4n)biops?)/ti,ab (630)

s (transrectal(w)ultraso? or trus)/ti,ab (2007)

s (needle(w)biops?)/ti,ab (4407)

s (core(w)biops? or biopsy(w)core?)/ti,ab (1478)

s (sextant(3n)biops?)/ti,ab (372)

s s4:s12 (15397)

s s3 and s13 (1970)

s s14/1980:2003 (1962)

The search was re-run on the Science Citation Index via Dialog OneSearch on 06/05/2004. To capture recent studies the search was limited to the period 2003 to 2004 and deduplication was undertaken online against MEDLINE. 55 records were downloaded.

1e. Pascal

Pascal was searched using the Dialog search interface on 30/10/2003. The search covered the period 1980 to 2003/Oct W3. 1540 records were identified.

s ((prostate or prostatic)(w)(cancer? or neoplas?))/de (71)

s ((prostate or prostatic)(2n)(cancer? or neoplas? or oncology? or malignan? or tumour? or tumor? or carcinoma? or adenocarcinoma? or adenoma? or sarcoma?))/ti,ab (18800)

s s1 or s2 (18811)

s (biopsy or biopsies)/de (33491)

s (transperineal(4n)biops?)/ti,ab (43)

s (transperineal(w)ultraso? or tpus)/ti,ab (94)

s (peripheral(3n)biops?)/ti,ab (251)

s (transrectal(4n)biops?)/ti,ab (467)

s (transrectal(w)ultraso? or trus)/ti,ab (1329)

s (needle(w)biops?)/ti,ab (2305)

s (core(w)biops? or biopsy(w)core?)/ti,ab (826)

s (sextant(3n)biops?)/ti,ab (289)

s s4:s12 (35950)

s s3 and s13 (1625)

s s14/1980:2003 (1540)

The search was re-run on Pascal via Dialog OneSearch on 06/05/2004. To capture recent studies the search was limited to the period 2003 to 2004 and deduplication was undertaken online against the databases MEDLINE and SciSearch. 33 records were downloaded.

1f. Biosis Previews

Biosis was searched using the Dialog search interface on 30/10/2003. The search covered the period 1980 to 2003/Oct W4. 3610 records were retrieved.

s ((prostate or prostatic)(w)(cancer? or neoplas?))/de (27307)

s ((prostate or prostatic)(2n)(cancer? or neoplas? or oncology? or malignan? or tumour? or tumor? or carcinoma? or adenocarcinoma? or adenoma? or sarcoma?))/ti,ab (38121)

s s1 or s2 (46333)

s (biopsy or biopsies)/de (45955)

s (transperineal(4n)biops?)/ti,ab (103)

s (transperineal(w)ultraso? or tpus)/ti,ab (66)

s (peripheral(3n)biops?)/ti,ab (547)

s (transrectal(4n)biops?)/ti,ab (696)

s (transrectal(w)ultraso? or trus)/ti,ab (2215)

s (needle(w)biops?)/ti,ab (4774)

s (core(w)biops? or biopsy(w)core?)/ti,ab (1089)

s (sextant(3n)biops?)/ti,ab (363)

s s4:s12 (51838)

s s3 and s13 (3698)

s s14/1980:2003 (3610)

The search was re-run on Biosis via Dialog OneSearch on 06/05/2004. To capture recent studies the search was limited to the period 2003 to 2004 and deduplication was undertaken online against the databases MEDLINE, SciSearch and Pascal. 297 records were downloaded.

1g. Current Contents Search

The database Current Contents was searched using the Dialog search interface on 30/10/2003 for the period 1990 to 2003/Oct 29. 2399 records were downloaded and saved as file prostate-current-contents.txt.

s ((prostate or prostatic)(w)(cancer? or neoplas?))/de (7719)

s ((prostate or prostatic)(2n)(cancer? or neoplas? or oncology? or malignan? or tumour? or tumor? or carcinoma? or adenocarcinoma? or adenoma? or sarcoma?))/ti,ab (31720)

s s1 or s2 (32367)

s (biopsy or biopsies)/de (8355)

s (transperineal(4n)biops?)/ti,ab (77)

s (transperineal(w)ultraso? or tpus)/ti,ab (144)

s (peripheral(3n)biops?)/ti,ab (431)

s (transrectal(4n)biops?)/ti,ab (751)

s (transrectal(w)ultraso? or trus)/ti,ab (2368)

s (needle(w)biops?)/ti,ab (3919)

s (core(w)biops? or biopsy(w)core?)/ti,ab (1564)

s (sextant(3n)biops?)/ti,ab (398)

s s4:s12 (15081)

s s3 and s13 (2399)

s s14/1980:2003 (2399)

The search was re-run on Current Contents via Dialog OneSearch on 06/05/2004. To capture recent studies the search was limited to the period 2003 to 2004 and deduplication was undertaken online against the databases MEDLINE, SciSearch, Pascal and Biosis. 1 record was downloaded.

1h. LILACS

LILACS was searched on the BIREME website on 31/10/2003. The following search terms were used:

prostat$ AND (cancer$ or neoplas$ or oncolog$ or malign$ or tumour$ or tumor$ or carcinoma$ or adencarcinoma$ or adenoma$ or sarcoma$) AND biops$

137 records were identified and scanned. 66 records were added to the Endnote Library.

The search was re-run on LILACS on 28/04/2004 to capture recent studies. 143 records were identified and scanned for duplicates. 5 records were added to the Endnote Library.

2. Conference Proceedings

2a. Inside Conferences

Inside Conferences was searched using the Dialog search interface on 28/10/2003 for the period 1993 to 2003. As abstracts are not included a broad search was used to identify papers. 54 records were identified.

Search Strategy:

---

s (prostate or prostatic)(2n)(cancer? or neoplas? or oncology? or malignan? or tumour? or tumor? or carcinoma? or adenocarcinoma? or adenoma? or sarcoma?) (2656)

s (biopsy or biopsies) (2145)

s s1 and s2 (54)

s s3/1980:2003 (54)

The search was re-run on Inside Conferences on 30/04/2004. In an attempt to capture recent studies the search was limited to the period 2003 to 2004. No additional records were identified.

3. Grey Literature

3a. SIGLE

SIGLE was searched via the ARC2 W WebSPIRS service on 24/10/2003. The dates searched were 1980 to 2003/06. 13 records were identified.

Search Strategy:
---

1. prostate near4 (cancer* or neoplas* or oncology* or malignan* or tumour* or tumor* or carcinoma* or adencarcinoma* or adenoma* or sarcoma*) (98 records)
2. prostatic near4 (cancer* or neoplas* or oncology* or malignan* or tumour* or tumor* or carcinoma* or adencarcinoma* or adenoma* or sarcoma*) (15 records)
3. #1 or #2 (109 records)
4. biopsy or biopsies (80 records)
5. diagnos* (6122 records)
6. #4 or #5 (6177 records)
7. #3 and #6 (13 records)

The search was re-run on SIGLE on 30/04/2004 to capture recent studies. 14 records were identified and scanned for duplicates. 1 record was added to the Endnote Library.

3b. National Technical Information Service (NTIS)

NTIS was searched using the Dialog search interface on 29/10/2003. The search covered the period 1980 to 2003/Oct W4. 12 records were downloaded and saved as file prostate-NTIS.txt.

s ((prostate or prostatic)(w)(cancer? or neoplas?))/de (652)

s ((prostate or prostatic)(2n)(cancer? or neoplas? or oncology? or malignan? or tumour? or tumor? or carcinoma? or adenocarcinoma? or adenoma? or sarcoma?))/ti,ab (730)

s s1 or s2 (760)

s (biopsy or biopsies)/de (550)

s (transperineal(4n)biops?)/ti,ab (0)

s (transperineal(w)ultraso? or tpus)/ti,ab (2)

s (peripheral(3n)biops?)/ti,ab (0)

s (transrectal(4n)biops?)/ti,ab (0)

s (transrectal(w)ultraso? or trus)/ti,ab (26)

s (needle(w)biops?)/ti,ab (25)

s (core(w)biops? or biopsy(w)core?)/ti,ab (4)

s (sextant(3n)biops?)/ti,ab (0)

s s4:s12 (588)

s s3 and s13 (17)

s s14/1980:2003 (16) saved as C:\Prostate\searching\searches\NTIS.txt

The search was re-run on National Technical Information Service (NTIS) on 30/04/2004. In an attempt to capture recent studies the search was limited to the period 2003 to 2004. 6 additional records were identified and entered on the Endnote Library.

3c. Dissertation Abstracts Online

Dissertation Abstracts Online was searched using the Dialog search interface on 29/10/2003. The search covered the period 1980 to 2003/Sep. 20 records were identified and saved as file prostate-dissabs.txt.

s ((prostate or prostatic)(w)(cancer? or neoplas?))/de (0)

s ((prostate or prostatic)(2n)(cancer? or neoplas? or oncology? or malignan? or tumour? or tumor? or carcinoma? or adenocarcinoma? or adenoma? or sarcoma?))/ti,ab (790)

s s1 or s2 (790)

s (biopsy or biopsies)/de (0)

s (transperineal(4n)biops?)/ti,ab (1)

s (transperineal(w)ultraso? or tpus)/ti,ab (5)

s (peripheral(3n)biops?)/ti,ab (6)

s (transrectal(4n)biops?)/ti,ab (3)

s (transrectal(w)ultraso? or trus)/ti,ab (31)

s (needle(w)biops?)/ti,ab (46)

s (core(w)biops? or biopsy(w)core?)/ti,ab (14)

s (sextant(3n)biops?)/ti,ab (1)

s s4:s12 (98)

s s3 and s13 (20)

s s14/1980:2003 (20)

The search was re-run on Dissertation Abstract Online on 05/05/2004. In an attempt to capture recent studies the search was limited to the period 2003 to 2004. Two additional records were identified, with one relevant record entered on the Endnote Library.

4. Internet

Searching the Internet was undertaken on 18/12/2003 using Google http://www.google.com and the following terms: (prostate OR prostatic) (cancer OR neoplasm) (biopsy OR biopsies)

This returned 87,700 hits of which the first 50 were searched for relevent information.

1. New Test May Reduce Need For Some Prostate Cancer Biopsies
   http://www.hopkinsmedicine.org/press/1998/MAY/980520.HTM
2. Prostate Cancer Biopsy Technique Adds Information
   http://www.meridianhealth.com/jsmc.cfm/MediaRelations/News/MensHealth/dec2003.cfm
3. Primer on prostate cancer, biopsy form f2
   http://www.phoenix5.org/books/Primer/FormF2biopsyform.html
4. Products - Prostate Cancer Biopsy Predictor
   http://www.xaim.com/medical_informatics05.html
5. Products- Prostate Cancer Biopsy Predictor (continued)
   http://www.xaim.com/medical_informatics06.html

6. Prostate Cancer -- Biopsy -- Printer-Friendly Version
http://www.upmccancercenters.com/cancer/prostate/pfv/biopsyneedle.html
7. Prostate Cancer, The Cancer Information Network
http://www.cancerlinksusa.com/prostate/
8. Prostate Cancer
http://www.prostate-cancer-info.com/
9. Microfocal prostate cancer: biopsy cancer volume does not predict ...
http://www.blackwell-synergy.com/links/doi/10.1046/j.1464-410x.1998.00661.x/full/
10. Cryosurgery in the Treatment of Prostate Cancer
http://www.cancernews.com/cryosurgery.htm
11. New model predicts likelihood of prostate cancer prior to biopsy
http://www.eurekalert.org/pub_releases/2003-08/ohs-nmp082103.php
12. DrTest | prostate cancer testing and biopsies
http://www.dr-test.com/catalog/%20prostate-cancer-testing-and-biopsies.htm
13. RCOG: Radiotherapy Clinics of Georgia http://www.prostrcision.com
14. What To Do If Prostate Cancer Strikes: A Helpbook for Patients
http://www.cancerresearch.org/prostatebook.html
15. New Prostate Cancer Test Reduces Need for Biopsies
http://my.webmd.com/content/article/75/89658.htm
16. Focal prostate cancer on biopsy does not predict focal prosate ...
http://www.marinurology.com/articles/cap/jurol-1995b.htm
17. Prostate Biopsy in the staging of prostate cancer
http://www.nature.com/cgi-taf/DynaPage.taf?file=/pcan/journal/v1/n2/abs/4500216a.html
18. Cancer.gov
http://www.cancer.gov/newscenter
Performed a search of the news releases using the term ‘prostate’ and limiting to Jan 1999 – Dec 2003
19. Prostate Cancer: Positive Biopsy
http://www.wmfurology.com/pcaposbx.htm
20. ACS :: How Is Prostate Cancer Diagnosed?
http://www.cancer.org/docroot/CRI/content/CRI_2_4_3X_How_is_prostate_cancer_diagnosed_36.asp?sitearea
21. Blood in semen after prostate biopsy --- HealthandAge
http://www.healthandage.com/Home/gm=6!gid7=513
22. The Prostate Biopsy: Examining Tissue for Cancer Cells
http://www.prostate-cancer-screening.com/html/tissue-biopsy.php3
23. Prostate Cancer Screening
http://www.prostate-cancer-screening.com
24. Biopsy, a Prostate Cancer Journal entry by Robert Vaughn Young
http://www.phoenix5.org/essaysry/rvycj1216biopsy.html?FACTNet
25. Predictors of prostate cancer on repeat prostatic biopsy in men ...
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12657099&dopt=Abstract
26. Science News: Baldness drug might avert prostate cancer
http://www.findarticles.com/cf_dls/m1200/26_163/105371515/p1/article.jhtml
27. Prostate Cancer Site Map
http://www.wmfurology.com/pcaweb.htm
28. Health 24 - News, Prostate
http://www.health24.co.za/news/Prostate/1-941,24387.asp
29. PSA Rising :: Prostate Cancer News, Info, Support
http://psa-rising.com
30. Optimal Biopsy Protocols for Prostate Cancer (ResearchIndex)
http://citeseer.nj.nec.com/494533.html
31. [PDF] A Statistical Atlas of Prostate Cancer for Optimal Biopsy
http://cisstweb.cs.jhu.edu/resources/publications/download/shen-etal-miccai-2001.pdf

32. More accurate test for prostate cancer can reduce invasive ...
http://www.umich.edu/~urecord/9697/Jan28_97/artcl23.htm
33. Health 24 - News, Prostate
http://www.health24.co.za/news/Prostate/1-941,22507.asp
34. Prostate Cancer Research Institute PC Forms & Software
http://www.prostate-cancer.org/tools/forms/biopsy_report.html
35. Prostate Cancer Research Institute
http://www.prostate-cancer.org/education/preclin/5region.html
36. [PDF] Statistically Optimized Biopsy Strategy for the Diagnosis of ...
http://www.rad.upenn.edu/sbia/papers/CBMS2001_Prostate_DGShen.pdf
37. Prostate Cancer Story -1
http://www.prostate-cancer-story.com
38. Optimized Needle Biopsy Strategies For Prostate Cancer Detection ...
http://citeseer.nj.nec.com/488354.html
39. Prostate cancer testing and biopsies
http://www.mrstest.com/disease/?ref=6&affiliate_banner_id=1
40. DRE Screening for Prostate Cancer [April 2000; 74-7]
http://www.jr2.ox.ac.uk/bandolier/band74/b74-7.html
41. The Prostate Cancer Charity Message Boards - Biopsy & ...
http://www.prostate-cancer.org.uk/supportServices/forums/topic.asp?TOPIC_ID=271
42. Optimal predictors of prostate cancer
http://www.astrazeneca.no/bibliotek/azmedica/onkologi/0201_prostata.html
43. CryoCarePCA - Prostate Cancer Advocates
http://www.cryocarepca.org
44. Predictive value of contralateral biopsies in unilaterally ...
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1538487&dopt=Abstract
45. Sloan-Kettering - High Dose Radiation Improves Outcome in ...
http://www.mskcc.org/mskcc/html/2400.cfm
46. Testing Method Misses Nearly 14 Percent Of Prostate Cancer Cases
http://www.acs.ohio-state.edu/researchnews/archive/prostest.htm
47. Prostate Cancer Tests Might Miss One In Seven Cases
http://unisci.com/stories/20013/0709012.htm
48. Cornell Urology - Pathology of Prostate Cancer
http://www.cornellurology.com/uro/cornell/prostate/evaluation/pathology.shtml
49. Using TRUS Effectively to Diagnose, Stage, Prostate Cancer
http://www.prostatepointers.org/prostate/lee/big/lee1.html
50. UM CCC - Prostate Cancer Screening and Diagnosis
http://www.cancer.med.umich.edu/prostcan/proscreening.htm

APPENDIX 2 FORM WITH EXPLICIT STUDY SELECTION CRITERIA

Explicit study selection criteria

Selection criteria		Inclusion			Exclusion
Study design		Any study design			---
		Include1	**Include2**	**Include3**	
Study topic A:	**Comparison of diagnostic value of different systematic prostate biopsy methods**	Classical test accuracy study (complete index test and complete gold standard for each participant) **Yes/No** ↓	Concordance study: a) Participants randomised to either test1 or test2 Or b) Sequential sampling for each participant (additional cores of test2 after application of test1) **Yes/No** ↓	Guidelines, clinical reviews (comparison of different biopsy methods) **Yes/No** ↓	No comparison of different biopsy methods main study topic: - DRE - PSA-testing - Prostate imaging as main topic (e.g. TRUS, MRI) - Fine needle aspiration of prostate tissue or comparison of fine needle aspiration vs. core biopsies - Comparison of lesion directed biopsies vs. lesion directed biopsies or vs. random systematic biopsy patterns - Biopsy taking in the assessment of the response to therapy or for cancer staging - Computer simulation models for biopsy or ex vivo biopsies of reshaped prostatectomy specimens - Histological workup
	Outcome measures (Study topic A)	Test accuracy: sufficient information to construct a 2 x 2 table (Adverse event data if available) **Yes/No** **(➔ ORDER)**	a) Respective cancer detection rate in each group Or b) Additional yield of cancers detected (for a or b: Adverse event data if available) **Yes/No** **(➔ ORDER)**	Qualitative reasoning and recommendations (Adverse event data if available) **Yes/No** **(➔ ORDER)**	Cancer detection rate of a *single* biopsy method in a chosen population (possibly in combination with repeat biopsies) without comparison to another biopsy method in this population

(page 2) Selection criteria		Inclusion			Exclusion
		AEONE	**AECR**	**BACKGROUND**	
Study topic B:	**Adverse events (AE) (systematic prostate biopsy methods)**	AE data of a study population, one systematic biopsy method, (no comparison between methods) **Yes/No** **(➔ hold on ordering)**	AE data, case report of one patient, ((no comparison between systematic methods) **Yes/No** **(➔ hold on ordering)**	Methodology, epidemiology, etc. **Yes/No** **(➔ ORDER)**	Studies comparing different methods of anesthesia for biopsy (AE: pain) Studies comparing different prophylactic antibiotic regimens (AE: infection) Studies examining enema application (AE: infection)
Population		Males, all age groups			---
Gold standard (GS) (applicable for Include 1)		Any reported gold standard			---
Intervention/ Index tests (IT)		a) Any systematic prostate biopsy technique used in the diagnosis of prostate cancer as *first* time biopsy b) Any systematic prostate biopsy technique used in the diagnosis of prostate cancer as repeat biopsy			*Transperineal* prostate biopsy method in patients with colitis or anus praeter naturalis.

APPENDIX 3 CHECKLIST FOR INCLUSION/EXCLUSION ASSESSMENT

Lead Reviewers*:*

Contact authors for further information?

☐ Yes ☐ No

PROSTATE REVIEW: Inclusion/exclusion by full text

1) **Paper** (first author, year & ENL identifier)

2) **Study topic A** (include: Comparison of diagnostic value of different systematic prostate biopsy methods as first time or repeat biopsies)
☐ Yes ☐ No

3) **Study design (topic A)**
☐ Yes ☐ No **Classical test accuracy study** (complete index test and complete gold standard for each participant) **INCLUDE1**

☐ Yes ☐ No **Concordance study** (Participants ***randomised*** to either test1 or test2) **INCLUDE2**

☐ Yes ☐ No **Concordance study** (***Sequential sampling*** for each participant (additional cores of test2 after application of test1) **INCLUDE2**

☐ Yes ☐ No **Guidelines, clinical reviews** (overview of different biopsy methods) **INCLUDE3**

4) **Outcome measures (topic A)**:
☐ Yes ☐ No **number of cancers** detected by test1 and test2
☐ Yes ☐ No **adverse event** data for test1 and test2
☐ Yes ☐ No **Qualitative reasoning** and recommendations

5) **Study topic B** (include: Adverse events (AE) of systematic prostate biopsy methods)
☐ Yes ☐ No

6) **Study design/outcome (topic B)**
☐ Yes ☐ No **AE data of a study population**, one systematic biopsy method (no comparison between systematic methods) **AEONE**
☐ Yes ☐ No **AE data, case report** of one patient (no comparison between systematic methods) **AECR**

7) **Design**

☐ Yes ☐ No **prospective data collection** (cohort of consecutive patients with randomised or extended sampling)

☐ Yes ☐ No **retrospective data collection** (cohort of consecutive patients with retrospective calculation of different schemes)

☐ Yes ☐ No **"case control design"**

☐ Yes ☐ No **other**

8) **Language** (if non-English):_____

9) **Decision**:

☐ Include1 ☐ Include2 ☐ Include3 ☐ AEONE ☐ AECR

☐ Background ☐ Exclude ☐ Unsure ☐ Foreign Lang. ☐ "Include2?"

10) **Reason** (if exclude or unsure):

11) **Bibliography checked:** ☐ Yes ☐ No ☐ N/A

Notes: _____ **Reviewer:** _____ **Date:**_____

APPENDIX 4 DATA EXTRACTION FORM

SR prostate biopsies: Date extraction form: items for access database

Form1

General information	***Item***	***Explicit criteria***
	Endnote number	*FIGURE*
	Endnote number of any related publication	*FIGURE*
	author	*TEXT*
	year	*FIGURE*
	extracted by	• *KE* • *JW* • *SH*
	checked by	• *KE* • *JW* • *SH*
	objective	*TEXT*
	country	• *USA* • *UK* • *Europe* • *TEXT*
	setting	• *Primary care* • *Secondary care* • *Combination* • *Not clear*
	Language (if not English)	*TEXT*
	methodological study approach:	• *test accuracy study* • *concordance study (randomisation)* • *concordance study sequential sampling)* • *adverse events (one method)* • *adverse events (case report)*
	study design	• *Prospective data collection* • *Retrospective data collection* • *"case control design"* • *TEXT*
	education level/skills of the examiner	• *Urologist* • *Radiologist* • *Nurses* • *Allied health professionals* • *TEXT* • *n.a.*
	Number of examiners	• *1* • *2* • *TEXT* • *N.a.*
	training of the examiner (case load: biopsies taken per year)	• *TEXT* • *N.a.*
	ultrasound equipment	• *monoplanar probe* • *biplanar probe* • *three dimensional probe* • *TEXT* • *N.a.*

	Brand of ultrasound equipment	• *Acuson* • *ATL* • *Bruel & Kjaer* • *Kretz* • *Philips* • *Siemens* • *Toshiba* • *TEXT*
	Scan frequency	• *Multifrequency probe (7-10MHz)* • *TEXT*
	Biopsy gun / needle	• *Manan* • *Bard* • *Bip* • *Travelol* • *TEXT*
	needle thickness (G)	• *FIGURE* • *N.a.*
	length of sample	• *FIGURE* • *N.a.*
	anesthesia method used	• *no anesthesia* • *Local anesthesia (injection)* • *Local anesthesia (gel)* • *Regional anesthesia (spinal)* • *General anesthesia* • *TEXT* • *N.a.*
	antibiotic prophylaxis	• *Yes* • *No* • *N.a.*
	enema application	• *Yes* • *No* • *N.a.*
Participant details		
	Total number of participants	*FIGURE*
	Age (mean)	• *FIGURE* • *n.a.*
	Age (min)	• *FIGURE* • *n.a.*
	Age (max)	• *FIGURE* • *n.a.*
	population	• *screening* • *transferral due to symptoms* • *mixed* • *TEXT*
	first / repeat biopsy?	• *Only first time biopsy population* • *only repeat biopsy population* • *mixed population* • *n.a.*
	biopsy indication	• *abnormal DRE and/or raised PSA* • *abnormal DRE only* • *raised PSA only* • *TEXT*
	PSA threshold for inclusion (ng/ml)	• *FIGURE* • *N.a.*
	PSA mean (ng/ml)	• *FIGURE* • *N.a.*
	PSA min (ng/ml)	• *FIGURE* • *N.a.*
	PSA max (ng/ml)	• *FIGURE* • *N.a.*

	PSA values age specified?	• *yes* • *no* • *n.a.*
	prostate volume threshold for inclusion (ml)	• *FIGURE* • *N.a.*
	prostate volume mean (ml)	• *FIGURE* • *N.a.*
	prostate volume min (ml)	• *FIGURE* • *N.a.*
	prostate volume max (ml)	• *FIGURE* • *N.a.*
Test details		
	Test1 (reference test): number of cores	*FIGURE*
	Biopsy access	• *transrectal* • *transperineal* • *transr. + transp.*
	Test1: needle angulation	• *FIGURE* • *TEXT* • *N.a.*
	Test1: anatomical location of cores (pattern number of systematic schemes)	• *MPZ (1)* • *TZ (2)* • *LPZ (3)* • *MPZ+TZ (+MLiPZ) (4)* • *LPZ+TZ (5)* • *MPZ+LPZ (6)* • *5-region (7)* • *TEXT*
	Test2: number of cores	*FIGURE*
	Biopsy access	• *transrectal* • *transperineal* • *transr. + transp.*
	Test2: needle angulation	• *FIGURE* • *TEXT* • *N.a.*
	Test2: anatomical location of cores (pattern number of systematic schemes)	• *MPZ (1)* • *TZ (2)* • *LPZ (3)* • *MPZ+TZ (+MLiPZ) (4)* • *LPZ+TZ (5)* • *MPZ+LPZ (6)* • *5-region (7)* • *TEXT*
	Test3: number of cores	*FIGURE*
	Biopsy access	• *transrectal* • *transperineal* • *transr. + transp.*
	Test3: needle angulation	• *FIGURE* • *TEXT* • *N.a.*
	Test3: anatomical location of cores (pattern number of systematic schemes)	• *MPZ (1)* • *TZ (2)* • *LPZ (3)* • *MPZ+TZ (+MLiPZ) (4)* • *LPZ+TZ (5)* • *MPZ+LPZ (6)* • *5-region (7)*

		• *TEXT*
	Test4: number of cores	*FIGURE*
	Biopsy access	• *transrectal* • *transperineal* • *transr. + transp.*
	Test4: needle angulation	• *FIGURE* • *TEXT* • *N.a.*
	Test4: anatomical location of cores (pattern number of systematic schemes)	• *MPZ (1)* • *TZ (2)* • *LPZ (3)* • *MPZ+TZ (+MLiPZ) (4)* • *LPZ+TZ (5)* • *MPZ+LPZ (6)* • *5-region (7)* • *TEXT*
Other items:	*"Comment overall" field for reviewer*	*TEXT* *(e.g. "only abstract available")*

Form 2

Results		
	Endnote number	*FIGURE*
	Sequential sampling :	
	number of patients biopsied (incl. LD)	*FIGURE*
	number of patients with cancer (incl. LD)	*FIGURE*
	Non randomised studies (sequential sampling): 2 x 2 table (= Template II)	*T1Ca+/T2Ca+ T1Ca+/T2Ca- T2Ca+/T1Ca- T2Ca-/T1Ca-*
	Further comparisons:	
	Non randomised studies (sequential sampling): 2 x 2 table (= Template II)	*T1Ca+/T3Ca+ T1Ca+/T3Ca- T3Ca+/T1Ca- T3Ca-/T1Ca-*
	Non randomised studies (sequential sampling): 2 x 2 table (= Template II)	*T1Ca+/T4Ca+ T1Ca+/T4Ca- T4Ca+/T1Ca- T4Ca-/T1Ca-*
	LD:	
	additional LD?	*Yes/no*
	number of cancers UNIQUELY detected by LD (sequ. sampl)	*FIGURE*
	Randomised studies :	
	number of patients randomised to Group1	*FIGURE*
	number of patients randomised to Group2	*FIGURE*
	number of patients biopsied Group1	*FIGURE*
	number of patients biopsied Group2	*FIGURE*
	difference randomised minus patients biopsied Group1	*FIGURE*
	difference randomised minus patients biopsied Group2	*FIGURE*
	number of patients with cancer Group1 (incl. LD)	*FIGURE*
	number of patients with cancer Group2 (incl. LD)	*FIGURE*
	Randomised studies: 2 x 2 table (= Template I)	*T1Ca+ T1Ca- T2Ca+ T2Ca-*
	Further comparisons:	
	number of patients biopsied Group3	*FIGURE*
	number of patients with cancer Group3(incl. LD)	*FIGURE*
	Randomised studies: 1 x 2 table (= Template I)	*T3Ca+ T3Ca-*
	number of patients biopsied Group4	*FIGURE*

	number of patients with cancer Group4incl. LD)	*FIGURE*
	Randomised studies: *1 x 2 table (= Template I)*	*T4Ca+* *T4Ca-*
	LD:	
	additional LD?	*Yes/no*
	number of cancers UNIQUELY detected by LD (randomised Group1)	*FIGURE*
	number of cancers UNIQUELY detected by LD (randomised Group2)	*FIGURE*
		•
	AE:	
	Adverse effects mentioned?	• *Yes* • *No*
	adverse effects sequential sampling (or Group2 or AEONE) in %	• *death* • *Infection major (bacteraemia, urosepsis, abscess)* • *Infection minor (fever)* • *prostatitis* • *urinary tract infections* • *voiding difficulties* • *bleeding major* • *hematuria (minor)* • *hematospermia (minor)* • *rectal bleeding (minor)* • *pain (details in "comment")* • *hospitalisation* • *other* • *none*
	adverse effects Group1 in %	• *death* • *Infection major (bacteraemia, urosepsis, abscess)* • *Infection minor (fever)* • *prostatitis* • *urinary tract infections* • *voiding difficulties* • *bleeding major* • *hematuria (minor)* • *hematospermia (minor)* • *rectal bleeding (minor)* • *pain (details in "comment")* • *hospitalisation* • *other* • *none*
	Adverse effects (case report)	*TEXT*
	Adverse effects (comments; details pain)	*TEXT*
	Results for subgroups available?	*Yes/no*

Form 3

Subgroups		
	Endnote number	*FIGURE*
	Subgroups sequential sampling	
	Subgroup 1: Criterion	• *PSA (crude measure)* • *First/repeat biopsy* • *Lesions (DRE and/or US) / no lesions* • *Prostate volume (ml)* • *TEXT*
	Criterion value	*TEXT*
	number of patients in subgroup 1?	*FIGURE*
	results subgroup 1 *Non randomised studies (sequential sampling): 2 x 2 table (= Template II)*	*T1Ca+/T2Ca+* *T1Ca+/T2Ca-* *T2Ca+/T1Ca-* *T2Ca-/T1Ca-/*
	Subgroup 2: Criterion	• *PSA (crude measure)* • *First/repeat biopsy* • *Lesions (DRE or US) / no lesions* • *Prostate volume* • *TEXT*
	Criterion value	*TEXT*
	number of patients in subgroup 2?	*FIGURE*
	Results subgroup 2 *Non randomised studies (sequential sampling): 2 x 2 table (= Template II)*	*T1Ca+/T2Ca+* *T1Ca+/T2Ca-* *T2Ca+/T1Ca-* *T2Ca-/T1Ca-/*
	Subgroup 3: Criterion	• *PSA (crude measure)* • *First/repeat biopsy* • *Lesions (DRE or US) / no lesions* • *Prostate volume* • *TEXT*
	Criterion value	*TEXT*
	number of patients in subgroup 3?	*FIGURE*
	Results subgroup 3 *Non randomised studies (sequential sampling): 2 x 2 table (= Template II)*	*T1Ca+/T2Ca+* *T1Ca+/T2Ca-* *T2Ca+/T1Ca-* *T2Ca-/T1Ca-/*
	Subgroup 4: Criterion	• *PSA (crude measure)* • *First/repeat biopsy* • *Lesions (DRE or US) / no lesions* • *Prostate volume* • *TEXT*
	Criterion value	*TEXT*
	number of patients in subgroup 4?	*FIGURE*
	Results subgroup 4 *Non randomised studies (sequential sampling): 2 x 2 table (= Template II)*	*T1Ca+/T2Ca+* *T1Ca+/T2Ca-* *T2Ca+/T1Ca-* *T2Ca-/T1Ca-/*
	Subgroups randomised studies	
	Subgroup 1: Criterion	• *PSA (crude measure)* • *First/repeat biopsy* • *Lesions (DRE and/or US) / no lesions* • *Prostate volume (ml)* • *TEXT*
	Criterion value	*TEXT*
	number of patients in subgroup 1?	*FIGURE*
	results subgroup 1 *Randomised studies:* *2 x 2 table (= Template I)*	*T1Ca+* *T1Ca-* *T2Ca+*

		T2Ca-
	Subgroup 2: Criterion	• *PSA (crude measure)* • *First/repeat biopsy* • *Lesions (DRE or US) / no lesions* • *Prostate volume* • *TEXT*
	Criterion value	*TEXT*
	number of patients in subgroup 2?	*FIGURE*
	results subgroup 2 *Randomised studies:* *2 x 2 table (= Template I)*	*T1Ca+* *T1Ca-* *T2Ca+* *T2Ca-*
	Subgroup 3: Criterion	• *PSA (crude measure)* • *First/repeat biopsy* • *Lesions (DRE or US) / no lesions* • *Prostate volume* • *TEXT*
	Criterion value	*TEXT*
	number of patients in subgroup 3?	*FIGURE*
	results subgroup 3 *Randomised studies:* *2 x 2 table (= Template I)*	*T1Ca+* *T1Ca-* *T2Ca+* *T2Ca-*
	Subgroup 4: Criterion	• *PSA (crude measure)* • *First/repeat biopsy* • *Lesions (DRE or US) / no lesions* • *Prostate volume* • *TEXT*
	Criterion value	*TEXT*
	number of patients in subgroup 4?	*FIGURE*
	results subgroup 4 *Randomised studies:* *2 x 2 table (= Template I)*	*T1Ca+* *T1Ca-* *T2Ca+* *T2Ca-*

Form 4

***Quality criteria* (Examples see definitions)**	*Endnote number*	*FIGURE*
QUADAS	*1 spectrum of patients representative?*	*Yes, No, not clear*
	2 selection criteria clearly described?	*Yes, No, not clear*
	8 index test (test2) described in sufficient detail to permit replication?	*Yes, No, not clear*
	9 reference test (test1) described in sufficient detail to permit replication?	*Yes, No, not clear*
	10 index test (test2) results interpreted without knowledge of results of reference test (test1)?	*Yes, No, not clear*
	11 reference test (test1) results interpreted without knowledge of results of index test (test2)?	*Yes, No, not clear*
	12 same clinical data available for test interpretation as in clinical practice?	*Yes, No, not clear*
	13 uninterpretable/intermediate test results reported?	*Yes, No, not clear*
	14 study withdrawals explained?	*Yes, No, not clear*
Clinical quality items	*Follow up long enough for important events to occur?*	*Yes, No, not clear*
	Each core specifically labelled for histologic work up?	*Yes, No, not clear*
	Method of histologic work up specified?	*Yes, No, not clear*
quality items for randomised studies only	*Was the method used to assign patients to the groups really random? (Examples see definitions….)*	*Yes, No, not clear*
	Was the allocation to the groups concealed? (Examples: see definitions….)	*Yes, No, not clear*
	Quality comments" field	*TEXT*

APPENDIX 5 APPLIED QUADAS QUALITY CRITERIA; CLINICAL AND METHODOLOGICAL QUALITY CRITERIA

SR Prostate Biopsies: Explicit definition of applied quality criteria
(For further details see: Whiting P. et al.: The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC medical Research Methodology 2003, 3:25) doi 101186/1471-2288-3-25

Selected QUADAS criteria:	
1 spectrum of patients representative?	*Yes: consecutive patients (or random sample) referred to biopsy due to abnormal PSA and/or abnormal DRE or screening population* *No: if the population does not fit in the group above* *not clear: insufficient information available*
2 selection criteria clearly described?	*Yes: inclusion criteria (at least 3 items of the following) described: biopsy indication (information about PSA and/or DRE reported); information if first or repeat biopsy; information if consecutive patients or sample of patients; exclusion criteria described* *No: none of all above items described* *not clear: if less than 3 above items described*
8 index test (test2) described in sufficient detail to permit replication?	*Yes: report about patient preparation (anaesthesia method for any bx.; antibiotic prophylaxis for transrectal bx.); needle thickness; biopsy access; number of cores taken, detailed anatomical regions of cores; labelling cores specifically (for sequential sampling only); (possibly US equipment; needle make)* *No: none of the above items described* *not clear: only some of the 6 above items described*
9 reference test (test1) described in sufficient detail to permit replication?	*Yes: (see criterion 8, test 2)* *No: (see criterion 8, test 2)* *not clear: (see criterion 8, test 2)*
10 index test (test2) results interpreted without knowledge of results of reference test (test1)?	*Yes: The histopathologist was blinded for the results of the cores taken by test1* *No: The histopathologist was not blinded* *not clear: insufficient information available*
11 reference test (test1) results interpreted without knowledge of results of index test (test2)?	*Yes: The histopathologist was blinded for the results of the cores taken by test2* *No: The histopathologist was not blinded* *not clear: insufficient information available*
12 same clinical data available for test interpretation as in clinical practice?	*Yes: clinical data available (for the urologist and/or the histopathologist) about PSA, US findings, DRE; prostate volume, patient age (at least 3 of them)* *No: less than 3 of the above mentioned data or additional data (like imaging techniques other than US)* *not clear: clinical data above not mentioned*
13 uninterpretable / intermediate test results reported?	*Yes: If it is clear that all test results, including results of incomplete sampling (e.g. due to complications) or results of cores that were not suitable for histopathologic analysis or results with unclear result are reported.* *No: If one thinks that such events have occurred but are not reported.* *not clear: If it is not clear whether all test results have been reported*
14 study withdrawals explained?	*Yes: If it is clear what happened to all the patients included in the study (no withdrawals or e.g. report about patients that denied biopsy after randomisation in randomised studies)* *No: If it appears that some participants who entered the study did not complete the biopsy and were not accounted for.* *not clear: If it is not clear whether all patients who entered the study were accounted for.*
Clinical quality items	
Follow up long enough for important events to occur?	*Yes: follow up long enough to discover delayed infectious complications (e.g. abscess): follow up by mailing (questionnaires) or patient examination* *No: follow up too short to discover delayed infectious complications*

	not clear: Follow up not reported at all
Each core specifically labelled for histologic work up?	*Yes: "each core specifically labelled for histological work up" or histological work up in randomised studies.* *No: "cores not specifically labelled"* *not clear: labelling not reported at all*
Method of histologic work up specified?	*Yes: description of embedding, staining and levels per tissue core examined* *No: no description at all* *not clear: only partly described*
Quality items for randomised studies only	
*Was the method used to assign patients to the groups really random?**	*Yes: (explicit examples are given.)* *No: (explicit examples are given.)* *not clear: no description of generation of sequence at all*
Was the allocation to the groups concealed?†	*Yes: (explicit examples are given.)* *No: (explicit examples are given.)* *not clear: no description of concealment at all*

(*Generation of random sequence: Computer generated random numbers and random number tables will be accepted as adequate, whilst inadequate approaches include the use of alternation, case record numbers, birth dates or days of the week.

(†Concealment of allocation: Adequate methods include centralised or pharmacy-controlled assignment or where the following are used: serially numbered containers, serially numbered opaque envelopes, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches include alternation, case record numbers, days of the week and open random number lists).

APPENDIX 6 APPLIED ANATOMIC MODEL OF PROSTATE REGIONS AND GROUPING OF PROSTATE BIOPSY METHODS

Proposal for an anatomic model of prostate regions and grouping of prostate biopsy schemes

This paper is a background paper for the review team.
Aim of the systematic review: To compare the diagnostic value of various prostate biopsy schemes in the diagnostic work up of patients with a raised PSA-test result for the evaluation of prostate cancer.

Aim of this proposal paper:
A) To select an (existing) anatomic model of the several prostate regions as reference for communication within the review team.
B) To define clinical meaningful patterns of distinct sampling schemes (i.e. grouping of studies which use similar sample strategies).

A) Selection of an anatomic model of prostate regions:
Histological zones of the prostate:
Two important histological zones of the prostate are well defined:

- Transition zone (where most, >90%, of benign hyperplasia develops)
- Peripheral zone (where most, >70%, of prostate carcinomas develop)

Anatomical regions for needle biopsies of the prostate:
The wording in the literature for the anatomic prostate regions is not fully consistent.
The "5-region anatomic model" of the prostate, described by Eskew[1], is used by several authors[2 3] for description of biopsy regions and seems to fit our needs for the review (see figure below).

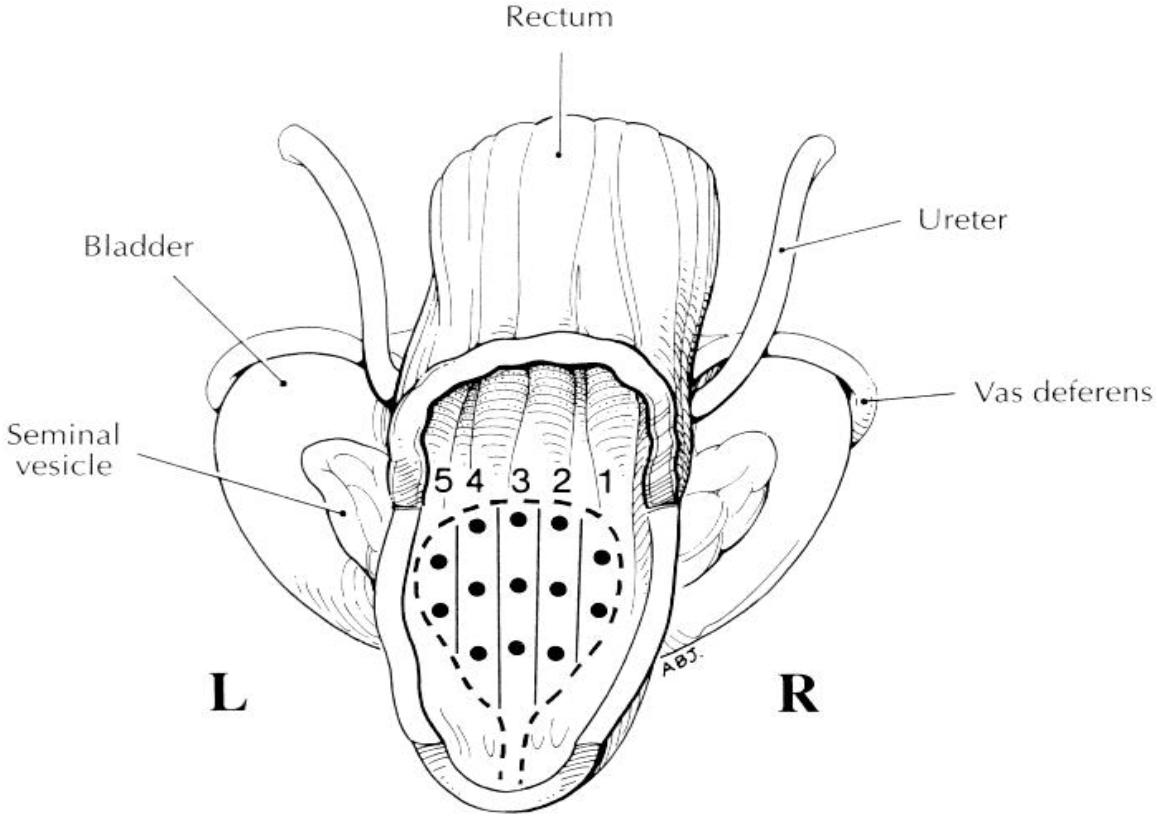


Figure 1: "5-region anatomic model" of the prostate in longitudinal plane.
Figure from Eskew[1]

Biopsies taken out of:

- region 1 sample tissue of the lateral peripheral zone
- region 2 sample tissue of the peripheral zone (mid-lobar)
- region 3 sample tissue of the transition zone (and possibly of the peripheral zone)
- region 4 sample tissue of the peripheral zone (mid-lobar)
- region 5 sample tissue of the lateral peripheral zone

Note: This is a simplified model! Depending on the core length and angle of the needle biopsies of one region may sample tissue out of the transition zone and the peripheral zone at the same time (e.g. in region 3).

Babaian et al.[4] distinguish base, mid and apex of the lateral zone and describe the very lateral regions of the prostate as anterior horns. The authors do also describe the mid-line zone as an explicitly region for biopsy. Depicted in a longitudinal plane, figure 2 shows the respective regions.

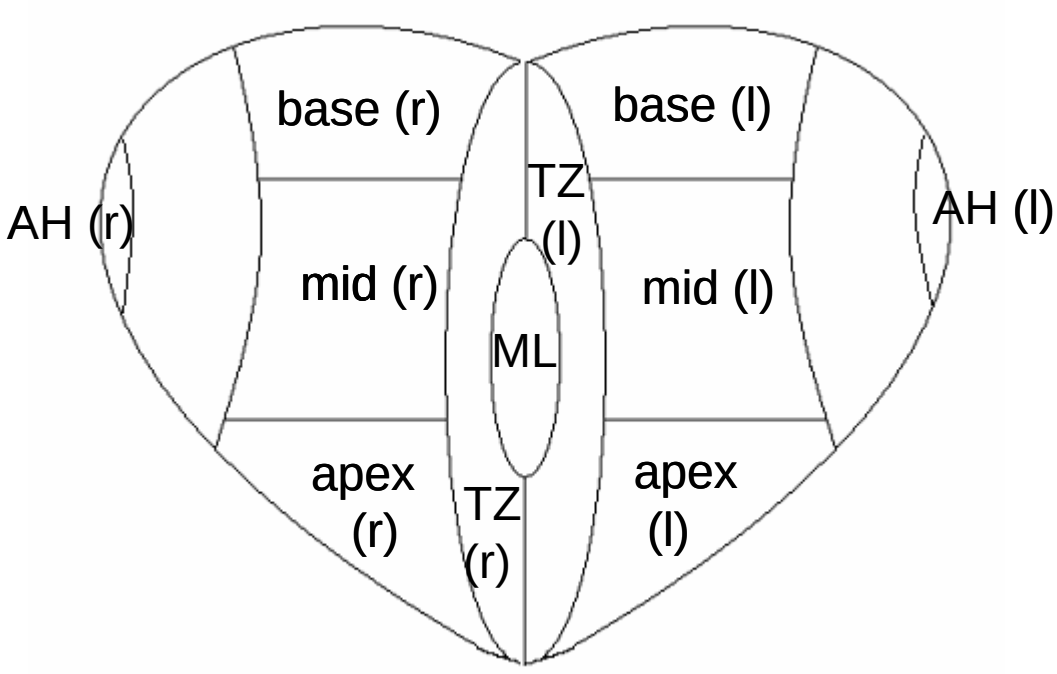


Figure 2: Five-region model with 11 biopsy sites.
Base (r): right base (sextant), mid (r): right mid (sextant), apex (r): right apex (sextant), AH (r): right anterior horn, TZ (r): right transition zone; (l): left respectively; ML: midline.

Durkan et al [5] describe a 12 core biopsy protocol with cores taken in the transition zone and the lateral peripheral zone additionally to the standard sextant scheme.

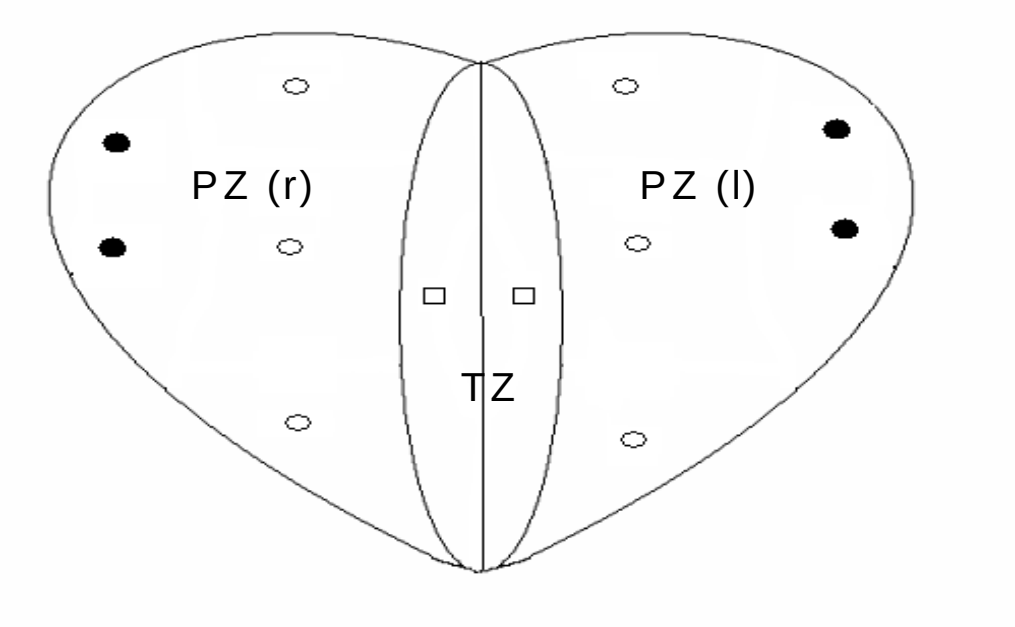


Figure 3: Twelve-core extended biopsy protocol.
With 6 routine sextant biopsies, 2 transition zone (TZ) biopsies and 4 lateral peripheral zone (PZ) biopsies.
Presti et al[6] show how the biopsy needle is guided for mid-lobar peripheral zone biopsies (region 4 and 2) and lateral peripheral zone biopsies (region 5 and 1).

Prostate in transverse plane.

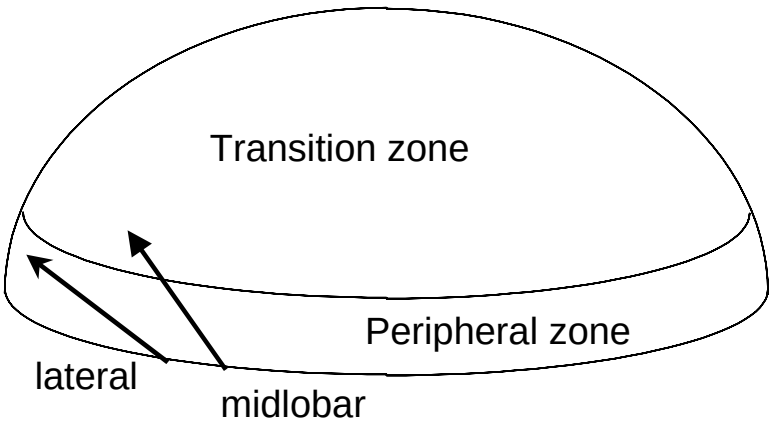


Figure 4: Needle trajectory in mid-lobar plane and lateral plane.

The corresponding 10-core scheme in coronal plane described by Presti et al[6] is depicted in figure 5.

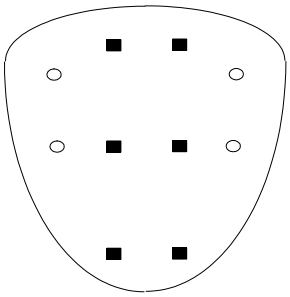


Figure 5: Ten-core biopsy scheme as described by Presti et al[6].
Standard sextant scheme plus 4 additional lateral biopsies.

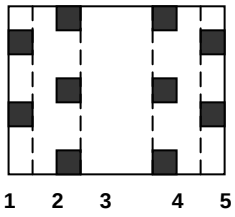
The following table tries to provide a synthesis of the schemes above:

Table 1: Scheme comparison

5-region model	**Babaian**	**Durkan**	**Presti**
Region 1 R	AH (r)	black dots	circles (Fig 5)) lateral (Fig 4)
Region 2	base (r), Mid (r), apex (r)	circles	squares (Fig 5) mid-lobar (Fig 4)
Region 3	TZ (r), TZ (l), ML	squares	(not described)
Region 4	base (l), mid (l), apex (l)	circles	squares (Fig 5) mid-lobar (Fig 4)
Region 5 L	AH (l)	black dots	circles (Fig 5) lateral (Fig 4)

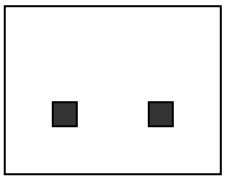
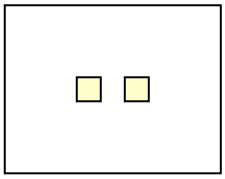
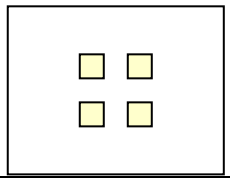
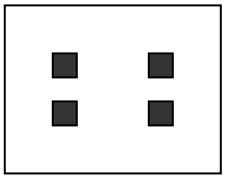
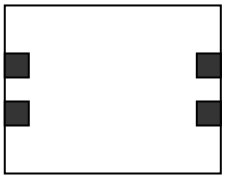
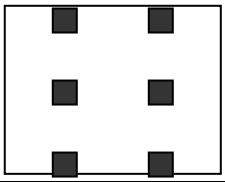
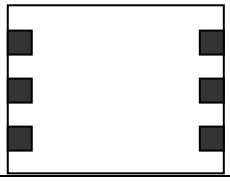
B) Clinical meaningful patterns of distinct sampling schemes:
A big number of different prostate biopsy schemes are described in the literature.
The following table provides an overview. Some schemes are sampling up to 30 cores per session (depending on prostate gland size). Those more extensive schemes are not described in the table. They are building up on the most extensive schemes described in the table by adding additional cores out of already sampled regions.
Possible lesion directed biopsies are not covered with the following table.
A schematic figure is used in the table to provide a better optical pattern. This figure is indicating the number of cores taken out of the respective region.

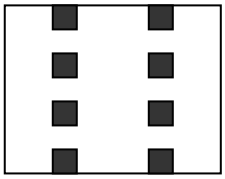
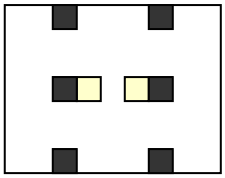
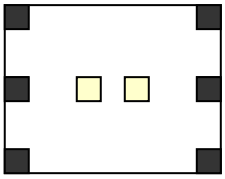
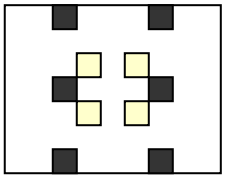
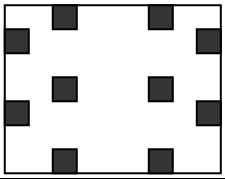
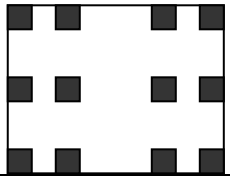
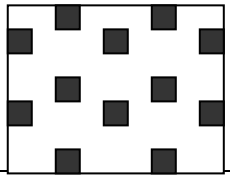
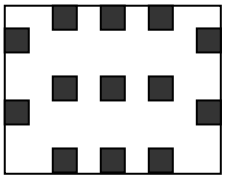
Example:

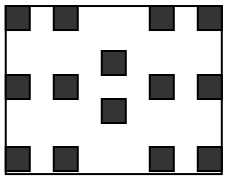
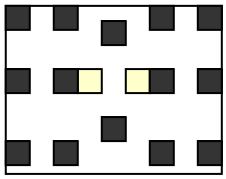
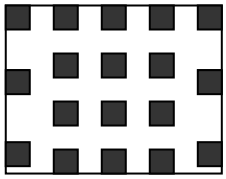
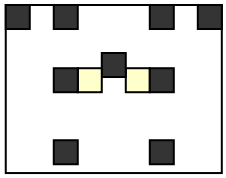


For this “10-core scheme” the following samples are taken:
Two lateral peripheral zone left side, **three** mid-lobar peripheral zone left side, **none** of the transition zone (or midline peripheral zone), **three** mid-lobar peripheral zone right side, **two** lateral peripheral zone right side.

Table: **Described prostate biopsy schemes** (an overview)
Peripheral zone biopsies are marked with black squares: ■
Transition zone biopsies are marked with light squares: □
(References: *Chen 1999; §Bauer 1999)

Scheme	**Total cores**	**Anatomic regions**	**figure**
Near apical*	2	2 mid-lobar peripheral zone	
TZ§	2	2 transition zone (light squares)	
Four transition zone*	4	4 anterior transition zone (light squares)	
Quadrant*	4	4 mid-lobar peripheral zone	
4-core scheme§	4	4 lateral peripheral zone	
Sextant* (6-Core scheme§)	6	6 mid-lobar peripheral zone	
6L-Core scheme§	6	6 lateral peripheral zone	

Octant*	8	8 mid-lobar peripheral zone	
Sextant and two transition zone*	8	6 mid-lobar peripheral zone 2 anterior transition zone (light squares)	
„6L + 2TZ“ (Damiano 2003)	8	6 lateral peripheral zone 2 transition zone (light squares)	
Sextant and four transition zone*	10	6 mid-lobar peripheral zone 4 anterior transition zone (light squares)	
10-core scheme[§]	10	6 mid-lobar peripheral zone 4 lateral peripheral zone	
12-core scheme[§]	12	6 mid-lobar peripheral zone 6 lateral peripheral zone	
5-region[§]	12	6 mid-lobar peripheral zone 2 midline peripheral zone 4 lateral peripheral zone	
Five region peripheral zone (13 minimum cores)*	13	6 mid-lobar peripheral zone 3 midline peripheral zone 4 lateral peripheral zone	

14-core scheme[§]	14	6 mid-lobar peripheral zone 6 lateral peripheral zone 2 midline peripheral zone	
16-core scheme[§]	16	6 mid-lobar peripheral zone 6 lateral peripheral zone 2 midline peripheral zone 2 transition zone (light squares)	
Five region peripheral zone (13 minimum cores plus one extra core per region)*	18	8 mid-lobar peripheral zone 4 midline peripheral zone 6 lateral peripheral zone	
Eleven-core multisite-directed*	11	6 mid-lobar peripheral zone 2 anterior horn (lateral peripheral zone) 1 midline 2 anterior transition zone (light squares)	

Based on the above defined regions, on already used biopsy schemes[1 4-7] and computer simulation studies[3 8] a grouping of biopsy schemes to patterns has to be a reasonable, pragmatic compromise as follows:

Each pattern has to be as homogenous as possible, i.e. included biopsy schemes should after clinical suggestion provide a similar diagnostic value and be technically similar to apply in clinical practice.
Patterns have to be distinct enough between each other, i.e. each group should after clinical suggestion provide a different diagnostic value and be technically distinct enough from other groups to be reliably applied as a distinct group of schemes in clinical practice.

Proposal for grouping of prostate biopsy schemes according to anatomical regions included:
(MPZ: mid-lobar peripheral zone; LPZ: lateral peripheral zone; MLiPZ: midline peripheral zone TZ: transition zone)

Group	**MPZ**	**TZ**	**LPZ**	**MPZ+TZ (+MLiPZ)**	**LPZ+TZ (+MliPZ)**	**MPZ+LPZ**	**5 region MPZ+LPZ+TZ (+MLiPZ)**
Cores	2-8	2-4	4-6	8-10	8	8-10-12	11-18
Region1			**X**		**X**	**X**	**X**
Region2	**X**			**X**		**X**	**X**
Region3		**X**		**X**	**X**		**X**
Region4	**X**			**X**		**X**	**X**
Region5			**X**		**X**	**X**	**X**

Considerations behind this proposal:
This grouping confers to the to anatomical regions included in the different biopsy schemes (from a relative few regions up to samples taken out of all 5 regions).
The crude number of cores taken in each scheme does not seem to be a good criterion for the grouping of schemes as prostate cancers are cancers often found in the lateral regions of the peripheral zone.
We have no proposal for a more detailed sub-grouping of the schemes in the "5-region group". Regarding the schemes in this group they look quite similar beside the number of cores taken. The number of cores taken should be an important co-variable for this group.

Open questions:

➔ Is the anatomic model correct and applicable for biopsy taking in clinical practice?
➔ Are there some clinical important biopsy schemes missed in the table?
➔ Makes this grouping sense from a clinical urologic perspective?
➔ Makes this grouping sense from a diagnostic perspective?
➔ Makes this grouping sense from the data analysis perspective?

Klaus Eichler, 03rd March, 2004
Discussed with experts of the advisory panel, April 2004
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APPENDIX 7 INCLUDED STUDIES AND RESULTS OF DATA EXTRACTION

Study details and design	**Participants details**	**Biopsy details**			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Arger2002 (EN4933) **Country:** USA **Aim:** To evaluate variations in prostate cancer detection relevant to the number and areas of biopsy cores. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **49** **Mean age (age range):** 65 (53-85) **First or repeat biopsy:** n.a. **PSA mean (range)** 9.6 (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 11 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** n.a. **Biopsy gun/needle brand:** Bard **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results				
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	**General comments** Although 90 pts were enrolled, only 49 had the 11-core biopsy and were suitable for data extraction. The remaining 41 pts had a 6-core biopsy performed by a different urology surgeon. **Adverse events comments** **Quality comments** No report about patient preparation.
Number of patients biopsied: 49 **Number of detected cancers: 21** **test1 pos/test2 pos: 13** **test1pos/test2 neg: 0** **test1neg/test2 pos: 8** **test1neg/test2 neg: 28** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Aus2001 (EN5096) **Country:** Sweden **Aim:** To evaluate the cancer detection rate of six systematic prostate biopsies with mid-lobar biopsies taken far laterally in the prostate. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **692** **Mean age (age range):** n.a. (50-66) **First or repeat biopsy:** First time biopsy population **PSA mean (range)** 7.4 (3-220) **Mean prostate volume (range):** 42.4 (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 4 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 6 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **4** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 692 **Number of detected cancers: 164** **test1 pos/test2 pos: 139** **test1pos/test2 neg: 0** **test1neg/test2 pos: 25** **test1neg/test2 neg: 528** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos: 133** **test1pos/test3 neg: 6** **test1neg/test3 pos: 25** **test1neg/test3 neg: 528**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Out of 727 randomly selected males with elevated PSA 692 accepted further diagnostic work-up. 636 males had six biopsies, 56 males had only four or fewer biopsies. 171 men turned out to have cancer, but only 164 men were analysed due to incomplete data.

Adverse events comments
56 of 692 pts had only 4 or fewer bipsies most often due to discomfort at the examination.

Quality comments
56 of 692 patients with incomplete sampling. Results are given for the whole population only. 7 of 171 patients with diagnosed cancer were excluded.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Babaian2000 (EN5587) **Country:** Canada, USA **Aim:** To evaluate the diagnostic value of an 11-core multisite directed biopsy scheme including the sextant scheme for the detection of prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **362** **Mean age (age range):** 63.7 (39-80) **First or repeat biopsy:** Mixed population **PSA mean (range)** 10.2 (0.5-49.5) **Mean prostate volume (range):** 68.5 (18-235.5)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 11 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** Travelol **Needle thickness (G):** 18 **Anaesthesia method:** no anesthesia **Antibiotic prophylaxis:** Yes
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 362 **Number of detected cancers: 110** **test1 pos/test2 pos: 74** **test1pos/test2 neg: 0** **test1neg/test2 pos: 36** **test1neg/test2 neg: 252** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		**General comments** Group 1 had 183 pts from MD Anderson Cancer Center (Huston, Texas) and Group 2 had 179 pts from Toronto General Hospital. For 2 pts no PSA values available. **Adverse events comments** The authors comment that the 11-core biopsy was tolerated by patients without need for sedation. **Quality comments**

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Balaji2003 (EN1139) **Country:** USA **Aim:** To evaluate the need for routine use of additional lateral biopsies at the time of standard sextant prostatic biopsy to reduce the false negative rates. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **23** **Mean age (age range):** 62.2 (41-74) **First or repeat biopsy:** n.a. **PSA mean (range)** 8.1 (n.a.-n.a.) **Mean prostate volume (range):** 40 (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** 7 MHZ **Biopsy gun/needle brand:** Bard **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		**General comments** 1 of the 23 pts. was biopsied twice. **Adverse events comments** None of the pts. were admitted to the hospital for a biopsy-related complication. **Quality comments** No details about the patient who was biopsied twice.
Number of patients biopsied: 24 **Number of detected cancers: 8** **test1 pos/test2 pos: 6** **test1pos/test2 neg: 0** **test1neg/test2 pos: 2** **test1neg/test2 neg: 16** **cancers detected uniquely by LD** (if any proceeded): **0**	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Balbontin2000 (EN2923) **Country:** Chile **Aim:** To compare 12 biopsy cores versus only 6 biopsy cores in the diagnosis of prostate cancer. **Study design:** concordance study (sequential sampling)	**Number of participants**: **49** **Mean age (age range):** 63.7 (48-85) **First or repeat biopsy:** n.a. **PSA mean (range)** 10.7 (2.46-38.6) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Aloka **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes

Results				**General comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	
Number of patients biopsied: 49 **Number of detected cancers: 27** **test1 pos/test2 pos: 17** **test1pos/test2 neg: 0** **test1neg/test2 pos: 10** **test1neg/test2 neg: 22** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: 0 Infection (major): 0 Infection (minor): 0 Prostatitis: Urinary tract infection: 0 Voiding difficulties: 2.04 Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	**Adverse events comments** nothing significant, no infection, 1 patient needed an uretro-vesical cathetherisation (retencion completa). **Quality comments**

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Bazinet1996 (EN4722) **Country:** Canada **Aim:** To determine the value of performing 2 systematic transition zone biopsies in addition to systematic sextant peripheral zone biopsies for early detection of prostate cancer. **Study design:** concordance study (sequential sampling)	**Number of participants**: **847** **Mean age (age range):** 64 (38-83) **First or repeat biopsy:** Mixed population **PSA mean (range)** 7.9 (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** Travelol **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 847 **Number of detected cancers: 279** **test1 pos/test2 pos: 271** **test1pos/test2 neg: 0** **test1neg/test2 pos: 8** **test1neg/test2 neg: 568** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
1 patient biopsied with unremarkable DRE and PSA but risk group affiliation

Adverse events comments

Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Beurton2000 (EN4168) **Country:** France **Aim:** In order to increase prostate cancer detection a prospective study comparing the diagnostic value of 12 versus 6 core biopsies was undertaken. **Study design:** Concordance study (randomisation)	**Number of participants**: **194** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (4.0-< 20) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: **Randomised to test1: 96** **Randomised to test2: 98** **Number of detected cancers:** **test1: 17** **test2 : 30** **cancers detected uniquely by LD** (if any proceeded):			*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		**General comments** Only abstract available for data extraction. Some details directly retrieved from author. **Adverse events comments** **Quality comments** Only abstract available

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Borboroglu2000 (EN5586) **Country:** USA **Aim:** To present experience with extensive transrectal ultrasound prostate biopsy in men in whom previous sextant biopsy was negative. **Study design:** concordance study (sequential sampling)	**Number of participants**: **57** **Mean age (age range):** 61.4 (47-72) **First or repeat biopsy:** Repeat biopsy **PSA mean (range)** 8.6 (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ+LPZ (6) **Number of cores:** 18 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 23 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** intravenous sedation **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 57 **Number of detected cancers: 17** **test1 pos/test2 pos: 16** **test1pos/test2 neg: 0** **test1neg/test2 pos: 1** **test1neg/test2 neg: 40** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): 0 Infection (minor): 0 Prostatitis: 0 Urinary tract infection: 0 Voiding difficulties: 10.5 Bleeding (major): 0 Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): 1.8 Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Test 1 (reference test): 4 to 6 cores were taken from the far lateral and mid zone bilaterally (18 cores is averaged by the reviewer). Test 2: Additionally at least 2 cores from most medial zones from TZ (4 to 6 per patient) resulting in 22.5 cores.

Adverse events comments
Authors report that no "significant hematuria" ocurred (coded by reviewers as "bleeding major").
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Broessner1999 (EN5568) **Country:** Austria **Aim:** To compare a TRUS-guided sextant biopsy technique, which puts more emphasis on the apical region of the prostate where most prostate carcinomas develop, with the standard sextant biopsy technique. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **280** **Mean age (age range):** 67 (40-87) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **5-region (7)** **Number of cores:** **6** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Siemens **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** Bip **Needle thickness (G):** 18 **Anaesthesia method:** no anesthesia **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 280 **Number of detected cancers: 72** **test1 pos/test2 pos: 66** **test1pos/test2 neg: 0** **test1neg/test2 pos: 6** **test1neg/test2 neg: 208** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos: 60** **test1pos/test3 neg: 6** **test1neg/test3 pos: 6** **test1neg/test3 neg: 208**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: 2.5 Voiding difficulties: 0.4 Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): 0.7 Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
PSA values are given only for pts with PrCa (mean 58.3 ng/ml; range: 2-970 ng/ml). Beside 6 standard sextant cores 6 cores were taken in a fan-shaped technique (from left to right lateral prostate margin always penetrating the apex in the same angle).

Adverse events comments
UTI: 2 out of 7 pts with urinary tract infection needed rehospitalization. Rectal bleeding: Prolonged bleeding that ceased spontaeously.
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Cam2001 (EN1541) **Country:** Turkey **Aim:** To define the diagnostic contribution and significance of TRUS guided biopsies from hypoechoic PZ lesions, and systematic TZ bx additionally to standard sextant bx in diagnosing prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **271** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** First time biopsy population **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** n.a.	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** n.a. **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** Bard **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes

Results				
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	**General comments** **Adverse events comments** **Quality comments** Poor reporting of patient characteristics.
Number of patients biopsied: 271 **Number of detected cancers: 89** **test1 pos/test2 pos: 86** **test1pos/test2 neg: 0** **test1neg/test2 pos: 0** **test1neg/test2 neg: 185** **cancers detected uniquely by LD** (if any proceeded): **3**	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Chang1998 (EN6054) **Country:** USA **Aim:** To define the role of systematic transition zone biopsies for the detection of prostate cancer in prostates larger than 50cc. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **213** **Mean age (age range):** 70.8 (65-76) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** 70 (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Siemens **Scan frequency:** 5.0-7.5 MHz **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** Local, injection **Antibiotic prophylaxis:** n.a.

Results				
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	**General comments** PSA values given as medians for subgroups (Pts without Ca: 7.6ng/ml; Pts with Ca: 10.6ng/ml;). **Adverse events comments** **Quality comments**
Number of patients biopsied: 213 **Number of detected cancers: 55** **test1 pos/test2 pos: 48** **test1pos/test2 neg: 0** **test1neg/test2 pos: 7** **test1neg/test2 neg: 158** **cancers detected uniquely by LD** (if any proceeded): **0**	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Chang1998 (EN4299) **Country:** USA **Aim:** To evaluate the usefulness of adding 4 lateral biopsies of the peripheral zone to the routine sextant biopsy regimen for prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **273** **Mean age (age range):** 70 (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** 6.6 (n.a.-n.a.) **Mean prostate volume (range):** 44 (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **LPZ (3)** **Number of cores:** **4** **Index test (test4) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **6**	**Ultrasound brand:** Siemens **Scan frequency:** 5-7.5 MHz **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** Local, injection **Antibiotic prophylaxis:** n.a.
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 273 **Number of detected cancers: 121** **test1 pos/test2 pos: 99** **test1pos/test2 neg: 0** **test1neg/test2 pos: 17** **test1neg/test2 neg: 157** **cancers detected uniquely by LD** (if any proceeded): **1**	**test1 pos/test3 pos: 68** **test1pos/test3 neg: 31** **test1neg/test3 pos: 17** **test1neg/test3 neg: 157**	**test1 pos/test4 pos: 89** **test1pos/test4 neg: 10** **test1neg/test4 pos: 17** **test1neg/test4 neg: 157**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		**General comments** Pts with prostates >50cc (n=97) also underwent syst. TZ biopsies (6 cores). All identified hypoechoic lesions were biopsied. Thus between 10 and 20 cores were taken (average: 12.6 cores). 4 Ca (out of 121 Ca) detected by TZ, 1 Ca detected by LD-bx. **Adverse events comments** **Quality comments**

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Chon2002 (EN4869) **Country:** USA **Aim:** To examine the potential impact of extended systematic biopsy schemes in patients with a prior negative prostate biopsy. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **185** **Mean age (age range):** 64 (n.a.-n.a.) **First or repeat biopsy:** Repeat biopsy **PSA mean (range)** 8.4 (n.a.-n.a.) **Mean prostate volume (range):** 58 (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **8** **Index test (test4) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **6**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** 7 MHz **Biopsy gun/needle brand:** Bard **Needle thickness (G):** 18 **Anaesthesia method:** local, gel **Antibiotic prophylaxis:** Yes
Results					**General comments** Pts with high grade PIN were excluded. A subgroup of 111 patients also underwent 6 anteriorly directed biopsies (at apex, midgland, base) which uniquely detected 2 out of 67 cancers. Authors collected all relevant clinical data retrosp. by chart review. **Adverse events comments** **Quality comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 185 **Number of detected cancers: 67** **test1 pos/test2 pos: 49** **test1pos/test2 neg: 0** **test1neg/test2 pos: 16** **test1neg/test2 neg: 120** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos: 47** **test1pos/test3 neg: 2** **test1neg/test3 pos: 16** **test1neg/test3 neg: 120**	**test1 pos/test4 pos: 41** **test1pos/test4 neg: 8** **test1neg/test4 pos: 16** **test1neg/test4 neg: 120**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Damiano2003 (EN3950) **Country:** Italy **Aim:** To understand the value of specific sites in extended peripheral and transition zone biopsy schemes for the detection of prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **165** **Mean age (age range):** 64.5 (n.a.-n.a.) **First or repeat biopsy:** First time biopsy population **PSA mean (range)** 7.24 (n.a.-n.a.) **Mean prostate volume (range):** 57 (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 14 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Kretz **Scan frequency:** n.a. **Biopsy gun/needle brand:** Tru-Cut **Needle thickness (G):** 18 **Anaesthesia method:** no anesthesia **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 165 **Number of detected cancers: 66** **test1 pos/test2 pos: 51** **test1pos/test2 neg: 0** **test1neg/test2 pos: 13** **test1neg/test2 neg: 101** **cancers detected uniquely by LD** (if any proceeded): **2**	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): 1.8 Infection (minor): 3.6 Prostatitis: Urinary tract infection: Voiding difficulties: 5.4 Bleeding (major): Hematuria (minor): 33.3 Hematospermia (minor): Rectal bleeding (minor): 7.9 Pain (details see comment): 35.7 Hospitalisation: Other (details see comment): 4.8 None:

General comments
Authors recommend an 8 core scheme with a cancer detection rate of 61/165 pts (36.9%); not enough data available to create a 2x2-table. Data of subgroup results partly inconsistent and not extracted.

Adverse events comments
Pain = discomfort on examination (35.7%). Other: vasovagal episodes (4.8%). Older pts tolerated the procedure with less discomfort than younger pts. VAS data (for 8 core and 14 core bx.; overlapping population) in #4409.

Quality comments
Q 13: Data of subgroup results partly inconsistant and not extraced.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
de la Taille2003 (EN4423) **Country:** France **Aim:** To prospectively evaluate the diagnostic yield of a 21-sample US-guided needle biopsy in patients with elevated PSA and/or abnormal DRE. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **303** **Mean age (age range):** 65.6 (48-82) **First or repeat biopsy:** Mixed population **PSA mean (range)** 9.2 (0.7-40) **Mean prostate volume (range):** 46.1 (10-235)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 21 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **12** **Index test (test4) (pattern):** **5-region (7)** **Number of cores:** **18**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** local, gel **Antibiotic prophylaxis:** Yes
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 303 **Number of detected cancers: 95** **test1 pos/test2 pos: 69** **test1pos/test2 neg: 0** **test1neg/test2 pos: 26** **test1neg/test2 neg: 208** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos: 69** **test1pos/test3 neg: 0** **test1neg/test3 pos: 17** **test1neg/test3 neg: 217**	**test1 pos/test4 pos: 69** **test1pos/test4 neg: 0** **test1neg/test4 pos: 24** **test1neg/test4 neg: 210**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: 1 Urinary tract infection: Voiding difficulties: 2 Bleeding (major): 0.3 Hematuria (minor): 84 Hematospermia (minor): 60 Rectal bleeding (minor): 45 Pain (details see comment): Hospitalisation: Other (details see comment): None:		**General comments** Sextant biopsies were taken in standard 45 degree angle; 6 biopsies of the PZ were taken at an 80 degree angle. **Adverse events comments** The mean pain score measured immediately after the procedure was VAS 4.56 (0 = no pain; 10 = intense pain). Data derived for HU, HSp, and RBm was derived from 90 consecutive pts (questionnaire completed after 6wks). **Quality comments**

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Deliveliotis2002 (EN4930) **Country:** Greece **Aim:** To evaluate the necessity of performing transitional zone biopsies additionally to the standard sextant biopsy procedure in order to detect prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **420** **Mean age (age range):** 64 (42-88) **First or repeat biopsy:** Mixed population **PSA mean (range)** 10 (3.2-88) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 420 **Number of detected cancers: 143** **test1 pos/test2 pos: 132** **test1pos/test2 neg: 0** **test1neg/test2 pos: 11** **test1neg/test2 neg: 277** **cancers detected uniquely by LD** (if any proceeded): n.a.	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): 6.9 Prostatitis: Urinary tract infection: Voiding difficulties: 1.9 Bleeding (major): Hematuria (minor): 71.4 Hematospermia (minor): 27.8 Rectal bleeding (minor): 33.8 Pain (details see comment): Hospitalisation: Other (details see comment): 1.1 None:

General comments
If a suspicious area was found elsewhere in the prostate then more biopsies were taken. Results of any additional lesion directed biopsies are not included in this report.

Adverse events comments
No significant complications occurred after the biopsies. No episode of epididimoorchitis was reported. Other complications: 1.1% of the pts required hospitalisation.

Quality comments
Cores were not individually labelled but grouped and labelled by zone (TZ/PZ).

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Durkan2002 (EN4925) **Country:** UK **Aim:** To investigate whether taking two transition zone and four lateral periperal zone biopsies in addition to routine sextant biopsies would improve detection rates in men with suspected prostate cancer. **Study design:** concordance study (sequential sampling)	**Number of participants**: **493** **Mean age (age range):** 68.7 (44-89) **First or repeat biopsy:** n.a. **PSA mean (range)** 10.2 (0.5-901) **Mean prostate volume (range):** 42 (11-172)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **10** **Index test (test4) (pattern):** **MPZ+TZ (+MLiPZ) (4)** **Number of cores:** **8**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** no anesthesia **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 493 **Number of detected cancers: 164** **test1 pos/test2 pos: 133** **test1pos/test2 neg: 0** **test1neg/test2 pos: 31** **test1neg/test2 neg: 329** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos: 133** **test1pos/test3 neg: 0** **test1neg/test3 pos: 14** **test1neg/test3 neg: 346**	**test1 pos/test4 pos: 133** **test1pos/test4 neg: 0** **test1neg/test4 pos: 21** **test1neg/test4 neg: 339**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): 0.4 Infection (minor): Prostatitis: 0.2 Urinary tract infection: 0.8 Voiding difficulties: 0.8 Bleeding (major): Hematuria (minor): 0.8 Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): 0.6 None:

General comments
The method genarally allowed any area of DRE abnormality or suspicious hypoecoic lesion noted on TRUS to be incorporated into the biopsy protocol.

Adverse events comments
Only figures for serious complications requiring hospital admission after biopsy (other = Epididymo-orchitis).
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Egawa1998 (EN6155) **Country:** Japan **Aim:** To examine the usefulness of and indication for transition zone biopsy in addition to standard systematic sextant peripheral zone biopsy for Japanese males. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **344** **Mean age (age range):** 67.6 (32-89) **First or repeat biopsy:** Mixed population **PSA mean (range)** 5.5 (1.0-20'100) **Mean prostate volume (range):** 41.8 (12.9-144.7)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 344 **Number of detected cancers: 55** **test1 pos/test2 pos: 53** **test1pos/test2 neg: 0** **test1neg/test2 pos: 2** **test1neg/test2 neg: 289** **cancers detected uniquely by LD** (if any proceeded): n.a.	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): 67.8 Hematospermia (minor): 2 Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
PSA values: median 5.5 ng/ml; mean 88.7 ng/ml. In certain cases additional LD biopsies were carried out but no extracable results are reported.

Adverse events comments
No pts experienced febrile complications due to bacteriemia. Hematuria was noted for up to 2wks following biopsy. No cystoscopy or clot evacuation was required.

Quality comments
Of 629 consecutive pts 344 pts were included. Indication for TZ bx: partly based on preprostatectomy evaluation or on patient tolerance/condition.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Ellis2002 (EN9317) **Country:** USA **Aim:** To evaluate the utility of anterior apical biopsies in the detection of prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **164** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** LPZ (3) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **LPZ (3)** **Number of cores:** **8** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.
Results					**General comments** Only abstract available. 12 core scheme: base and mid prostate both laterally and mid-sagittal, apex laterally and anteriorely. Authors propose 8 core scheme: 6 lat. sextant bx. and 2 apex anteriorely. Anterior apex was grouped to lateral PZ for analysis. **Adverse events comments** **Quality comments** Only abstract available, poor reporting about test details and patient data.
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 164 **Number of detected cancers: 71** **test1 pos/test2 pos: 53** **test1pos/test2 neg: 0** **test1neg/test2 pos: 18** **test1neg/test2 neg: 93** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos: 53** **test1pos/test3 neg: 0** **test1neg/test3 pos: 14** **test1neg/test3 neg: 97**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Emiliozzi2003 (EN4480) **Country:** Italy **Aim:** To compare the efficacy of transperineal versus transrectal six-core prostate biopsy in the diagnostic work-up for prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **107** **Mean age (age range):** 68 (52-88) **First or repeat biopsy:** n.a. **PSA mean (range)** 8.2 (4.1-240) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 12 **Access:** transrectal+transperineal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **6** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Toshiba **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** Tru cut **Needle thickness (G):** 18 **Anaesthesia method:** Local, injection **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 107 **Number of detected cancers: 43** **test1 pos/test2 pos: 34** **test1pos/test2 neg: 0** **test1neg/test2 pos: 9** **test1neg/test2 neg: 64** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos: 32** **test1pos/test3 neg: 2** **test1neg/test3 pos: 9** **test1neg/test3 neg: 64**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): 31 Hematospermia (minor): 54 Rectal bleeding (minor): Pain (details see comment): 6 Hospitalisation: Other (details see comment): None:

General comments
The 6 transrectal biospies were taken according to Hodge. The 6 specimens from the transperineal area of the prostate were taken using a "fan" scheme close to midline, mid-lobar, and lateral for each lobe.

Adverse events comments
AE can not be attributed to one of the two applied tests specifically. Pain: 6% of patients described mild postbiopsy perineal discomfort. None of the patients with AE had to be hospitalised.

Quality comments
Duration of follow up not explicitly stated but authors report about AE (hematospermia) lasting up to 3 months.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Emiliozzi2004 (EN9417) **Country:** Italy **Aim:** To conduct a randomised controlled trial comparing 6- and 12-core transperineal ultrasound guided prostate biopsy for the detection of prostate cancer. **Study design:** Concordance study (randomisation)	**Number of participants**: **214** **Mean age (age range):** 67.5 (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** 8.1 (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transperineal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 12 **Access:** transperineal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Toshiba **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** Bard **Needle thickness (G):** 18 **Anaesthesia method:** Local, injection **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: **Randomised to test1: 107** **Randomised to test2: 107** **Number of detected cancers:** **test1: 41** **test2 : 55** **cancers detected uniquely by LD** (if any proceeded):			*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): 0 Prostatitis: Urinary tract infection: Voiding difficulties: 0 Bleeding (major): Hematuria (minor): 43 Hematospermia (minor): 74 Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
All DRE and TRUS suspicious areas were included in the specimens obtained.

Adverse events comments
No patient required hospitalisation after the procedure in either group.
AE data (%) for reference test 1:
Infection (minor): 0
Voiding difficulties: 0
Hematuria (minor): 45
Hematospermia (minor): 79

Quality comments
Authors report about adverse events up to 3 mth but do not state how they collected the data.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Eskew1997 (EN1070) **Country:** USA **Aim:** To determine if a 5 region prostate biopsy technique significantly increases the chances of finding carcinoma of the prostate compared to the sextant biopsy technique. **Study design:** concordance study (sequential sampling)	**Number of participants**: **256 (with 1999-update)** **Mean age (age range):** 65.8 (45-82) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (4.0-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 13 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** 6.5 MHz **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** intravenous sedation **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 256 **Number of detected cancers: 133** **test1 pos/test2 pos: 91** **test1pos/test2 neg: 0** **test1neg/test2 pos: 42** **test1neg/test2 neg: 123** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): 0 Infection (minor): Prostatitis: Urinary tract infection: 0 Voiding difficulties: Bleeding (major): 0 Hematuria (minor): 80 Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
For prostates with > 50 cc often an additional core biopsy per region was taken. Participant details, test details and acverse events taken from 1997 publication (n=119 patients).

Adverse events comments
All patientes underwent cystoscopy after biopsy to assess the degree of hematuria caused by taking additional cores (no results reported; 80% gross hematuria were self limiting events).
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Eskicorapci2004 (EN8974) **Country:** Turkey **Aim:** To evaluate the efficacy of TRUS guided 10-core biopsy strategy for Turkish patients who had biopsy of the prostate for the first time. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **303** **Mean age (age range):** 63 (43-80) **First or repeat biopsy:** First time biopsy population **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **8** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Falcon **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** Local, injection **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 303 **Number of detected cancers: 94** **test1 pos/test2 pos: 70** **test1pos/test2 neg: 0** **test1neg/test2 pos: 24** **test1neg/test2 neg: 209** **cancers detected uniquely by LD** (if any proceeded): **0**	**test1 pos/test3 pos: 64** **test1pos/test3 neg: 6** **test1neg/test3 pos: 24** **test1neg/test3 neg: 209**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): 0.9 Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
PSA given as medians (pts with Ca: 6.94; pts without Ca: 9.18). Authors also determined detection rate of different 8-core schemes (data extracted for 8-core scheme with highest detection rate: left and right parasagittal mid+base, lateral mid+base).

Adverse events comments
3 serious infectious complications required hospitalisation (controlled by antibiotics). All of the patients tolerated the procedure well and none needed intravenous sedation or narcotic analgesics.
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Eskicorapci2004 (EN10169) **Country:** Turkey **Aim:** To present the repeat biopsy resutls with 14-core biopsy strategy in the repeat biopsy population. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **130** **Mean age (age range):** 62 (46-78) **First or repeat biopsy:** Repeat biopsy **PSA mean (range)** 8.7 (1.28-30) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ+LPZ (6) **Number of cores:** 10 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 14 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 130 **Number of detected cancers: 40** **test1 pos/test2 pos: 39** **test1pos/test2 neg: 0** **test1neg/test2 pos: 1** **test1neg/test2 neg: 90** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		**General comments** Only abstract available for data extraction. 150 biosy sessions were done in 130 patients thus some patients were counted several times. 67 pts had undergone previous sextant biopsy, 63 pts had undergone previous 10-core biopsy. **Adverse events comments** **Quality comments** Only abstract available for quality assessment.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Fleshner2002 (EN4818) **Country:** Canada **Aim:** To determine the role of extensive prostate biopsy ("saturation biopsy"; i.e. 32 to 38 cores) among selected men with unexplained worrisome prostate-specific antigen (PSA) parameters. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **37** **Mean age (age range):** 62.4 (39-75) **First or repeat biopsy:** Repeat biopsy **PSA mean (range)** 22.4 (7.8-73.8) **Mean prostate volume (range):** 54.1 (18.4-145.8)	**Reference test (test1) (pattern):** LPZ (3) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** LPZ+TZ (5) **Number of cores:** 32 **Access:** transrectal + transurethrally **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **LPZ (3)** **Number of cores:** **18** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** n.a. **Biopsy gun/needle brand:** Manan and Cook **Needle thickness (G):** 18 **Anaesthesia method:** general (n=36) or spinal (n=1) **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 37 **Number of detected cancers: 5** **test1 pos/test2 pos: 2** **test1pos/test2 neg: 0** **test1neg/test2 pos: 3** **test1neg/test2 neg: 32** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos: 2** **test1pos/test3 neg: 0** **test1neg/test3 pos: 3** **test1neg/test3 neg: 32**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): 0 Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): 0 Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
All pt. with at least 3 prior neg.sets of biopsies. Saturation bx: 24 cores (4x6) from LPZ, 6-12 cores from TZ (2 add. cores from lat.prost.lobes transurethrally via resectoscope). No cancer was uniquely detected by TZ- or by transurethrally biopsies.

Adverse events comments
All 37 patients were sent home with urinary catheter (removal after week 1; in 4 pt. not removable before week 3). Outwided antibiotic prophylaxis (ciprofloxacin, ampicillin, gentamycin).

Quality comments
Samples were separately labelled in groups of six so that marginal benefit of biopsies could be determined.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Fowler1996 (EN97) **Country:** USA **Aim:** To assess the results of additional diagnostic procedures in men with prostate specific antigen more than 10 ng/ml and a peripheral zone prostate biopsy negative for cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **12** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** Repeat biopsy **PSA mean (range)** n.a. (10-50) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 12 **Number of detected cancers: 7** **test1 pos/test2 pos: 7** **test1pos/test2 neg: 0** **test1neg/test2 pos: 0** **test1neg/test2 neg: 5** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Only a subgroup of 12 patients suitable for data extraction. Sextant biopsy of PZ plus 1-2 TZ biopsies were performed of the right and the left TZ each. Thus the total number of cores varied between 8 and 10 in these 12 patients.

Adverse events comments

Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Fuganti2002 (EN1321) **Country:** Brazil **Aim:** To evaluate the sensitivity of 12-core biopsy in the diagnosis of prostate cancer compared to the standard sextant biopsy. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **78** **Mean age (age range):** 69 (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** 17.3 (n.a.-n.a.) **Mean prostate volume (range):** 35.4g (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Mitsubishi **Scan frequency:** 6.5MHz **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 78 **Number of detected cancers: 28** **test1 pos/test2 pos: 26** **test1pos/test2 neg: 0** **test1neg/test2 pos: 2** **test1neg/test2 neg: 50** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Poor reporting of patient characteristics and test procedures so little detail is available for additional data extraction.

Adverse events comments

Quality comments
Poor reporting of patient characteristics and test procedures.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Garber1994 (EN533) **Country:** Canada **Aim:** To determine the diagnostic advantage of obtaining six sextant samples rather than only four quadrant samples and confirm utility of syst. TRUS guided biopsies in the detection of prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **669** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ (1) **Number of cores:** 4 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Aloka **Scan frequency:** 5.0 MHz and 7.5 MHz **Biopsy gun/needle brand:** Bard **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 669 **Number of detected cancers: 233** **test1 pos/test2 pos: 215** **test1pos/test2 neg: 18** **test1neg/test2 pos: 0** **test1neg/test2 neg: 436** **cancers detected uniquely by LD** (if any proceeded): n.a.	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: 0 Infection (major): 0 Infection (minor): 0 Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): 0 Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Cores taken from four quadrants (bilateral bases and apices, mid-lobar parasagittal) with the aim of including any localized abnormality detected by US or DRE. Two additional cores were obtained from the midzone region of each side. Occasionally add. LD-bx

Adverse events comments
Although the authors used no formal pain scale it was their impression that patient discomfort increased with additional biopsy samples. There were no cases of hospital admission and clinical significant bleeding or infection.
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Garcia2001 (EN5206) **Country:** France **Aim:** To compare TRUS guided transrectal biopsies with finger guided transperineal biopsies in the detection of prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **51** **Mean age (age range):** 67 (53-79) **First or repeat biopsy:** n.a. **PSA mean (range)** 15.7 (4.6-63) **Mean prostate volume (range):** 43.8g (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transperineal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** 7 MHz **Biopsy gun/needle brand:** Biopty Gun **Needle thickness (G):** 18 (transrectal), 14 (transperineal) **Anaesthesia method:** general anesthesia without intubation **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 51 **Number of detected cancers: 23** **test1 pos/test2 pos: 14** **test1pos/test2 neg: 3** **test1neg/test2 pos: 6** **test1neg/test2 neg: 28** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): 0 Infection (minor): 0 Prostatitis: 0 Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): 17.6 Hematospermia (minor): Rectal bleeding (minor): 2 Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
6 transperineal biopsies (with intrarectal guidance of the left forefinger) were taken before the TRUS guided 6 transrectal biopsies. 4 pts had fewer biopsies due to technical problems.

Adverse events comments
Some patients experienced haematospermia (no figures provided).
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Gómez Veiga1999 (EN4173) **Country:** Spain **Aim:** To evaluate prospectively the role of systematic TZ biopsies in patients with PSA range 4-10 for the detection of prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **238** **Mean age (age range):** 66 (48-88) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (4-10) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 238 **Number of detected cancers: 52** **test1 pos/test2 pos: 47** **test1pos/test2 neg: 0** **test1neg/test2 pos: 5** **test1neg/test2 neg: 186** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		**General comments** Only abstract available for data extraction. **Adverse events comments** **Quality comments** Only abstract available for quality assessment.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Gore2001 (EN5165) **Country:** USA **Aim:** To systematically evaluate the contribution to the cancer detection rate of prostate biopsy cores from all sextant and lateral regions to establish an optimal biopsy regimen. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **104** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** First time biopsy population **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **10** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Vingmed or Hitachi **Scan frequency:** 6.5 MHz or 7.0 MHz **Biopsy gun/needle brand:** Manan **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 104 **Number of detected cancers: 45** **test1 pos/test2 pos: 32** **test1pos/test2 neg: 0** **test1neg/test2 pos: 13** **test1neg/test2 neg: 59** **cancers detected uniquely by LD** (if any proceeded): **0**	**test1 pos/test3 pos: 32** **test1pos/test3 neg: 0** **test1neg/test3 pos: 13** **test1neg/test3 neg: 59**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Total population: 396 pts with first bx, repeat bx or staging bx after diagnosis of PrCa. Data extraction only for 104 pts with full 12 core bx at first biopsy (whole study group of 396 pts.: age 61.4; PSA 5.9) Optimal 10 core: 6LPZ, 4MPZ (base +apex).

Adverse events comments

Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Harewood1996 (EN9228) **Country:** Australia **Aim:** To assess whether a technique specifically biopsying the peripheral zone at the lateral margin of the prostate results in an increased rate of disgnosis of prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **124** **Mean age (age range):** 65.7 (49-83) **First or repeat biopsy:** n.a. **PSA mean (range)** 8.7 (n.a.-n.a.) **Mean prostate volume (range):** 46 (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 4 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 124 **Number of detected cancers: 38** **test1 pos/test2 pos: 19** **test1pos/test2 neg: 0** **test1neg/test2 pos: 19** **test1neg/test2 neg: 86** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		**General comments** Abstract only, hence very few details can be extracted for this study. Included 124 pts did not have palpable abnormality of the prostate or hypoechoic lesions. A subgroup of 59 pts also recieved 2 TZ bx (recommended best 6-core pattern: 4LPZ + 2TZ). **Adverse events comments** **Quality comments** Abstract only, hence very few details can be extracted for this study.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Horninger1999 (EN4174) **Country:** Austria **Aim:** To determine whether prostate cancer detection rates in PSA first-line screening can be improved by increasing the number of biopsies from 10 to 14. **Study design:** Concordance study (randomisation)	**Number of participants**: **222** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** 4.8 (1.25-10) **Mean prostate volume (range):** 30.5 (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 10 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 14 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: **Randomised to test1: 111** **Randomised to test2: 111** **Number of detected cancers:** **test1: 27** **test2 : 24** **cancers detected uniquely by LD** (if any proceeded):			*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): 64.8 Hospitalisation: Other (details see comment): None:

General comments
Only abstract available.

Adverse events comments
The authors state that for patients undergoing 14 biopsies, the incidence of discomfort during biopsy was higher (no information about pain measurement of pain intensity).
AE data (%) for reference test 1:
Pain (details see comment): 27.9

Quality comments
Study details lacking (only abstract available)..

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Ishizuka2002 (EN4787) **Country:** Japan **Aim:** To analyse the efficacy of routine transition zone biopsies in patients undergoing ultrasound-guided systematic prostate biopsies for the first time because of a suspicious DRE or elevated PSA test. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **192** **Mean age (age range):** 70 (39-90) **First or repeat biopsy:** First time biopsy population **PSA mean (range)** 10.5 (0.7-6530) **Mean prostate volume (range):** 36 (4.4-112)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** GE Yokogawa **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** local, gel **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 192 **Number of detected cancers: 72** **test1 pos/test2 pos: 69** **test1pos/test2 neg: 0** **test1neg/test2 pos: 3** **test1neg/test2 neg: 120** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Patients received 2-4 TZ biopsies. PSA value stated is the median (10.5) not the mean (105.6).

Adverse events comments

Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Ito2002 (EN4603) **Country:** Japan **Aim:** To evaluate a new age-adjusted and prostate volume adjusted biopsy method combined with transperineal and transrectal routes for the detection of prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **100** **Mean age (age range):** 68.2 (50-79) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (4.1-10) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal+transperineal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 20 **Access:** transrectal+transperineal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** 5 to 7.5MHz **Biopsy gun/needle brand:** Bard **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 100 **Number of detected cancers: 46** **test1 pos/test2 pos: 31** **test1pos/test2 neg: 0** **test1neg/test2 pos: 15** **test1neg/test2 neg: 54** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Study reports table with matrix of numbers of cores taken dependent on age and prostate volume. Between 8 and 20 cores were taken by transrectal/transperineal approach (on average 12.8 cores per patient). Add. results for age subgroups (<=64 vs. >64 yr.).

Adverse events comments

Quality comments
Intransparent reporting about patient preparation and applied biopsy patterns.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Karakiewicz1996 (EN45) **Country:** Canada **Aim:** To assess the potential difference in positive biopsy rates between four-sector and six-sector biopsy methods. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **749** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ (1) **Number of cores:** 4 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** Bard **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results				
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	**General comments** 749 pts (neg DER and TRUS; elevated PSA) out of 3538 consecutive pts were included . Diff.4 sector biopsy solutions were simulated out of the 6 sector biopsies by computer simulation. Results are based on the average undetected Ca of 1000 simulations. **Adverse events comments** **Quality comments** Index test not specified: 4 sector pattern was simulated by randomly reducing the 6 sector cores (taken in vivo) by computer simulation.
Number of patients biopsied: 749 **Number of detected cancers: 156** **test1 pos/test2 pos: 137** **test1pos/test2 neg: 19** **test1neg/test2 pos: 0** **test1neg/test2 neg: 593** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Karakiewicz1995 (EN9229) **Country:** Canada **Aim:** To determine the value of two systematic TZ biopsies performed in addition to systematic, sextant PZ biopsies. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **847** **Mean age (age range):** 63.7 (38-83) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 847 **Number of detected cancers: 279** **test1 pos/test2 pos: 271** **test1pos/test2 neg: 0** **test1neg/test2 pos: 8** **test1neg/test2 neg: 568** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		**General comments** Abstract only, hence very few details can be extracted for this study. PSA values: 8.5% pts < 4ng/ml; 59.3% pts between 4.1ng/ml and 10ng/ml ; 32.2% pts > 10ng/ml. **Adverse events comments** **Quality comments** Abstract only, hence very few details can be extracted for this study. 113 of 960 pts referred to the authors during the study did not undergo biopsy.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Kawakami2003 (EN9121) **Country:** Japan **Aim:** To evaluate the diagnostic yield and safety of a TRUS-guided 22 core (transperineal-14 + transrectal 8) systematic biopsy technique for the detection of prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **254** **Mean age (age range):** 68 (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** 8.3 (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 22 **Access:** transrectal+transperineal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **8** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Aloka **Scan frequency:** 5/7.5 MHz **Biopsy gun/needle brand:** Bard **Needle thickness (G):** 18 **Anaesthesia method:** regional (saddle block) **Antibiotic prophylaxis:** n.a.
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 254 **Number of detected cancers: 80** **test1 pos/test2 pos: 48** **test1pos/test2 neg: 0** **test1neg/test2 pos: 32** **test1neg/test2 neg: 174** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos: 48** **test1pos/test3 neg: 0** **test1neg/test3 pos: 14** **test1neg/test3 neg: 192**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): 1.6 None:		**General comments** Author provided updated data of a poster (study in press: Kawakami et.al.: Int J Urol). Authors propose that an optimal biopsy scheme is (TP-8 plus TR-4) 12-cores; this procedure maintains 60% improvement of cancer detection rate over sextant biopsy. **Adverse events comments** During 4 weeks period after biopsy incidence of any biopsy related complications that required hospitalisation was 1.6% (no further details provided). **Quality comments** Abstract, updated poster and unpublished study available for quality assessment.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Keetch1995 (EN294) **Country:** USA **Aim:** To examine the diagnostic value of performing routine TZ biopsies in men with elevated serum PSA levels and prior biopsies that showed no evidence of cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **166** **Mean age (age range):** 66 (50-87) **First or repeat biopsy:** Repeat biopsy **PSA mean (range)** 6.39 (4.1-n.a.) **Mean prostate volume (range):** 56.6 (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 4 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.
Results					**General comments** Population derived from 2 screening trials. PSA values are levels before first biopsy that took place about 6 months before repeat biopsy. 37 patients with 4-6 PZ biopsies plus 4 TZ. 129 patients with 4 PZ biopsies (or LD biopsies) plus 4 TZ. **Adverse events comments** **Quality comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 166 **Number of detected cancers: 19** **test1 pos/test2 pos: 17** **test1pos/test2 neg: 0** **test1neg/test2 pos: 2** **test1neg/test2 neg: 147** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Keetch1996 (EN9230) **Country:** USA **Aim:** To examine the value of performing routine peripheral and transitional zone biopsies in men from a community screening population. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **227** **Mean age (age range):** n.a. (50-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (4.1-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 4 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 227 **Number of detected cancers: 52** **test1 pos/test2 pos: 47** **test1pos/test2 neg: 0** **test1neg/test2 pos: 5** **test1neg/test2 neg: 175** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Abstract only, hence very few details can be extracted for this study. 4 to 6 PZ cores and 2 TZ cores were taken.

Adverse events comments

Quality comments
Abstract only, hence very few details can be extracted for this study.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Kitamura2002 (EN4847) **Country:** Japan **Aim:** To clarify the clinical efficacy of TZ biopsy. **Study design:** concordance study (sequential sampling)	**Number of participants**: **139** **Mean age (age range):** 69 (50-88) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal+transperineal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** 7 MHz **Biopsy gun/needle brand:** Bard **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results				**General comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	
Number of patients biopsied: 139 **Number of detected cancers: 40** **test1 pos/test2 pos: 40** **test1pos/test2 neg: 0** **test1neg/test2 pos: 0** **test1neg/test2 neg: 99** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	**Adverse events comments** **Quality comments**

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Kojima M.2001 (EN5144) **Country:** Japan **Aim:** To determine the clinical value of transperineal 12-core systematic prostate biopsy guided by TRUS in the detection of prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **541** **Mean age (age range):** 70.0 (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** 52.5 (n.a.-n.a.) **Mean prostate volume (range):** 33.3 (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transperineal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 12 **Access:** transperineal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Aloka **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** regional (spinal) **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 541 **Number of detected cancers: 130** **test1 pos/test2 pos: 112** **test1pos/test2 neg: 0** **test1neg/test2 pos: 18** **test1neg/test2 neg: 411** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): 5.2 Prostatitis: Urinary tract infection: Voiding difficulties: 7.2 Bleeding (major): Hematuria (minor): 2.6 Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Only the most recent 541 of 679 reported patients suitable for data extraction. 4 cores of the 12 core pattern taken from the "anterior portion" of the prostate (no specification if PZ or TZ).

Adverse events comments
Complications in association with biopsy were collected from clinical records.
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Kojima Y.2000 (EN5494) **Country:** Japan **Aim:** To analyse the impact of 4 systematic TZ and 2 systematic apex (AP) biopsies in addition to systematic sextant biopsies for the detection of early prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **130** **Mean age (age range):** 70 (48.4-86.3) **First or repeat biopsy:** n.a. **PSA mean (range)** 13.8 (0.7-92.4) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 8 **Access:** transperineal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 12 **Access:** transperineal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** regional (epidural) **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 130 **Number of detected cancers: 41** **test1 pos/test2 pos: 37** **test1pos/test2 neg: 0** **test1neg/test2 pos: 4** **test1neg/test2 neg: 89** **cancers detected uniquely by LD** (if any proceeded): **0**	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): 0.8 Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Biopsies were also taken of other prostate sites where TRUS had revealed abnormalities. No result of lesion directed biopsies provided.

Adverse events comments
Macroscopic haematuria in one case, but no serious complications of biopsy were seen in any patient.
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Kravchick2004 (EN9621) **Country:** Israel **Aim:** To compare color Doppler (CD)-targeted biopsy with systematic sextant, laterally directed biopsy cores and different combinations of biopsy regimens for detection of prostate cancer **Study design:** Concordance study (sequential sampling)	**Number of participants**: **120** **Mean age (age range):** 65.1 (52-77) **First or repeat biopsy:** n.a. **PSA mean (range)** 7.3 (2.3-15) **Mean prostate volume (range):** 41.5 (18-150)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **LPZ (3)** **Number of cores:** **6** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** gray scale and CD: 7.5MHz; **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 120 **Number of detected cancers: 43** **test1 pos/test2 pos: 23** **test1pos/test2 neg: 0** **test1neg/test2 pos: 9** **test1neg/test2 neg: 88** **cancers detected uniquely by LD** (if any proceeded): **11**	**test1 pos/test3 pos: 15** **test1pos/test3 neg: 8** **test1neg/test3 pos: 9** **test1neg/test3 neg: 88**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): 47.8 Hematospermia (minor): Rectal bleeding (minor): 7.4 Pain (details see comment): 33.3 Hospitalisation: Other (details see comment): 11.5 None:

General comments
After colour Doppler examination syst. biopsies (standard sextant and 4-6 LPZ cores depending on prostate volume) were taken by an urologist unaware of CD findings. Lesion directed biopsies were taken in suspicious CD areas and focal lesions thereafter.

Adverse events comments
(other: 4% vasovagal episodes; 7.5% urethrorrhagia); AE data 10 days after biopsy: dysuria 14.2%, persist. hematuria 5.8%, urinary retention 1.6%, h-spermia 12.5%, persist. rectal bleeding 3.3%, fever and UTI 1.6%, disturbed sexual function 0.8%.
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Leibovich2000 (EN9335) **Country:** USA **Aim:** To evaluate the cancer detection rate of sextant and a new 10-core biopsy technique in a prospective, internally controlled study. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **125** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** Repeat biopsy **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** n.a.	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 10 **Access:** n.a. **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results				
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	**General comments** Abstract only, hence very few details can be extracted for this study. Poor reporting of patient data. Participants: Men with PIN and no cancer diagnosed on prior biopsy. **Adverse events comments** **Quality comments** Abstract only, hence very few details can be extracted for this study. Poor reporting of patient data and test details.
Number of patients biopsied: 125 **Number of detected cancers: 30** **test1 pos/test2 pos: 16** **test1pos/test2 neg: 0** **test1neg/test2 pos: 14** **test1neg/test2 neg: 95** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Levine1998 (EN6062) **Country:** USA **Aim:** To investigate the role of performing 2 consecutive sets of transrectal ultrasound guided sextant biopsies of the prostate in a single office visit as the protocol for detecting prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **137** **Mean age (age range):** 65 (n.a.-n.a.) **First or repeat biopsy:** First time biopsy population **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ (1) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** 7 MHz **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 137 **Number of detected cancers: 43** **test1 pos/test2 pos: 30** **test1pos/test2 neg: 0** **test1neg/test2 pos: 13** **test1neg/test2 neg: 94** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): 0.7 Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: 1.5 Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
84% of pts had PSA values <=10ng/ml.

Adverse events comments
Only significant AE reported: 1 pt with E.coli bacteriemia (infection major); 2 pt with voiding difficulties due to clot retention.
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Limitone1998 (EN6026) **Country:** Italy **Aim:** A new fashion of prostate transperineal biopsy (seven cores from each lobe) is described, in order to evaluate a potential increase of prostate cancer detection rate. **Study design:** concordance study (sequential sampling)	**Number of participants**: **247** **Mean age (age range):** 63.4 (48-83) **First or repeat biopsy:** n.a. **PSA mean (range)** 23.5 (2.3-355) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ+LPZ (6) **Number of cores:** 6 **Access:** transperineal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 14 **Access:** transperineal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Ansaldo AU 920 **Scan frequency:** 5 MHz **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** Local, injection **Antibiotic prophylaxis:** n.a.

Results				**General comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	
Number of patients biopsied: 247 **Number of detected cancers: 107** **test1 pos/test2 pos: 93** **test1pos/test2 neg: 0** **test1neg/test2 pos: 14** **test1neg/test2 neg: 140** **cancers detected uniquely by LD** (if any proceeded): n.a.	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): 0 Prostatitis: Urinary tract infection: 0 Voiding difficulties: 4.9 Bleeding (major): Hematuria (minor): 5.3 Hematospermia (minor): 24.7 Rectal bleeding (minor): Pain (details see comment): 6.9 Hospitalisation: Other (details see comment): None:	**Adverse events comments** pain: % of patients with severe pain (method of measurement not specified). **Quality comments**

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Liu2001 (EN4962) **Country:** USA **Aim:** To evaluate the diagnostic value of additional anteriorly directed TZ biopsies for diagnosing prostate cancer in a series of contemporary patients of the PSA era. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **390** **Mean age (age range):** 65.1 (53-83) **First or repeat biopsy:** Mixed population **PSA mean (range)** 12.4 (4.2-66.9) **Mean prostate volume (range):** 66.8 (32.2-220)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** Bard **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 390 **Number of detected cancers: 85** **test1 pos/test2 pos: 70** **test1pos/test2 neg: 0** **test1neg/test2 pos: 15** **test1neg/test2 neg: 305** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		**General comments** The number of TZ biopsies taken depended on the size of the prostate. In the 390 patients of this study 4 to 10 biopsies (mean 5.6) were taken from the TZ. **Adverse events comments** **Quality comments**

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Lui1995 (EN428) **Country:** USA **Aim:** To define the indications for TZ biopsies for the detection of prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **187** **Mean age (age range):** 67.4 (52-86) **First or repeat biopsy:** Mixed population **PSA mean (range)** 34.6 (0.8-457) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** Bard **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results				
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	**General comments** PSA values measured by polyclonal radioimmunoassay. **Adverse events comments** **Quality comments**
Number of patients biopsied: 187 **Number of detected cancers: 72** **test1 pos/test2 pos: 53** **test1pos/test2 neg: 0** **test1neg/test2 pos: 19** **test1neg/test2 neg: 115** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Maeda1997 (EN6194) **Country:** Japan **Aim:** To evaluate routine transition zone biopsies additionally to quadrant biopsies for the detection of prostate cancer in a community based urology practice. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **217** **Mean age (age range):** 70.8 (n.a.-n.a.) **First or repeat biopsy:** Mixed population **PSA mean (range)** 9.4 (n.a.-n.a.) **Mean prostate volume (range):** 38.1 (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 4 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 6 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Toshiba **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 217 **Number of detected cancers: 68** **test1 pos/test2 pos: 66** **test1pos/test2 neg: 0** **test1neg/test2 pos: 2** **test1neg/test2 neg: 149** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
In select cases, additional biopsies were directed toward suspicious areas noted on the ultrasound image. These site-directed biopsies were excluded from this analysis. The 217 pts consisted of 196 pts with first biopsy and 21 pts with repeat biopsy.

Adverse events comments

Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Manseck2001 (EN9339) **Country:** Germany **Aim:** To evaluate the diagnostic value of performing 4 additional transition zone biopsies in patients undergoing routine sextant biopsy of the prostate. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **324** **Mean age (age range):** 64.7 (37-88) **First or repeat biopsy:** Mixed population **PSA mean (range)** 8.3 (0.4-3773) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Siemens **Scan frequency:** 7.5 MHz **Biopsy gun/needle brand:** Urotech **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 324 **Number of detected cancers: 110** **test1 pos/test2 pos: 100** **test1pos/test2 neg: 0** **test1neg/test2 pos: 10** **test1neg/test2 neg: 214** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
If there was a suspicious ultrasound finding, the biopsy needle was directed into this area. (Some test details extracted from related paper: Manseck et al., Onkologie 2000; 23: 151-156)

Adverse events comments

Quality comments
(Some test details extracted from related paper: Manseck et al., Onkologie 2000; 23: 151-156)

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Meng2003 (EN9770) **Country:** USA **Aim:** To determine the utility of adding apical anterior horn biopsies to systematic prostate sampling regimens in detecting prostate cancer in men with measured prostate volume <=50cc. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **255** **Mean age (age range):** 67 (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** 6.0 (n.a.-n.a.) **Mean prostate volume (range):** 31.8 (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **8** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Siemens **Scan frequency:** 5-7.5MHz **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** Local, injection **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 255 **Number of detected cancers: 121** **test1 pos/test2 pos: 100** **test1pos/test2 neg: 0** **test1neg/test2 pos: 19** **test1neg/test2 neg: 136** **cancers detected uniquely by LD** (if any proceeded): **2**	**test1 pos/test3 pos: 95** **test1pos/test3 neg: 5** **test1neg/test3 pos: 19** **test1neg/test3 neg: 136**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
255 pts with prostate vol.<50cc (out of 407 consecutive pts) included. PSA and prostate vol. reported as medians. Bx of hypoechoic lesions taken before syst. bx. 2 cores were taken from anterior horn of PZ. Subgroup results not suitable for 2x2 table.

Adverse events comments
Authors report that the biopsy was well-tolerated. No increase in pain or complications after apical anterior biopsies occured (no figures provided).

Quality comments
Q 13 , Q14: no natural figures for cancer detection rates of different patterns provided.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Morote1999 (EN5766) **Country:** Spain **Aim:** To analyse the efficacy of routine transition zone biopsies in patients undergoing ultrasound-guided sextant biopsies for the first time due to suspicious DRE or elevated PSA. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **164** **Mean age (age range):** 69 (48-89) **First or repeat biopsy:** First time biopsy population **PSA mean (range)** 10.0 (0.4-574) **Mean prostate volume (range):** 48 (15-154)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** local, gel **Antibiotic prophylaxis:** n.a.
Results					**General comments** The mean PSA number is the reported median value. **Adverse events comments** **Quality comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 164 **Number of detected cancers: 77** **test1 pos/test2 pos: 75** **test1pos/test2 neg: 0** **test1neg/test2 pos: 2** **test1neg/test2 neg: 87** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Nakata1998 (EN5956) **Country:** Japan **Aim:** To evaluate the systematic biopsies (6 cores peripheral zone, 2 cores transition zone) performed on patients suspected of having prostate cancer **Study design:** concordance study (sequential sampling)	**Number of participants**: **83** **Mean age (age range):** 70.0 (48-86) **First or repeat biopsy:** n.a. **PSA mean (range)** 14.2 (0.5-124.6) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** n.a.	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** n.a. **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Aloka SSD-2000 **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		**General comments** Data extracted from English abstract and tables. **Adverse events comments** **Quality comments** Data extracted from engl abstract and tables
Number of patients biopsied: 83 **Number of detected cancers: 25** **test1 pos/test2 pos: 24** **test1pos/test2 neg: 0** **test1neg/test2 pos: 1** **test1neg/test2 neg: 58** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Naughton2000 (EN5457) **Country:** USA **Aim:** To compare 6 to 12 prostate biopsy cores to determine the impact on the cancer detection rate by performing a prospective randomized trial. **Study design:** Concordance study (randomisation)	**Number of participants**: **244** **Mean age (age range):** 65.5 (n.a.-n.a.) **First or repeat biopsy:** Mixed population **PSA mean (range)** 5.9 (2.5-20) **Mean prostate volume (range):** 42 (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 G **Anaesthesia method:** no anaesthesia **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: **Randomised to test1: 122** **Randomised to test2: 122** **Number of detected cancers:** **test1: 32** **test2 : 33** **cancers detected uniquely by LD** (if any proceeded):			*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): 4 Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): 55 Hematospermia (minor): 82 Rectal bleeding (minor): 23 Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Stanford sextant method used. Exclusion criteria: clinical prostatitis within 1 month, active UTI, patients who did not complete the questionnaire. Of the 288 eligible men 44 refused to participate. Thus 244 patients were prospectively randomized.

Adverse events comments
Pain and morb. data from 134 out of 160 randomized patients (Naughton, J Urol 2000; 163:168-171). Mean overall pain: 3-4 (VAS 0-10). Mod. or major problem: hematuria 9-11%; rectal bleeding: 7-14%; h-sperm.:13-20%. No sign. diff. between 6 and 12 core.
Quality of life (SF 36): No sign. differences after 4 weeks (Naughton, J Urol 2001; 165:100-103)
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Nava1997 (EN9235) **Country:** Italy **Aim:** To clarify the role of the number of transrectal biopsies to be performed for the detection of prostate cancer in an attempt to improve the dignostic accuracy. **Study design:** Concordance study (randomisation)	**Number of participants**: **120** **Mean age (age range):** 64 (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** 8.0 (4.1-9.9) **Mean prostate volume (range):** 55g (40g-70g)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **5-region (7)** **Number of cores:** **18** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** Tru cut **Needle thickness (G):** 18 **Anaesthesia method:** no anesthesia **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: **Randomised to test1: 40** **Randomised to test2: 40** **Number of detected cancers:** **test1: 6** **test2 : 7** **cancers detected uniquely by LD** (if any proceeded):	**Number of patients biopsied:** **Randomised to test1: 40** **Randomised to test3: 40** **Number of detected cancers:** **test1: 6** **test2 : 13** **cancers detected uniquely by LD** (if any proceeded):		*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Only patients with raised PSA and normal DRE and negative TRUS pattern were included. Abstract only, hence very few details can be extracted for this study (some details from Italian double publication #9387).

Adverse events comments
Complication rate was not significantly different among the three groups (no figures provided).

Quality comments
Abstract only, hence very few details can be extracted for this study (some details from Italian double publication #9387).

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Ng2002 (EN4647) **Country:** Singapore **Aim:** To evaluate if changing the biopsy regime to a 10-core strategy improves the positive predictive value of PSA (4-20 ng/ml) for the diagnosis of prostate carcinoma. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **191** **Mean age (age range):** 64.6 (38-85) **First or repeat biopsy:** n.a. **PSA mean (range)** 9.05 (0.7-19.6) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Aloka **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** Aloka Biopty **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 191 **Number of detected cancers: 47** **test1 pos/test2 pos: 37** **test1pos/test2 neg: 0** **test1neg/test2 pos: 10** **test1neg/test2 neg: 144** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): 2.6 Prostatitis: Urinary tract infection: Voiding difficulties: 2.6 Bleeding (major): 0.5 Hematuria (minor): 1.6 Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Pts with PSA >20 were not included. Short paper only, hence very few details can be extracted for this study. Subgroups shown but cannot be extracted because location of cancers is not stated.

Adverse events comments
Significant complications occured in 14 of 191 cases (7.3%). Other minor complications such as transient hematuria, hematospermia and orchitis were treated in the outpatient setting (no data provided).

Quality comments
There is a difference in total numbers in the table 2 (185 pts) compared to the 191 included in the study. A related abstract gave no addtl info.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Norberg1997 (EN4298) **Country:** Sweden **Aim:** To evaluate the sensitivity of the sextant biopsy protocol compared with a more extensive procedure for the detection of prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **512** **Mean age (age range):** 65 (34-81) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **8** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** 6 to 7.5 6 to 7.5MHz **Biopsy gun/needle brand:** Manan **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 512 **Number of detected cancers: 276** **test1 pos/test2 pos: 234** **test1pos/test2 neg: 0** **test1neg/test2 pos: 35** **test1neg/test2 neg: 243** **cancers detected uniquely by LD** (if any proceeded): **7**	**test1 pos/test3 pos: 234** **test1pos/test3 neg: 0** **test1neg/test3 pos: 31** **test1neg/test3 neg: 247**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): 2.3 Prostatitis: Urinary tract infection: Voiding difficulties: 0.8 Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Depending on the size of the gland, 8 to 10 biopsies were taken (81.4% of pts had a 10-core biopsy). Authors present results as sensitivities.

Adverse events comments
Complications derived from questionnaire mailed to all 512 patients 10 days after exam. All questionnaires completed and returned. 4 of the 18 pts with complications had to be hospitalised. Bleeding (without info. on location) occurred in 2 pts.
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
O'Connell2004 (EN9665) **Country:** Ireland **Aim:** To investigate the effect on prostate carcinoma detection of 12 versus 6 core biopsies at TRUS, when all biopsies are taken from the lateral peripheral zone. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **202** **Mean age (age range):** 62 (51-81) **First or repeat biopsy:** First time biopsy population **PSA mean (range)** 9.91 (1.1-98.4) **Mean prostate volume (range):** n.a. (18-141)	**Reference test (test1) (pattern):** LPZ (3) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** LPZ (3) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Toshiba or Accuson **Scan frequency:** 7.5-9.0 MHZ **Biopsy gun/needle brand:** Temno AHC **Needle thickness (G):** 18 **Anaesthesia method:** intravenous sedation **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 202 **Number of detected cancers: 78** **test1 pos/test2 pos: 72** **test1pos/test2 neg: 0** **test1neg/test2 pos: 6** **test1neg/test2 neg: 124** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): 0.5 Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: 0.5 Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Prostate was also examined with colour Doppler; no report about additional lesion directed biopsies.

Adverse events comments
Infection major 0.5%: one patient developed urinary sepsis and required hospitalisation (responded to treatment). AE data measured at routine office visit 2 weeks after biopsy; delayed complications assessed by review of office/emergency room records.

Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Onder1998 (EN5987) **Country:** Turkey **Aim:** To analyse the impact of 2 systematic transition zone biopsies in addition to systematic sextant biopsies in an effort to establish the importance of cancer detected in the transition zone. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **189** **Mean age (age range):** 66.8 (40-87) **First or repeat biopsy:** n.a. **PSA mean (range)** 27.3 (0.3-495.6) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Siemens **Scan frequency:** 7.5 MHz **Biopsy gun/needle brand:** Biopty-Cut **Needle thickness (G):** 18 **Anaesthesia method:** no anesthesia **Antibiotic prophylaxis:** n.a.

Results				**General comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	
Number of patients biopsied: 189 **Number of detected cancers: 52** **test1 pos/test2 pos: 51** **test1pos/test2 neg: 0** **test1neg/test2 pos: 1** **test1neg/test2 neg: 137** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): 1.1 Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): 5 Hematospermia (minor): Rectal bleeding (minor): 2 Pain (details see comment): Hospitalisation: Other (details see comment): 7.5 None:	**Adverse events comments** Minor complications occurred in 21 patients (11.1%). Other: 2% dizziness, 5% urethral bleeding 0.5% dysuria. **Quality comments** Patients were observed for 2 h before leaving the hospital (no further details provided about follow-up for adverse events after biopsy).

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Pagliarulo1996 (EN1081) **Country:** Italy **Aim:** To define the indications for transition zone biopsies in the detection of prostate cancer. **Study design:** concordance study (sequential sampling)	**Number of participants**: **112** **Mean age (age range):** 67.4 (56-84) **First or repeat biopsy:** Mixed population **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** n.a.	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 12 **Access:** n.a. **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.
Results					**General comments** The PSA values of 94 patients with elevated PSA levels and normal DRE were 16.2 on average (4.8 to 62.8). Origin of the samples of the PZ not specified in detail by authors (for further analysis grouped to MPZ). **Adverse events comments** Patients showed a slightly elevated intolerance depending on the number of cores taken. **Quality comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 112 **Number of detected cancers: 38** **test1 pos/test2 pos: 31** **test1pos/test2 neg: 0** **test1neg/test2 pos: 7** **test1neg/test2 neg: 74** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None: 100		

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Pasqualotto2000 (EN9345) **Country:** USA **Aim:** To evaluate the incidence of prostate cancer in patients with PIN, stratifying the diagnosis based on biopsy location. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **44** **Mean age (age range):** 66.7 (n.a.-n.a.) **First or repeat biopsy:** Repeat biopsy **PSA mean (range)** 7.0 (4.6-10.9) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** LPZ (3) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** LPZ+TZ (5) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 44 **Number of detected cancers: 20** **test1 pos/test2 pos: 20** **test1pos/test2 neg: 0** **test1neg/test2 pos: 0** **test1neg/test2 neg: 24** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		**General comments** Only abstract available. The sextant lateral-base technique consisted of 3 to 4 cores from each side of the PZ and 1 to 2 cores from each side of the TZ. All patients had a minimum of 8 biopsy cores. **Adverse events comments** **Quality comments** Only abstract available for quality assessment.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Patel2004 (EN9678) **Country:** USA **Aim:** To compare the outcome of lateral biopsies with parasagittal biopsies in detecting prostate cancer during repeat biopsies performed using "saturation" technique, which includes 24 cores per biopsy. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **100** **Mean age (age range):** 62.1 (n.a.-n.a.) **First or repeat biopsy:** Repeat biopsy **PSA mean (range)** 9.4 (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 8 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 24 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **LPZ (3)** **Number of cores:** **16** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** Local, injection **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 100 **Number of detected cancers: 25** **test1 pos/test2 pos: 9** **test1pos/test2 neg: 0** **test1neg/test2 pos: 16** **test1neg/test2 neg: 75** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos: 9** **test1pos/test3 neg: 0** **test1neg/test3 pos: 16** **test1neg/test3 neg: 75**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: 1 Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): 2 None:

General comments
Def. of lateral cores (on each side): 2 lat.base, 3 lat.mid and 3 apex. Parasagittal cores include 2 paras.base and 2 paras.mid. Authors recommend a 16-core lateral pattern. (The final 8 pts underwent 20-core saturation biopsy instead of 24-core).

Adverse events comments
AE other: Two pts developed self-limited light headedness after injection of 2% lidocaine local anesthesia (after change to 1% lidocaine no further complications).

Quality comments
Poor reporting of patient preparation and test details.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Paul2003 (EN9004) **Country:** Germany **Aim:** To investigate if there is a gain in the prostate cancer detection rate by adding median biopsies to a lateral directed sextant pattern. **Study design:** Concordance study (randomisation)	**Number of participants**: **200** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** LPZ (3) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: **Randomised to test1: 100** **Randomised to test2: 100** **Number of detected cancers:** **test1: 32** **test2 : 40** **cancers detected uniquely by LD** (if any proceeded):			*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): 2.2 Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): 72.0 Hematospermia (minor): 75.0 Rectal bleeding (minor): 29.3 Pain (details see comment): 33.0 Hospitalisation: Other (details see comment): None:

General comments
Only abstract available for data extraction. The 10 core pattern consisted of 6 cores from the LPZ and 4 cores from the MPZ.

Adverse events comments:
AE data: Paul et al.: European Urology 2004: 45: 450-456; pain (% of patients with moderate or severe pain during biopsy);
AE data (%) for reference test 1:
Infection (minor): 2.4
Hematuria (minor): 57.6
Hematospermia (minor): 65.3
Rectal bleeding (minor): 18.3
Pain (details see comment): 31.8
Other: chills: test1: 1.2%, test2: 3.3%.

Quality comments
Only abstract available for quality assessment. Additional information recieved from author.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Pepe2002 (EN1281) **Country:** Italy **Aim:** To investigate whether a larger number of prostate biopsies improves the rate of prostate cancer detection. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **190** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transperineal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 12 **Access:** transperineal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** 5MHz - 7.5 MHz **Biopsy gun/needle brand:** Tru cut **Needle thickness (G):** 16-18 **Anaesthesia method:** Local, injection **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 190 **Number of detected cancers: 84** **test1 pos/test2 pos: 66** **test1pos/test2 neg: 0** **test1neg/test2 pos: 18** **test1neg/test2 neg: 106** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: 0.5 Bleeding (major): Hematuria (minor): 5.5 Hematospermia (minor): 6.2 Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): 1.1 None:

General comments
Data extracted for subgroup of 190 patients. In some of those patients 2 additional TZ biopsies were performed if indicated (elevated PSA with negative DRE). No cancer was uniquely detected by those TZ biopsies.

Adverse events comments
other: 0.6% epididymitis monolateralis; 0.5% vagal syndome
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Perdona2000 (EN5279) **Country:** Italy **Aim:** We describe our experience with a 14 systematic multisite biopsy scheme to detect carcinoma of the prostate (stage T1c). **Study design:** concordance study (sequential sampling)	**Number of participants**: **177** **Mean age (age range):** 64.1 (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** 8.36 (4.0-13) **Mean prostate volume (range):** 49.3 (23.3-78.3)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 14 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **5-region (7)** **Number of cores:** **12** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Kretz **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** Tru-Cut **Needle thickness (G):** 18 **Anaesthesia method:** no anesthesia **Antibiotic prophylaxis:** Yes

Results				**General comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	
Number of patients biopsied: 177 **Number of detected cancers: 61** **test1 pos/test2 pos: 42** **test1pos/test2 neg: 0** **test1neg/test2 pos: 19** **test1neg/test2 neg: 116** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos: 42** **test1pos/test3 neg: 0** **test1neg/test3 pos: 19** **test1neg/test3 neg: 116**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): 3.9 Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): 95 Hematospermia (minor): 95 Rectal bleeding (minor): 95 Pain (details see comment): 18.6 Hospitalisation: Other (details see comment): 23.7 None:	**Adverse events comments** "general discomfort 18.6%" coded as pain by reviewer; other: "Dysuria 22.6%" and "vaso vagal episode 1.1%". Uretrorhagia (95%) coded together with Haematuria. **Quality comments**

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Philip2004 (EN10163) **Country:** UK **Aim:** To assess the prostate cancer detection rate with a 12-core biopsy protocol and develop an optimal biopsy regimen for detecting early prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **445** **Mean age (age range):** 64.5 (43-84) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (2.6-10) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **8** **Index test (test4) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **10**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** 7.5 MHz **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** Local, injection **Antibiotic prophylaxis:** Yes
Results					**General comments** Authors recommend a 10 core pattern (omitting the 2 parasagittal mid-zone biopsies of the 12 core pattern): 6 LPZ cores (base, mid, apex) and 4 MPZ cores (base and apex). Optimal 8-core pattern: 6 MPZ + 2 LPZ base. **Adverse events comments** **Quality comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 445 **Number of detected cancers: 142** **test1 pos/test2 pos: 102** **test1pos/test2 neg: 0** **test1neg/test2 pos: 40** **test1neg/test2 neg: 303** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos: 102** **test1pos/test3 neg: 0** **test1neg/test3 pos: 24** **test1neg/test3 neg: 319**	**test1 pos/test4 pos: 100** **test1pos/test4 neg: 2** **test1neg/test4 pos: 40** **test1neg/test4 neg: 303**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Presti2000 (EN4277) **Country:** USA **Aim:** To define the optimal systematic biopsy regimen to detect carcinoma of the prostate. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **483** **Mean age (age range):** 69.0 (n.a.-n.a.) **First or repeat biopsy:** First time biopsy population **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **8** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Siemens **Scan frequency:** 5-7.5 MHz **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** Local, injection **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 483 **Number of detected cancers: 202** **test1 pos/test2 pos: 161** **test1pos/test2 neg: 0** **test1neg/test2 pos: 33** **test1neg/test2 neg: 289** **cancers detected uniquely by LD** (if any proceeded): **5**	**test1 pos/test3 pos: 158** **test1pos/test3 neg: 3** **test1neg/test3 pos: 33** **test1neg/test3 neg: 289**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Authors advocate 8 cores taken f. apex, mid-lobar mid gland, lateral mid gland and lateral base. Pat with prost. vol >50cc received TZ bx (3 Ca uniquely detected). Normal DRE group: 75 cancers, only 73 by 10-core. Abnormal DRE: 127 cancers, 121 by 10-core

Adverse events comments

Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Ravery1999 (EN5765) **Country:** France **Aim:** To evaluate the improvement in the rate of detection of prostate cancer using an extensive protocol involving 10 transrectal biopsies. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **162** **Mean age (age range):** 66.2 (39-87) **First or repeat biopsy:** n.a. **PSA mean (range)** 16.8 (1-600) **Mean prostate volume (range):** 42.7 (10-182)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ (1) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes

Results				**General comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	
Number of patients biopsied: 162 **Number of detected cancers: 65** **test1 pos/test2 pos: 60** **test1pos/test2 neg: 0** **test1neg/test2 pos: 5** **test1neg/test2 neg: 97** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: 1.25 Urinary tract infection: Voiding difficulties: Bleeding (major): 0.6 Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	**Adverse events comments** 3 of 162 patients experienced complications: 1 pt with rectal bleeding requiring hospitalisation; 2 pts with confirmed prostatitis. **Quality comments** Poor reporting of test procedures so little detail is available for data extraction.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Ravery1998 (EN4176) **Country:** France **Aim:** To determine if additional biopsies significantly increases the chance of finding prostate cancer compared to the sextant biopsy technique. **Study design:** concordance study (sequential sampling)	**Number of participants**: **92** **Mean age (age range):** 66.4 (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** 13.3 (n.a.-n.a.) **Mean prostate volume (range):** 41.8 (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ (1) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results				**General comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	
Number of patients biopsied: 92 **Number of detected cancers: 34** **test1 pos/test2 pos: 30** **test1pos/test2 neg: 0** **test1neg/test2 pos: 4** **test1neg/test2 neg: 58** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	**Adverse events comments** No figures provided for AE ("there is no additional morbidity to this new technique") **Quality comments**

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Ravery2000 (EN5456) **Country:** France **Aim:** To evaluate the improvement in the rate of prostate cancer detection when using an extensive biopsy protocol involving peripheral cores. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **303** **Mean age (age range):** 64.3 (43-86) **First or repeat biopsy:** n.a. **PSA mean (range)** 11.3 (0.4-138) **Mean prostate volume (range):** 44.1 (6-147)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** no anesthesia **Antibiotic prophylaxis:** Yes
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 303 **Number of detected cancers: 118** **test1 pos/test2 pos: 98** **test1pos/test2 neg: 0** **test1neg/test2 pos: 20** **test1neg/test2 neg: 185** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: 0.7 Urinary tract infection: Voiding difficulties: Bleeding (major): 0.3 Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		**General comments** When prostate volume was >50ccm (in 63 of 303 pts) 2 additional biospies were taken at the periphery of the apex (i.e. 12 cores totally). **Adverse events comments** Bleeding major: rectal bleeding in 1 patient that required hospitalisation. **Quality comments** The cores out of each zone (two corresponding cores from each prostate lobe together) were were fixed and sent separately for histological analysis.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Reissigl1997 (EN1040) **Country:** Austria **Aim:** To evaluate the frequency and clinical significance of TZ cancers by adding two TZ biopsies to the routinely performed sextant biopsies. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **340** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (2.5-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Kretz **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** Bip **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results				**General comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	
Number of patients biopsied: 340 **Number of detected cancers: 98** **test1 pos/test2 pos: 70** **test1pos/test2 neg: 0** **test1neg/test2 pos: 28** **test1neg/test2 neg: 242** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	**Adverse events comments** **Quality comments** Representativity of patients: In this study only patients with clearly visible prostatic zones in three dimensional US were included.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Robles1999 (EN5613) **Country:** Spain **Aim:** To evaluate the effectiveness of routine biopsy of the transition zone in patients undergoing early systematic sextant prostate biopsy. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **164** **Mean age (age range):** 69 (48-89) **First or repeat biopsy:** n.a. **PSA mean (range)** 10 (0.4-574) **Mean prostate volume (range):** 48 (15-154)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** 6.5MHz **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** local, gel **Antibiotic prophylaxis:** Yes

Results				**General comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	
Number of patients biopsied: 164 **Number of detected cancers: 77** **test1 pos/test2 pos: 75** **test1pos/test2 neg: 0** **test1neg/test2 pos: 2** **test1neg/test2 neg: 87** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	**Adverse events comments** **Quality comments**

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Romagnoli2002 (EN4465) **Country:** Italy **Aim:** To evaluate the utility of lateral PZ biopsies in the diagnostic work-up for prostate cancer with the transperineal approach. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **666** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** Mixed population **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 6 **Access:** transperineal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 8 **Access:** transperineal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Esaote Eidos **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** Tru cut **Needle thickness (G):** 18 **Anaesthesia method:** Local, injection **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 666 **Number of detected cancers: 303** **test1 pos/test2 pos: 288** **test1pos/test2 neg: 0** **test1neg/test2 pos: 15** **test1neg/test2 neg: 363** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: 0.5 Bleeding (major): 0.6 Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): 2 None:

General comments
Author reports about 1352 patients. Only the subgroup of the most recent 666 patients suitable for data extraction.

Adverse events comments
AE data relate to the complete study population of 1352 patients with different biopsy patterns (Bleeding major: urinary catheter necessary due to urethrorhagia; other: vagal syndrome leading to interruption of biopsy.)
Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Rowe2002 (EN9356) **Country:** UK **Aim:** To determine whether whether the diagnostic yield for prostate cancer was increased in larger prostates, with a 12-core biopsy strategy to sample more of the lateral aspects of the prostate. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **52** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (n.a.-<20 ng/ml) **Mean prostate volume (range):** n.a. (>40cc-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 52 **Number of detected cancers: 20** **test1 pos/test2 pos: 13** **test1pos/test2 neg: 0** **test1neg/test2 pos: 7** **test1neg/test2 neg: 32** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Abstract only, hence very few details can be extracted for this study.

Adverse events comments

Quality comments
Qualita assessment based on information available in abstract.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Singh2003 (EN9135) **Country:** USA **Aim:** To examine the predictive diagnostic value of PSA measurement (discrimination between BPH and prostate cancer) for systematic 6 core and for systematic 12 core biopsies. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **336** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (4-10) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** n.a.	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 12 **Access:** n.a. **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 336 **Number of detected cancers: 127** **test1 pos/test2 pos: 95** **test1pos/test2 neg: 0** **test1neg/test2 pos: 32** **test1neg/test2 neg: 209** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Abstract only, hence very few details can be extracted for this study. Finger and ultrasound directed biopsy cores were excluded. Sensitivities and area under curve stats for PSA measurement are also reported in the abstract.

Adverse events comments

Quality comments
Abstract only, hence very few details can be extracted for this study.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Slongo2003 (EN1154) **Country:** Brazil **Aim:** To establish the efficacy of 6- and 12-core TRUS guided needle biopsies in low risk patients for prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **54** **Mean age (age range):** 57.7 (41-80) **First or repeat biopsy:** n.a. **PSA mean (range)** 6.5 (2.7-10) **Mean prostate volume (range):** 34.7 (17-49)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **10** **Index test (test4) (pattern):** **LPZ (3)** **Number of cores:** **6**	**Ultrasound brand:** Siemens **Scan frequency:** 6.5MHz **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** intravenous sedation **Antibiotic prophylaxis:** Yes
Results					**General comments** Pts were selected from 240 pts, giving a sample of 54 pts who met the inc. criteria. Additional LD samples were taken of suspicious areas and were included in the systematic sampling count. (10 core pattern: 12 minus 2 basal parasagittal cores) **Adverse events comments** **Quality comments**
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: 54 **Number of detected cancers: 22** **test1 pos/test2 pos: 11** **test1pos/test2 neg: 0** **test1neg/test2 pos: 11** **test1neg/test2 neg: 32** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos: 11** **test1pos/test3 neg: 0** **test1neg/test3 pos: 11** **test1neg/test3 neg: 32**	**test1 pos/test4 pos: 9** **test1pos/test4 neg: 2** **test1neg/test4 pos: 11** **test1neg/test4 neg: 32**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Soramoto1999 (EN1822) **Country:** Japan **Aim:** Evaluation of systematic biopsies in the diagnosis of prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **56** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (0.8-2360) **Mean prostate volume (range):** n.a. (11-98)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 4 **Access:** n.a.	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 6 **Access:** n.a. **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results				
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	**General comments** Data extracted from Japanese abstract and the partly translated full text. **Adverse events comments** **Quality comments** Only English abstract and partly translared full text available.
Number of patients biopsied: 56 **Number of detected cancers: 26** **test1 pos/test2 pos: 24** **test1pos/test2 neg: 0** **test1neg/test2 pos: 2** **test1neg/test2 neg: 30** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): 1.8 Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): 26.8 Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Sur2002 (EN9362) **Country:** USA **Aim:** To perform a randomised prospective comparison of the sextant biopsy procedure with a more extensive biopsy technique using I.V. conscious sedation. **Study design:** Concordance study (randomisation)	**Number of participants**: **197** **Mean age (age range):** n.a. (42-82) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ+LPZ (6) **Number of cores:** 10 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 24 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** local, gel (Gr1) vs. IV conscious sedation (Gr2) **Antibiotic prophylaxis:** n.a.
Results					
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)		
Number of patients biopsied: **Randomised to test1: 88** **Randomised to test2: 94** **Number of detected cancers:** **test1: 34** **test2 : 39** **cancers detected uniquely by LD** (if any proceeded):			*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:		**General comments** Abstract only, very few patient and test details provided. 197 pts initially randomized, 15 pts withdrew, 182 pts analysed. In Gr.1 6-12 cores were taken (on average 10.1 cores). **Adverse events comments** Urinary iritative/obstructive symptoms, hematospermia, hematechezia, hematuria, biopsy pain and satisfaction were assessed on the day prior to and 1 day, 1wk and 2wks after biopsy. Pain was stat. sign. less and satisfaction higher with conscious sedation. **Quality comments** Withdrawals = 15 pts, not included in the analysis. Abstract only, hence very few details can be extracted for this study.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Tan2001 (EN9364) **Country:** Canada **Aim:** To investigate the diagnostic yield of additional biopsies which in addition to sextant biopsies include biopsies of the TZ, suspicious areas on DRE or TRUS and hypervasc. areas on colour doppler US. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **126** **Mean age (age range):** n.a. (n.a.-n.a.) **First or repeat biopsy:** Repeat biopsy **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** 66.5. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** Yes	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 126 **Number of detected cancers: 53** **test1 pos/test2 pos: 49** **test1pos/test2 neg: 0** **test1neg/test2 pos: 4** **test1neg/test2 neg: 73** **cancers detected uniquely by LD** (if any proceeded): **0**	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Abstract only, hence very few details can be extracted for this study. Additional data available for DRE, TRUS and doppler effectiveness in locating prostate cancer. 2 TZ cores taken from only 105 out of 126 pts. Addtl data extracted from study 9363.

Adverse events comments

Quality comments
Abstract only, hence very few details can be extracted. 2 addtl. PZ biopsies taken in only 105 out of 126 pts (selection criteria not described).

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Terris1997 (EN6200) **Country:** USA **Aim:** To determine if prostate cancer detection could be improved by obtaining more laterally placed biopsies (lateral sextant) additionally to the standard mid-lobar parasagittal sextant biopsies. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **41** **Mean age (age range):** 67.5 (49-79) **First or repeat biopsy:** n.a. **PSA mean (range)** 10.9 (0.3-37.4) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** LPZ (3) **Number of cores:** 6 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **MPZ+LPZ (6)** **Number of cores:** **12** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Bruel & Kjaer **Scan frequency:** n.a. **Biopsy gun/needle brand:** Bard **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** Yes

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 41 **Number of detected cancers: 28** **test1 pos/test2 pos: 19** **test1pos/test2 neg: 3** **test1neg/test2 pos: 6** **test1neg/test2 neg: 13** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos: 22** **test1pos/test3 neg: 0** **test1neg/test3 pos: 6** **test1neg/test3 neg: 13**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Pts unable to tolerate 12 biopsies were excluded as were pts with obvious stage C or D cancer.

Adverse events comments

Quality comments
Histologic work up: Only embedding and staining method of the cores reported.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Terris1997 (EN1069) **Country:** USA **Aim:** To examine the efficacy of routine transition zone and seminal vesicle biopsies for the detection of prostate cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **161** **Mean age (age range):** 69.6 (51-82) **First or repeat biopsy:** n.a. **PSA mean (range)** 26.2 (1.2-225) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** Multifrequency probe (7-10MHz) **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results				
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	**General comments** 1-3 TZ cores were taken depending on prostate volume. Data for seminal vesicle biopsies that evaluated the extent of cancer were not extracted. **Adverse events comments** **Quality comments**
Number of patients biopsied: 161 **Number of detected cancers: 55** **test1 pos/test2 pos: 54** **test1pos/test2 neg: 0** **test1neg/test2 pos: 1** **test1neg/test2 neg: 106** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Tokumitsu2000 (EN10152) **Country:** Japan **Aim:** To evaluate the improvement in the detection rate of prostate cancer with a modified 5-region biopsy technique. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **73** **Mean age (age range):** 70.9 (50-88) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 12 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** Aloka **Scan frequency:** 5.0 MHz **Biopsy gun/needle brand:** Biopty **Needle thickness (G):** 18 **Anaesthesia method:** regional (saddle anesthesia) **Antibiotic prophylaxis:** n.a.

Results				
Outcome index test2	**Outcome index test3** (if any extracted data)	**Outcome index test4** (if any extracted data)	**Adverse events** (% of patients; index test2)	**General comments** Abstract only. Poor reporting of patient data. The 5-region biopsy reported by Eskew (13 cores) was modified to a 5-region biopsy with 12 cores by reducing the number of cores from the mid zone (region 3) from 3 to 2 cores. **Adverse events comments** **Quality comments** Quality assessment based on information available in abstract.
Number of patients biopsied: 73 **Number of detected cancers: 30** **test1 pos/test2 pos: 27** **test1pos/test2 neg: 0** **test1neg/test2 pos: 3** **test1neg/test2 neg: 43** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events* ***(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:	

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Traverso2001 (EN4164) **Country:** Italy **Aim:** To perform a prospective study where prostate biopsy is performed trans-perineally. **Study design:** concordance study (sequential sampling)	**Number of participants**: **668** **Mean age (age range):** 68.9 (n.a.-n.a.) **First or repeat biopsy:** Mixed population **PSA mean (range)** 10.3 (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transperineal	**Index test (test2) (pattern):** MPZ+TZ (+MLiPZ) (4) **Number of cores:** 8 **Access:** transperineal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 668 **Number of detected cancers: 296** **test1 pos/test2 pos: 270** **test1pos/test2 neg: 0** **test1neg/test2 pos: 26** **test1neg/test2 neg: 372** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Origin of the samples of the PZ not specified in detail by authors (for further analysis grouped to MPZ).

Adverse events comments

Quality comments

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Tsai2000 (EN9369) **Country:** USA **Aim:** To determine if additional biopsies of the extreme lateral zones of the prostate increase the rate of prostate cancer detection. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **173** **Mean age (age range):** 66 (n.a.-n.a.) **First or repeat biopsy:** n.a. **PSA mean (range)** 6.9 (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** MPZ+LPZ (6) **Number of cores:** 10 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 173 **Number of detected cancers: 66** **test1 pos/test2 pos: 59** **test1pos/test2 neg: 0** **test1neg/test2 pos: 7** **test1neg/test2 neg: 107** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Abstract only, hence very few details can be extracted for this study. Biopsy results were stratified for presence or absence of hypoechoic lesions, prostate volume (<40cc vs. >40cc) and PSA (4-10, 10-20, >20ng/ml). These results are not reported.

Adverse events comments
No complications resulted from additional biopsies (authors do not provide further details for adverse events).

Quality comments
Abstract only, hence very few details can be extracted for this study.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Vakar-Lopez2002 (EN9370) **Country:** USA **Aim:** To evaluate 10-11 core biopsies to determine the predictors of prostate cancer in repeat biopsy and to establish recommendations for it use in pts with an initial extended biopsy negative for cancer. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **89** **Mean age (age range):** 60.4 (44-74) **First or repeat biopsy:** Repeat biopsy **PSA mean (range)** 7.9 (0.7-36.1) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** n.a.	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 11 **Access:** n.a. **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** n.a. **Biopsy gun/needle brand:** n.a. **Needle thickness (G):** n.a. **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 89 **Number of detected cancers: 15** **test1 pos/test2 pos: 8** **test1pos/test2 neg: 0** **test1neg/test2 pos: 7** **test1neg/test2 neg: 74** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Abstract only. Very few details could be extracted from the report.

Adverse events comments

Quality comments
Abstract only, hence very few data could be extracted for this study.

Study details and design	Participants details	Biopsy details			
		Reference test (test1)	**Index test (test2)**	**Additional index tests** (if any):	**Biopsy equipment; patient preparation**
Zhong2003 (EN9373) **Country:** China **Aim:** To evaluate the clinical value of transrectal ultrasound guided systematic 13-core prostate biopsy. **Study design:** Concordance study (sequential sampling)	**Number of participants**: **213** **Mean age (age range):** n.a. (48-87) **First or repeat biopsy:** n.a. **PSA mean (range)** n.a. (n.a.-n.a.) **Mean prostate volume (range):** n.a. (n.a.-n.a.)	**Reference test (test1) (pattern):** MPZ (1) **Number of cores:** 6 **Access:** transrectal	**Index test (test2) (pattern):** 5-region (7) **Number of cores:** 13 **Access:** transrectal **Additional lesion directed biopsies:** 0	**Index test (test3) (pattern):** **Number of cores:** **Index test (test4) (pattern):** **Number of cores:**	**Ultrasound brand:** n.a. **Scan frequency:** 5.5 to 7.5 MHz **Biopsy gun/needle brand:** Bard **Needle thickness (G):** 18 **Anaesthesia method:** n.a. **Antibiotic prophylaxis:** n.a.

Results

Outcome index test2	Outcome index test3 (if any extracted data)	Outcome index test4 (if any extracted data)	Adverse events (% of patients; index test2)
Number of patients biopsied: 213 **Number of detected cancers: 66** **test1 pos/test2 pos: 52** **test1pos/test2 neg: 0** **test1neg/test2 pos: 14** **test1neg/test2 neg: 147** **cancers detected uniquely by LD** (if any proceeded):	**test1 pos/test3 pos:** **test1pos/test3 neg:** **test1neg/test3 pos:** **test1neg/test3 neg:**	**test1 pos/test4 pos:** **test1pos/test4 neg:** **test1neg/test4 pos:** **test1neg/test4 neg:**	*Adverse events **(if any mentioned by authors):*** Death: Infection (major): Infection (minor): Prostatitis: Urinary tract infection: Voiding difficulties: Bleeding (major): Hematuria (minor): Hematospermia (minor): Rectal bleeding (minor): Pain (details see comment): Hospitalisation: Other (details see comment): None:

General comments
Data extraction from English abstract. 53.5% of participants had a PSA value > 10 ng/ml.

Adverse events comments
There were no severe complications reported for the patients undergoing 13-core biopsies.
Quality comments
Quality assessment based on data extraction from English abstract.

Author	year	T1_cores	T1_pattern	T2_cores	T2_pattern	Q1 Spectrum representative?	Q2 selection criteria	Q8 index test (test2) details	Q9 reference test (test1) details	Q10 index test (test2) review bias?	Q11 reference test (test1) review bias?	Q12 same clinical data available?	Q13 uninterpreatable results?	Q14 withdrawals?	Q20 follow-up long enough?	Q21 cores specifically labelled?	Q22 histologic work up	Q-ran1 random sequence	Q-ran2 concealment	Quality comments
Arger	2002	6	MPZ (1)	11	MPZ+TZ (+MLiPZ) (4)	?	?	?	?	?	?	+	+	+	?	?	-			No report about patient preparation.
Aus	2001	4	MPZ (1)	6	MPZ+LPZ (6)	+	+	?	?	?	?	+	-	+	?	+	-			56 of 692 patients with incomplete sampling. Results are given for the whole population only. 7 of 171 patients with diagnosed cancer were excluded.
Babaian	2000	6	MPZ (1)	11	5-region (7)	?	+	+	+	?	?	+	+	+	?	+	-			
Balaji	2003	6	MPZ (1)	10	MPZ+LPZ (6)	+	?	?	?	?	?	+	?	+	?	+	?			No details about the patient who was biopted twice.
Balbontin	2000	6	MPZ (1)	12	MPZ+LPZ (6)	?	?	?	?	?	?	+	+	+	?	?	-			
Bazinet	1996	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	+	?	?	?	?	?	+	+	+	?	?	-			
Beurton	2000	6	MPZ (1)	12	MPZ+LPZ (6)	?	?	?	?	?	?	+	+	+	?	+	-	+	+	Only abstract available
Borboroglu	2000	18	MPZ+LPZ (6)	23	5-region (7)	+	+	+	+	?	?	+	+	+	-	+	-			
Broessner	1999	6	MPZ (1)	12	5-region (7)	?	?	+	+	?	?	+	+	+	?	+	+			
Cam	2001	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	?	?	?	?	?	?	+	+	+	?	?	-			Poor reporting of patient characteristics.
Chang	1998	6	MPZ (1)	10	MPZ+LPZ (6)	+	?	?	?	?	?	+	+	+	?	+	-			
Chang	1998	6	MPZ (1)	12	MPZ+TZ (+MLiPZ) (4)	+	+	?	?	?	?	+	+	+	?	+	-			
Chon	2002	6	MPZ (1)	10	MPZ+LPZ (6)	+	+	+	+	?	?	+	+	+	?	+	-			
Damiano	2003	6	MPZ (1)	14	5-region (7)	+	+	+	+	?	?	+	?	+	+	+	-			Q 13: Data of subgroup results partly inconsistant and not extraced.
de la Taille	2003	6	MPZ (1)	21	5-region (7)	+	+	+	+	?	?	+	+	+	+	+	-			
Deliveliotis	2002	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	+	+	?	?	?	?	+	+	+	?	+	-			Cores were not individually labelled but grouped and labelled by zone (TZ/PZ).

Author	year	T1_cores	T1_pattern	T2_cores	T2_pattern	Q1 Spectrum representative?	Q2 selection criteria	Q8 index test (test2) details	Q9 reference test (test1) details	Q10 index test (test2) review bias?	Q11 reference test (test1) review bias?	Q12 same clinical data available?	Q13 uninterpreatable results?	Q14 withdrawals?	Q20 follow-up long enough?	Q21 cores specifically labelled?	Q22 histologic work up	Q-ran1 random sequence	Q-ran2 concealment	Quality comments
Durkan	2002	6	MPZ (1)	12	5-region (7)	+	?	+	+	?	?	+	+	+	+	+	-			
Egawa	1998	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	-	?	?	?	?	?	+	+	+	+	?	-			Of 629 consecutive patients 344 patients were included. Indication for TZ bx: partly based on preprostatectomy evaluation or on patient tolerance/condition.
Ellis	2002	6	LPZ (3)	12	MPZ+LPZ (6)	+	?	?	?	?	?	+	+	+	?	?	-			Only abstract available, poor reporting about test details and patient data.
Emiliozzi	2004	6	MPZ (1)	12	MPZ+LPZ (6)	?	?	+	+	?	?	+	+	+	+	+	-	?	?	Authors report about adverse events up to 3 mth but do not state how they collected the data.
Emiliozzi	2003	6	MPZ (1)	12	MPZ+LPZ (6)	?	+	?	?	?	?	+	+	+	+	?	-			Duration of follow up not explicitly stated but authors report about AE (hematospermia) lasting up to 3 months.
Eskew	1997	6	MPZ (1)	13	5 region (7)	?	?	+	+	?	?	+	+	+	?	+	-			
Eskicorapci	2004	10	MPZ+LPZ (6)	14	5-region (7)	?	?	?	?	?	?	+	?	+	?	?	-			Only abstract available for quality assessment.
Eskicorapci	2004	6	MPZ (1)	10	MPZ+LPZ (6)	+	+	?	?	?	?	+	+	+	?	+	-			
Fleshner	2002	6	LPZ (3)	32	LPZ+TZ (5)	?	+	+	+	?	?	+	+	+	+	+	-			Samples were separately labelled in groups of six so that marginal benefit of biopsies could be determined.
Fowler	1996	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	?	+	?	?	?	?	+	+	+	?	?	-			
Fuganti	2002	6	MPZ (1)	12	5-region (7)	+	?	?	?	?	?	+	+	+	?	?	+			Poor reporting of patient characteristics and test procedures.
Garber	1994	6	MPZ (1)	4	MPZ (1)	?	?	?	?	?	?	+	+	+	?	+	?			
Garcia	2001	6	MPZ (1)	6	MPZ (1)	?	?	?	?	?	?	+	+	+	?	?	-			
Gómez Veiga	1999	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	+	?	?	?	?	?	+	+	+	?	?	-			Only abstract available for quality assessment.
Gore	2001	6	MPZ (1)	12	MPZ+LPZ (6)	?	?	?	?	?	?	+	+	+	?	+	?			
Harewood	1996	4	MPZ (1)	8	MPZ+LPZ (6)	+	?	?	?	?	?	+	+	+	?	?	-			Abstract only, hence very few details can be extracted for this study.

Author	year	T1_cores	T1_pattern	T2_cores	T2_pattern	Q1 Spectrum representative?	Q2 selection criteria	Q8 index test (test2) details	Q9 reference test (test1) details	Q10 index test (test2) review bias?	Q11 reference test (test1) review bias?	Q12 same clinical data available?	Q13 uninterpreatable results?	Q14 withdrawals?	Q20 follow-up long enough?	Q21 cores specifically labelled?	Q22 histologic work up	Q-ran1 random sequence	Q-ran2 concealment	Quality comments
Horninger	1999	10	MPZ+TZ (+MLiPZ) (4)	14	MPZ+TZ (+MLiPZ) (4)	+	-	-	-	?	?	+	+	+	?	?	-	?	?	Study details lacking (only abstract available)..
Ishizuka	2002	6	MPZ (1)	10	MPZ+TZ (+MLiPZ) (4)	+	+	?	?	?	?	+	+	+	?	?	-			
Ito	2002	6	MPZ (1)	20	5-region (7)	?	?	?	?	?	?	+	?	+	?	?	-			Intransparent reporting about patient preparation and applied biopsy schemes.
Karakiewicz	1996	6	MPZ (1)	4	MPZ (1)	?	?	?	?	?	?	+	+	+	?	?	-			Index test not specified: 4 sector scheme was simulated by randomly reducing the 6 sector cores (taken in vivo) by computer simulation.
Karakiewicz	1995	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	+	?	?	?	?	?	+	+	+	?	?	-			Abstract only, hence very few details can be extracted for this study. 113 of 960 patients referred to the authors during the study did not undergo biopsy.
Kawakami	2003	6	MPZ (1)	22	5-region (7)	?	?	?	?	?	?	+	+	+	+	?	-			Abstract, updated poster and unpublished study available for quality assessment.
Keetch	1995	4	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	+	+	?	?	?	?	+	+	-	?	?	-			
Keetch	1996	4	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	+	?	?	?	?	?	+	+	+	?	?	-			Abstract only, hence very few details can be extracted for this study.
Kitamura	2002	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	+	?	?	?	?	?	+	+	+	?	?	-			
Kojima M.	2001	6	MPZ (1)	12	5-region (7)	+	?	?	?	?	?	+	+	+	?	?	-			
Kojima Y.	2000	8	MPZ (1)	12	MPZ+TZ (+MLiPZ) (4)	?	?	?	?	?	?	+	+	+	?	?	-			
Kravchick	2004	6	MPZ (1)	12	MPZ+LPZ (6)	+	?	?	?	?	?	+	+	+	+	+	-			
Leibovich	2000	6	MPZ (1)	10	MPZ+LPZ (6)	?	?	?	?	?	?	?	+	+	?	?	-			Abstract only, hence very few details can be extracted for this study. Poor reporting of patient data and test details.
Levine	1998	6	MPZ (1)	12	MPZ (1)	+	+	?	?	+	+	+	+	+	?	+	-			
Limitone	1998	6	MPZ (1)	14	5-region (7)	?	?	+	+	-	-	+	+	+	?	+	-			
Liu	2001	6	MPZ (1)	10	MPZ+TZ (+MLiPZ) (4)	?	?	?	?	?	?	+	+	+	?	+	?			

Author	year	T1_cores	T1_pattern	T2_cores	T2_pattern	Q1 Spectrum representative?	Q2 selection criteria	Q8 index test (test2) details	Q9 reference test (test1) details	Q10 index test (test2) review bias?	Q11 reference test (test1) review bias?	Q12 same clinical data available?	Q13 uninterpreatable results?	Q14 withdrawals?	Q20 follow-up long enough?	Q21 cores specifically labelled?	Q22 histologic work up	Q-ran1 random sequence	Q-ran2 concealment	Quality comments
Lui	1995	6	MPZ (1)	12	MPZ+TZ (+MLiPZ) (4)	?	?	?	?	?	?	+	+	+	?	+	+			
Maeda	1997	4	MPZ (1)	6	MPZ+TZ (+MLiPZ) (4)	+	+	?	?	?	?	+	+	+	?	?	-			
Manseck	2001	6	MPZ (1)	10	MPZ+TZ (+MLiPZ) (4)	?	+	?	?	?	?	+	+	+	?	+	-			Some test details extracted from related paper: Manseck et al., Onkologie 2000; 23: 151-156.
Meng	2003	6	MPZ (1)	12	MPZ+LPZ (6)	-	?	?	?	?	?	+	+	+	?	+	-			Q 13 , Q14: no natural figures for cancer detection rates of different schemes provided.
Morote	1999	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	+	+	?	?	?	?	+	+	+	?	?	-			
Nakata	1998	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	?	?	?	?	?	?	+	+	+	?	?	?			Data extracted from English abstract and tables
Naughton	2000	6	MPZ (1)	12	MPZ+LPZ (6)	+	+	+	+	?	?	+	+	+	+	+	-	+	+	
Nava	1997	6	MPZ (1)	12	MPZ+TZ (+MLiPZ) (4)	+	?	?	?	?	?	+	+	+	?	?	-	?	?	Abstract only, hence very few details can be extracted for this study. Ssome details extraced from Italian double publication: Nava L, Rigatti P. La biopsia prostática ecoguidata: tecnica di esecuzione, aghi utilizzati, numero dei prelievi. Acta Urologica Italica 1998;1(suppl. 12):47-53.
Ng	2002	6	MPZ (1)	10	MPZ+LPZ (6)	+	+	?	?	?	?	+	?	-	+	+	-			There is a difference in total numbers in the table 2 (185 patients) compared to the 191 included in the study. A related abstract gave no addtl info.
Norberg	1997	6	MPZ (1)	10	5-region (7)	+	+	?	?	?	?	+	+	+	+	+	+			
O'Connell	2004	6	LPZ (3)	12	LPZ (3)	?	?	+	+	?	?	+	+	+	+	+	?			
Onder	1998	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	+	+	?	?	?	?	+	+	+	-	+	-			Patients were observed for 2 h before leaving the hospital (no further details provided about follow-up for adverse events after biopsy).
Pagliarulo	1996	6	MPZ (1)	12	MPZ+TZ (+MLiPZ) (4)	?	?	?	?	?	?	+	+	+	?	+	+			
Pasqualotto	2000	6	LPZ (3)	8	LPZ+TZ (5)	?	?	?	?	?	?	+	+	+	?	?	-			Only abstract available for quality assessment.
Patel	2004	8	MPZ (1)	24	MPZ+LPZ (6)	?	?	?	?	?	?	+	+	+	?	?	-			Poor reporting of patient preparation and test details.
Paul	2003	6	LPZ (3)	10	MPZ+LPZ (6)	?	-	?	?	?	?	+	+	+	?	?	-	+	-	Only abstract available for quality assessment. Additional information recieved from author.

Author	year	T1_cores	T1_pattern	T2_cores	T2_pattern	Q1 Spectrum representative?	Q2 selection criteria	Q8 index test (test2) details	Q9 reference test (test1) details	Q10 index test (test2) review bias?	Q11 reference test (test1) review bias?	Q12 same clinical data available?	Q13 uninterpreatable results?	Q14 withdrawals?	Q20 follow-up long enough?	Q21 cores specifically labelled?	Q22 histologic work up	Q-ran1 random sequence	Q-ran2 concealment	Quality comments
Pepe	2002	6	MPZ (1)	12	MPZ+LPZ (6)	?	?	?	?	?	?	+	+	+	?	?	-			
Perdona	2000	6	MPZ (1)	14	5-region (7)	+	?	+	+	?	?	+	+	+	?	+	-			
Philip	2004	6	MPZ (1)	12	MPZ+LPZ (6)	+	?	+	+	?	?	+	+	+	?	+	-			
Presti	2000	6	MPZ (1)	10	MPZ+LPZ (6)	+	+	?	?	?	?	+	+	+	?	+	-			
Ravery	1998	6	MPZ (1)	10	MPZ (1)	?	+	-	-	?	?	+	?	+	?	?	-			
Ravery	2000	6	MPZ (1)	10	MPZ+LPZ (6)	+	?	+	+	?	?	+	+	+	?	+	-			The cores out of each zone (two corresponding cores from each prostate lobe together) were were fixed and sent separately for histological analysis.
Ravery	1999	6	MPZ (1)	10	MPZ (1)	+	?	?	?	?	?	+	+	+	?	+	-			Poor reporting of test procedures so little detail is available for data extraction.
Reissigl	1997	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	+	+	?	?	?	?	+	+	+	?	+	-			Representativity of patients: In this study only patients with clearly visible prostatic zones in three dimensional ultrasound were included.
Robles	1999	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	+	?	?	?	?	?	+	+	+	?	?	-			
Romagnoli	2002	6	MPZ+TZ (+MLiPZ) (4)	8	5-region (7)	?	?	+	+	?	?	+	+	+	?	+	-			
Rowe	2002	6	MPZ (1)	12	MPZ+LPZ (6)	?	?	?	?	?	?	+	+	+	?	+	-			Qualita assessment based on information available in abstract.
Singh	2003	6	MPZ (1)	12	MPZ+LPZ (6)	+	?	?	?	?	?	+	+	+	?	?	-			Abstract only, hence very few details can be extracted for this study.
Slongo	2003	6	MPZ (1)	12	MPZ+LPZ (6)	+	+	+	+	?	?	+	+	+	?	+	+			
Soramoto	1999	4	MPZ (1)	6	MPZ+TZ (+MLiPZ) (4)	?	?	?	?	?	?	+	+	+	?	?	-			Only English abstract and partly translared full text available.
Sur	2002	10	MPZ+LPZ (6)	24	5-region (7)	?	?	?	?	?	?	+	+	+	+	?	-	?	?	Withdrawals = 15 pts, not included in the analysis. Abstract only, hence very few details can be extracted for this study.
Tan	2001	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	+	?	?	?	?	?	+	-	+	?	+	-			Abstract only, hence very few details can be extracted. 2 additional PZ biopsies taken in only 105 out of 126 patients (selection criteria not described).

Author	year	T1_cores	T1_pattern	T2_cores	T2_pattern	Q1 Spectrum representative?	Q2 selection criteria	Q8 index test (test2) details	Q9 reference test (test1) details	Q10 index test (test2) review bias?	Q11 reference test (test1) review bias?	Q12 same clinical data available?	Q13 uninterpreatable results?	Q14 withdrawals?	Q20 follow-up long enough?	Q21 cores specifically labelled?	Q22 histologic work up	Q-ran1 random sequence	Q-ran2 concealment	Quality comments
Terris	1997	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	+	?	?	?	?	?	+	+	+	?	+	+			
Terris	1997	6	MPZ (1)	6	LPZ (3)	?	+	?	?	?	?	+	+	+	?	+	?			Histologic work up: Only embedding and staining method of the cores reported.
Tokumitsu	2000	6	MPZ (1)	12	5-region (7)	?	?	?	?	?	?	+	+	+	?	+	-			Quality assessment based on information available in abstract.
Traverso	2001	6	MPZ (1)	8	MPZ+TZ (+MLiPZ) (4)	+	+	?	?	?	?	+	+	+	?	?	-			
Tsai	2000	6	MPZ (1)	10	MPZ+LPZ (6)	+	?	?	?	?	?	+	+	+	?	?	-			Abstract only, hence very few details can be extracted for this study.
Vakar-Lopez	2002	6	MPZ (1)	11	5-region (7)	?	?	?	?	?	?	+	+	+	?	?	-			Abstract only, hence very few data could be extracted for this study.
Zhong	2003	6	MPZ (1)	13	5-region (7)	?	?	?	?	?	?	+	+	+	?	?	-			Quality assessment based on data extraction from English abstract.