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Prostate Cancer

Ten- and 15-yr Prostate Cancer-specific Mortality in Patients with Nonmetastatic Locally Advanced or Aggressive Intermediate Prostate Cancer, Randomized to Lifelong Endocrine Treatment Alone or Combined with Radiotherapy: Final Results of The Scandinavian Prostate Cancer Group-7

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Abstract

Background: In high-risk prostate cancer (PCa), no study with observation times beyond 10 yr has demonstrated survival improvement after addition of prostatic radiotherapy (RAD) to endocrine treatment (ET) alone.
Objective: To compare mortality rates in patients receiving ET alone versus ET + RAD.
Design, settings, and participants: From 1996 to 2002, 875 Scandinavian patients with high-risk (90%) or intermediate PCa were randomized to ET or ET + RAD (The Scandinavian Prostate Cancer Group-7). After 3 mo with total androgen blockade in all patients, all individuals continued lifelong antiandrogen monotherapy. Those randomized to ET + RAD started prostate radiotherapy (70 Gy) at 3 mo.
Outcome, measurements and statistical analysis: PCa-specific 15-yr mortality represented the primary endpoint. Assessment of the combination treatment effect and prognostic factors was performed in competing risk analyses and Cox proportional-hazard models.
Intervention: RAD added to ET.
Results and limitations: With a median observation time of 12 yr, the 15-yr PCa-specific mortality rates were 34% (95% confidence interval, 29–39%) and 17% (95% confidence interval, 13–22%) in the ET and ET + RAD arms respectively ($p < 0.001$). Compared with the ET arm, the median overall survival in the ET + RAD arm was prolonged by 2.4 yr. Treatment with ET alone, age ≥65 yr and increasing histology grade independently increased the risk of PCa-specific and overall mortality. Limitations include nonformal evaluation of comorbidity, the inability to calculate progression-free survival, and lack of information about salvage therapy and toxicity.

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Conclusions: In patients with nonmetastatic locally advanced or aggressive PCa, ET + RAD reduces the absolute risk of PCa-specific death by 17% at 15 yr compared with ET alone; the comparable 15-yr PCa-specific mortality rates being 17% and 34%. The results warrant a phase 3 study comparing ET + RAD with radical prostatectomy in high-risk PCa.
Patient summary: Adding prostatic therapy to lifelong antiandrogen therapy halves the absolute risk of death from prostate cancer from 34% to 17% 15 yr after diagnosis.

1. Introduction

Multiple studies have proven that pelvic radiotherapy (RAD) combined with androgen deprivation therapy (ADT) prolongs survival compared with radiotherapy alone in patients with locally advanced prostate cancer (PCa) [1]. Nevertheless, endocrine therapy (ET) alone (medical or surgical castration or oral antiandrogens) may still be viewed as a therapeutic option in patients with locally advanced PCa, at least on the basis of the favorable long-term results of The Scandinavian Prostate Cancer Group (SPCG)-6 [2].

Two of three randomized trials [3–5] with median observation times below 10 yr have indicated that RAD combined with ET improves overall and PCa-specific survival compared with ET alone. Nevertheless, more mature survival results are desirable for final assessment of the role of combined treatment.

From 1996 to 2002 the SPCG conducted a phase 3 trial (SPCG-7; ISRCTN01534787) with the primary objective to compare PCa-specific survival in patients with nonmetastatic advanced stage or aggressive localized PCa treated with life-long ET with patients receiving similar ET combined with RAD (ET + RAD). After a median follow-up of 7.6 yr, mortality results were published in 2009 [3]. We now report mature mortality results with a median follow-up of more than 13 yr in surviving patients.

2. Patients and methods

2.1. Patients

Details of trial performance, participants, and compliance with the Consolidated Standards of Reporting Trials criteria have been published previously [3]. Briefly, consenting eligible patients included from 47 centers in Norway, Sweden, and Denmark fulfilled the following criteria: (1) age $<$ 75 yr, (2) clinically estimated life expectancy $\geq$10 yr, (3) clinical tumor stage 1 or 2 (TNM-classification, 1992) [6] if World Health Organization (WHO) histological grade II, or clinical tumor stage 3 combined with any grade (Gleason score was not yet used throughout Scandinavia when this study was initiated), (4) prostate-specific antigen (PSA) $\leq$70 ng/ml, (5) M0 by bone scan and chest x-ray, and (6) N0 (PSA $\leq$10 ng/ml, or by bilateral obturatory lymphadenectomy [n = 693]). For the purpose of the present study, patients were retrospectively classified into National Comprehensive Cancer Network risk groups [7] with the following approximation: WHO grade I → Gleason score 6; WHO grade II → Gleason score 7; WHO grade III → Gleason score $\geq$8 (low risk: T1; WHO grade I; PSA level $<$10 ng/ml; intermediate risk: intraprostatic tumors with WHO grade II were regarded as "moderately aggressive". High risk: T3 or WHO grade III or PSA level $>$20 ng/ml).

2.2. Randomization and treatment

From 1996 to 2002, 875 eligible patients were randomized to ET alone (N = 439; Arm 1) or ET + RAD (N = 436; Arm 2), with stratification according to study center, T stage, and grade with a block size of four. To ensure allocation concealment, randomization was by computer through a telephone service at the Oncology Centre at Umeå University. After randomization all patients underwent a 3-mo period of ADT with a luteinizing hormone-releasing hormone agonist (Procren, Abbott, Solna, Sweden) combined with flutamide (250 mg $\times$ 3 oral administration daily; Eulexin, Schering-Plough, Stockholm, Sweden). Medical castration was discontinued after 3 mo in both arms and patients in Arm 2 started pelvic RAD. All patients continued with flutamide 750 mg daily. The daily flutamide dose was reduced to 500 mg or transiently discontinued in case of toxicity. Alternatively, bicalutamide (Casodex, Astra-Zeneca, Mölndal, Sweden) 150 mg oral administration daily was prescribed. The majority of patients also received breast irradiation to prevent gynecomastia [8].

Standard three-dimensional conformal RAD using customized blocks with 2 Gy per fraction was given to the prostate and the seminal vesicles with a central target dose of 50 Gy followed by a 20-Gy boost to the prostate (total dose to the prostate 70 Gy). During the study period, the protocol was amended and a total dose of 74–78 Gy was allowed (given to 6% [27/436]) of the patients in Arm 2).

In case of progression, pelvic RAD was allowed in Arm 1. For patients in Arm 2, ADT was recommended. Initially, progression was defined as symptomatic loco-regional growth or the development of distant metastases. From 2002, a PSA increase above 10 ng/ml was accepted as a criterion for progression. Subsequently, on the introduction of the American Society for Therapeutic Radiation and Oncology criteria, a PSA increase above the nadir by $\geq$2 ng/ml was applied. These amendments are not expected to have modified PCa-specific or overall mortality.

2.3. Follow-up assessment

At the time of the present analysis, complete individual long-term data on biochemical and clinical progression were not available. Therefore, the study steering committee in 2014 decided to restrict this final trial analysis to PCa-specific and overall mortality.

2.4. Statistical analyses

All analyses were performed according to the intention-to-treat principle. The primary end point of the present study was death from prostate cancer (with death from other causes treated as competing risk) [9]. Death from any cause was the secondary endpoint. Gray's test was applied to assess treatment effects [10]. Treatment effect sizes were quantified by determining differences in cumulative incidence and relative risks (both with 95% confidence intervals [CI]), estimated with the use of Cox proportional-hazard models. CI for the difference in cumulative incidence was computed assuming a normal distribution with the asymptotic variance estimated according to Aalen [11]. Number needed to treat to avert one PCa-specific death was calculated as the

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