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Urologic Oncology: Seminars and Original Investigations 26 (2008) 533–541

UROLOGIC ONCOLOGY

Seminar article

Screening for prostate cancer (PC)—an update on recent findings of the European Randomized Study of Screening for Prostate Cancer (ERSPC)☆★

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Abstract

Introduction for screening for prostate cancer as a healthcare policy is desirable provided its effectiveness can be shown in terms of decreasing prostate cancer mortality at an acceptable price in terms of quality of life and costs. The European Randomized Study of Screening for Prostate Cancer (ERSPC) was initiated in 1993 and should in 2008 have the power to produce the required information.

The structure and status of ERSPC. ERSPC is a randomized controlled trial running in eight European countries (Belgium, Finland, France, Italy, The Netherlands, Spain, Sweden, and Switzerland). A total of 267,994 have been randomized to screening vs. control. An interim look at the data has taken place in 2006; the advice of the Data Monitoring Committee was to continue the study. This was based on a total of 23,794 deaths in both study groups, 6,033 cases of prostate cancer detected in both groups of which about 1, 200 had died.

Contributions to a better understanding of the screening methodology. ERSPC has contributed with a large number of publications, either coming from individual centers or combining data of several centers. A complete listing can be found at www.erspc.org.

Lead-time and overdiagnosis with the screening regimen utilized in ERSPC Rotterdam were established to amount to 10.3 years and 54%. This information is of great importance for the development of further screening strategies. During the process of ERSPC, digital rectal examination was omitted and replaced by the inclusion of PSA 3–4 as a biopsy indication. The data on which this decision has been based were published and validated. Overdiagnosis and overtreatment have an adverse influence on quality of life, as it will be included in the evaluation of ERSPC. The recent development of a nomogram for the identification of indolent disease is a major step to improve on this outcome parameter. The application of this nomogram to screen detected cases allows the the advice "active observation" to about 30% of such patients.

ERSPC is set to show or exclude at least a 25% reduction in prostate cancer mortality through screening. Many pending problems still have to be resolved prior to the introduction of populations based screening as a worldwide healthcare policy.

Keywords: Prostate cancer; Screening trial; Preliminary results; Screening tests

Introduction

Level I evidence for the effectiveness of screening for prostate cancer in terms of lowering prostate cancer mortality is still not available. Two major randomized studies, the Prostate, Lung, Colon, and Ovary (PLCO) screening trial [1] and the European Randomized Study of Screening for Prostate Cancer (ERSPC) [2] are far advanced and are expected to produce final answers to the pending questions. The purpose of the present paper is to give an update on the status of ERSPC up to the end of the year of 2006. In addition, a number of important findings of the study will be summarized. A complete review of all publications is available on the ERSPC website www.erspc.org, which also contains a listing of all publications that have resulted from the study and associated projects.

The status of ERSPC up to December 2006

ERSPC was initiated in 1993 with Belgium and The Netherlands being the first countries to participate. Six other

☆ This work was supported by ERSPC International: EU grant 5th Framework Program, Beckman Coulter Hybritech, various sources in participating countries, ERSPC The Netherlands: Dutch Cancer Society and the Netherlands Organization for Health Research and Development.

★ Summary of findings presented in part during the Charles Huggins lecture given at the Annual Meeting of the Society of Urological Oncology, Bethesda, MD, December 1, 2006.

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1078-1439/08/$ – see front matter © 2008 Published by Elsevier Inc.
doi:10.1016/j.urolonc.2008.03.011

countries followed: Finland, France, Italy, Spain, Sweden, and Switzerland. There were clearly defined criteria for participation, which included the conduct of pilot studies to test all important aspects of feasibility including randomization. All centers signed up to the obligation of producing biannually data to be delivered to the independent data center according to an agreed minimal dataset. All centers were allowed to publish interim data of their study. Publication of data related to the endpoint prostate cancer mortality by mutual agreement is not allowed for any center. These data are under the control of the central Data Monitoring Committee, and are subject to the published monitoring and evaluation plan [3]. Some of the pilot studies have been described in early publications [4,5]. In Rotterdam, 5 pilot studies were conducted between 1991 and 1993 prior to entering the main protocol. These studies have a very long follow-up; the patients were followed according to the standard protocol and testing procedures varied from pilot to pilot. The pilot studies show an encouraging difference in the rate of metastases and prostate cancer specific survival, which may or may not be predictive of the outcome of ERSPC as a whole [6].

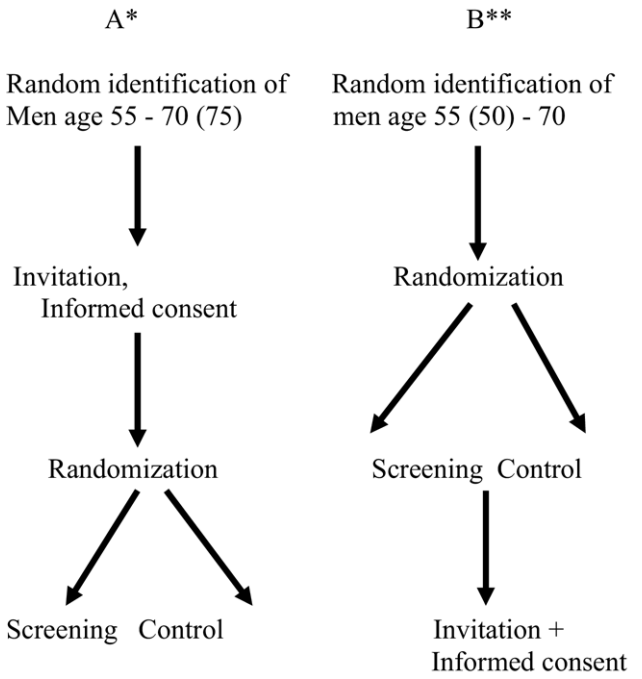

Fig. 1. Randomization procedures in ERSPC. *Belgium, The Netherlands, Italy, Switzerland; **Finland, Sweden.

The structure of ERSPC

ERSPC is a randomized controlled trial of screening for prostate cancer vs. unscreened controls with the main endpoint of showing a difference in prostate cancer mortality between the screening and control arm. The study is powered to show a difference of 25% with a follow-up of 10 years taking into account at least 20% of noncompliance and/or contamination in the control arm [7]. The first complete evaluation is planned when the follow-up data for the year 2008 are complete. Three interim analyses are planned on the basis of the data up to the end of 2002, 2004, and 2006. Both interim analyses conducted so far have resulted in the advice to the study group to continue ERSPC.

Within ERSPC two randomization schemes are utilized which are in line with national regulations. The randomization procedures are reproduced in Fig. 1. Belgium, The Netherlands, Spain, and Switzerland by law have to utilize an upfront informed consent. The studies in Italy, France, Finland, and Sweden are population based in the sense that men are randomized without prior knowledge. Men randomized to screening are subsequently invited. Outcomes of men in the control group are evaluated through registry data.

Data collection within ERSPC is decentral. The study is run by the Scientific Committee and the committee of voting members. Other committees relate to quality control (Epidemiology Committee, Quality Control Committee, Pathology Committee, PSA Committee, Data Monitoring Committee). All committees report to the Scientific Committee and to the voting members. Members of the Data Monitoring Committee are independent experts. The ERSPC Scientific Committee and voting members meet twice yearly and receive updated information on the status of ERSPC from the central database in line with the agreed dataset. Data on prostate cancer mortality are blinded with respect to the study arm.

Recruitment

Recruitment and rescreening after an interval of 2 years (in Sweden) and 4 years (all other centers) has been completed. In the screening arm, a total of 5,588 cancers were detected. Up to the end of 2005, 3,373 cancers were detected in the control arm. France was a latecomer within ERSPC and entered only in 2001. The first screen is still ongoing in the two French centers. Table 1 shows that due to the type of randomization applied, compliance is lower in Finland, Italy, and Sweden. Description of recruitment, cancer detection, and cancer characteristics have been subject to publication from the individual centers [8–15]. Other more specific reports can be found in the bibliography of ERSPC (www.erspc.org).

Endpoints

The main endpoint of ERSPC is prostate cancer mortality. Special effort is taken to review causes of deaths in