Early Versus Delayed Endocrine Treatment of T2-T3 pN1-3 M0 Prostate Cancer Without Local Treatment of the Primary Tumour: Final Results of European Organisation for the Research and Treatment of Cancer Protocol 30846 After 13 Years of Follow-up (A Randomised Controlled Trial)

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Abstract

Background: The timing of endocrine treatment (ET) for prostate cancer (PCa) remains controversial. The issue is addressed in European Organisation for the Research and Treatment of Cancer (EORTC) protocol 30846 for patients with lymph node–positive (pN1-3) cancer without local treatment of the primary tumour.

Objective: To evaluate the effect of early versus delayed treatment in pN1-3 PCa.

Design, setting, and participants: Two hundred thirty-four patients with histologically proven PCa and nodal metastases (pN1-3) were randomized to immediate versus delayed ET without treatment of the primary tumour. ET consisted of a depot luteinising hormone-releasing hormone (LHRH) agonist and 1 mo of an anti-androgen or surgical castration. The trial's main objective was to show non-inferiority of delayed ET to immediate ET by ruling out a hazard ratio (HR) of 1.50 for overall survival (OS), with 85% power at one-sided α = 5%.

Measurements: All but three patients were treated as randomized. The median follow-up is 13 yr. The median protocol treatment duration was 2.7 yr in the delayed and 3.2 yr in the immediate ET groups.

Results and limitations: Overall, 193 patients (82.5%) have died (97 on delayed ET and 96 on immediate ET), 59.4% of them as a result of PCa. The intention-to-treat analysis shows a 22% increase in the hazard of death of those randomized to delayed treatment (HR = 1.22, 95% confidence interval [CI]: 0.92, 1.62). The difference is not statistically significant, but non-inferiority is also not proved.

The median OS on immediate ET is 7.6 yr (95% CI, 6.3–8.3 yr) versus 6.1 yr (95% CI, 5.7–7.3 yr) in the delayed ET group. The 10-yr cumulative incidence of death resulting from PCa was 55.6% in the delayed ET group versus 52.1% with immediate ET group. Similar conclusions hold for PCa-specific survival.

Conclusions: After 13 years of follow-up, survival or PCa-specific survival between immediate and delayed ET appear similar, but the trial is underpowered to reach its goal of showing non-inferiority.

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1. Introduction

This study was designed between 1984 and 1986 to compare delayed endocrine treatment (DET) to early endocrine treatment (EET) in patients with lymph node–positive (pN+) prostate cancer (PCa). At that time, little was known about the survival of men with pN+ PCa. Kramer et al described a 5-yr overall survival (OS) of 39.5% in patients with pN+ PCa treated initially by surveillance [1]. This information, which was in line with institutional data of the principal investigator [2], was the basis for the sample size calculation of this protocol. Because of observations showing more favourable response (volume reduction) of the primary tumour than of the metastatic disease and because of the side effects of radical prostatectomy (RP) and radiotherapy (RT) at that time, it was decided not to treat the primary tumour [3,4].

Earlier studies conducted by the Veterans Administration Cooperative Urological Research Group (VACURG) had allowed indirect comparison of early versus delayed treatment in locally advanced PCa [5,6]. These studies had never been confirmed in a prospective randomized trial using EET versus DET as the primary treatment options. On this background, European Organisation for the Research and Treatment of Cancer (EORTC) protocol 30846 intended to contribute to a better understanding of this issue in managing node-positive disease and M0 PCa patients. This report presents the definitive study results, as 82.5% of the patients have died and further follow-up is not expected to change the conclusions. Earlier results were reported in 2004 [7]; thus, details—specifically, those relating to the criteria at entry—are not repeated here.

2. Methods

2.1. Randomisation and follow-up scheme

This trial recruited 302 participants from February 1986 to November 1998. Temporarily, from June 1988 until March 1993, 68 men who refused randomisation were registered in the study as a separate stratum and followed according to protocol. These results are not included in the present analysis. A total of 234 men with locally confined or locally advanced PCa (category T2-T3) and histologically or cytologically confirmed lymph node metastases were randomized between DET and EET. Eligibility criteria allowed N1-3 (TNM 1972) but not N4 disease (computed tomography [CT] scan was mandatory), no previous treatment other than lymph node dissection or lymph node biopsy, no evidence of further metastatic disease (assessed by bone scan and CT scan), and a World Health Organization (WHO) performance status (PS) of 0–2. The primary histologic diagnosis was left to the institutional pathologist.

The randomization and treatment scheme is shown in Table 1. Endocrine treatment consisted of 3.6 mg of Zoladex (AstraZeneca, London, UK) given subcutaneously every 4 wk and cyproterone acetate (CPA) 50 mg given orally 3 times per day for the first 4 wk of treatment. Change from DET to endocrine treatment was indicated upon clinical progression.

<table>
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<th>Table 1 – Randomisation, treatment, and decision points in EORTC protocol 30846</th>
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<td><strong>Treatment scheme for EORTC Protocol 30846</strong></td>
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| A | N | | |
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| T | O | | |
| M | | | |
| Institution | | | |
| IET | | Treatment according to investigator’s discretion |
| ET | | OR | |
| Zoladex: 3.6 mg subcutaneously every 4 wk + CPA: 50 mg tid first 4 wk | | | |
| **OR** | | **Orchidectomy (as of 7 February 1991)** |

EORTC, European Organisation for the Research and Treatment of Cancer; WHO, World Health Organization; DET, delayed endocrine treatment; ET, endocrine treatment; CPA, cyproterone acetate.
or, at the investigators discretion upon subjective progression, based on a rise of serum prostate-specific antigen (PSA) or an increase in the T category or prostatic volume.

2.2. Treatment

Endocrine treatments in the DET arm were identical to the EET given initially in the EET arm. According to the study scheme, two progression endpoints were defined in the DET arm. If progression occurred under endocrine treatment, further management was at the discretion of the investigator. However, there was a strong recommendation to continue endocrine treatment. PCa as cause of death was determined by the institutional investigators.

2.3. Follow-up

Patients were initially followed every 3 mo. After 2 yr of endocrine treatment and unstable situations, six monthly follow-up visits were allowed. Patients who concluded protocol treatment were followed yearly until death. Follow-up investigations included acid phosphatase (and since 1988, PSA) plasma testosterone, liver function tests, rectal examination, ultrasound measurements of the prostate, and yearly bone scans. Only the last three parameters but not PSA were the indicators of clinical progression and indicated ET in the DET arm (increase in T category, increase in transrectal ultrasound–measurable prostate volume under ET, and new lesions on bone scans continued by x-ray).

2.4. Endpoints

The primary trial endpoint is OS counted from randomization to the day of death. Cancer-specific and non-cancer mortality were likewise counted, considering only death of the cause of interest as events and censoring the others as a competing risk.

2.5. Statistical objectives

The trial was designed to prove non-inferiority of DET to EET. Non-inferiority was originally defined as a decrease of <15% in 4-yr survival rates, based on the assumption of a 50% OS at 4 yr with immediate treatment (one-sided t test at α = 5% with 85% power, hazard ratio [HR] = 1.50, 180 events needed). Three hundred twenty patients were considered required. The same number of patients and events was also sufficient to rule out an equivalent 10% decrease in the 4-yr survival rate from a more realistic 75% to 65%.

Since the trial was launched, the conception of what might be called equivalence or non-inferiority has evolved and now allows only much smaller survival losses and smaller false positive error rates (HR ≤ 1.25 and one-sided α = 2.5%), so that the original sample size calculation would now be considered unethical. Furthermore, the recruitment was difficult, so that not even the originally planned 320 evaluable men were recruited. Thus, in spite of having now reached the benchmark for data analysis, according to the original protocol, a survival loss that would result in statistically significant non-inferiority according to the original design may be regarded as clinically relevant to current-day practice [8,9].

2.6. Statistical analysis

OS rates were estimated by the Kaplan-Meier method and cause-specific mortality by cumulative incidence [10]. Treatment effects are summarized by HRs, with 95% confidence intervals (CI) estimated from the Cox proportional hazards model. The analysis was performed on all randomized patients (intention to treat) as well as on eligible patients according to treatment received. Because the data of the two analyses did not show any major differences, we only report the intention-to-treat analysis.

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**Fig. 1 – EORTC study 30846. Recruitment 1986–1998; median follow-up: 13 yr (randomized group).**

DET, delayed endocrine therapy; IET, immediate endocrine therapy; PCa, prostate cancer.
3. Results

The flow diagram of the study (consort diagram) is provided in Fig. 1. Five men were ineligible (three in the DET arm and two in the EET arm). Assigned protocol treatment was never started in 14 men—9 in the DET arm and 5 in the EET arm. The analysis was conducted on all 234 men randomized; the registered cohort is not included.

3.1. Baseline characteristics

Baseline characteristics were detailed in the previous publication [7] and are also shown in Table 2. The two groups were well balanced except for small differences for some factors: the median age was 66.6 yr for the EET arm and 64.3 yr for the DET arm. In the EET arm, 29.4% of the tumours were poorly differentiated (WHO grade 3) versus 33.9% in the DET arm, but T3-4 (TNM 1972) were seen in 68.1% of the patients in the EET arm versus 62.6% in the DET arm.

3.2. Treatment

Fig. 2 shows the Kaplan-Meier projections of protocol treatment duration for the two arms, with two curves relating to respectively time to treatment start and end of protocol for the DET arm. In the DET arm, the median duration of protocol treatment was 4.8 yr (95% CI, 3.9–5.7 yr), and the maximum time to the discontinuation of treatment was 15.9 yr. In the EET arm, the median time on treatment was 5.1 yr (95% CI, 3.9–6.5 yr), and the maximum duration of treatment was 19.4 yr. The median time to the initiation of treatment in the DET arm was 1.8 yr (95% CI, 1.4–2.1 yr), and the longest time to start of DET was 9.2 yr. At the time of this analysis, protocol treatment was still ongoing in 13 patients in the DET arm and 19 patients in the EET arm. Reliable information concerning the treatment modalities, which were applied at the investigators’ discretion at the time of progression under endocrine treatment, is not available. However, yearly follow-up indicates that 50% of the patients in the delayed and immediate group, respectively, continued the same treatment as per protocol after they reached the end of the protocol treatment.

As Fig. 2 indicates, there is no difference in the total duration on protocol treatment between the two treatment arms.

3.3. Survival

At 13 yr median follow-up, 193 of the 234 randomized patients (82.5%) have died (97 in the DET arm (84.3%) and 96 in the EET arm (80.7%); see Table 3. In both arms, roughly 60% of the deaths were the result of PCa. Cardiovascular deaths were also equally distributed between the two arms in spite of prolonged endocrine treatment. Deaths resulting from other cancers, infectious disease, and other causes of death, including cardiovascular diseases, were also balanced between the treatment arms.

There is no statistically significant difference between OS rates in the two treatment arms (Fig. 3); the median survival for delayed endocrine treatment was 6.1 yr and for immediate treatment 7.6 yr (Table 4). The HR of 1.22 indicates a 22% relative increase in the risk of death in the DET arm compared to the EET arm. This difference, however,
considering the inclusion of 1.0 inside the 95% CIs, is not statistically significant. The 95% CI represents the range of plausible differences between the two groups. The lower limit of the interval (optimistic bound) of 0.92 represents an 8% relative advantage (relative decrease in the risk of death) in favour of the group allocated to DET. In contrast, the upper 95% limit of the CI (pessimistic bound) of 1.62 indicates a 62% relative increase in the hazard of death in the DET group compared to the EET group. The upper bound being >1.5, the study cannot demonstrate non-inferiority according to the original protocol objectives.

Fig. 4 shows Kaplan-Meier projections of overall mortality, cancer-specific mortality, and non-cancer mortality. The 5-yr cumulative incidence of PCa mortality was 28.0% in the delayed arm and 23.2% in the immediate treatment arm. The respective data after 10 yr amount to 55.6% and 52.1%, respectively, indicating a number of patients needed to treat of 20.8 to spare one life by year 5 and of 28.6 to spare one life by year 10. Neither cancer-related nor
overall mortality differed significantly. The mortality curves for non-cancer mortality in the two treatment arms are overlapping. This is in line with Table 3, which shows that there is no difference in absolute numbers of death resulting from cardiovascular events or other causes.

4. Discussion

At present, EORTC protocol 30846 can be considered mature: 82.5% of all participants have died, and the median follow-up is 13 yr. We calculated that even if all patients in the study were dead, the
information gain would not bring the lower bound of the CI above 1, which would prove benefit of immediate treatment. To detect a difference in the magnitude observed in the trial (22%), many more events would be required than can be produced by this study.

The study shows that in men with regional lymph node metastases, delay of endocrine treatment will result in clinical progression after an average of 1.8 yr. During this period of time, patients enjoy their normal lifestyle, including sexual activity. Unfortunately, quality of life (QoL) was not studied in this protocol. The advantage of remaining eugonad may, however, be negatively influenced by the anxiety resulting from knowledge about the presence of their untreated cancer.

Clinical progression in this trial triggered the initiation of ET in the DET arm and the end of protocol treatment in both arms. The expected variations of the identification and timing of progression may have influenced the outcome of the study in either direction.

Randomisation to this protocol was very difficult. Patients were expecting to undergo RP and, in addition to the disappointment resulting from the presence of lymph node metastases that excluded the possibility of radical treatment, it was then explained to them that it did not matter whether immediate endocrine treatment was installed. These conversations took a long time and often had to be repeated. In 1998, the protocol was finally discontinued because of the absence of inclusion.

4.1. Other, related evidence

The Eastern Cooperative Oncology Group (ECOG) conducted this trial as an intergroup study, protocol 3886, which differed from the present EORTC study by the predominant inclusion of locally confined PCa and because RP was performed in both the EET and the DET treatment arms. That study was last reported in 2006 [11]; it also encountered major difficulties in recruitment and could not meet the expected sample size of 220 participants. Eventually, 100 men were randomized between early and delayed endocrine treatment. At a median follow-up of 11.9 yr, a persisting significant benefit for early treatment was seen in OS (HR = 1.84, 95% CI, 1.01–3.35, p = 0.04; in cancerspecific survival [CSS], HR = 4.09, 95% CI, 1.76–9.49, p = 0.0004). Among several possible explanations for these major differences in outcome, the most obvious is the application of RP to the ECOG protocol. The persistence of clonal populations of cells in the primary tumour that have the capability of metastasizing is a very sensible explanation offered by Messing et al [12]. This working hypothesis is also confirmed by the outcome of several RT studies of localized and locally advanced PCa, mostly without precise knowledge of lymph node involvement. Most prominently, EORTC protocol 22863, a study of RT with and without adjuvant endocrine treatment for a period of 3 yr, showed an OS difference of 16% and of 34%, respectively, in disease-free 5-yr survival [13]. Other studies conducted in Europe and the United States confirm these results. A complete recent review is found in Lawton et al [14]. The present study may, because of a lack of power, miss a clinically relevant difference.

Present evidence shows that immediate endocrine treatment in locally confined or locally advanced disease with a proven or high likelihood of lymph node metastases improves OS and CSS if combined with surgical removal or RT of the primary tumour. It is unlikely that hormonal treatment alone might have similar effects. It is, however, regrettable that the RT and surgical studies using adjuvant endocrine treatment have not also included an endocrine treatment–only arm. An attempted meta-analysis on this subject has never been published in a peer-reviewed setting [15]. The preliminary data include a mixture of trials treating the primary tumour aggressively and others that do not. A more complete review of the issue, including QoL aspects, has recently been published [16]. A possible beneficial effect of EET in localised PCa without treatment of the primary tumour remains hypothetical. In spite of the small numbers, it is remarkable that there is no difference in cardiovascular deaths between the two arms. Also, other side effects were similar in the two arms but were not extensively studied.

5. Conclusion

This underpowered study does not show non-inferiority of DET to ET applied to men with T2-3PN1-3 M0 PCa.

Author contributions: Fritz H. Schröder 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: Schröder, Collette.
Acquisition of data: Kurth, Fossa, Hoekstra, Karthaus.
Analysis and interpretation of data: De Prijck, Collette.
Drafting of the manuscript: Schröder.
Critical revision of the manuscript for important intellectual content: Schröder, Kurth, Fossa, Hoekstra, Karthaus, De Prijck, Collette. Statistical analysis: Collette.

Obtaining funding: Schröder, Data Center EORTC.

Administrative, technical, or material support: De Prijck.

Supervision: Schröder, Collette.

Other (specify): M. H. van der Linde for typing, revision, and submission.

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