Early detection of prostate cancer. What do we tell our patients?

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Introduction: *Early detection of prostate cancer is possible; overdetection of early disease that may never surface clinically during a lifetime is likely. On the other hand, early detection measures will detect life-threatening disease of which some maybe amenable to cure, while otherwise it would kill the patient. Proof of effectiveness of early detection is unavailable. Those who decide to be screened and those who decide not to be screened take risks that are difficult to balance against each other. How do we deal with this situation? What do we tell our patients?*

Discussion: *Ongoing randomized studies are likely to produce definitive answers on the question of whether screening will save men from prostate cancer deaths within a few years. The trials will also provide answers to the optimal way of screening and to the question of how to avoid overdiagnosis and treatment. In the meantime, however, men who are considering to undergo testing have a difficult decision to make. Our profession is obliged to provide assistance. The information provided unfortunately at this time cannot be the simple message: if you undergo testing your cancer will be detected early and be curable, so you will resolve the problem. It is necessary to stress the potential benefits and also the downside of testing. Elements of such information are provided in this article. Benefits may include the reassurance resulting from a normal test result, the early diagnosis of aggressive and still-curable cancer, and the avoidance of the consequences of advanced prostate cancer such as the occurrence of metastatic disease. The downside includes the possibility of missing prostate cancer and providing a false reassurance, the fact that screening may lead to unnecessary anxiety and medical tests when no cancer is present, and the fact that it may detect slow-growing cancer that may never cause any symptoms or shorten lifespan. All treatments have side effects to which men will be exposed, even those who do not have life-threatening cancer. In addition, there is no certainty that treatment will be successful.*

Conclusion: *In the present situation, it is important to emphasize to patients that capabilities are being developed to identify those prostate cancers that may not cause any harm and to exclude them from immediate treatment. This recent development is a very important aspect for those who consider to be tested outside ongoing trials.*

Key Words: prostate cancer, detection, testing, screening

Introduction

There is ample proof that the use of prostate-specific antigen (PSA) as a screening test will lead to an important shift of prostate cancers detected clinically towards those with more favorable stages. Much has been learned about this since the initial publications by Catalona.[1] Still, our knowledge is incomplete, and the use of PSA as a screening test remains controversial.[2] We still do not know the optimal way in which a PSA test might be used to detect prostate cancer, and it remains unresolved whether or not screening for prostate cancer will decrease mortality from this disease. Randomized studies to investigate this are ongoing and approaching completion.[3,4] In the meantime, in a situation of uncertainty, PSA testing cannot be refused to well-informed men who wish to be screened and accept the potential uncertainties and disadvantages of testing.

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Wait for evidence from randomized trials?

In this context, a brief review of the ongoing studies seems warranted. The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial has recently issued interim reports.[5,6] These mainly concentrate on screening test performance characteristics, which have been subject of intense discussion. The trial started in 1994, and results of the prostate arm are not expected before conclusion of a follow-up of up to 13 years after recruitment.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) has issued extensive publications, which can be retrieved from their website at www.erspc.org. The ERSPC trial was initiated in 1993 in the Netherlands and Belgium. Six other European countries joined in subsequent years. The main endpoints of the ERSPC trail are the demonstration of differences in prostate cancer mortality, prostate cancer morbidity, quality of life, and quality-adjusted life years (QALYs) between the screening and control arms. Screening intervals vary between 2 and 4 years depending on the countries involved (Belgium, Finland, France, Italy, Netherlands, Spain, Sweden, and Switzerland). Study power considerations are based on showing a 20% or 25% difference in prostate cancer mortality for the core age group of 55-70 years.[7] Several countries also recruit men aged 50 to 55 and 70 to 75 and this data will be included in additional analyses. The study's power calculation allows a 20% contamination rate and corrects for non-compliance rates found per country. At the time of the last reporting to the ERSPC datacenter in October 2005, about 250,000 men had been randomized, which rises to almost 268,000 men when the latecomer France is added. The median follow-up is about 6 years. More than 7,500 prostate cancer cases have been diagnosed, a detection rate of 4.1%, and 12.5% of these men have died so far. In almost 30% of the time, an external review confirmed that prostate cancer was the cause of death. The Data Monitoring Committee of the ERSPC study has carried out a first interim analysis of data up to the end of 2002. Their advice was to continue the study.

If the original power calculations are applied, in 2008, a 25% difference in prostate cancer mortality for the core age group should be detectable with a power of 80% or higher. If it is necessary to rely on cancer registry data, this will be delayed until the end of 2009. Recent knowledge on the natural history of locally confined disease suggests that a longer follow-up may be necessary.[8-10]

While the randomized studies are likely to produce the level 1 evidence that is necessary to convince healthcare suppliers to introduce prostate cancer screening around the world, other evidence — epidemiological data from areas where screening is prevalent, data from a number of case-control studies, and information coming from the so-called "Innsbruck study"[11] — are suggestive that screening has an affect on prostate cancer mortality. In this situation, and even in the case of a negative outcome from the ongoing randomized studies, there will be men who wish to be tested for prostate cancer. The simple conclusion that the availability of early detection will also lead to individual benefit is so convincing that the subject of this article, "What do we tell the patient who wishes to be screened?" will remain an important issue.

Epidemiological changes and stage shift

In areas where prostate cancer screening — with a PSA test and/or a digital rectal examination (DRE) — is very prevalent, important changes in prostate cancer incidence and in the incidence-to-mortality ratio have occurred. These are reflected in the geographical comparisons given in Table 1. The data shown in the

TABLE 1. **Incidence and mortality of prostate cancer in different areas of the world (Globocan 2002). Ref. www.clip.iarc.fr**

	Incidence		Mortality		Ratio
	Cases (n)	Crude rate	Deaths (n)	Crude rate	Incid/mort
World	679,023	21.7	221,002	7.1	3.1
South Africa	4,778	19.3	2,648	10.7	1.8
Eastern Asia	29,472	3.9	14,535	1.9	2.1
Northern Europe	46,974	100.4	16,771	35.9	2.8
Northern America	257,943	163.7	36,447	23.1	7.1

Table are based on the year 2002. At that time, the incidence-to- mortality ratio in the United States had risen to 7.1. According to the most recent estimates, this year in the United States there will be 232,090 cases of prostate cancer diagnosed, and mortality will have decreased, by about 4% per year since 1994, to 30,500. This is almost identical to the 30,520 deaths from prostate cancer in 1989. The incidence-to-mortality ratio will have risen to 7.6. It is estimated that almost 70% of all American men above the age of 50 make use of PSA testing.[2,12] These changes show that screening is effective in terms of diagnosing more prostate cancer, which is usually locally confined, specifically in populations that have been screened repeatedly. Even prior to the introduction of screening, it was a well-recognized phenomenon that about 50% of men diagnosed with prostate cancer would die from other causes. It is inherent to screening that this incidence-to-mortality proportion increases. Our profession, however, is burdened with the need to give an answer to the question: "How much overdiagnosis is acceptable in the present situation of uncertainty about the benefits of screening?" The possibility of finding cancer in a large proportion of men who may not be otherwise aware of the presence of this disease and who are not at risk of suffering or dying of prostate cancer is obviously an important issue to be discussed with men who wish to be screened.

Ideally, the information to be used, if opportunistic screening is requested, should be field tested for understanding and should be balanced with respect to the outcome of its use. The outcome should reflect the present situation of uncertainty, meaning that about half the men who take note of this information should agree to be tested and the other half should refuse. Attempts to evaluate such patient information in the United Kingdom and in The Netherlands will be discussed later.

Information to be discussed with candidates for PSA testing

PSA testing may provide men with reassurance of the absence of prostate cancer. This reassurance, however, may be false. On the other hand, testing may find prostate cancer before symptoms develop. The prostate cancer that may be diagnosed, however, may never lead to the development of symptoms. If prostate cancer is found early on, treatment may be successful. However, more advanced asymptomatic prostate cancer may be diagnosed, and early detection of such cancers may prolong the period of suffering. These are some of the elements to be provided to potential screenees. Some aspects of this will be further discussed.

Overdiagnosis and "underdiagnosis"

Overdiagnosis can be defined as the diagnosis of cancer that otherwise would not be diagnosed during a lifetime. Several estimates of overdiagnosis are available in the current literature.[13,14] The estimates depend on age, estimates of lead-time, and other factors, and vary between 15% and 93%. Overdiagnosis in the ERSPC study — utilizing a 4-year screening interval and the age group 55-74 — has been determined to be 54%. This rate is associated with a mean lead-time of 10.3 years and an increase in lifetime risk of 105%.[15] This actually means that more than 50% of men diagnosed using the screening regimens applied to the ERSPC study centers would never experience prostate cancer during their lifetimes and are treated unnecessarily. This is a heavy burden, which will enter into calculations of quality of life and QALYs in the case of a positive outcome from this large randomized study. The identification of overdiagnosed cases and application of less aggressive regimens would be an obvious way to avoid these difficulties. Details of lead-time and overdiagnosis in the ERSPC Rotterdam study are given in Table 2.[15]

Next to the occurrence of overdetection, there is the phenomenon of cancers that are clinically detected during the screening interval (interval cancers). It is likely that the rate of detection of interval cancers can be decreased by shortening the screening intervals. However, even with the most aggressive types of screening reported in the literature —testing every 6 months, and biopsy indications ranging from PSA values above 2.5 ng/mL to above 4.0 ng/mL in conjunction with abnormal DREs— cancers will be diagnosed that are too advanced for effective treatment.[16]

The remarkable series of Catalona of 3,478 men treated by radical prostatectomy contained 1,774 (51%) of men with T1c cancers. These were by definition detected by screening. The median follow-up was 65 ± 50 months, Kaplan Meier projections ran to 10 years. In spite of intensive screening, PSA progression after 10 years approached 20%. This phenomenon has been termed "underdiagnosis." The term implies that with more aggressive diagnostic testing, men with prostate cancer might altogether avoid escape from effective treatment. This hypothesis is untested and not in line with the observation of the phenomenon of interval cancers in the setting of screening for other types of cancers.

TABLE 2. **Lead-time and overdiagnosis by screening in ERSPC. Rotterdam Draisma et al. BJUI 2003.**

Screening	Mean lead-time* Years	Detection per 1000 men	Overdetection	
			% of detection lifetime risk	% increase
Single screen test at age				
55	12.3	15	27	6
65	9.5	52	47	38
75	6.0	54	56	47
Screening with regular interval				
55-67, annual	12.3	103	50	80
55-67, 4 year interval	11.2	87	48	65
55-75, 4 year interval	10.3	123	54	105

*time elapsed from screen-detection to either clinical diagnosis or death from other causes in the situation without screening

Considering present uncertainties about the best methodology for screening and the best screening interval, the phenomenon of overdiagnosis is real and will be an important consideration for healthcare authorities if they were to consider the introduction of screening for prostate cancer in countries where healthcare adheres to strict budgetary regulations and where certain priorities have to be met. It is unlikely that in the near future overdiagnosis can be avoided. The remaining part of this article presents and examines available evidence that may allow the avoidance of aggressive treatment in potentially overdiagnosed cases.

Ways out of the dilemma

Identify overdiagnosed cases

The ideal situation we may hope for would be a serum test that would allow us to differentiate between the presence of more aggressive and less aggressive prostate cancers. This would avoid overdiagnosis as a result of the identification of potentially nonaggressive cancers. Recent progress in proteomics is promising in this respect, but experience has shown that a long time is necessary to establish a new marker in a clinical setting.[18]

Evidence cited above has shown that screening in at-risk age groups will result in overdiagnosis in about 50% of cases. Can overdiagnosed cases be identified with reasonable certainty on the basis of pre-treatment evidence? Kattan and co-workers[19] applied a decision-making analytical approach to the identification of "indolent prostate cancer" in a series of radical prostatectomy cases derived from two different institutions. Clinically diagnosed and screening-detected cancers were not differentiated. A total of 20% of the cases were identified as being indolent cancers. Depending on the model used, the accuracy of their identification amounted to a maximum of 80%.

Using the same criteria, this analysis has recently been repeated in a series of screening-detected cases derived from the ERSPC Rotterdam study. It turned out that 121 (49%) of the 247 cases were identified as having indolent cancer by using the Kattan criteria. Using the complete model, the area under the operating characteristic curve was 0.76, and depending on the intake characteristics, the model allowed the identification of up to 83% of cases as indolent cases, with acceptable confidence intervals. The natural history of these cases is unknown at this time. However, the selection criteria are virtually identical to those utilized in recent prospective and retrospective studies of active surveillance.[21-24] The parameters classifying cancers, which turned out to be independent variables in multivariate analyses,[19,20] are serum PSA, ultrasound prostatic volume, Gleason score, and millimeters of cancerous tissue and non-cancerous tissue in the biopsy cores. While the parameters classifying cases in radical prostatectomy specimens as indolent are arbitrary, it is likely that those cases that will not otherwise be diagnosed during a lifetime will fall within these classifications of "indolent cancers."

Avoid overtreatment

The crucial question is whether it is safe to use watchful waiting in prostate cancer cases that are identified as being indolent on the basis of pre-treatment criteria. Definitive answers to this question

TABLE 3. **Should I have the PSA test?**

Benefits of PSA testing	
	It may provide reassurance if the test result is normal
	It may find cancer before symptoms develop
	It may detect cancer at an early stage when treatments could be beneficial
	If treatment is successful, the consequences of more advanced cancer is avoided
Downside of PSA testing	
	It can miss cancer, and provide false reassurance
	It may lead to unnecessary anxiety and medical tests when no cancer is present
	It might detect slow-growing cancer that may never cause any symptoms or shortened life span
	The main treatments of prostate cancer have significant side-effects, and there is no certainty that the treatment will be successful

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will come from ongoing phase II studies and, hopefully, from controlled randomized trials. This, however, will take a minimum of 15 years. For the time being, other study results are promising. In the context of this contribution, only two ongoing studies will be referred to. Klotz and co-workers[21] evaluated 299 cases on watchful waiting over an 8-year period and found a prostate cancer-specific survival of 99%. Two men died of prostate cancer, each at 5 years after entering the study. Both cases had a PSA doubling time of less than 2 years. Within the ERSPC study Rotterdam section, an active surveillance study is being conducted. Within this protocol, during the initial years of the first round of screening, 64 consecutive men had chosen watchful waiting. Their mean follow-up was 80.8 months. This study evaluated 8-year prostate cancer-specific survival. None of the 64 cases showed progression to metastatic disease, and none of these men died from prostate cancer. The salvage regimens that were utilized were clearly effective.[24]

When a decision-making analytical approach to pre-treatment depending on the characteristics of cancers detected by screening is combined with a controlled watchful waiting regimen, this seems to be effective in avoiding treatment in many cases and in avoiding prostate cancer mortality. At this time, whether watchful waiting policies are cost effective and what their impact will be on the quality of life for a particular individual remains unclear. However, data coming from the only randomized trial comparing watchful waiting to radical prostatectomy show, in an extensive quality of life analysis, that there are no important differences.[25]

What do we tell our patients?

The crucial decision to be taken by men who are in the age groups at risk of prostate cancer is whether to be tested by having their serum PSA measured and having a DRE. In the present situation of uncertainty, risks and potential benefits of screening must be considered equally distributed. Information supplied to potential participants in screening programs or to men who consider themselves candidates for opportunistic screening should be understandable and balanced with respect to the resulting options. Table 3 is derived from the information material published by Cancer Research UK. Such patient information material, its effect on decision-making and the psychosocial aspect of testing have recently been studied.[26] As in the United Kingdom, attempts to develop balanced information material have been carried out in the Netherlands. The short brochure is available in Dutch on the website of the Dutch Cancer Foundation KWF Kankerbestrijding (www.kwfkankerbestrijding.nl). This text has been evaluated with respect to understanding the content and, in a limited way, the impact of decisions. Further evaluations are planned.

Conclusion

In the present situation of uncertainty, there is an ethical obligation to provide balanced information to men who are considering opportunistic screening or participation in ongoing early-detection programs for prostate cancer. Available patient information

materials may not be perfect, but attempt to present the potential advantages and disadvantages of PSA testing. This is in line with a recent important statement by Carroll who considers the decrease of overtreatment to be an important ethical obligation of our profession.[27] □

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