

# Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer: Part 2. Final evaluation of the Scandinavian Prostatic Cancer Group (SPCG) Study No. 5

Dr Per Olov Hedlund, Jan-Erik Damber, Inger Hagerman, Svein Haukaas, Peter Henriksson, Peter Iversen, Robert Johansson, Peter Klarskov, Finn Lundbeck, Finn Rasmussen, Eberhard Varenhorst, Jouko Viitanen, The Spcg-5 Study Group, Dr Per Olov Hedlund, Jan-Erik Damber, Inger Hagerman, Svein Haukaas, Peter Henriksson, Peter Iversen, Robert Johansson, Peter Klarskov, Finn Lundbeck, Finn Rasmussen, Eberhard Varenhorst, Jouko Viitanen & The Spcg-5 Study Group

To cite this article: Dr Per Olov Hedlund, Jan-Erik Damber, Inger Hagerman, Svein Haukaas, Peter Henriksson, Peter Iversen, Robert Johansson, Peter Klarskov, Finn Lundbeck, Finn Rasmussen, Eberhard Varenhorst, Jouko Viitanen, The Spcg-5 Study Group, Dr Per Olov Hedlund, Jan-Erik Damber, Inger Hagerman, Svein Haukaas, Peter Henriksson, Peter Iversen, Robert Johansson, Peter Klarskov, Finn Lundbeck, Finn Rasmussen, Eberhard Varenhorst, Jouko Viitanen & The Spcg-5 Study Group (2008) Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer: Part 2. Final evaluation of the Scandinavian Prostatic Cancer Group (SPCG) Study No. 5, *Scandinavian Journal of Urology and Nephrology*, 42:3, 220-229, DOI: [10.1080/00365590801943274](https://doi.org/10.1080/00365590801943274)

To link to this article: <https://doi.org/10.1080/00365590801943274>



Published online: 09 Jul 2009.



Submit your article to this journal [↗](#)



Article views: 225



Citing articles: 36 View citing articles [↗](#)

ORIGINAL ARTICLE

## Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer: Part 2. Final evaluation of the Scandinavian Prostatic Cancer Group (SPCG) Study No. 5

PER OLOV HEDLUND<sup>1</sup>, JAN-ERIK DAMBER<sup>2</sup>, INGER HAGERMAN<sup>3</sup>,  
SVEIN HAUKAAS<sup>4</sup>, PETER HENRIKSSON<sup>5</sup>, PETER IVERSEN<sup>6</sup>, ROBERT JOHANSSON<sup>7</sup>,  
PETER KLARSKOV<sup>8</sup>, FINN LUNDBECK<sup>9</sup>, FINN RASMUSSEN<sup>8</sup>,  
EBERHARD VARENHORST<sup>10</sup>, JOUKO VIITANEN<sup>11</sup> & THE SPCG-5 STUDY GROUP\*

<sup>1</sup>Department of Urology, Karolinska University Hospital Solna, Sweden, <sup>2</sup>Department of Urology, Sahlgrenska University Hospital, Gothenburg, Sweden, <sup>3</sup>Department of Cardiology, Karolinska University Hospital, Huddinge, Sweden, <sup>4</sup>Diakonissehjemmet Hospital, Bergen, Norway, <sup>5</sup>Department of Medicine, Danderyd University Hospital, Danderyd, Sweden, <sup>6</sup>Department of Urology, Rigshospitalet, Copenhagen, Denmark, <sup>7</sup>Oncologic Center, Umeå University Hospital, Umeå, Sweden, <sup>8</sup>Department of Urology, Herlev University Hospital, Herlev, Denmark, <sup>9</sup>Department of Urology, Skejby University Hospital, Aarhus, Denmark, <sup>10</sup>Department of Urology, Linköping University Hospital, Linköping, Sweden, and <sup>11</sup>Department of Urology, North Karjala Central Hospital, Joensuu, Finland

### Abstract

**Objective.** To compare parenteral estrogen therapy in the form of high-dose polyestradiol phosphate (PEP; Estradurin<sup>®</sup>) with combined androgen deprivation (CAD) in the treatment of prostate cancer patients with skeletal metastases. The aim of the study was to compare anticancer efficacy and adverse events, especially cardiovascular events. **Material and methods.** In total, 910 eligible patients with T0–4, NX, M1, G1–3 prostate cancer with an Eastern Cooperative Oncology Group performance status of 0–2 were randomized to treatment with either PEP 240 mg i.m. twice a month for 2 months and thereafter monthly, or flutamide (Eulexin<sup>®</sup>) 250 mg t.i.d. per os in combination with either triptorelin (Decapeptyl<sup>®</sup>) 3.75 mg i.m. per month or on an optional basis bilateral orchidectomy. **Results.** At this final evaluation of the trial 855 of the 910 patients were dead. There was no difference between the treatment groups in terms of biochemical or clinical progression-free survival or in overall or disease-specific survival. There was no difference in cardiovascular mortality, but a significant increase in non-fatal cardiovascular events in the PEP arm ( $p < 0.05$ ) predominantly caused by an increase in ischemic heart and heart decompensation events. There were 18 grave skeletal events in the CAD group but none in the PEP group ( $p = 0.001$ ). **Conclusions.** PEP has an anticancer efficacy equal to CAD and does not increase cardiovascular mortality in metastasized patients, but carries a significant risk of non-fatal cardiovascular events, which should be balanced against the skeletal complications in the CAD group. It is feasible to use Estradurin in the primary or secondary endocrine treatment of metastasized patients without prominent cardiac risk factors and especially those with osteoporosis.

**Key Words:** Cardiovascular complications, combined androgen deprivation, multicenter study, parenteral estrogen, primary endocrine therapy, prostate cancer, randomized trial, skeletal metastases

### Introduction

In the mid-1980s there was renewed interest in estrogen treatment of prostate cancer, since pilot studies indicated that parenteral administration of this therapy was practically free from the cardiovas-

cular toxicity seen after oral estrogen treatment [1]. Two Finnish studies showed that polyestradiol phosphate (PEP, Estradurin<sup>®</sup>; Pharmacia, Sweden) given at a dose of 160 mg i.m. per month did not lead to higher cardiovascular mortality or morbidity

\*A complete list of the members of the SPCG-5 Study Group is given in the Appendix.

Correspondence: Dr Per Olov Hedlund, Skogsstigen 22, SE-131 42 Nacka, Sweden. E-mail: krea@beta.telenordia.se

(Received 1 October 2007; accepted 15 January 2008)

than bilateral orchiectomy [2] or gonadotrophin-releasing hormone analogue therapy [3]. This dose of Estradurin did, however, have inferior anticancer efficacy in terms of progression-free survival. This may be explained by the fact that it did not decrease serum testosterone to castration levels [4]. In a Swedish pilot study it was found that PEP given at a dose of 240 mg per month i.m. decreased serum testosterone to castration levels and that this was most rapidly achieved by giving PEP 240 mg every second week during the first 2 months [5]. In an open study of 40 prostate cancer patients no increase in cardiovascular toxicity was noted during the first 3 years [6].

The aim of the present study was to compare PEP with combined androgen deprivation (CAD) with overall survival as the primary endpoint. Secondary objectives were to compare time to biochemical and clinical progression, cancer-specific survival, cardiovascular toxicity, other adverse events and quality of life.

Previous interim analysis [7] showed that progression-free, disease-specific and overall survival were similar in the two treatment groups. There was, however, a significant increase in non-fatal heart decompensation and ischemic heart events in the PEP group, but no significant increase in cardiovascular mortality.

This paper presents the results of the final evaluation of the trial, done when 855 of the 910 patients included in the study were dead.

## Material and methods

Between December 1992 and June 1997, 915 men with hormone-naive, T any, Nx, M1, G any prostate cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 from 63 Nordic urological centers were randomized to receive treatment with either PEP or CAD. All patients had skeletal metastases as evaluated by bone scans supplemented with X-rays when needed. The primary tumor was staged by digital rectal examination according to the TNM classification of 1987, and graded according to the World Health Organization (WHO) system, either on the base of fine-needle aspiration cytology [8] or histologically from transurethral resection specimen and needle biopsies [9]. The extent of bone disease was calculated from pretreatment bone scans according to a modified Soloway score [10] as follows: score 1, total area of hot spots is less than three bodies of a lumbar vertebra; score 2, the total area of hot spots is larger of that of score 1, but less than 75% of the total scan; and score 3, superscan.

Exclusion criteria were as follows: patients who had received previous systemic therapy for prostate cancer or with another malignancy of any kind with the exception of basal cell carcinoma of the skin, patients who had suffered a myocardial infarction or cerebral infarction within 1 month prior to randomization in the study, patients with current or previous liver disease with a bilirubin or alanine aminotransferase value above the upper limit of normal, and patients who it was felt would not be able to comply with the study protocol. The patients were given oral and written information about the study and gave their oral consent to participate.

The patients were stratified according to country, with Iceland included in the Norwegian group, ECOG performance status 0–1 versus 2, an alkaline phosphatase under versus over 1.25 times the upper normal limit, and whether they had or not had a previous or current history of cardiovascular disease (Table I). Randomization was done by the Oncologic Center of the Karolinska University Hospital Stockholm, where the eligibility of the patients was initially checked. Patients were allocated to treatment according to their position on the stratification list.

Polyestradiol phosphate was given as i.m. injections of 240 mg twice a month for 2 months and thereafter once a month. CAD was given as flutamide (Eulexin®; Schering-Plough, Stockholm, Sweden) 250 mg per os t.i.d. in combination with either triptorelin (Decapeptyl®; Ferring, Malmö, Sweden) 3.75 mg i.m. per month, or bilateral orchiectomy at the choice of the patient and trialist. Flutamide was started 1 week before the first Decapeptyl injection.

Table I. Parameters of stratification.

| Parameter                       | PEP<br>(n=455) | CAD<br>(n=455) |
|---------------------------------|----------------|----------------|
| Country                         |                |                |
| Denmark                         | 105            | 106            |
| Finland                         | 46             | 44             |
| Norway and Iceland              | 51             | 51             |
| Sweden                          | 252            | 254            |
| Performance status              |                |                |
| ECOG 0–1                        | 375            | 384            |
| ECOG 2                          | 80             | 71             |
| Alkaline phosphatase            |                |                |
| <1.25 × UNL                     | 230            | 233            |
| >1.25 × UNL                     | 224            | 222            |
| Previous cardiovascular disease | 78             | 66             |
| Ischemic heart disease          | 46             | 40             |
| Heart decompensation            | 13             | 12             |
| Ischemic cerebral disease       | 6              | 4              |
| Venous thromboembolism          | 11             | 8              |
| Intermittent claudication       | 2              | 2              |

PEP = polyestradiol phosphate; CAD = combined androgen deprivation; ECOG = Eastern Cooperative Oncology Group; UNL = upper normal limit.

Irradiation of the breasts prior to therapy was optional.

The patients were followed by visits to the trialist 1, 3 and 6 months after randomization and thereafter every 6 months until clinical progression was clearly established. At every visit the patients were questioned and evaluated with regard to symptoms and signs of disease progression and adverse events. Blood pressure, body weight, performance status and pain and analgesic scores (Table II) were noted, and levels of hemoglobin, creatinine, prostate-specific antigen (PSA) and liver enzymes including alkaline phosphatase were measured. Digital rectal examination and bone scan or X-rays were done only if considered necessary for the evaluation of the disease status. In between these 6 month visits the PSA was measured so that the patients were monitored for PSA every 3 months. If required, the

patients could attend for extra checks. When clinical progression was definitely established, treatment and follow-up of the patient were at the discretion of the individual trialist.

Patients were usually given other forms of endocrine therapy, sometimes with known cardiovascular toxicity, or chemotherapy. Time and cause of death were recorded.

Monitoring was done by research nurses or monitoring specialists by means of visits to the trialist at least once a year for the first 5 years. After this, monitoring was done only by means of telephone contacts or correspondence. Some centers with many patients in the study were monitored more closely. To check compliance with the medication the patients had to return empty vials of Eulexin and charts were kept by the nurses of all injections of Estradurin or Decapeptyl. A statement by the trialist regarding compliance was included in the Case Report Form.

Table II. Other demographic characteristics at entry.

| Characteristic                           | PEP              | CAD              |
|--|------------------|------------------|
| Age (years) <sup>a</sup>                 | 72.9 (46.5–88.9) | 73.3 (41.8–93.4) |
| Body weight (kg) <sup>a</sup>            | 75 (46–143)      | 76 (47–129)      |
| Pain score <sup>b</sup>                  |                  |                  |
| 0  | 192              | 185              |
| 1  | 137              | 145              |
| 2  | 94               | 98               |
| 3  | 29               | 24               |
| 4  | 3                | 3                |
| T-stage                                  |                  |                  |
| T0                                       | 1                | 4                |
| T1                                       | 14               | 19               |
| T2                                       | 68               | 78               |
| T3                                       | 244              | 249              |
| T4                                       | 110              | 98               |
| Grade of malignancy                      |                  |                  |
| 1  | 67               | 69               |
| 2  | 211              | 203              |
| 3  | 163              | 177              |
| Soloway category of bone metastases [10] |                  |                  |
| 1  | 152              | 167              |
| 2  | 250              | 233              |
| 3  | 49               | 49               |
| Pretreatment                             | 234              | 67               |
| irradiation of breasts                   |                  |                  |
| B-hemoglobin (g/l) <sup>c</sup>          | 92 (86–98)       | 91 (86–99)       |
| S-creatinine (μl/l) <sup>c</sup>         | 98 (94–102)      | 102 (97–106)     |
| S-testosterone (nmol/l) <sup>c</sup>     | 14 (13–14)       | 14 (13–15)       |
| S-PSA (μg/l) <sup>c</sup>                | 823 (632–1014)   | 719 (597–841)    |
| S-PSA (μg/l) <sup>a</sup>                | 235 (2.7–28500)  | 225 (1.8–8631)   |

<sup>a</sup> Median (range).

<sup>b</sup> 0 = no pain; 1 = slight pain, non-opioid analgesics occasionally; 2 = moderate pain, non-opioid analgesics regularly; 3 = severe pain, opioids occasionally; 4 = intolerable pain, opioids regularly.

<sup>c</sup> Mean (95% confidence interval).

PEP = polyestradiol phosphate; CAD = combined androgen deprivation; PSA = prostate-specific antigen.

#### Definition of endpoints

Time to biochemical progression was the time from randomization to the time when the first rise of PSA from nadir was observed and followed by a continuous rise in consecutive measurements. Time to clinical progression was the time from randomization to the first suspicion of clinical deterioration of the disease which could be supported by further clinical deterioration in consecutive evaluations [11].

Clinical deterioration was thus based on symptoms, most commonly pain and decreased performance status, but also in some cases on increasing micturition problems ( $n=11$ ), local extension of the prostate ( $n=16$ ), lymph edema ( $n=5$ ), uremia ( $n=9$ ), skeletal complications ( $n=5$ ) or solely on progression seen on bone scans performed on the request of some patients ( $n=34$ ). Overall survival was the time from randomization to death from any cause. Analysis of disease-specific survival included all the typical deaths from prostatic cancer with progressive cachexia, etc., but also deaths from another disease with significant contribution from the prostatic malignancy meaning that clinical progression of the cancer was established [11]. For patients who died of another disease and had no symptoms of their prostate cancer, the cause of death was counted as without contribution of the prostatic malignancy.

Patients found dead in their homes where no examination had been done shortly before death or no post-mortem examination was done were classified as dead of unknown cause.

*Evaluation of cardiovascular toxicity; the blind observer*

Strict criteria for heart decompensation, ischemic heart disease, ischemic cerebral disease, intermittent claudication and venous thromboembolism were set out in the study protocol (for details see previous paper [12]). All such events were evaluated by a "blind observer", a cardiologist with special interest in cardiovascular side-effects of estrogen therapy. When a cardiovascular event was suspected, the patient's file, blinded for the anticancer therapy the patient was receiving, was sent to the blind observer, who decided whether the event qualified as a cardiovascular event or not, according to the criteria of the trial. A non-fatal cardiovascular event was only counted the first time it happened in a patient, even if the same kind of cardiovascular event occurred several times. If the event was ultimately the cause of death it was counted again in the cause-of-death evaluation.

*Evaluation of other toxicity*

Gastrointestinal and liver toxicity as well as allergic cutaneous manifestations were graded according to the WHO scale [13]. Hot flushes were evaluated in terms of frequency and both according to Frödin et al. [14]. The extent of gynecomastia was recorded as follows: slight, only involving mammary gland and nipple; moderate, involving the mammary gland and including lipomastia; and severe, area of the breast involved is larger than the patient's fist.

Before locking the data bank after the patient's death a final check of all CRFs was done by a data quality committee consisting of experienced urologists from the Nordic countries. The trial was analyzed on an intention-to-treat basis. The study was performed in accordance with the recommendations of the Helsinki Declaration (World Medical Assembly, Helsinki 1964; amended in Tokyo 1975, Venice 1983 and Hong Kong 1989). The study was approved by the ethical committee of the Karolinska Institute, Stockholm, and by the local ethical committees of the participating centers.

*Statistical methods*

The aim of the study, according to the protocol, was to show that the PEP treatment was equally effective as CAD in terms of overall medium survival by testing the hypothesis using two one-sided levels [15]. A difference in time to death of <20% was not considered clinically significant. To demonstrate an equivalence in median survival with a power of 80% and at an alpha level of 5%, 371 deaths were needed per group. A total of 900 randomized patients was

recommended to obtain the necessary number of deaths.

A Cox proportional hazard regression model was used to estimate the relative effects of treatments with regard to overall survival. The hypothesis stated in the protocol (assuming a constant hazard) corresponds to a relative hazard expressed as  $e^B = \lambda_{\text{PEP}}(t) / \lambda_{\text{CAD}}(t) < 1.25$ , where  $B$  was estimated from Cox regression. These estimations were also done for disease-specific survival and time to progression.

In these analyses testing for differences between the two treatment groups was done, and these tests were also done for disease-specific survival. A  $p$ -value of 0.05 was considered significant.

Kaplan–Meier plots were performed for overall survival, disease-specific survival, and time to biochemical and clinical progression. Differences between the two treatment groups regarding non-fatal adverse events were tested using chi-squared tests. Analyses for adverse events were based on information obtained from the total available material from all randomized patients. The software used for all analyses was SPSS 15.0 for Windows (SPCC, Cary, NC, USA) and the plots were drawn in S-PLUS 6.0.

**Results**

Five patients were excluded, two who were found to be M0 and three who were shown to have performance status 3 at randomization. Twenty patients were lost to follow-up and therefore excluded from survival data. At this final evaluation 855 of the 910 patients had died. Median time from randomization to cessation of follow-up was 11.7 (10.1–13.7) years. Thirty-five patients were still alive at the data cut-off date a median of 11.0 (10.2–12.6) years after randomization, 14 in the PEP group and 21 in the CAD group. Parameters of stratification and other demographic data are shown in Tables I and II. In spite of the stratification there were more patients with previous cardiovascular morbidity in the PEP group. Statistical correction of this imbalance changed the results only marginally. Other baseline characteristics were well balanced. In the CAD group 158 patients (35%) underwent orchidectomy and 297 (65%) were treated with triptorelin.

Time to clinical and biochemical progression is shown in Figures 1 and 2. There was no significant difference between the groups. Patients who died of another disease without having progressed ( $n = 82$ ), and patients where PSA values were missing ( $n = 14$ ) were censored. Overall and disease-specific survival are shown in Figures 3 and 4. There was no difference between the two treatment groups. The cause of death is shown in Table III. Causes of death other than prostatic cancer with and without contribution

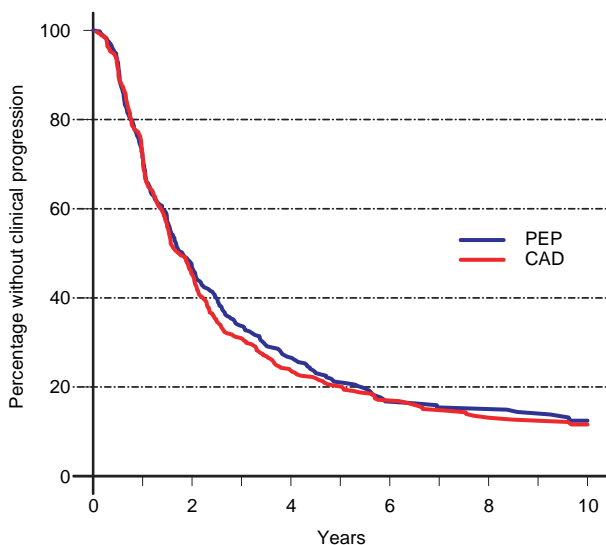


Figure 1. Kaplan–Meier estimates of time to biochemical progression. Median time polyestradiol phosphate (PEP) 13.7 (12.3–15.1), combined androgen deprivation (CAD) 13.8 (12.4–15.2) months. Relative risk = 1.05 (0.91–1.21),  $p=0.54$ .

of the prostatic malignancy are shown in Table IV. There was no difference in cardiovascular mortality between the two groups. The non-fatal cardiovascular events are listed in Table V. There were more ischemic heart and heart decompensation events in the PEP group, but there was a statistically significant difference between the two treatment groups only if all cardiovascular events were added ( $p < 0.05$ ). This increased cardiovascular morbidity is based wholly on adverse cardiac events. The principal investigator advised stopping PEP treatment in four patients who suffered a myocardial infarction, since this was

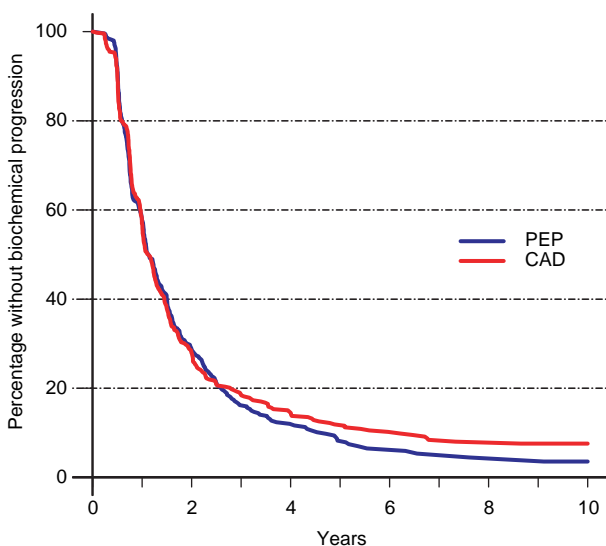


Figure 2. Kaplan–Meier estimates of time to clinical progression. Median time polyestradiol phosphate (PEP) 21.7 (18.9–24.6), combined androgen deprivation (CAD) 21.0 (18.2–23.8) months. Relative risk = 0.95 (0.82–1.11),  $p=0.53$ .

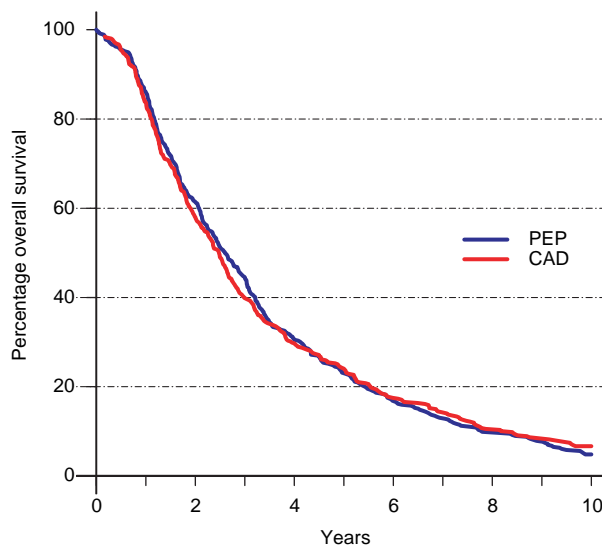


Figure 3. Kaplan–Meier estimates of overall survival. Median time polyestradiol phosphate (PEP) 31.1 (27.4–34.9), combined androgen deprivation (CAD) 29.7 (27.0–32.4) months. Relative risk = 1.01 (0.88–1.15),  $p=0.91$ .

considered to be in the interest of the patients. The onset of the non-fatal and fatal cardiovascular events is shown in Table VI. The majority of these events occurred during the first 3–4 years after the start in both treatment groups. Other non-fatal events are listed in Tables VII and VIII. The 18 skeletal events included nine femoral neck fractures, seven spinal cord compressions, one grave osteoporosis and one olecranon fracture. No skeletal adverse events were reported in the PEP group. The reasons for temporary or persistent reduction of the dosage or cessation of therapy are shown in Table IX. There was a number

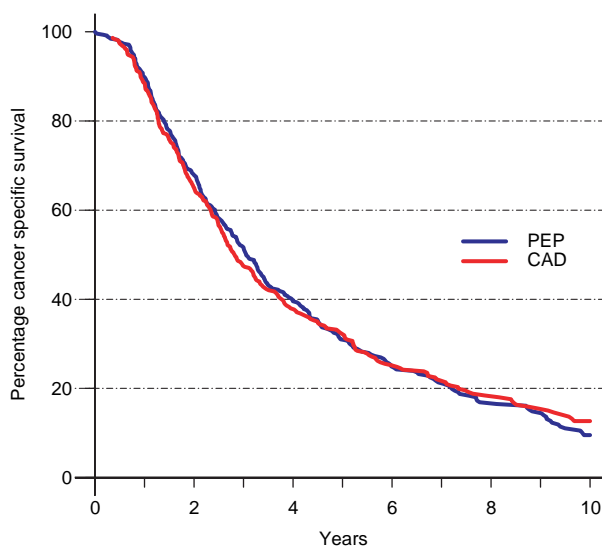


Figure 4. Kaplan–Meier estimates of cancer-specific survival. Median time polyestradiol phosphate (PEP) 36.7 (32.9–40.4), combined androgen deprivation (CAD) 33.9 (30.0–37.7) months. Relative risk = 1.01 (0.87–1.18),  $p=0.90$ .

Table III. Cause of death.

| Cause of death  | PEP | CAD | Total | <i>p</i> |
|---|-----|-----|-------|----------|
| Prostate cancer                                       | 337 | 324 | 661   | 0.99     |
| Other disease with contribution of prostate cancer    | 32  | 49  | 81    | 0.035    |
| Other disease without contribution of prostate cancer | 46  | 36  | 82    | 0.30     |
| Unknown   | 20  | 11  | 31    | 0.09     |

PEP =polyestradiol phosphate; CAD =combined androgen deprivation.

of cases with increased liver enzymes, but only two cases had a more serious event with jaundice and were taken into hospital. One of them was found to have a liver abscess and a gallbladder stone; he recovered after medical treatment. The other had alcohol problems and a gallbladder stone, and also recovered after medical treatment. In both cases the trialists considered that the flutamide treatment contributed to the events.

**Discussion**

The study shows that this PEP regimen has an anticancer efficacy equal to that of CAD. As can be seen from pretreatment PSA values and Soloway score there were many patients in the trial with extensive tumor burden, which may explain the relatively short progression-free survival.

No significant increase in cardiovascular mortality was observed. There was, however, a statistically significant increase in non-fatal cardiovascular, mainly cardiac events, although the incidence was much lower than previously seen after oral estrogen therapy [16]. These results are partly in accordance with the Finnprost 6 study, where the same dose of PEP was compared with bilateral orchidectomy in locally advanced (*n*=240) and metastasized (*n*=200) prostate cancers [17]. In that study there was a significant increase in cardiovascular morbidity

and mortality in patients with locally advanced tumors, but no significant increase in the metastasized patients. The different results for patients with and without metastases can probably be explained by the high competing cancer mortality for patients with more advanced disease and also the length of treatment in patients with smaller tumor burden. This study was evaluated on an intention-to-treat basis according to the protocol. In reality, however, five of the non-fatal cardiovascular events in the PEP group and 12 in the CAD group occurred during second-line therapy, making the difference in incidence during the primary randomized treatment 66 to 38 (*p*=0.005). It has been shown that the grave deviations of coagulation parameters due to the induction of liver metabolism by oral estrogen therapy [18,19] can nearly be avoided by parenteral administration [20]. In the present study, as in the Finnprost 6 study, the onset of cardiovascular adverse events was mainly spread over the first 3–4 years, contrary to what was seen after oral estrogen therapy [16], when 50% of the cardiovascular events occurred within 2 months of treatment start and 85% within the first year. This may indicate that the parenteral therapy has a more protracted effect on liver metabolism, so that with longer parenteral treatment the induction of liver metabolism may be more significant. However, there seem to be no studies of coagulation parameters for longer than 3–6 months during parenteral estrogen therapy. It has been shown that ischemic complications of oral estrogen therapy can be reduced by prophylactic aspirin treatment [21], but no data are available for the high-dose PEP therapy used in this

Table IV. Cause of death, other disease with and without contribution of the prostate cancer.

| Cause of death            | PEP | CAD | <i>p</i> |
|---------------------------|-----|-----|----------|
| Ischemic heart disease    | 12  | 10  | 0.59     |
| Heart decompensation      | 18  | 11  | 0.17     |
| Ischemic cerebral disease | 8   | 10  | 0.43     |
| Pulmonary embolism        | 0   | 2   | 0.47     |
| Cerebral hemorrhage       | 1   | 5   | 0.13     |
| Total cardiovascular      | 39  | 38  | 0.99     |
| Pneumonia                 | 4   | 14  | 0.029    |
| Pulmonary insufficiency   | 3   | 2   | 0.69     |
| Other malignancy          | 16  | 13  | 0.78     |
| Benign gastrointestinal   | 4   | 6   | 0.21     |
| Septicemia                | 3   | 3   | 0.99     |
| Miscellaneous             | 7   | 8   |          |

PEP =polyestradiol phosphate; CAD =combined androgen deprivation.

Table V. Non-fatal cardiovascular adverse events.

| Event                     | PEP | CAD | <i>p</i> |
|---------------------------|-----|-----|----------|
| Ischemic heart disease    | 20  | 11  | 0.12     |
| Heart decompensation      | 23  | 12  | 0.06     |
| Ischemic cerebral disease | 13  | 13  | 0.99     |
| Venous thromboembolism    | 12  | 8   | 0.37     |
| Intermittent claudication | 2   | 4   | 0.41     |
| Retinal thrombosis        | 1   | 2   | 0.99     |
| Total                     | 71  | 50  | 0.05     |

PEP =polyestradiol phosphate; CAD =combined androgen deprivation.

Table VI. Time of onset of fatal and non-fatal cardiovascular events with or without contribution of the prostate cancer.

| Year after start | PEP <i>n</i> (%) | CAD <i>n</i> (%) |
|------------------|------------------|------------------|
| 1                | 40 (36)          | 20 (26)          |
| 2                | 27 (24)          | 18 (24)          |
| 3                | 17 (15)          | 11 (14)          |
| 4                | 11 (9)           | 9 (12)           |
| 5                | 4 (4)            | 6 (8)            |
| 6                | 5 (4)            | 0 (0)            |
| 7                | 4 (4)            | 3 (4)            |
| 8-13             | 3 (3)            | 3 (4)            |

PEP =polyestradiol phosphate; CAD =combined androgen deprivation.

trial. Patients with advanced prostate cancer can have a hypercoagulable state with increases in fibrinogen, factor V and von Willebrand's factor even before treatment [19], and androgen deprivation therapy in prostate cancer patients carries a risk of developing the metabolic syndrome which per se is a cardiovascular risk factor [22]. Keating et al., in a survey of 73 196 Medicare enrollees, found that gonadotropin-releasing hormone therapy was associated with significantly increased risks of diabetes, coronary heart disease, myocardial infarction and sudden cardiac death, while bilateral orchiectomy was likely to lead to diabetes but no cardiac adverse events [23]. A risk for cardiac adverse events has even been discussed after non-steroidal antiandrogen treatment [24]. In this perspective cardiovascular adverse events in prostate cancer patients seem to be multifactorial events, also connected to androgen deprivation per se and not only to hormone-induced changes in coagulation parameters. A total of 144 patients with previous cardiovascular disease accord-

Table VIII. Other non-fatal adverse events.

| Event                      | PEP | CAD | <i>p</i> |
|----------------------------|-----|-----|----------|
| Skeletal                   | 0   | 18  | 0.001    |
| Pneumonia                  | 1   | 1   |          |
| Skin, including infections | 1   | 3   |          |
| Benign gastrointestinal    | 2   | 1   |          |
| Mental-neurological        | 2   | 3   |          |
| Septicemia                 | 1   | 0   |          |
| Edema                      | 2   | 0   |          |
| Miscellaneous              | 4   | 1   |          |

PEP =polyestradiol phosphate; CAD =combined androgen deprivation.

ing to the strict criteria of the trial were included in the study, 78 in the PEP group and 66 in the CAD group. In addition many patients with non-protocol-defined cardiovascular conditions such as hypertension, atrial fibrillation or general atherosclerosis were randomized in the study. It is well known that previous cardiovascular disease is a strong risk factor for cardiovascular complications during oral estrogen therapy [16]. A detailed evaluation of cardiovascular events including previous cardiovascular morbidity, with the aim of determining prognostic risk factors, will be carried out later.

There has been a tremendous decrease in patients with widespread skeletal metastases at the time of diagnosis owing to PSA screening [25]. Endocrine therapy will, however, remain an important treatment modality in prostate cancer after failure of curative therapy [26]. As a whole, the cardiovascular morbidity from parenteral estrogen therapy to metastasized prostate cancer patients may be considered a modest problem, given that the responsible doctor will be closely monitoring and providing

Table VII. Other non-fatal events stratified by severity and presented as percentages of the groups as PEP (*n* =447)/CAD (*n* =451).

| Event                               | Severity |       |       |         |       |
|-------------------------------------|----------|-------|-------|---------|-------|
|                                     | 0        | 1     | 2     | 3       | 4     |
| Nausea <sup>a</sup>                 | 80/75    | 15/17 | 4/5   | 1/2     | 0/0.2 |
| Diarrhea <sup>b</sup>               | 90/74    | 8/11  | 2/7   | 0.4/8   | 0/0.4 |
| Allergy cutaneous <sup>c</sup>      | 96/95    | 2/2   | 1/2   | 0.2/0.2 | 0.2/0 |
| Flush frequency <sup>d</sup>        | 70/26    | 27/41 | 3/25  | 0/8     |       |
| Flush bother <sup>e</sup>           | 74/33    | 21/30 | 5/29  | 0.7/8   |       |
| Gynecomastia <sup>f</sup>           |          |       |       |         |       |
| Prophylactic irradiation            | 40/52    | 49/45 | 10/3  | 2/0     |       |
| No irradiation                      | 16/64    | 52/31 | 28/5  | 4/0.3   |       |
| Pain of drug injection <sup>g</sup> | 99/100   | 0.2/0 | 0.7/0 | 0/0     |       |

<sup>a</sup> 0 =none; 1 =nausea; 2 =transient vomiting; 3 =vomiting requiring therapy; 4 =intractable vomiting.

<sup>b</sup> 0 =none; 1 =slight; 2 =moderate; 3 =severe, requiring therapy; 4 =intolerable.

<sup>c</sup> 0 =none; 1 =erythema; 2 =dry desquamation/pruritus; 3 =ulceration; 4 =exfoliative dermatitis.

<sup>d</sup> 0 =none; 1 =1-3/day; 2 =4-10/day; 3 = > 10/day.

<sup>e</sup> 0 =none; 1 =slight; 2 =moderate; 3 =great.

<sup>f</sup> 0 =none; 1 =slight, only mammary gland; 2 =moderate, including lipomastia; 3 =severe, breast bigger than the patient's fist.

<sup>g</sup> 0 =none; 1 =slight, lasting some hours; 2 =moderate, couple of days; 3 =severe, need for therapy.

PEP =polyestradiol phosphate; CAD =combined androgen deprivation.

Table IX. Cause of temporary or persistent dose reduction/termination of the primary treatment due to adverse events: number of patients.

| Adverse event          | PEP  | CAD   |
|------------------------|------|-------|
| Nausea                 | 0/2  | 7/11  |
| Diarrhea               | 0/0  | 18/38 |
| Liver reaction         | 0/0  | 12/22 |
| Gynecomastia           | 0/3  | 0/0   |
| Flush                  | 0/0  | 0/6   |
| Pain of PEP injections | 2/5  | 0/0   |
| Allergic skin reaction | 0/2  | 4/2   |
| Cardiovascular events  | 1/20 | 1/3   |
| Impotence              | 0/0  | 0/2   |
| Patient's wish         | 0/0  | 2/0   |
| Misunderstanding       | 1/1  | 2/0   |
| Miscellaneous          | 2/4  | 4/4   |

PEP =polyestradiol phosphate; CAD =combined androgen deprivation.

information to the patient. It should also be considered that CAD therapy is five to six times as expensive as PEP.

There are ongoing studies of parenteral estrogen using transcutaneous patches, but so far no data (P Abel, personal communication). The blind observer was consulted on more than 300 occasions and her evaluation proved to be of great importance. Metastatic pain in the legs or chest may easily be misinterpreted for intermittent claudication, venous thrombosis, or cardiac or pulmonary morbidity.

Tables VII and VIII show well-known differences in side-effects of the two therapies. The difference in skeletal complications between the groups should be important when choosing therapy. It may seem surprising that so many patients in the PEP group experienced slight or moderate nausea and even diarrhea. It was also unexpected that so many PEP patients reported slight hot flushes, as estrogen often is used to alleviate flushes in castrated patients. This phenomenon, which has also been reported in other trials [27,28], is dealt with in a separate publication of this study [29].

Prophylactic irradiation of the breasts seemed to have more effect in the PEP group than in the CAD group, but could only partly prevent gynecomastia. In most patients with increased liver enzymes the increase was very modest, and the only two cases with jaundice recovered uneventfully after hospital treatment. It is probable that the registration of painful reactions to the PEP injections is not complete. From personal experience, slight or moderate pain during the day and sometimes the day after injection is rather common even if the injection is given slowly and with care. A quality-of-life evaluation is currently being prepared.

In summary, the PEP regimen used in this trial had an anticancer efficacy equal to that of CAD, and

was not associated with increased cardiovascular mortality. Significantly more non-fatal ischemic heart and heart decompensation events occurred in the PEP group which, however, had a higher prevalence of pretreatment cardiovascular morbidity. Even with this higher risk of non-fatal cardiovascular events it seems appropriate to use Estradurin in the primary or secondary hormonal therapy of metastasized prostate cancer patients without prominent cardiovascular morbidity, and especially in those with osteoporosis.

### Acknowledgements

We acknowledge statisticians Lena Damber and Örjan Nordle, monitors Marie Botilsrud, Maria Concha, Hildeburg Eriksson, Charlotte de Molade, Thea Nieminen, Kerstin Paulsson, Paula Saari, Britt Tryde and Lena Wiman, data technician Gunilla Andersson, and secretaries Anneli Lahtinen and Hilikka Lindberg. This study was financially supported by Ferring AB, Malmö, Sweden, Ferring Laegemidler A/S Copenhagen, Denmark, Pharmacia AB, Sweden, and Schering-Plough AB, Stockholm, Sweden.

### References

- [1] Henriksson P, Blombäck M, Eriksson A, Stege R, Carlström K. Effect of parenteral estrogen on the coagulation system in patients with prostatic carcinoma. *Br J Urol* 1990;65:282-5.
- [2] Aro JL, Happpainen RK, Rannikko SA, Alftan OS. High dose polyestradiol phosphate with and without acetosalicylic acid versus orchiectomy in the treatment of prostatic cancer. Finnprostate Group. *Br J Urol* 1989;63:512-4.
- [3] Lukkarinen O, Kontturi M, Finnish Zoladex Multicentre Study Group. Comparison of long-acting LHRH agonist and polyestradiol phosphate in the treatment of advanced prostatic carcinoma. *Scand J Urol Nephrol* 1994;28:171-8.
- [4] Stege R, Carlström K, Collste L, Eriksson A, Henriksson P, Pousette A. Single-drug parenteral estrogen treatment in prostatic cancer: a study of two maintenance-dose regimens. *Prostate* 1989;14:183-8.
- [5] Henriksson P, Carlström K, Pousette A, Gunnarsson PO, Johansson CJ, Eriksson B, et al. Time for revival of estrogens in the treatment of advanced prostatic carcinoma? Pharmacokinetics and endocrine and clinical effects of a parenteral estrogen regimen. *Prostate* 1999;40:76-82.
- [6] Henriksson P, Eriksson A, Stege R, Collste L, Pousette A, von Schoultz B, et al. Cardiovascular follow-up of patients with prostatic cancer treated with single-drug polyestradiol phosphate. *Prostate* 1988;13:257-61.
- [7] Hedlund PO, Henriksson P, Scandinavian Prostatic Cancer Group (SPCG)-5 Trial Study Group. Parenteral estrogen versus total androgen ablation in the treatment of advanced prostatic carcinoma: effects on overall survival and cardiovascular mortality. *Urology* 2000;55:328-33.
- [8] Esposti P. Cytologic malignancy grading of prostatic carcinoma by transrectal aspiration biopsy. *Scand J Urol Nephrol* 1971;5:199-209.

- [9] Mostofi FK, Sesterhenn IA, Sobin LH. Histologic typing of prostate tumors. Geneva: World Health Organization; 1980. p. 17–21.
- [10] Soloway MS. The importance of prognostic factors in advanced prostate cancer. *Cancer* 1990;66:1017–21.
- [11] Andersson L. Design of clinical trials on prostate cancer. *Urology* 1997;49(Suppl 4A):39–45.
- [12] Hedlund PO, Ala-Opas Martti, Brekkan E, Damber JE, Damber L, Hagerman I, et al. Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer. *Scand J Urol Nephrol* 2002;36:405–13.
- [13] Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207–14.
- [14] Frödin T, Ålund G, Varenhorst E. Measurement of skin blood-flow and water evaporation as a means of objectively assessing hot flushes after orchidectomy in patients with prostatic cancer. *Prostate* 1985;7:203–8.
- [15] Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm* 1987;15:657–80.
- [16] Hedlund PO, Gustafson H, Sjögren S. Cardiovascular complications to treatment of prostate cancer with estramustine phosphate (Estracyt®) or conventional estrogen. *Scand J Urol Nephrol Suppl* 1980;55:103–5.
- [17] Mikkola A, Aro J, Rannikko S, Oksanen H, Ruutu M. Cardiovascular complications in patients with advanced prostatic cancer treated by means of orchidectomy or polyestradiol phosphate. *Scand J Urol Nephrol* 2005;39:294–300.
- [18] Henriksson P, Blombäck M, Bratt G, Edhag O, Eriksson A, Vesterqvist O. Effects of oestrogen therapy and orchidectomy on coagulation and prostanoid synthesis in patients with prostatic cancer. *Med Oncol Tumor Pharmacother* 1989;3:219–25.
- [19] Blombäck M, Hedlund PO, Säwe U. Changes in blood coagulation and fibrinolysis in patients on different treatment regimens for prostatic cancer – predictors for cardiovascular complications? *Thromb Res* 1988;49:111–21.
- [20] Henriksson P, Blombäck M, Eriksson A, Stege R, Carlström K. Effect of parenteral oestrogen on the coagulation system in patients with prostatic carcinoma. *Br J Urol* 1990;65:282–5.
- [21] Eisen M, Napp HE, Vock R. Inhibition of platelet aggregation caused by estrogen treatment in patients with carcinoma of the prostate. *J Urol* 1975;114:93–7.
- [22] Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. *J Clin Oncol* 2006;24:3979–83.
- [23] Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006 Sep 20;24:4448–56.
- [24] Sternberg CN. Apples and oranges. RE: 7.4 year update of the ongoing bicalutamide early prostate cancer (EPC) trial program. *Br J Urol Int* 2006;97:435–8.
- [25] Adolfsson J, Garmo H, Varenhorst E, Ahlgren G, Ahlstrand C, Andren O, et al. Clinical characteristics and primary treatment of prostate cancer in Sweden between 1996 and 2005. *Scand J Urol Nephrol* 2007;41:456–77.
- [26] Aus G, Abbou CC, Bolla M, Heidenreich L, Schmid HP, Van Poppel H, et al. EAU guidelines on prostate cancer. *Eur Urol* 2005;48:546–51.
- [27] Leuprolide Study Group. Leuprolide versus diethylstilbestrol for metastatic prostate cancer. *N Engl J Med* 1984;311:1281.
- [28] Cox RL, Crawford D. Estrogens in the treatment of prostate cancer. *J Urol* 1995;154:1991–8.
- [29] Spetz AC, Hammar M, Lindberg B, Spångberg S, Varenhorst E. Prospective evaluation of hot flushes during treatment with parenteral estrogen or complete androgen ablation for metastatic carcinoma of the prostate. *J Urol* 2001;166:518.

## Appendix A: Participants in the SPCG-5 Trial

### Denmark

Aalborg Hospital: Torben Krarup; Bispebjerg Hospital: Valdemar Hvidt, Peter Mogensen; Frederiksberg Hospital: Michael Luke; Frederikshavn Hospital: Ole Sörensen; Gentofte Hospital: Cai Frimodt-Möller, Henrik Willumsen; Glostrup Hospital: Peter Klarskov, Svend Mortensen; Herlev Hospital: Jesper Rue Andersen, Finn Rasmussen; Holbaek Hospital: Palle Rosenkilde; Hvidovre Hospital: Hans Georg Iversen; Naestved Hospital: Erik Larsen; Nykøbing Hospital: Paul Skaarup; Odense Hospital: John Farber, Niels Svoggaard; Randers Hospital: Sören Mommsen; Rigshospitalet: Peter Iversen, Jørgen Kvist Kristensen; Skejby Hospital: Finn Lundbeck, Hans Wolf; Viborg Hospital: Arne Højsgaard.

### Finland

Diakonissa Hospital: Antero Halme; Helsinki University Hospital: Mirja Ruutu, Jaakko Salo; Hyvinkaa Hospital: Eero Kasinen; Jorvi Hospital: Harri Juusela; Kuopio Hospital: Martti Ala-Opas; Lohja Hospital: Risto Salminen; Mikkeli Hospital: Tapani Liukkonen; Joensuu Hospital: Jouko Viitanen; Päijät Hämeen Hospital: Martti Talja; Lappenranta Hospital: Jaakko Permi, Veli-Matti Puolakka; Turku Hospital: Martti Nurmi; Vaasa Hospital: Erkki Hansson.

### Iceland

Borgarspítalinn Hospital: Guðmundur Geirsson.

### Norway

Bergen Hospital: Svein Haukaas, Per Aage Høisaeter; Levanger Hospital: Fredrik Hesselberg, Karsten Vada; Stavanger Hospital: Ilker Tasdemir, Sigmund Vaage; Trondheim Hospital: Per Lundmo; Ullevål Hospital: Carl-Johan Ribbegren, Per Ögreid.

### Sweden

Boden Hospital: Andrzej Owczarski; Eskilstuna Hospital: Leif Borck, Torsten Lindeborg; Hudiksvall Hospital: Stig Susskind; Karlshamn Hospital: Bo Hedberg; Karlstad Hospital: Björn Kihl, Jan-Olof Olsson; Karolinska Hospital: Per Olov Hedlund, Lars Häggarth; Kristinehamn Hospital: Bruno Larsson; Kungälv Hospital: Sture Carlsson, Bengt Lind-

berg; Linköping Hospital: Inge Höjgaard, Anders Spångberg; Lund Hospital: Peter Elfving, Rolf Lundgren; Mora Hospital: Bengt Hahne; Norrtälje Hospital: Richard Ideström; Sahlgrens Hospital: Jan-Erik Damber, Hans Hedelin; Sala Hospital: Bengt Andersson; Sandviken Hospital: Torsten Sandin; Säffle Hospital: Mauritz Wallden, Ole Sörensen; Trelleborg Hospital: Ronnie Olsson, Ebbe Telhammar; Umeå Hospital: Torvald Granfors, Pär Stattin; Uppsala Hospital: Einar Brekkan, Bo Johan Norlen; Varberg Hospital: Jan Hammarsten; Värnamo Hospital: Ib Mikkelsen, Anders Ramsing; Västervik Hospital: Inger Wall; Växjö Hospital: Lars Adell, Agneta Ullman; Ystad Hospital: Curt-Erik Nelson; Ängelholm Hospital: Susanne Ljungeryd; Örebro Hospital: Sven-Olof Andersson, Jan Erik Johansson.

*Members of the scientific committee*

Kjell Carlström, Department of Endocrinology, Huddinge University Hospital, Sweden; Jan-Erik Damber, Department of Urology, Sahlgrens University Hospital, Gothenborg, Sweden; Lena Damber, Oncology Center, Umeå University Hospital, Umeå, Sweden; Per Olov Hedlund, Department of Urology, Karolinska University Hospital, Stockholm, Sweden; Peter Henriksson, Department of

Internal Medicine, Danderyd University Hospital, Danderyd, Sweden; Per Aage Höisaeter, Department of Urology, Haukeland University Hospital, Bergen, Norway (Chairman); Peter Iversen, Department of Urology, Rigshospitalet, Copenhagen University, Denmark (Secretary); Jan Erik Johansson, Department of Urology, Örebro University Hospital, Örebro, Sweden; Ole Steen Nielsen, Department of Oncology, Århus Community Hospital, Århus, Denmark; Bo Johan Norlen, Department of Urology, Uppsala University Hospital, Uppsala, Sweden; Åke Pousette, Laboratory for Reproductive Health, Karolinska University Hospital, Stockholm, Sweden; Sakari Rannikko, Department of Urology, Helsinki University Hospital, Helsinki, Finland; Finn Rasmussen, Department of Urology, Herlev University Hospital, Copenhagen, Denmark; Reinhard Stege, Department of Urology, Huddinge University Hospital, Huddinge, Sweden (Co-chairman); Teuvo Tammela, Department of Urology, Tampere University Hospital, Tampere, Finland; Eberhard Varénhorst, Department of Urology, Linköping University Hospital, Linköping, Sweden; Hans Wolf, Department of Urology, Skejby University Hospital, Århus, Denmark.