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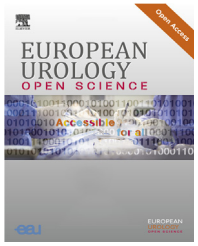

European Association of Urology

Prostate Cancer

# Intervention-related Deaths in the European Randomized Study of Screening for Prostate Cancer

*Rebecka Arnsrud Godtman*[a], *Sebastiaan Remmers*[b], *Gunnar Aus*[c], *Vera Nelen*[d], *Liesbet van Eycken*[e], *Arnauld Villers*[f], *Xavier Rebillard*[g], *Maciej Kwiatkowski*[h,i,j,*], *Stephen Wyler*[h,i], *Donella Puliti*[k], *Giuseppe Gorini*[k], *Alvaro Paez*[l], *Marcos Lujan*[m], *Teuvo Tammela*[n], *Chris Bangma*[b], *Anssi Auvinen*[o], *Monique J. Roobol*[b]

[a] *Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Göteborg, Göteborg, Sweden;* [b] *Department of Urology, Erasmus Medical Centre, Rotterdam, The Netherlands;* [c] *Department of Urology, Carlanderska Sjukhuset, Göteborg, Sweden;* [d] *Provinciaal Instituut voor Hygiëne-Antwerpen, Antwerp, Belgium;* [e] *Belgian Cancer Registry, Brussels, Belgium;* [f] *Department of Urology, Univ. Lille, CHU Lille, Lille, France;* [g] *Clinique Beau Soleil, Montpellier, France;* [h] *Department of Urology, Cantonal Hospital Aarau, Aarau, Switzerland;* [i] *Faculty of Medicine, University of Basel, Basel, Switzerland;* [j] *Department of Urology, Academic Hospital Braunschweig, Braunschweig, Germany;* [k] *ISPRO Oncological Network, Prevention, and Research Institute, Florence, Italy;* [l] *Department of Urology, Hospital Universitario de Fuenlabrada, Madrid, Spain;* [m] *Department of Urology, Hospital Infanta Cristina Parla, Madrid, Spain;* [n] *Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland;* [o] *Prostate Cancer Research Center, Faculty of Social Sciences, University of Tampere, Tampere, Finland*

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**Abstract**

***Background:*** Identification of intervention-related deaths is important for an accurate assessment of the ratio of benefit to harm in screening trials.
***Objective:*** To investigate intervention-related deaths by study arm in the European Randomized Study of Prostate Cancer Screening (ERSPC).
***Design, setting, and participants:*** ERSPC is a multicenter trial initiated in the 1990s to investigate whether screening on the basis of prostate-specific antigen (PSA) can decrease prostate cancer mortality. The present study included men in the core age group (55–69 yr: screening group n = 112 553, control group n = 128 681) with 16-yr follow-up.
***Outcome measurements and statistical analysis:*** Causes of death among men with prostate cancer in ERSPC were predominantly evaluated by independent national committees via review of medical records according to a predefined algorithm. Intervention-related deaths were defined as deaths caused by complications during the screening procedure, treatment, or follow-up. Descriptive statistics were used for the results.
***Results and limitations:*** In total, 34 deaths were determined to be intervention-related, of which 21 were in the screening arm and 13 in the control arm. The overall risk of intervention-related death was 1.41 (95% confidence interval 0.99–1.99) per 10 000 randomized men for both arms combined and varied among centers from 0 to 7.0 per 10 000 randomized men. A limitation of this study is that differences in procedures among centers decreased the comparability of the results.

* Corresponding author. Urologische Klinik, Kantonsspital Aarau, Tellstrasse 25, 5001 Aarau, Switzerland. Tel. +41 62 8384759; Fax: +41 62 8384753.
E-mail address: maciej.kwiatkowski@unibas.ch (M. Kwiatkowski).

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***Conclusions:*** Intervention-related deaths were rare in ERSPC. Monitoring of intervention-related deaths in screening trials is important for assessment of harms.
***Patient summary:*** We investigated deaths due to screening or treatment to assess harm in a trial of prostate cancer screening. Few such deaths were identified.


## 1. Introduction

The European Randomized Study of Prostate Cancer Screening (ERSPC) is a multicenter trial initiated in the early 1990s to investigate whether screening on the basis of prostate-specific antigen (PSA) might decrease prostate cancer (PC) mortality. In 2009, ERSPC demonstrated a 20% reduction in the relative risk of PC mortality in the screening arm compared to the control arm [1]. This finding has been corroborated with longer follow-up periods [2–4]. However, the decrease in mortality is accompanied by an increase in PC incidence. On the basis of 16 yr of ERSPC follow-up data, the number needed to invite and the number needed to screen to prevent one PC death were 570 and 18 respectively [4]. If the screening tests, diagnostic interventions, and/or treatments for the target disease have lethal complications, and if any intervention-related deaths are not identified as screening-related deaths but instead are falsely attributed to other causes (misclassification), major adverse effects of screening could be strongly underestimated. For ERSPC, independent committees have determined the cause of death using medical records and predefined criteria for men with PC in a blinded fashion to minimize bias [5]. In addition, intervention-related deaths have been included in the definition of disease-specific mortality. The aim of the present study was to assess the frequency and clinical characteristics of intervention-related deaths within ERSPC by study arm and center.

## 2. Patients and methods

### 2.1. ERSPC trial

The ESRPC trial protocol has been described in detail previously [1]. In Finland, Italy, and Sweden, men were randomized before informed consent (effectiveness trial), whereas in Belgium, the Netherlands, Switzerland, and Spain, only men who provided consent were randomized (efficacy trial). Men assigned to the screening arm were invited to PSA testing every fourth year (or every second year in Sweden). A PSA threshold of 3.0 ng/ml was used in most centers, but auxiliary tests, such as the free PSA/total PSA ratio and digital rectal examination, were used in some centers for patients with low PSA levels. A positive screen led to referral for prostate biopsies. Transrectal ultrasound-guided sextant biopsy was the standard in most centers. The upper age limit for invitation ranged from 67 to 78 yr among centers. The number of screening rounds was two in Belgium and France; three in Finland, Italy, Spain, and Switzerland; five in the Netherlands; and up to 10 in Sweden. Men allocated to the control arm were not invited to PSA testing but received standard care. The present report included men within the predefined core age group (55–69 yr at randomization) who were followed up to December 31, 2014. The two French centers were included, resulting in a larger study population than in previous publications based on the core age group (241 234 vs 162 389) [4].

### 2.2. Determination of cause of death in ERSPC

PC cases were identified by linkage with cancer registers and review of medical records and death certificates. Medical records, including relevant imaging, histopathology reports, and autopsy protocols, were collected for all men diagnosed with PC who died. The investigators were blinded to trial arm allocation, screening history, and official cause of death. An algorithm, which has been described in depth previously, was used to determine the causes of death [5]. In summary, an intervention-related death was defined as a death caused by complications during treatment or follow-up, or complications during screening/biopsy. The algorithm included several decision points describing the clinical course of the disease: progressive metastases, progressive local recurrence, intervention-related death, and possible doubts as to whether these were the cause of death. Causes of death were assigned into seven categories: definitely PC, probable PC, possible PC, intervention-related, PC as a contributory factor, unlikely to be PC, and definitely not PC. Definitely PC, probable PC, and intervention-related death were regarded as PC deaths in the analysis of the trial.

### 2.3. Local cause-of-death committees

According to the ERSPC protocol [6], the cause of death for all men with PC in both the screening and control arms were to be evaluated by an independent committee reviewing medical records according to the predefined algorithm [5]. Therefore, each center formed a committee with at least three members who were not involved in any other aspect of the trial (except in Spain; see the Supplementary material). Each committee member individually reviewed the records and assigned the cause of death using the predefined algorithm. If the committee members did not agree on the cause of death, the case was discussed with the aim of reaching consensus. If a disagreement could not be resolved, the case was referred to the international committee, consisting of members from each local committee, or was left pending. The international committee convened annually in the early years of the trial and thereafter when needed. A detailed description of the national cause-of-death committees can be found in the Supplementary material. Results from the Finnish, Dutch, and Swedish cause-of-death committees have been published [7–10].

### 2.4. Statistical analysis

Descriptive statistics were used for the results in the present study. Confidence intervals (CIs) for proportions were calculated using the method proposed by Wilson [11,12]. Statistical analyses were performed with SPSS v25.0.0 (IBM Corp., Armonk, NY, USA).

## 3. Results

Table 1 shows the number of intervention-related deaths in the two arms combined and separately by study arm. There were more intervention-related deaths in the screening arm than in the control arm (between-arm difference 0.86, 95% CI −0.10 to 1.94 per 10 000 randomized men). Although the number of intervention-related deaths was small, the

differences among centers were relatively large. Two centers had no intervention-related deaths; in the remaining centers, the number of intervention-related deaths ranged from 0.4 to 7.0 per 10 000 randomized men. Fisher's test showed a significant difference ($p < 0.001$) in the proportion of intervention-related deaths between centers.

Table 2 summarizes all the intervention-related deaths (both arms combined). There was only one death registered as being associated with the screening or diagnostic pathway; this case is described below (Case 1). For men dying after radical prostatectomy, the median time from treatment to death was 0.6 mo (interquartile range [IQR] 0.16–3.8). Lethal complications within 30 days after radical prostatectomy were typically cardiovascular events and included postoperative bleeding, cardiac infarction, and pulmonary embolism. Later complications included one case of urosepsis and one case of epidural abscess (Table 1). For men who underwent radiotherapy, the median time from treatment to death was longer, at 94 mo (IQR 0.7–147). Intervention-related deaths after radiotherapy included bleeding due to radiation cystitis and complications after fistula surgery. Deaths after treatment for advanced disease were due to complications (ie, cardiac arrests and infections) after palliative transurethral resection of the prostate, orchidectomy, and infectious complications after nephrostomy and chemotherapy.

Three cases are described to exemplify difficulties in capturing and determining what constitutes an intervention-related death.

### 3.1. Case 1: death associated with the screening/diagnostic pathway

A man in the screening group was diagnosed with screen-detected low-risk PC (cT1cN0M0). For staging purposes, he underwent abdominal computed tomography, which detected an asymptomatic 6.5-cm abdominal aortic aneurysm. During aneurysm surgery, the patients experienced a cerebrovascular insult that led to death. According to the official death certificate, the cause of death was cerebrovascular insult.

### 3.2. Case 2: death from late complications of primary treatment

A man in the control group who had multiple comorbidities was diagnosed with cT3N0M0 high-risk PC, for which he received external radiation therapy. Some 10 yr later, he was diagnosed with bilateral ureteral strictures and underwent nephrostomies. The patient experienced several episodes of febrile urinary tract infection. His PSA increased slowly, and after suspicious findings on a bone scan, he started luteinizing hormone–releasing hormone (LHRH)-agonist treatment. The man responded to this treatment. However, his overall condition deteriorated and he became bedridden. The patient died suddenly in his home 12 yr after his primary treatment. According to the official death certificate, the cause of death was cardiac failure.

### 3.3. Case 3: death from complications of treatment for advanced disease

A man in the screening group was diagnosed (not screen-detected) with cT1cN1Mx high-risk PC. He received primary treatment with a LHRH agonist, but after several years his PSA began to increase and an orchidectomy was performed. Several months later, the patients developed macrohematuria due to advanced PC and underwent palliative transurethral resection of the tumor and palliative radiotherapy. These treatments were complicated by an urosepsis episode, for which bilateral nephrostomies were performed. His condition did not improve and the man died 3 yr after diagnosis. According to the official death certificate, the cause of death was PC.

## 4. Discussion

In this study, we found that ERSPC intervention-related deaths were rare, accounting for only 2.3% of all PC-related deaths, but relatively large differences existed among centers. More intervention-related deaths were found in the screening group than in the control group, reflecting the larger number of men diagnosed and treated for PC in the screening group than in the control group.

We described three cases as examples of situations in which identifying an intervention-related death can be difficult, even for experienced reviewers who have access to medical records and are using a standardized algorithm.

**Table 2 – Summary of intervention-related deaths**

| Cause of death | Number |
|---|---|
| Complications in the diagnostic pathway | 1 |
| Complications after radical prostatectomy within 30 d | 15 |
| Complications after radical prostatectomy after >30 d | 5 |
| Complications after radiotherapy | 7 |
| Complications after treatment for advanced disease | 6 |
| Total | 34 |

**Table 1 – Number of intervention-related deaths in both arms combined and by study arm**

| | Overall cohort ($n$ = 241 234) | Screening arm ($n$ = 112 553) | Control arm ($n$ = 128 681) |
|---|---|---|---|
| Deaths ($n$) | 34 | 21 | 13 |
| Deaths per 10 000 randomized, $n$ (95% CI) | 1.41 (0.99–1.99) | 1.87 (1.22–2.85) | 1.01 (0.59–1.73) |
| Deaths per 10 000 prostate cancers ($n/N$) | 16 (34/20,872) | 19 (21/10 909) | 13 (13/9963) |
| Percentage of prostate cancer deaths, % ($n/N$) | 2.3 (34/1466) | 3.5 (21/598) | 1.5 (13/868) |
| Median age at death, yr (IQR) | 69 (66–74) | 69 (67–73) | 69 (64–76) |
| Median time for diagnosis to death, mo (IQR) | 6 (3–37) | 6 (3–36) | 4 (2–61) |

CI = confidence interval; IQR = interquartile range.

Case 1 demonstrates how a screening or diagnostic process can result in incidental findings that prompt a cascade of new examinations and treatments that could lead to complications and, at worst, death. In this case, it might be argued that an aortic aneurysm of 6.5 cm carries a high risk of rupture and death without intervention, but a chance finding could just as well be a less severe condition but with a fatal treatment complication. An intervention-related death, such as the one described, is unlikely to be identified as intervention-related if the cause of death is based on the death certificate alone. Case 2 demonstrates another difficulty in identifying intervention-related deaths, in that such deaths could occur many years after treatment. In this case, a man with multiple comorbidities died, probably because of complications from his primary treatment, 12 yr later. Without access to medical records for the entire course of the disease(s) and a thorough review, such a death would probably not have been identified as intervention-related. Case 3 involves a man diagnosed outside the screening program who received noncurative treatment for advanced PC with complications leading to death. A fourth situation for which cause of death can be difficult to determine is cardiovascular deaths in men treated with androgen deprivation (ADT) therapy. Observational studies have suggested an increase in the risk of cardiovascular disease during ADT [13]. However, cardiovascular disease is also a common cause of death for men with PC and in an individual case it is impossible to know whether the cardiovascular death was directly caused by ADT or not. In the present study there was one man with metastasized PC who was treated with ADT who died from cardiac arrest. In this case, PC was not mentioned on the death certificate, but the local committee identified this as an intervention-related death. According to the algorithm used in ERSPC, all fatal complications of screening, treatment, or follow-up were considered as intervention-related deaths, including complications of interventions for advanced disease.

Whether the latter group of deaths should be attributed to the screening program could be a matter of discussion. The chain of events leading to death would be likely to occur even in the absence of screening. The aim of a screening program is to decrease disease-specific mortality by introducing a stage shift whereby tumors are detected at earlier stages, when they are amenable to curative treatment. When reviewing the work of the local cause-of-death committees, we found that some committees interpreted deaths during treatment for advanced PC as being intervention-related, whereas others interpreted them as deaths due to PC. Because both categories are included in PC mortality, these local differences should not have affected the main endpoint (PC mortality), but they could explain, at least in part, differences in the number of intervention-related deaths among centers. Other explanations may be that some centers had terminated the work of the local committee and relied on the official cause of death, which was probably less likely to capture intervention-related deaths; differences in the availability and quality of medical records between countries; and variation in the proportion of men receiving curative treatment among centers [14]. A central cause-of-death committee reviewing all deaths in men with PC in all centers would probably have reduced variation between centers, but this was not possible, as it would have required translation and review of complete medical records spanning many years for thousands of individuals. However, local committees could send difficult cases to an international central committee for discussion.

An alternative method to avoid the pitfalls in cause-of-death ascertainment is to use overall mortality as the primary endpoint in screening studies instead of disease-specific mortality [15,16]. The main argument against the use of this method is that it is not feasible if the disease being screened for constitutes the cause of death in only a small proportion (often 3–5%) of all deaths; therefore, a trial powered to demonstrate a significant difference in overall mortality would require millions of individuals [17]. A more feasible method would be to investigate differences in excess mortality rates between the intervention and control arms. Excess mortality comparisons are unaffected by cause-of-death ascertainments but require accurate estimates of the expected mortality. In ERSPC, excess mortality analyses have indicated unbiased cause-of-death determination and no major effects from intervention-related deaths [18,19].

Several ERSPC centers have published results from their local cause-of-death committee [7,9,10]. In Sweden, for example, the agreement between committee results and death certificates was 96% ($\kappa = 0.92$), and comparable levels of agreement were found in the two study arms (screening arm 97%, control arm 95%) [10]. Similar results have been reported from the Dutch and Finnish ERSPC sections [7,9]. The overall accuracy of the ERSPC cause-of-death coding was recently investigated by Walter and colleagues [20]. Although observer variation was present, the authors ruled out that a biased cause-of-death assignment could explain the mortality reduction due to screening. Furthermore, no systematic differences in the accuracy of cause-of-death assessment were observed in country-specific analyses [8,10].

The importance of a death review process in identifying intervention-related deaths has also been demonstrated in the PLCO trial [21]. Unfortunately, the review process ceased in 2012, before all deaths requiring a review had been processed. Overall, a high level of agreement was found between the committee and death certificates. The committee assessed that almost 9% of PC deaths were intervention-related. A difference in intervention-related deaths was found between the arms, with 11% of deaths classified as intervention-related in the intervention arm, compared with 6% in the control arm. Without a review process, these deaths indirectly caused by the screening process would have remained unknown, and thus caused biased estimates of the screening effects. The UK Cluster randomized trial of PSA testing for PC (CAP) trial, which used a similar cause-of-death assignment to that in ERSPC [22], found that an expert committee and the death certificates agreed on the cause of death in 92% of cases. The committee attributed 0.6% (3/523) of PC deaths to intervention-related causes. The proportion of intervention-related PC deaths found in the present study

(2.3%) is lower than reported from the PLCO trial but higher than in the CAP trial. Possible explanations for this wide span (0.5–9%) include differences in age and treatment distributions, length of follow up, access to and quality of medical records, and different methods for reviewing records and assigning cause of death.

One limitation in the ERSPC methodology used to identify intervention-related deaths is that lethal complications during the screening procedure were not captured for men without a PC diagnosis. Only deaths in men with a PC diagnosis were reviewed by the committees. However, we previously reported that prostate biopsies were not associated with any excess mortality and that fatal complications after prostate biopsies were rare in ERSPC [23]. Similar findings from the PLCO trial have been published by Pinsky et al [24]. We therefore argue that this limitation should not have biased the main endpoint of the ERSPC. Another limitation is that several centers terminated the work of the committees and relied on the official cause of death, which possibly increased the risk of missing intervention-related deaths. This limitation probably explains some of the differences seen among centers. With the small numbers of intervention-related deaths, including those in the centers that used a committee during the entire period, this limitation should not have affected the main endpoint (PC mortality) of the ERSPC trial.

## 5. Conclusions

In conclusion, intervention-related deaths were rare in ERSPC, but relatively large differences in the number of deaths classified as intervention-related were observed among centers. Standardized, carefully conducted cause-of-death reviews are important to identify intervention-related deaths and should be used in screening trials. However, as demonstrated in this study, even with great care and effort, identification of these deaths is difficult.

***Author contributions:*** Maciej Kwiatkowski had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design*: Arnsrud Godtman, Remmers, Auvinen, Roobol.
*Acquisition of data*: Arnsrud Godtman, Remmers.
*Analysis and interpretation of data*: Arnsrud Godtman, Remmers, Roobol.
*Drafting of the manuscript*: Arnsrud Godtman, Remmers.
*Critical revision of the manuscript for important intellectual content*: Arnsrud Godtman, Remmers, Aus, Nelen, van Eycken, Villers, Rebillard, Kwiatkowski, Wyler, Puliti, Gorini, Paez, Lujan, Tammela, Bangma, Auvinen, Roobol.
*Statistical analysis*: Arnsrud Godtman, Remmers.
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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2021.09.014.

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