Screening for Prostate Cancer: Current Status of ERSPC and Screening-Related Issues

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Abstract

The "European Randomized Study of Screening for Prostate Cancer" (ERSPC) was initiated in 1993 and up to 1998 six other European countries were joined. The main goal is to establish the effect of Prostate Specific Antigen (PSA)-based screening on prostate cancer (PCa) mortality with morbidity as secondary end point. At present, with 11 and 12 years of follow-up significant relative reductions of 21 % and 31 % relating to both end points have been reported. The diagnosis of non-life threatening PCA (over diagnosis) is estimated to be in the range of 50 % and represents the main "harm", which prevents the introduction of population-based screening. As a result, the prevention of over diagnosis is now given top research priority. PSA as a screening test has poor performance characteristics including a low specificity. With the cut-off value of 3.0 ng/ml chosen within ERSPC, about 25 % of men aged 55–69 test positively, 75 % have "negative" test results, which do not definitely exclude the presence of PCa. Research to establish empirical schemes of follow-up based on PSA levels and other parameters are ongoing worldwide. In the meantime, we are, by approximation, capable to identify over diagnosed PCa detected by screening. Active surveillance can be applied to avoid side effects and expenses of treatment and is, among others, based on the grade of differentiation determined on biopsies. The assignment of the most favorable "Gleason score 6" is a crucial decision element. Unfortunately, biopsy pathology underestimates the true degree of PC aggressiveness by 25–30 % which establishes the need of careful follow-up.

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Screening for prostate cancer remains controversial in spite of increasing evidence of effectiveness in terms of mortality reduction of prostate cancer and of metastatic disease (Schröder et al. 2012a, b). These issues will be addressed in this brief chapter based on the European Randomized study of Screening for Prostate Cancer (ERSPC) and data reporting on 11- and 12-year follow-up periods (mortality and metastatic disease, respectively). In spite of the described effects on mortality and morbidity of prostate cancer the authors are, in line with healthcare providers and officials, convinced that the time for introducing population-based screening has not arrived because of harms of screening which only recently have been addressed and which will also be briefly reviewed within this chapter. In addition to that, the contribution aims to address a number of predefined questions related to the authors prior to the Prostate Cancer Prevention Consensus Conference held in connection with the annual meeting of the European Association of Urology (EAU) in Milano, March 2013.

1 Current Status of ERSPC

The ERSPC study is being conducted in eight European countries. All methodological details and results can be found in (Schröder et al. 2012a). The study was initiated in 1993. France was excluded from the most recent analysis because of a short follow-up period. All rules of participation including the common assignment of a core age group, age 55–69, the minimal dataset and the decision to contract an external data centre in a non-participating country were taken in 1995 and are documented in the criteria for participation which have been published (Schröder et al. 2012a, appendix). A total of 240,000 men age 55–74 were randomised to an upfront agreed core age group of ages 55–69. Of these, after the exclusion of France, 162, 160 men were included in the most recent analysis. The screen interval was 4 years for all centres, except Sweden where a 2-year screening interval was used (13 % of all participants). During the year of 1997 a common screening procedure was introduced indicating a lateralized sextant prostate biopsy in men who had a PSA $\geq$ 3.0 ng/ml. Our data showed a rate ratio of prostate cancer death of 0.79, a 21 % relative risk reduction, $p = 0.001$. The data translated into an absolute risk reduction of 1.07 prostate cancer deaths per 1,000 men. The numbers needed to identify and the numbers needed to diagnose amounted to 936 and 33 in excess of the control group. After adjustment for non-

compliance in men actually screened a relative prostate cancer mortality reduction of 29 % was found for men who participated and were screened.

The ERSPC study group agreed early to also study quality of life and the effects of screening on prostate cancer morbidity. A subgroup of four ERSPC centres found a relative reduction of M+ disease of 31 % in the intention-to-screen analysis and of 42 % in screened men. This translated into numbers needed to identify and numbers needed to diagnose to prevent one case of metastatic disease within 12 years of 328 and 12.

In conclusion, with a median follow-up of 11 years the ERSPC study shows a modest but significant prostate cancer mortality reduction of 21 % in the intention-to-screen analysis and of 29 % after adjustment for non-compliance. The reduction of metastatic disease amounted to 31 % with a 12-year follow-up. Since more than 70 % of all men randomised to the ERSPC study are still alive and since follow-up continues, our data must be considered as preliminary, analyses of data with a 13-year follow-up is ongoing.

The following sections will address a number of questions which are directly related to the subject of this contribution and which have been pre-assigned by the organisers of the consensus meeting.

2 Do Harms of Screening Outweigh Benefits?

The relative weight of benefits and harms of screening was recently evaluated by Heijnsdijk et al. (2012). A modelling approach was used applying the MISCAN system which allows predictions for populations of men during their whole lifetime. Quality of life adjusted life years (Qaly's) was calculated using weight-estimates of health effects of screening (utilities). The study used the 11-year ERSPC follow-up data. For 1,000 screened men aged 55–69 followed for life, a prostate cancer mortality reduction of 28 % was estimated, which translated into 73 life years gained per 1,000 men. When this was applied to a 4-year screening interval, the adjustment due to loss of quality of life was estimated to be 20 %. This resulted in 52 life years and 41 Qaly's gained by screening. Overdiagnosis and overtreatment had a large negative impact on Qaly's gained. The study was criticised because of uncertain assumptions of weights of utilities, the use of preliminary follow-up data of the ERSPC study and the use of the older literature-based assumptions on side effects of treatment. The authors acknowledge that future updating is needed.

3 How to Deal with High PSA Values After a Negative Biopsy?

This question addresses a situation which is extremely common worldwide. Regional estimates in the United States show that about 75 % of all older men had at least one PSA determination, similar data are in the range of 25–40 % for a number of European countries. With commonly used PSA-driven screening and cut-off

values indicating biopsies cancer is being diagnosed in 25–35 % of cases, depending on whether screening or clinical indications are applied. This means that 65–75 % of men are confronted with this question. A recent study from ERSPC Rotterdam presented at the 2013 EAU meeting (Zhu et al. 2013) addressed the issue by comparing prostate cancer mortality in 654 and 526 men who were diagnosed with prostate cancer in the first and second rounds of screening. After truncating the data at a 7-year follow-up period available from the second round population of men and after adjustment for known prognostic parameters the hazard ratio of prostate cancer death of the first versus second round amounted to 0.51 (95 % CI 0.27–0.95). This suggests an almost two-fold lower chance of death for cancers detected with repeat screening in men who had an elevated PSA 4 years earlier. The information can be used in shared decision taking between men and their physicians.

4 How to Manage Gleason 6 Cancer?

Prostate cancers classified into the most favourable prognostic group, Gleason score ≤ 6 on biopsy are considered to have clinically insignificant disease and are often advised to be managed by active surveillance. This has led to an ongoing discussion whether Gleason ≤ 6 cancers detected on biopsy might not be considered as cancer at all. Available published data, however, suggest to the contrary. Several studies show that 25–45 % of Gleason ≤ 6 prostate cancers are undergraded if biopsy findings are compared to the histological examination of radical prostatectomy specimens. Within the ERSPC study Rotterdam in 23.3, 41.7 and 33.3 % of Gleason ≤ 6 prostate cancers diagnosed during the first, second and third rounds of screening, either metastatic disease or death from prostate cancer occurred (Zhu et al. 2011). Furthermore, in a study modelling the development of screen-detected prostate cancer over time, progression of Gleason six prostate cancer to more aggressive disease was shown (Draisma et al. 2006).

How then should we deal with Gleason ≤ 6 prostate cancer? We cannot assume the presence of insignificant disease if Gleason ≤ 6 prostate cancer is found on biopsy. Major efforts, including risk stratification based on PSA, prostate volume, the amount of cancer on biopsies and other potentially available prognostic factors should be used to rule-out more aggressive disease. Advanced imaging studies applying multi-parametric MRI technology should be considered prior to or during active surveillance if this choice is made.

5 Final Conclusions

Screening for prostate cancer was shown to significantly reduce its mortality in the ERSPC study. Harms and their weights have been identified and quantified. Harms decrease but do not exceed the benefits of screening with presently available data. To reduce the most important harm, overdiagnosis and overtreatment, is a top

clinical and research priority. Men with elevated PSA and negative previous biopsies should be followed carefully and not a priori be considered to have insignificant disease. The time of population-based screening has not (yet) come. In the meantime, shared decision taking for well-informed men who wish to undergo PSA-driven testing cannot be denied.

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