

The ERSPC: frequently asked questions

Introduction

This European Randomized Study on Screening for Prostate Cancer was launched now a decade ago and supported by the European Community for its centralized databank and by eight centers from eight different European countries. It involves a major logistic undertaking by randomizing close to 200.000 aging males in the European community and it is only comparable to a similar study in the USA (the PLCO study) where 60.000 males are randomized.

There is no question in the minds of screening public health experts that this study is needed to provide a clear answer to an important health policy question "Do men over fifty years of age need screening for prostate cancer". The answer is not known as stated in the last 2003 publication of the European Code against Cancer.

However, we live in an era of fast track communication where little patience is shown to a study that takes the 15 year natural history of prostate cancer into account and where innovations in diagnosis and treatment of prostate cancer are often seen as giving the answer to the question of screening and where questions on public health are sometimes met with suspicion on its stand towards the individual.

There is now a situation of compromise in the medical community that the individual man requesting the well known PSA-test should be fully informed on its consequences.

These consequences are all part of the study in asymptomatic men aged between 55 and 70 years of age where not only survival but also quality of life and cost/benefit to public health are involved but where aspects of pathology, marker biology and quality control of all aspects of the disease and the study are involved.

The multinational, ten-year-old mega study is awaited with high expectations but impatience or ignorance on its complex undertaking are raised by the medical community as well by patient organizations.

Rather than remain in the ivory tower of science a PR document was made, composed of skeptic or enthusiastic questions on population screening for prostate cancer. Answers will not be a plea or a defense for or against the study but an objective state of the art answering service following evidence-based principles. The ERSPC will welcome any new questions that may arise as we all feel that a repeat of the seismic discussions on the value of mammographic screening for female breast cancer should be avoided in the finish of this study.

Prof. dr. L. Denis

1. *How long will it take before the ERSPC study will show results on mortality reduction? - Harry de Koning*

With the current numbers enrolled, the ERSPC trial has sufficient power to detect a significant difference in prostate cancer mortality between the two arms if the true reduction in mortality by screening is 25% or more (or, if contamination remains limited to 10 % if the true effect is 20 % or more (de Koning 2002). These results can be expected between 2007 and 2010.

2. *What screening tests are used within the ERSPC? – Monique Roobol*

For a screening test to be useful, certain conditions must be met: firstly the screening test must indicate subjects with the condition (sensitivity) and those without (specificity).

A good screening test preferably has a high sensitivity and specificity and must be acceptable for the population screened, rapid and ideally noninvasive.

In prostate cancer screening there are basically three tests available which serve as indicators for the need of further testing. These tests are the digital rectal examination (DRE), the transrectal ultrasonography (TRUS) and the serum prostate specific antigen (PSA) level.

DRE:

There is a tendency to detect larger tumors with DRE, and the risk of detecting clinically insignificant tumors with DRE is low, but depends strongly on the PSA level. On the other hand, small multi focal lesions with an aggressive biologic potential are not detected with DRE alone. The general opinion is that DRE is highly subjective, and variable between different examiners.

Several studies have already questioned the use of DRE in screening programs and found little or no additional beneficial effect of a DRE in men with PSA levels ≥ 4.0 ng/ml (Catalona 1994, Rietbergen 1997). It is thought that the DRE can have an additional value in detecting (clinically significant) cancer in men with a low "normal" range of PSA (< 4.0 ng/ml) (Eastham 1999, Han 2004).

TRUS:

Similar to the DRE the interpretation is highly dependent on the investigator. Several studies have shown that the value of TRUS as a screening test is limited to detect cancer, but is indispensable for guiding prostatic biopsies and assessing the prostate volume.

PSA:

PSA is a protein, that is almost exclusively produced by the epithelial cells of the prostate, in normal and pathologic conditions, such as infection, urinary retention, enlargement of the prostate cancer. Approximately 40% of the patients with organ confined prostate cancer, show no elevation of serum PSA.

The problem with PSA testing is the choice of a cut off value for the decision to continue with more invasive examinations such as the prostate biopsy.

F/T PSA ratio:

To increase the specificity of PSA as a screening tool derivatives from PSA are studied.

Total PSA consists of Complex PSA (cPSA) and Free PSA (fPSA). cPSA is serum PSA that is bound to circulating proteins. It has been shown that the proportion of circulating cPSA is higher in patients with carcinoma than in those with benign enlargement. Studies comparing the diagnostic efficacy of cPSA with total PSA and the free to total (F/T) ratio report diverging results.

Screening tests are used to identify men with an elevated risk of having prostate cancer. This suspicion must however be confirmed. The gold standard to prove the presence or absence of prostate cancer is the surgical removal of the entire prostate followed by a histological analysis of the entire gland. Next to this clinically and ethically impossible maneuver, there is no superior method to prove the presence or absence of prostate cancer than a prostate biopsy, although it is known that prostate cancers will be missed with this procedure due to sampling errors. Within ERSPC prostate biopsies are taken (6 to 9 cores) laterally to the mid plain in the peripheral zone where most prostate cancers are located (Stamey1995). The prostate biopsy is a general safe procedure.

3. Why are different screening intervals within the ERSPC? – Jonas Hugosson

The optimal screening interval is still to be established. The screening interval has varied between 6 months (Catalona) up to studies with only one time screening (Gustafsson). The screening interval is usually determined from the lead-time assessments. Lead-time for PSA detected cancers are long, in the range 3-11 years, and vary according to PSA level. Cancers detected at a lower PSA level have longer lead-time compared to cancers detected at higher PSA levels (Törnblom). As most prostate cancers in a screening situation are detected at a low PSA level (< 10 ng/mL) one may argue that a long screening interval is sufficient. However, particularly in prostate it is important to diagnose the fast-growing prostate cancers at an early stage while they still are curable. The reason is that these cancers probably are those who are responsible for a lot of the mortality while slow-growing cancers are indolent to most of the patients. Such considerations led different ERSPC centres to choose different screening interval (between 1 and 4 years). These differences will give ERSPC an unique

possibility in the future to establish an optimal screening interval provided that screening is efficacious.

4. What are the risks of screening? - Schröder

The value of screening, the use of early detection measures on the basis of the whole population, can only be proven by showing a reduction in the chance of dying of prostate cancer at an acceptable price in terms of quality of life. This has not been done. At this time screening offers the possibility to diagnose early aggressive prostate cancer that may lead to suffering and death from this disease. On the other hand, screening may also detect cancers, which do not form a threat to the patients' life. Finding such cases cannot be avoided at present. It has been estimated that for screening in the general population the number of such minimal cancers is more than 50 % (Draisma 2003). Their diagnosis is actually unnecessary and leads to unnecessary treatment which may be associated with side effects.

5. What are the benefits of screening? – Fritz Schröder

Screening has the potential to find aggressive and potentially killing cancers at an early, still curable stage. Surgery and radiotherapy are the potentially curative forms of management that are commonly applied. There is now evidence from a randomized trial showing that radical prostatectomy decreases the change of dying of prostate cancer with respect to delayed treatment by suppressing the male hormone testosterone. However, even in the delayed treatment group at 8 years only about 25% of men are at risk of developing metastatic disease. Up to now it is impossible to diagnose up front those cases that may not progress and whose carriers may die of some other cause rather than from prostate cancer. It has not been shown that the same favorable results of surgery can be achieved in men whose prostate cancer has been detected by screening. Uncertainty therefore remains. Men who decide to be screened take a chance. However, men who are well informed about the potential risks and benefits of screening and subsequent treatment should not be denied the early diagnostic tests.

6. What is the policy regarding screening for prostate cancer in Europe? – Anssi Auvinen

The council recommendation on cancer screening for the European Union accepted in 2003 states that PSA testing for prostate cancer, though promising, does not meet the criteria of having proved to decrease the cancer-specific mortality, or well known and acceptable benefits and risks, as well as cost-effectiveness. Therefore, prostate cancer screening is not recommended. The statement emphasizes the importance of on-going randomized trials and specifically cites the ERSPC in this respect.

This position is consistent with the recommendations of an expert panel organized by the World Health Organization (WHO) and the International Cancer Union, which stated that sufficient evidence showing the benefits of prostate cancer screening in terms of mortality

reduction has not emerged yet. Therefore, offering screening as part of health care policy was not recommended.

Similar conclusions about withholding screening due to lack of evidence have also been reached in assessments of the U.S. Preventive Services Task Group and the U.S. National Cancer Institute.

Nevertheless, screening does take place even if it is not part of the policy. This is done on the basis of judgment and the responsibility of individual physicians and their patients, who may in some circumstances regard the possibility of benefit as more important than lack of demonstrated effectiveness.

7. Why are treatment regimens different between the ERSPC centres? –Stijn Roemeling

Historically, for men diagnosed with prostate cancer two curative treatment options were available, namely radical prostatectomy and radiotherapy. Although the value of watchful waiting is still being heavily disputed in the literature, watchful waiting, with the possibility of deferred curative treatment, has completed those two as a third option. When prostatic carcinoma has metastasized, endocrine therapy is available for palliative treatment. Although immunotherapy and gene therapy are promising, they have yet no place in everyday practice. There seems to be no role for chemotherapy in the treatment of prostate cancer. All treatment modalities seem to have their own indications, benefits and disadvantages. Furthermore, screen detected carcinoma has a more favorable prognosis than clinically detected cancer and long-term follow up is mandatory to evaluate treatment outcome. Therefore evidence based long term follow up data comparing different curative therapy modalities is limited and when available does not evidently show an advantage of one therapy over the other. Thus, in a lot of cases it is still not clear what the best treatment modality is. Whether doctors and individual patients join in new developments, is really a matter of beliefs and traditional differences. Moreover, not every treatment is easily available in all countries, due to lack of facilities and/or proper equipment. European guidelines are currently not widely used for treatment decisions.

8. What information is available for patients within Europe? - Ida Korfage

Governments as well as advocates such as general physicians, urologists, and cancer funds supply guidelines for early detection of prostate cancer by PSA-testing. According to most European guidelines PSA-testing should not be offered to asymptomatic men. After request it should only be offered following full counseling about the implications.

For men who consider PSA-testing a number of websites are available, which offer not only guidelines but also information on prostate cancer, prevalence, mortality, treatment options, and pros and cons of PSA-testing. For example:

the National Health Service in the UK (<http://www.cancerscreening.nhs.uk/prostate/psa-tests.html>)

Ministry of Health, New Zealand: Information for Men and their Families

<http://www.nhc.govt.nz/publications/ProstateCancer.htm> (April 2004)

Dutch Cancer Society KWF

(http://www.kwfkankerbestrijding.nl/content/pages/English_information.html)

Packs of clear information sheets (double sided A-4) for distribution by primary care staff to patients are available from the National Health Service in the UK. To order: email doh@prolog.uk.com

9. What are the other ongoing studies worldwide that contribute to the questions of screening? - Fritz Schröder

The great hope is vested on two ongoing studies, the European Randomized Study of Screening for Prostate Cancer (ERSPC) and, in the United States, the Prostate, Lung, Colon and Ovary screening trial (PLCO). In both trials lottery decides about participation in the screening arm or in a control arm where screening is not offered. A difference in the rate of deaths from prostate cancer is the most important endpoint in both trials. If a relevant difference exceeding 20% is shown in these trials at an acceptable cost in terms of quality of life and money, it can be expected that governments worldwide will introduce screening programs for prostate cancer which will then be included into paid healthcare policy packages. The great hope of all investigators is that this in fact will happen and that early diagnosis can be offered to all men at risk to decrease the burden of suffering and potential death from prostate cancer.