Features of prostate cancers detected during a prevalence screening round. The Rotterdam experience

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VAN DER KWAST TH H, POSTMA R, HOEDEMAEKER RF, VAN LEENDERS GJLH, SCHRODER FH. Features of prostate cancers detected during a prevalence screening round. The Rotterdam experience. The Canadian Journal of Urology. 2005;12(Supplement 2):16-20.

Introduction: *Prostate-specific antigen (PSA) testing of asymptomatic men may lead to the detection of "minimal" prostate cancers that are less likely to be associated with morbidity or mortality.*

Objective: *To examine the significance of various diagnostic outcomes from needle biopsies of the prostate in an asymptomatic population of men.*

Methods: *Prostatic needle biopsy findings were matched with those from radical prostatectomy specimens using data from the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC). Men, aged between 55 and 75 years, with elevated PSA levels underwent lateralized sextant needle biopsies. In corresponding radical prostatectomy specimens, the tumor categories (minimal, moderate, or advanced) were determined.*

Results: *Prostate cancer was diagnosed in 5.1% of 19,970 screened men, and 31.6% of the men had cancers that were categorized as "minimal." Repeat biopsies performed after initial diagnoses of either isolated prostatic intra-epithelial neoplasia (PIN) or "suspicious for malignancy," detected adenocarcinoma in 12.1% and 36.5% of the men, respectively. In a substudy of 510 men with a benign biopsy outcome 12 months previously, repeat biopsies detected adenocarcinoma in 12.4% of the men. Of men who were subsequently treated with radical prostatectomy, the cancers were classified as "minimal" in 27.8% of the men with previously benign biopsies and in 47.4% of the men with previously suspicious lesions.*

Conclusions: *The chance of finding a "minimal" prostate cancer in an asymptomatic population is substantial and increases when a repeat biopsy is performed following a biopsy with a suspicious outcome.*

Key Words: prostate cancer, screening, minimal cancer, PIN

Introduction

The introduction of the serum prostate-specific antigen (PSA) test as a diagnostic tool has allowed detection of prostate cancer at an early stage, as can be seen from histopathological examination of needle biopsy samples of the prostate. As a consequence, the digital rectal examination (DRE) has lost a great deal of its impact as a diagnostic tool for prostate cancer.[1] Although the biopsy procedure with the contemporary technique continues to be unpleasant and may lead to complications like haematospermia and fever,[2] the threshold for this procedure has been lowered considerably compared to the time when thick, 14-gauge needle biopsies were employed. In part as a consequence of the large increase in the number of men subjected to a needle biopsy of the prostate — prompted by finding an elevated serum PSA level — in most Western countries the incidence of prostate cancer has increased substantially, while mortality from this cancer has remained unchanged, or tended to decrease in some countries.[3]

Since needle biopsies of the prostate are generally not targeted at a suspect lesion, the chance to detect a cancer is dependent on the size of the prostate

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cancer in relation to the prostate volume. In addition, the quality of the needle biopsies and the tissue processing by the pathology laboratory may also influence the chance of detecting a cancer.[4] A review of a series of negative prostate biopsies derived from seven European screening centers estimated that the percentage of suspicious lesions or prostate cancer diagnoses missed by the pathologist was about 5%.[5] It may therefore be anticipated that after a negative (or benign) biopsy outcome, repeat biopsies will lead to the identification of a prostate cancer in some cases. The increase in the number of diagnostic needle biopsies of the prostate has led to the identification of lesions whose clinical significance may not always be very clear.[6] Examples are lesions suspicious for adenocarcinoma or for the precursor lesion of prostate cancer, i.e., prostatic intra-epithelial neoplasia (PIN). In these cases, multiple rounds of repeat biopsies may be performed in order to demonstrate the presence of an adenocarcinoma. The clinical relevance of these cancers detected after repeat biopsies remains unclear, however. Based on the clinical and pathological findings from the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC),[7] we will highlight the significance of the various prostate biopsy diagnoses.

Material and methods

Population characteristics

In the Rotterdam section of the ERSPC, 42,376 participants, aged 55 to 75, were randomized to a screening arm (n=21,210) or control arm (n=21,166). In the first screening round, which took place from November 1993 to December 1999, a total of 19,970 men were screened. The database of the Rotterdam section of the ERSPC contains pathologic findings (tumor volume, differentiation grade, and pathologic stage) of prostatectomy specimens of screened participants. The screening consisted of determination of serum PSA levels, and, before May 1997, transrectal ultrasonography (TRUS) and DRE results. A sextant needle biopsy procedure was prompted by a PSA > 4 ng/mL, or positive DRE or TRUS tests. Since analysis of earlier results revealed a poor predictive power of DRE and TRUS, starting in May 1997, these tests were omitted, and a PSA cutoff value of > 3.0 ng/mL was employed. This change did not influence the detection frequency of prostate cancer.

A small group of 510 men with an initial negative needle biopsy prostate cancer diagnosis underwent another sextant needle biopsy procedure one year after the initial screening. After an interval of 4 years, men in the same cohort who had not reached the age of 75 years and were not yet diagnosed with cancer were again screened for prostate cancer.[7]

Categorization of prostate cancers

Radical prostatectomy specimens were inked and serially sectioned at 4-mm intervals and totally embedded in paraffin blocks. Two uropathologists (THvdK and GJLHvL) determined the pathologic stage (TNM 1992 classification) and Gleason score of the samples. Tumor volume was measured by morphometry, as described previously.[1] After the first screening round, radical prostatectomy was performed in 401 patients. Tumors were categorized according to a previously reported arbitrary model that was based on histopathological tumor characteristics,[8-9] comprising three categories: 1) minimal tumor: tumor < 0.5 ml, containing no Gleason pattern 4 or 5, and organ-confined; 2) moderate tumors: tumors ≥ 0.5 ml, or organ-confined tumor containing any amount of Gleason pattern 4 or 5, or tumor with extra-capsular extension without Gleason pattern 4 or 5; or 3) advanced tumors: tumors with extra-capsular extension containing Gleason pattern 4 or 5, and seminal vesicle invasion or bladder neck invasion.

Results

Prostate biopsy diagnosis of adenocarcinoma

During the prevalence screening round at the Rotterdam section of the ERSPC, prostate cancer was detected in 5.1% of participants. Histopathologic examination revealed that 81.6% of men treated by prostatectomy had "minimal" or moderate (potentially curable) prostate cancer; 31.6% had "minimal" cancer with its highly favorable features Table 1 and Figure 1.

Negative prostate biopsy outcome

A negative prostate biopsy result includes the pathology diagnoses of "no abnormalities, (granulomatous) inflammation, hyperplasia and/or atrophy." In a subgroup study, 510 men with a PSA level > 4 ng/mL and/or abnormal TRUS or DRE and a negative prostate biopsy outcome underwent a repeat sextant biopsy one year later[7] and in 12.4% (n=63) of the men a diagnosis of adenocarcinoma was reported. Eighteen of these men were treated by radical prostatectomy; in five men (27.8%) a minimal cancer was found, while five men had an advanced cancer. In the second screening round 4 years later,

TABLE 1. **Number (%) of men and categories of prostate cancers detected***

Prostate cancer category	1st (prevalence) screening round	Cancer after 1-year interval; negative biopsy in 1st round	Cancer after 4-year interval; negative biopsy in 1st round	Cancer after 4-year interval; no previous biopsy	Cancer after repeat biopsy for suspicious lesion
Minimal	122 (31.6)	5 (27.8)	14 (45.2)	55 (41.7)	9 (47.4)
Moderate	193 (50.0)	8 (44.4)	15 (48.4)	58 (43.9)	9 (47.4)
Advanced	71 (18.4)	5 (27.8)	2 (6.5)	19 (14.4)	1 (5.3)
All categories	386	18	31	132	19

*The 1st screening round from the Rotterdam section of the European Randomized study of Screening for Prostate Cancer screened 19,970 men, and 401 men had prostatectomies. In a substudy, 510 men with negative prostate needle biopsies in the 1st round underwent repeat biopsies 1 year. The entire cohort was rescreened at 4 years after the initial screening (n=12,520 men).

the proportion of minimal cancers increased significantly ($p < 0.03$). However, no significant difference was observed between men with a negative biopsy outcome during the prevalence screening round (n=31) compared to men who had never been biopsied before (n= 132) Table 1.

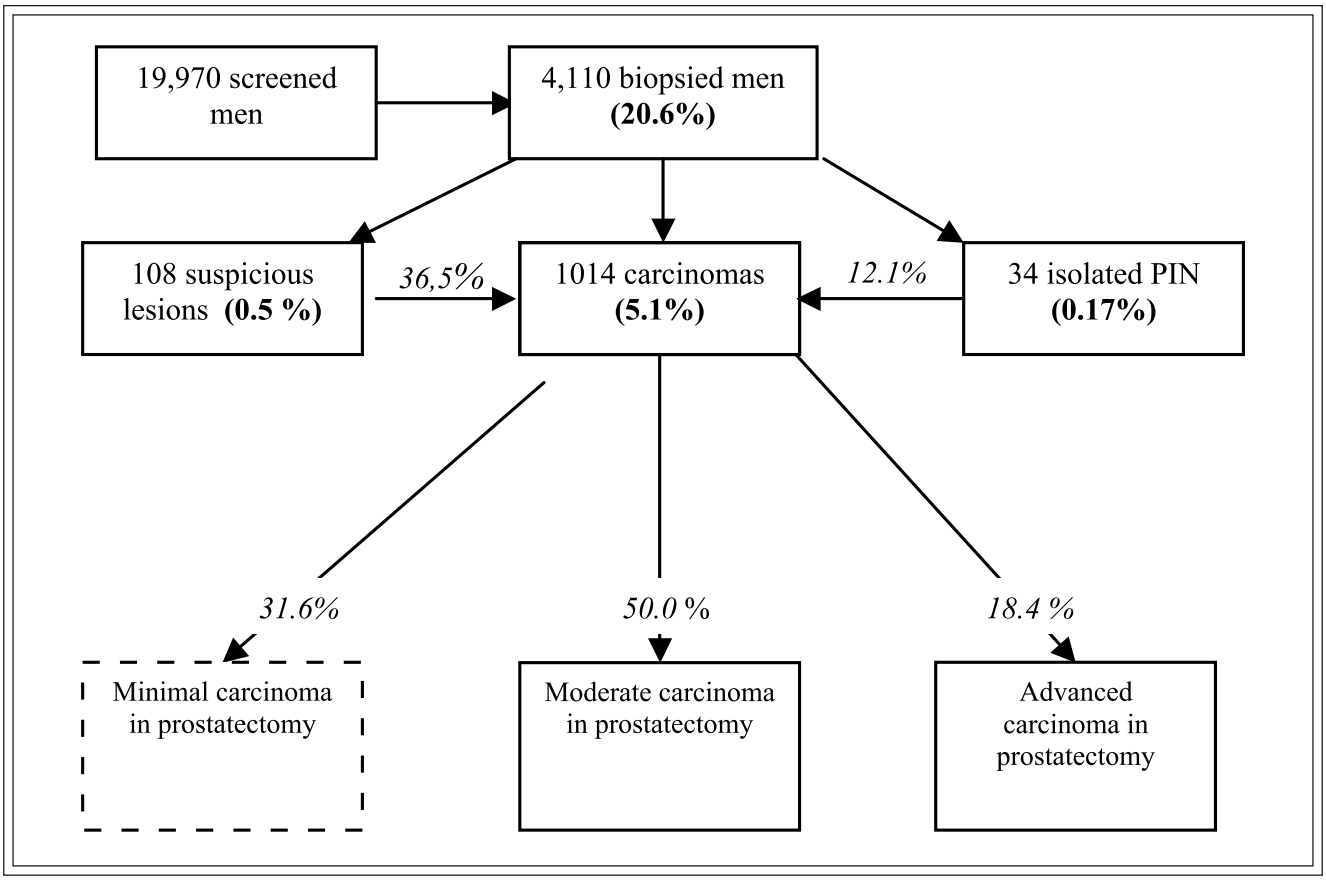

Figure 1. Flow chart of prostate screening results during the prevalence screening round. From the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC).

Prostate biopsy with a diagnosis suspicious for cancer

If – according to the pathologist – a lesion found in a needle biopsy sample shows some features reminiscent of malignancy, but insufficient features to warrant a definite diagnosis of cancer, the lesion is reported as "suspicious for malignancy." In the ERSPC prevalence screening round, these lesions were found in 108 (2.6%) of the 4110 sextant needle biopsy samples Figure 1. Repeat biopsies, generally done within 6 weeks, from the same location, yielded a definite diagnosis of adenocarcinoma in 36.5% of the men.[10] A radical prostatectomy was performed in 19 men, and the proportion of minimal cancer was 47.4%. Only in one man was an advanced cancer detected in the radical prostatectomy specimen Table 1.

Prostate biopsy diagnosis of high-grade PIN

During the prevalence screening round of the Rotterdam section of the ERSPC, isolated PIN was found in 34 of 4110 biopsy samples (0.8%).[10] In follow-up biopsies after a diagnosis of PIN, an adenocarcinoma was detected in 12.1% of the men Figure 1. This percentage is not really increased as compared to the percentage of cancers detected after an initial negative biopsy outcome (see above). In 7 of 9 men who underwent a radical prostatectomy a minimal cancer was found.

Discussion

The discrepancy between the incidence of prostate cancer detected from autopsy studies (30%-50%)[11,12] versus the incidence from the prevalence screening round of the Rotterdam section of the ERSPC (5.1%) suggests that a lot of cancers may be missed by a screening procedure based on PSA testing in combination with a sextant needle biopsy procedure. Several authors reported that ex vivo sextant needle biopsies taken from prostatectomies missed prostate cancer in about 30% of cases.[13,14] These observations led to recommendations to increase the number of needle biopsy samples from the usual 6 to 7 (sextant needle) biopsy samples to for example, 10 to 14 biopsy samples.[13] Arguments against trying to find all cancers are the risk of overtreatment in the case of very small cancers and empirically, the relatively low chance of detecting an advanced cancer during the screening interval or at the second screening round after 4 years.[15] Other reasons to be somewhat conservative in the early detection of prostate cancers are the relatively high age at which a prostate cancer is detected in association with age-related comorbidity and the long leadtime of about 9 years from the time cancers are detected by screening until the time of death.[16] We should remember that, as yet, no definite evidence has been provided for the actual reduction of prostate cancer mortality or the improvement of quality of life by prostate cancer screening.

The reported frequency of 0.8% of isolated PIN in the ERSPC study is low compared to data from large biopsy series in the literature that report various frequencies up to 4.1%.[10] The incidence reported in our series was determined without reviewing cases reported as benign; therefore, the actual PIN incidence might be higher than reported here. Other explanations for the lower PIN incidence in our study include: 1) in a general population-based screening sample, lower PIN incidence rates may occur compared to that in a population referred by urologists; 2) "only" sextant biopsies were performed, which represent a limited sample size; and 3) tissue preparation/staining variables may influence the detection of isolated PIN. The detection of a similar percentage of prostate cancer in repeat biopsies compared to the percentage observed if no evidence of malignancy was reported in previous biopsies detracts somewhat from the clinical relevance of isolated PIN. A recent paper by Bishara et al[17] also found a limited predictive value of isolated PIN for detection of prostate cancer in subsequent prostate needle biopsies (21% versus 14%). In contrast, other, particularly older, studies mentioned higher percentages of adenocarcinoma (up to 58%) in follow-up biopsies after a diagnosis of PIN, although comparison with repeat biopsies after an initial negative biopsy outcome are lacking in most studies.[10,17] With regard to the pathological features of the prostate cancers detected after an initial isolated PIN diagnosis, our data suggest that the majority (7 of 9 examined cases) represent "minimal" cancers.

After a diagnosis of suspicious, but not definite prostate cancer — also referred to as atypical small acinar proliferation (ASAP) — in 2.6% of the biopsied men, repeat biopsies yielded a definite diagnosis of prostate cancer in a much higher proportion of men (36.5%) as compared to men with a previous diagnosis of isolated PIN (12.1%). This percentage fits well within the range reported in literature.[8] More recently, however, we noted that during the second screening round, the predictive value of suspicious lesions for finding a subsequent prostate cancer was reduced to about 17%.[18] Probably, the further downsizing of prostate cancers during subsequent screening rounds precludes their ready detection in repeat biopsies for suspicious lesions. The observation that about 50%

of the cancers detected after a suspicious lesion represent a minimal cancer (i.e., a volume <0.5 ml) would be in line with this view.

Repeat biopsies performed within 1 year after an initially benign sextant needle biopsy result lead to detecting prostate cancer in about 12% of men. The same proportion of these cancers had the favorable features of a "minimal" cancer compared to men diagnosed with cancer during the prevalence screening round. In contrast, men with a cancer detected during the second screening round had an increased chance of "minimal cancer," irrespective of their biopsy history in the prevalence screening round. Why cancers detected within 12 months after an initially benign biopsy do not show favorable tumor characteristics compared to cancers detected in the prevalence screening round remains unclear. One possibility is that in this subset of patients a treatment bias occurred, with a selection of adverse features for those to undergo prostatectomy.

Our data suggest that in an asymptomatic population aged between 55 and 75 years, the chance of finding a "minimal" prostate cancer by PSA testing and the sextant needle biopsy procedure is considerable. This chance even further increases in cases where a repeat biopsy is being performed for a suspicious lesion. Pretreatment identification of such "minimal" carcinomas on the basis of needle biopsy findings and clinical parameters would have saved these men an immediate prostatectomy or radiotherapy. Unfortunately, the correlation is too low between, on the one hand, the extent of cancer involvement and tumor differentiation grade in needle biopsies and, on the other hand, tumor volume and differentiation grade of the tumor in the prostate. This hampers a prediction of the presence of a "minimal" cancer in individual patients.[19] □

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