TOPIC PAPER

Overdiagnosis and overtreatment of early detected prostate cancer

C. H. Bangma · S. Roemeling · F. H. Schröder

Abstract Early detection of prostate cancer is associated with the diagnosis of a considerable proportion of cancers that are indolent, and that will hardly ever become symptomatic during lifetime. Such overdiagnosis should be avoided in all forms of screening because of potential adverse psychological and somatic side effects. The main threat of overdiagnosis is overtreatment of indolent disease. Men with prostate cancer that is likely to be indolent may be offered active surveillance. Evaluation of active surveillance studies and validation of new biological parameters for risk assessment are expected.

Keywords Rationale for screening · Overdiagnosis · Overtreatment · Prostate cancer · Active surveillance

Introduction

What is the rationale for screening?

Screening for diseases, especially cancer, has become part of modern medicine. Screening for breast, cervical and colorectal cancer is already normal practice in some countries, and will probably become routine in other countries in the future. Screening for prostate, melanoma and lung cancer are subject to ongoing studies [1–5]. The rationale behind screening is simple: to detect cancers at an early stage, when they are still curable. Screening is currently performed using one of the three methods: mass screening (i.e. large scale screening of an entire population), selective screening (i.e. screening of high-risk populations) or opportunistic screening (e.g. incorporated as part of a medical consultation). Diagnostic testing differs from screening because it attempts to identify the disease in the presence of symptoms, while screening is offered to symptom-free individuals.

In any population screened for cancer, four basic groups of patients exist: those diagnosed with cancer who would not have developed cancer symptoms during their lifetime (overdiagnosis); those diagnosed with cancer at an early stage that might otherwise have led to symptoms and/or the need for more aggressive curative treatment; those diagnosed with cancer at a curable stage with aggressive disease that might otherwise have progressed to metastatic disease at the time of diagnosis; and those whose cancer is diagnosed by screening at the same stage as it would have been diagnosed through clinical routines, and that involves cancers that are too late for curative therapy. Ideally, screening should reduce the number of patients in the fourth group (that cannot be cured), and increase those in the second and third group. The window of opportunity for decreasing cancer-mortality by screening for cancer lies with the second and third group. Randomized clinical trials, considered the gold standard for the evaluation of a screening test, have to show how sizeable the window of opportunity is. The difference between the first group and the second is however not always clear at the time of initial diagnosis. Any screening procedure carries a risk of overdiagnosis and overtreatment, which should be balanced against the benefits for those in

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which the cancers are diagnosed at a curative stage. Whether this balance is justifiable depends on more than mortality differences of randomized study groups only, but also on quality of life issues measured against the cultural background of the population studied.

Incidence

Does screening influence prostate cancer incidence?

Since the potential value of PSA for the early detection of prostate cancer was described in the early 1990s, both prostate cancer incidence and mortality rates have changed profoundly [6]. Between 1989 and 2003, for example, the age-standardized incidence rate of prostate cancer increased by 48.4% in The Netherlands (reaching an incidence of 93.2 cases per 100,000 men). Based on rates from 2001 to 2003, 17.1% of U.S. men born today will be diagnosed with cancer of the prostate at some time during their lifetime [http://www.cancer.gov]. It is now the most frequently diagnosed non-cutaneous cancer, with 225,000 new cases reported each year in Europe alone [7]. This increase of incidence suggests that this is due to the detection of cancers in the first three groups described above. This is supported by the reports on autopsy studies. These autopsy studies have revealed that histologic prostate cancer occurs in an even larger proportion of men compared to the screening incidence: up to 55% of men in their fifties, and 64% of men in their seventies have prostate cancer diagnosed at autopsy, while only 5–10% are detectable in a screening setting during life [8].

A number of influences might have contributed to the increase of cancer diagnosis over the last decades, apart from the structured screening studies that have been initiated at various places. First, the PSA thresholds for biopsy appears to have been reduced gradually in some areas of the world due to the detection of significant cancers in the low PSA range [9]. Most guidelines, however, still mention the traditional cut-off of 4 ng/ml as an indication for biopsy. Secondly, an increase in the number of core samples per biopsy have been advocated, based on the observation that more cancers are diagnosed when more biopsies are taken. Thirdly, awareness of prostate cancer within the general population has increased stimulated by the information obtained predominantly from the urologic profession [10]. If these current trends continue, the number of living men diagnosed with prostate cancer will increase even further [11].

Mortality

What happens to prostate cancer mortality by screening and detecting indolent tumors?

Despite this rising incidence, the age-standardized prostate cancer mortality rate has decreased in many countries around the world with or without early detection programs. In The Netherlands, for example, rates fell by 11% between 1989 and 2003, to 28.4 deaths per 100,000 men or 2,349 in total [http://www.cancer.gov]. It is however unclear whether the stage and grade migration observed in screening studies results in a reduction in the mortality, although case-control studies with conflicting results are available [12–14]. A decrease of mortality shown in randomized studies would form a strong argument in favor of population screening.

Screening results in the more frequent detection of small volume, low grade and organ confined prostate cancers, which are diagnosed earlier in their course [6, 15]. Many of these tumors have the histological characteristic of autopsy tumors, that is, tumors that have not become symptomatic during life [16]. They have been called indolent or clinically insignificant cancers. Various definitions of clinically insignificant tumors have been designed based on the characteristics of the autopsy studies, of which the Epstein definition is widely known [17]. Detecting such tumors will increase the detection frequency of cancer, but it is unlikely that they will influence the prostate cancer specific mortality, as they do not alter the course of life.

Early diagnosis

Screen detected tumors are diagnosed more early

Screen detected tumors are not only diagnosed more often, but can be expected more early during their natural course. Lead-time is defined as the time period from detection by a screening procedure to the time of diagnosis in absence of screening due to symptoms. If the patient dies during the lead-time period of the tumor, the lead-time is indefinite and therefore equal to overdiagnosis.

Early detection by PSA advances prostate cancer diagnosis in time (i.e. lead time) [18]. For men aged 55–75 years lead time amounts to 12.3 years in a screening setting [19]. The lead-time is likely to be shorter for aggressive cancers and longer for indolent ones. Early detection also causes a significant stage shift towards more locally confined and less aggressive cancers [20]. The long lead-time, stage reduction and natural history data cited above indicate that for properly selected cases there is a long 'time-window' during which obser-

vation is safe without losing the opportunity for cure. This is supported by evidence from nomograms, prognostic tables, and by the only available randomized study of observation against radical prostatectomy [21].

The impact of overdiagnosis and unnecessary treatment and of its side effects on patient health is also unclear; however, application of a mathematical model (the Miscan model) on data from the ERSPC has shown that, in an annual screening program for men aged 55–67 years, 56% of diagnosed cases would constitute instances of overdiagnosis [22]. If this estimate proves to be realistic (as it appears to be the case), nationwide screening programs may not be acceptable using the present screening regimens, even if benefits in terms of mortality reduction were shown. Research aimed at the development of more selective screening tools is therefore very important.

The natural course of screen-detected cancers

The current knowledge of the natural history of prostate cancer is mainly based on clinically detected cases, diagnosed by disease-related symptoms, or coincidentally at the time of unrelated symptoms of the urinary tract. Natural history data on screen-detected cases of prostate cancer will be created as a result of the large ongoing screening studies worldwide in which tumors might have been treated without invasive therapy [1]. Most studies show histological and cytological grade to be the most important prognostic variable [23, 24]. There is a steep decline in the 5-, 10- and 15-year cancer-specific survival with increasing grade. Most prostate cancer cases diagnosed with present diagnostic techniques fall into the moderately differentiated group (grade 2, Gleason 6), of which the cancer-specific 10–15-year mortality is 18–30%. This is even lower in the group of prostate cancers diagnosed with grade 1 and 2 or Gleason 4–6, and there are subgroups of patients who are not at risk of dying from prostate cancer even within 15 years. Overall mortality is then determined by comorbidity. The majority of these men are currently treated for their prostatic disease with invasive procedures, which might not be needed. Adequate prediction of the outcome of comorbid diseases would be of great support in predicting the outcome of the prostate cancer patient.

Overdiagnosis

Overdiagnosis and overtreatment, what does it mean?

During recent years, increased interest has risen to the possibility that increased detection of prostate cancer may lead to the diagnosis of cancers that rather should not have been diagnosed, and certainly should not have been treated, as their detection and subsequent treatment is unlikely to benefit patients, or even might harm them. Related to this, the terms 'overdiagnosis' and 'overtreatment' are being used. So, when is prostate cancer overdiagnosed?

By using the clinical definition of overdiagnosis, that is diagnosing tumors that would otherwise remain clinically unrecognized until the individual died from other causes, it is clear that this definition can only be applied in retrospect in the evaluation of studies. There are currently no clinical or biological parameters that can identify such tumors 100% adequately at the time of diagnosis. By studying the natural course of prostate cancer, and comparing autopsy results with findings from screened populations, clinical and histological parameters can be identified that predict indolent tumors best. Those indolent tumors are likely to be only a subset of the tumors that are overdiagnosed in retrospect.

Overdiagnosis is predominantly being associated with early detection or screening programs. Overdiagnosis appears to be especially harmful when it results in invasive treatment of the tumors that would unlikely to be harmful. This is called overtreatment.

Overdiagnosis occurs when screening detects small tumors that would otherwise remain clinically unrecognized until the individual dies from other causes. Such tumors are predominantly found in the low PSA ranges. Unfortunately, an unknown number of biologically more aggressive cancers may hide between the larger number of detectable tumors with favorable stages. Though some of the aggressive tumors can be diagnosed by adverse histological criteria such as high Gleason score in the biopsy, some of these features might be missed due to the heterogeneity of prostate cancers and their representation in the biopsy sampling. This might justify the amount of overtreatment that has been practiced in various areas of the world. Overtreatment is thus defined as unnecessary invasive treatment with respect to the outcome of the natural course of the tumor in combination with its host.

One can wonder what number needed-to-treat to prevent one prostate cancer death we are prepared to accept. Based on the Swedish randomized trial of radical prostatectomy versus watchful waiting [22], the Connecticut observation series [15], and the Toronto active surveillance experience [25], a number needed to treat analysis of the benefit of radical treatment of all newly diagnosed favorable-risk prostate cancer patients, compared with a strategy of active surveillance with selective delayed intervention, has been
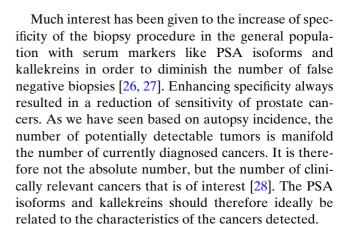
presented by Klotz [25]. This suggested that approximately 73 patients will require radical treatment for each prostate cancer death averted. This translates into a 3- to 4-week survival benefit, unadjusted for quality of life. If any, the number of life-years gained will be small, because of the fact that prostate cancer is a disease of old age. This should be contrasted to the side-effects of all applied treatments. As a minimum, the number of men needed to treat should be higher than the number of men dying from intervention related causes.

Informed decision making, reduction of unnecessary prostate biopsies

The increasing number of diagnostic procedures and subsequently of prostate cancer diagnosis in various areas of the world is partly fed by an increased awareness of prostate cancer and the anxiety raised of suffering from a devastating disease at the end of life. Men should ask themselves if they are at specific risk for having prostate cancer, and if they want to follow the step wise procedure of PSA testing, urologic investigations, prostate biopsies, and potential treatment. Balanced information regarding this procedure and its consequences should be offered to every man considering prostate testing. Validated information (that is: well understandable text that delivers the information that is required) has been made available in several countries around the world, and it has been shown that such information reduces the number of men who initially wanted to be screened.

Based on population data it is possible to provide risk assessments for every step of the screening procedure. Such assessments produce an individual risk calculation based on relevant risk parameters. This might support patients and doctors in their decision to follow or refrain from further steps, dependent on their interpretation of the risk calculated. At the time of cancer diagnosis, it may provide information on the risk of the presence of an indolent tumor, as discussed above.

Current risk calculators have incorporated family history, age, micturition complaints, PSA, DRE, TRUS results, and histologic features of the prostate biopsies into their assessment. With an increasing number of relevant parameters, the level of predictive accuracy is enhanced. It is likely that new parameters might be added once tested in population-based biorepositories. Candidate parameters therefore obviously are serum and urine markers for the early diagnostic steps, and histologic markers at the time that biopsies have been taken.

Much interest has been given to the increase of specificity of the biopsy procedure in the general population with serum markers like PSA isoforms and kallekreins in order to diminish the number of false negative biopsies [26, 27]. Enhancing specificity always resulted in a reduction of sensitivity of prostate cancers. As we have seen based on autopsy incidence, the number of potentially detectable tumors is manifold the number of currently diagnosed cancers. It is therefore not the absolute number, but the number of clinically relevant cancers that is of interest [28]. The PSA isoforms and kallekreins should therefore ideally be related to the characteristics of the cancers detected.

Screening efficiency

A small number of studies already have provided evidence that supports strategies to reduce the number of screens in the general population. Such strategies will inevitably lead to the reduction of overdiagnosis of prostate cancer.

Information obtained from population based screening studies illustrates that the absolute value of serum PSA is related to the proportion of detectable carcinomas in subsequent screening rounds. Data from the ERSPC as well as from the PLCO [29, 30] showed that men with a PSA less than 1 ng/ml did not develop invasive cancer over the time period of more than 5 years of repeated check-ups. In the Rotterdam site of the ERSPC, 1703 men with an initial PSA of less than 1 ng/ml men were followed during two consecutive 4 year screening rounds. Eighty percent of men attended the second screening round, and 77% the third round. In total, only 8 cancers were found in 47 prostate biopsies on the indication of PSA of >3 ng/ml. In the PLCO screening, every 5 years for baseline PSA less than 1 ng/ml and every 2 years for PSA 1–2 ng/ml could result in a 50% reduction in PSA tests and in less than 1.5% of men missing earlier positive screens.

In men who were enrolled onto a cardiovascular study in Sweden, 21,277 men aged <50 years old were assessed over a period of more than 20 years starting between 1974 and 1986. Two decades later, 498 (2.3%) were eventually diagnosed with prostate cancer (outside a structured screening procedure). In retrospect, the level of serum kallikreins (hK2, total PSA, and free PSA) at baseline and thereafter were strongly associated with emerging prostate cancer. This supports the idea of risk stratification for screening on prostate cancer in an early age, that is during the fourth decade of life. Men at low risk may refrain from frequent serum testing for long periods of time based on their individual risk assessment that incorporates the information

obtained from currently available and newly validated parameters.

Overtreatment

Side effects of treatment are substantial

Treatment for prostate cancer may involve surgery, external beam radiation therapy, brachytherapy, high intensity focused ultrasound (HIFU), watchful waiting, active surveillance, chemotherapy, cryosurgery, hormonal therapy, or combinations. The most frequently applied treatments for organ confined prostate cancer are radical prostatectomy, external beam radiotherapy and brachytherapy.

Although, severe or life-threatening complications with radical prostatectomy are rare, the adverse effects of greatest concern are damage to the urinary sphincter and erectile nerves (nervi erigenti), resulting in urinary incontinence and impotence, respectively. Complete incontinence is uncommon after radical prostatectomy, although a significant number of men experience some degree of stress-urinary incontinence [31–33]. In the Prostate Cancer Outcomes Study, a population-based study of 1,291 men who underwent radical prostatectomy for localized prostate cancer and were followed for 2 years, 1.6% reported no urinary control at 24 months following surgery (compared with 0.7% at baseline prior to surgery), while 7 and 42% reported frequent and occasional leakage, respectively (compared with 2 and 9% at baseline) [32]. Age had an impact on the degree of incontinence; 14% of men aged between 75 and 79 years experienced the highest level of incontinence compared with 0.7–4% of younger men. In the Prostate Cancer Outcomes Study, 42% of men reported that sexual performance was a moderate to large problem at 24 months (compared with 18% at baseline); 60% were not able to have erections firm enough for sexual intercourse (compared with 16% at baseline) [32]. At 24 months postoperatively, men over the age of 60 were more likely to be impotent than younger men (78–85 vs. 61%, respectively).

Complications after external beam radiotherapy include bladder irritation (urgency, pain, frequency) in up to 5% of men, and impotence in 40–50% [34]. In contrast to surgery, these complications tend to increase over time. The reported incidence of radiation proctitis ranges from 2 to 39%, depending upon the definition used, and the dose field, and technique of radiotherapy. Prostate inflammation and swelling can occur acutely following brachytherapy, suggesting that men with significant urinary symptoms or a large

prostate are not good candidates. Urinary retention can be severe enough to require self-catheterization; transurethral resection to improve micturition is contraindicated until a substantial portion of the radioactivity (usually five half-lives) has dissipated because of the risk of incontinence and radiation risks to the surgeon and pathologist. Later complications include irritative voiding symptoms, urinary retention, rectal urgency, bowel frequency, rectal bleeding or ulceration, and prostatorectal fistulas [35–37]. The incidence of erectile dysfunction ranges from 14 to 52%, depending on whether it is physician- or patient-reported.

It is obvious that invasive treatment may influence the quality of life of men with prostate cancer and their families substantially. But so does a potential threat of prostate cancer that is not actively treated or not even diagnosed yet. It is unlikely that quality of life studies will be able to indicate the best balance between these points of view for management decisions on an individual patient level.

Active surveillance as alternative to invasive treatment

Because not all cancers diagnosed require treatment, one of the major challenges for the future is to determine which diagnosed cancers should be treated, and which can be managed by active surveillance. Active Surveillance manages selected men with prostate cancer expectantly with curative intent. This means men are carefully selected and subsequently actively observed in order to have the possibility to offer them deferred curative treatment once the tumor seems to progress. Active surveillance should be clearly differentiated from watchful waiting. Watchful waiting entails a strategy for all men who are managed expectantly, whereas active surveillance focuses on men for whom therapy is delayed until the tumor becomes progressive and curative treatment can be offered. This offers an attitude of active control over the cancer diagnosed for patients and their doctors. The stage migration that screening provides has resulted in an over-representation of low-risk cancers. Therefore, studies which validate monitoring algorithms in active surveillance regimens are ongoing [38].

Risk stratification for indolent disease

Over the last decade, a number of nomograms have been composed to predict the presence of an indolent cancer [39, 40]. The identification of indolent cancers was strongly based on histologic information of prostate biopsies, and power of Gleason score as a predictive parameter for aggressiveness of prostate cancer

was unsurpassed. As a single serum parameter at the time of diagnosis, the level of PSA contributed most to prognosis.

These nomograms were based on extensive clinical series. A new nomogram recently appeared based on information obtained from a screening series of the general population [41]. Screening series differ from clinical studies, as the incidence of indolent cancer is almost 50% compared to maximal 20% in multicentred clinical series. With the use of the nomogram, at a 70% probability cut-off, at least 69% of all indolent cancers would be diagnosed as such, and be treated with active surveillance.

Conclusions

It is still too early to say whether population-based prostate cancer screening is a useful tool with regard to cancer mortality. We must wait until the results of ongoing prostate cancer screening trials are available. Until then, opportunistic screening should not be encouraged and those men who do want a PSA test should participate in carefully designed, balanced information program. Even if PSA screening is found to reduce prostate-cancer-specific mortality, levels of overdiagnosis may remain unacceptable for population-based screening.

To reduce overdiagnosis in a screening setting, markers are needed that reduce the risk on a positive prostate biopsy, increasing the specificity of this procedure. Men from the age of forty, as well as their advising doctors, need instruments to reduce their doubts and anxiety of the potential presence of a prostate cancer. This, together with balanced information about the benefits and risks of the individual outcome of screening procedures, might induce a more selective and step-wise screening action. Risk assessment, incorporating the main determinants known for the presence of prostate cancer from the age of 50, such as age, family history, and micturition complaints, should form the base of an individual screening approach. Objective values of serum markers might enhance the accuracy of such of risk predictors.

Various efforts are performed to find new markers in the proteome and genome of blood and urine. Based on large and longitudinal serum collections of men diagnosed with prostate cancer in screening settings, the EC-sponsored P-MARK consortium evaluates candidate markers as prognostic tools [42].

Until alternative screening tools are found, PSA will continue to be used, and overdiagnosis will remain an unavoidable drawback of prostate cancer screening. The current challenge is to ensure that in the still growing numbers of men diagnosed with prostate cancer world-wide, overdiagnosis does not result in over-treatment. To this end, research efforts presently focus on clarifying which cancers can be managed through active surveillance.

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