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Survival benefit of early androgen receptor inhibitor therapy in locally advanced prostate cancer: Long-term follow-up of the SPCG-6 study

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Abstract ***Background:*** The optimal timing of endocrine therapy in non-metastatic prostate cancer (PCa) is still an issue of debate.
Methods: A randomised, double-blind, parallel-group trial comparing bicalutamide 150 mg once daily with placebo in addition to standard care in patients with hormone-naïve, non-metastatic PCa. Kaplan–Meier analysis was used to estimate overall survival (OS) and multivariate Cox proportional hazard model was performed to analyse time-to-event (death).
Findings: A total of 1218 patients were included into the Scandinavian Prostate Cancer Group (SPCG)-6 study of which 607 were randomised to receive bicalutamide in addition to their standard care and 611 to receive placebo. Median follow-up was 14.6 years. Overall, 866 (71.1%) patients died, 428 (70.5%) in the bicalutamide arm and 438 (71.7%) in the placebo arm, $p = 0.87$. Bicalutamide significantly improved OS in patient with locally advanced disease (hazard ratios (HR) = 0.77 (95% confidence interval (CI): 0.63–0.94, $p = 0.01$), regardless of baseline prostate-specific antigen (PSA), with a survival benefit which was apparent throughout the study period. In contrast, survival favoured randomisation to the placebo arm in patients with localised disease (HR = 1.19 (95% CI: 1.00–1.43), $p = 0.056$). However, a survival gain from bicalutamide therapy was present in patients with localised disease and a baseline PSA greater than 28 ng/mL at randomisation. In multivariate Cox

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proportional hazard model, only including patients managed on watchful waiting as their standard of care ($n = 991$) OS depended on age, World Health Organisation (WHO) grade, baseline PSA, clinical stage and randomised treatment.

Interpretation: Throughout the 14.6 year follow-up period the addition of early bicalutamide to standard of care resulted in a significant OS benefit in patients with locally advanced PCa. In contrast, patients with localised PCa and low PSA derived no survival benefit from early bicalutamide. The optimal timing for initiating bicalutamide in non-metastatic PCa patients is dependent on disease stage and baseline PSA.

1. Introduction

Two randomised studies, COU-AA-302 and PREVAIL, have recently shown that androgen synthesis inhibition (abiraterone acetate) and inhibition of androgen receptor signalling (enzalutamide) can increase overall survival (OS) in patients with chemo-naïve metastatic castration resistant prostate cancer (PCa) [1,2]. The efficacy of these new compounds in hormone-naïve PCa is currently investigated in phase II + III trials [3] (ClinicalTrials.gov identifier: NCT01715285). Although endocrine manipulation is not first line therapy in non-metastatic PCa [4], this new development has documented that endocrine manipulation may prolong survival and it revives the old controversy of what constitutes the optimal timing of endocrine manipulation in management of PCa [5].

The Scandinavian Prostate Cancer Group (SPCG)-6 study was conducted as a randomised, double-blinded, placebo-controlled trial in Denmark, Finland, Norway, and Sweden. The SPCG-6 study was one of three trials included in the Early Prostate Cancer (EPC) programme evaluating the efficacy of bicalutamide 150 mg/day in addition to standard care in patients with hormone-naïve, non-metastatic PCa [6]. Previous separate analyses of the SPCG-6 trial indicated that the efficacy of bicalutamide depended on clinical stage and baseline prostate-specific antigen (PSA) at randomisation [7,8]. Patients with locally advanced (tumour category (T) 3–4, any N; or any T, N+) PCa randomised to bicalutamide had a significant improvement in progression-free survival (PFS) and OS, while survival non-significantly favoured placebo in patients with localised PCa (T1–2, N0/NX).

We report long-term survival update of the SPCG-6 study with a median follow-up of 14.6 years and an overall mortality rate of 71%.

2. Materials and methods

2.1. Study details

A detailed methodology of the SPCG-6 study has been described previously [7,9]. Between October 1995 and July 1998, 1218 males aged 18–75 years were included in 62 Nordic centres. Eligible patients had histologically confirmed localised (T1–2, N0/NX) or locally advanced (T3–4, any N; or any T, N+) hormone-naïve PCa with no evidence of distant metastases. Histological evaluation was performed according to the World Health Organisation (WHO) criteria. Their standard care before randomisation is listed in Table 1.

Patients were randomised on a 1:1 basis to receive either bicalutamide 150 mg or placebo once daily. Randomised treatment continued until disease progression. Patients were assessed every 12 weeks for primary tumour, distant metastases, clinical symptoms and PSA levels. The primary endpoints were PFS and OS. The second analysis of the EPC programme with 5.4 year follow-up demonstrated a significant reduction in PFS in patients receiving bicalutamide [10]. Consequently, the independent data and safety committee along with the trial steering committee recommended that randomised trial therapy should be stopped. Investigators and patients should be informed of the findings, and that the treatment code should be broken. The investigators could at their discretion continue patients on open-label bicalutamide, switch to alternative therapy or receive no further therapy.

2.2. Present study update

Between 2012 and 2014 the study was updated for survival status. In all of the 188 men who had died since the last update, the date and cause of death (PCa or other cause mortality) were recorded. Updated survival information could not be retrieved in 154 (28.6%) of the 538 patients alive at the last data lock 30th August 2008 [6]. The 154 patients were therefore censured on that date. Retroactively, body mass index (BMI) and Charlson co-morbidity index at entry were calculated based on baseline physical examination, medical history and concurrent medication. The dataset was locked 1st February 2014. The median follow-up of patients alive was 14.6 (10.2–18.3) years.

2.3. Statistical analysis

Continuous data are presented as median with range unless indicated otherwise. Chi-square test was used to test for independence. Kaplan–Meier analysis was used to estimate OS and competing risk analysis was used

Table 1
Demographic and baseline tumour characteristics at entry. Unless stated otherwise, values shown represent numbers of patients, with percentages of the total randomised cohort in parentheses.

	Bicalutamide 150 mg/daily plus standard care $n = 607$	Placebo plus standard care $n = 611$
Median age (years)	70 (range 46–87)	70 (range 52–77)
Median body mass index	22.3 (range 13.5–40.0)	22.6 (range 14.1–36.2)
Charlson co-morbidity index		
0	443 (73.0)	450 (73.6)
1	134 (22.1)	135 (22.1)
2	26 (4.3)	22 (3.6)
3–4	4 (0.7)	4 (0.7)
Median prostate-specific antigen (PSA)	13.8 (range 1–291)	12.6 (range 1–3107)
Tumour category[a]		
T1	120 (19.8)	137 (22.4)
T2	241 (39.7)	233 (38.1)
T3	236 (38.9)	226 (37.0)
T4	9 (1.5)	14 (2.3)
Unknown	1 (0.2)	1 (0.2)
WHO grading		
Well differentiated	259 (42.7)	264 (43.2)
Moderately differentiated	265 (43.7)	276 (45.2)
Poorly differentiated	72 (11.9)	68 (11.1)
Unknown	11 (1.8)	3 (0.5)
Nodal status		
N0	132 (21.7)	122 (20.0)
N+	28 (4.6)	26 (4.3)
Unknown	447 (73.6)	463 (75.8)
Disease stage[b]		
Localised	351 (57.9)	360 (59.0)
Locally advanced	255 (42.1)	250 (41.0)
Standard care received		
Radical prostatectomy	77 (12.7)	76 (12.4)
Radiotherapy/Brachythereapy	39 (6.4)	26 (4.3)
Watchful waiting	486 (80.1)	505 (82.7)
Other[c]	5 (0.8)	4 (0.7)

[a] In patients undergoing radical prostatectomy, disease stage was determined histopathologically, whereas in the remaining patients it was determined clinically.
[b] Patients with unknown tumour stage are excluded.
[c] Includes cryotherapy/cryosurgery and radical prostatectomy plus radiotherapy.

to account for PCa-specific and other cause mortality. Log-rank test was used to compare between the randomised groups. Results are presented with 95% confidence interval (CI). The efficacy of bicalutamide in localised and locally advanced PCa and as a function of baseline PSA, has again been analysed according to results found in previous publications [7,8]. Moreover, we have analysed the efficacy of bicalutamide according to a modification of the NCCN risk classification [11]: low-risk: T1, PSA <10 ng/mL, and well differentiated WHO; intermediate-risk: T2 and/or PSA 10–20 ng/mL and/or moderately differentiated WHO; and high-risk: T3 and/or, PSA >20 ng/mL and/or poorly differentiated WHO. Patients with T4 or lymph node metastasis were excluded from these analyses. A multivariate Cox proportional hazard regression model was performed to analyse time-to-event (death), including randomised treatment (categorical), locally advanced disease (categorical), PSA (continuous, log2 transformed), age (continuous) and histology grade (categorical). Test for distribution between covariates was done using chi-square statistics. Results are presented by hazard ratios (HR) with 95% CI. The expected overall survival was calculated using vital statistics from Statistics Denmark (www.statistikbanken.dk), Statistics Finland (tilastokeskus.fi), Statistics Norway (www.ssb.no), and Statistics Sweden (www.statistikdatabasen.scb.se), matched by age and year of consent. Two sided p-value <0.05 was considered significant. Statistical analysis was performed with SAS (v 9.2, SAS Institute, Cary, NC, USA).

3. Results

A total of 1218 non-metastatic PCa patients were included into the SPCG-6 study of which 607 were

randomised to receive bicalutamide and 611 to receive placebo in addition to their standard care. Baseline characteristics were well balanced between the two treatment arms, including BMI, Charlson co-morbidity, and PCa management before entry (Table 1). The majority of included patients (81.4%) had undergone watchful waiting (WW) before randomisation. Baseline characteristics in patients with localised and locally advanced PCa are available in Supplementary Table 1.

Overall, 866 (71.1%) patients died, 428 (70.5%) in the bicalutamide arm and 438 (71.7%) in the placebo arm (Table 2). The median survival for patients randomised

Table 2
Exposure to bicalutamide and androgen deprivation therapy and mortality data. Unless stated otherwise, values shown represent numbers of patients, with percentages in parentheses.

	Bicalutamide 150 mg/daily plus standard care $n = 607$	Placebo plus standard care $n = 611$
Exposure to bicalutamide[a]		
Number of patients	605 (99.0)	60 (9.8)
Median time to initiation (years)	0 (range 0–1.0)	6.0 (range 3.1–7.8)
Median duration (years)	5.3	3.2
Exposure to androgen-deprivation therapy or open label bicalutamide[a]		
Number of patients	461 (75.9)	425 (69.6)
Median time to initiation (years)	5.6 (range 0.1–8.7)	3.8 (range 0–8.0)
Mortality		
Death by any cause	428 (70.5)	438 (71.7)
Prostate cancer specific mortality	221 (36.4)	229 (37.5)
Other cause mortality	207 (34.1)	209 (34.2)
Mortality localised disease		
Death by any cause	242 (68.9)	236 (65.6)
Prostate cancer specific mortality	98 (27.9)	104 (28.9)
Other cause mortality	144 (41.0)	132 (36.7)
Mortality locally advanced disease		
Death by any cause	186 (72.9)	201 (80.4)
Prostate cancer specific mortality	123 (48.2)	124 (49.6)
Other cause mortality	63 (24.7)	77 (30.8)

[a] Data only available until 30th August 2008.

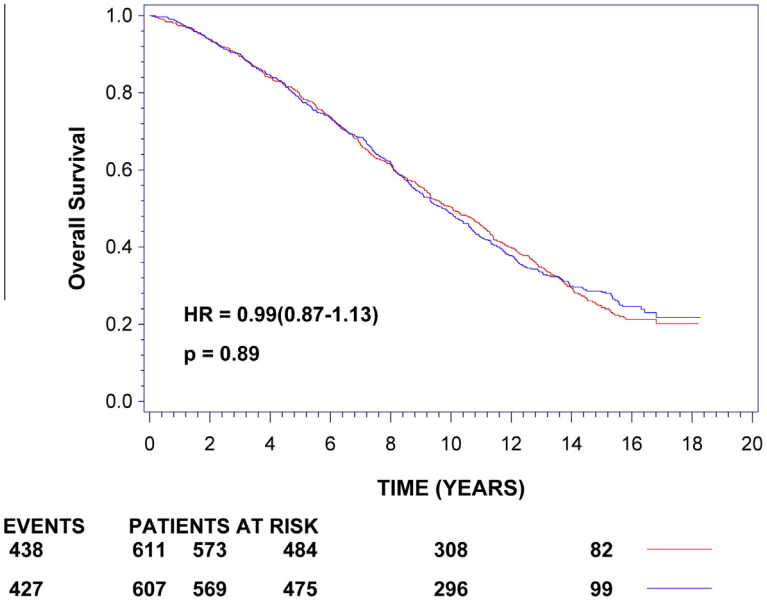

Fig. 1. Kaplan–Meier estimated overall survival for patients randomised to bicalutamide (blue line) or placebo (red line) presented with hazard ratio (HR) and 95% confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

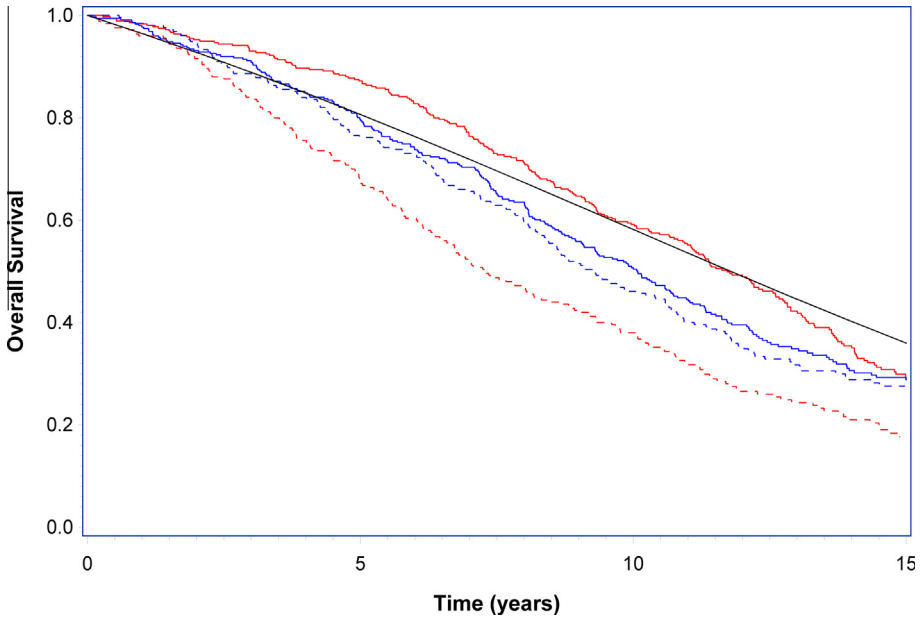

Fig. 2. Kaplan–Meier estimated overall survival stratified according to clinical tumour stage (localised [solid lines], locally advanced [dotted lines]) presented for randomised groups (bicalutamide [blue lines], placebo [red lines]) and the expected survival (black line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

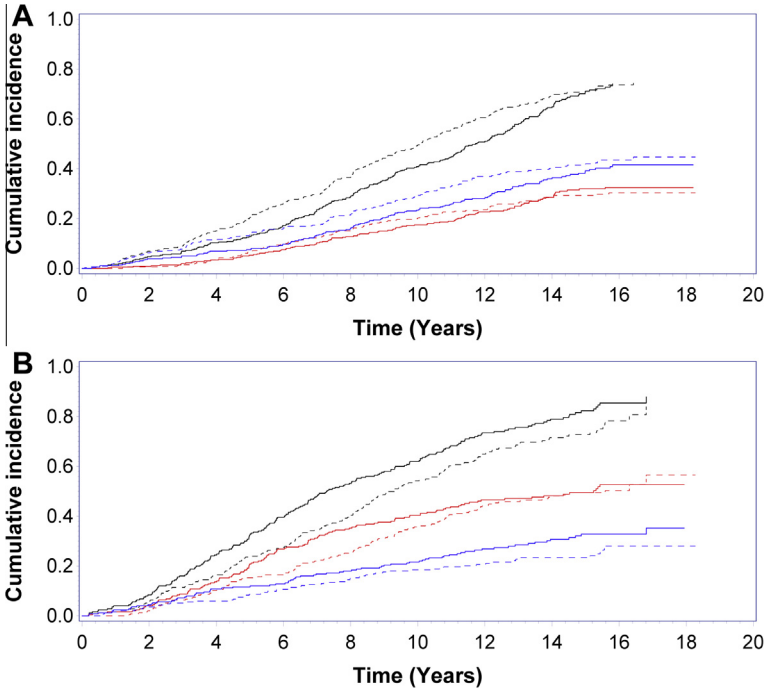

Fig. 3. Cumulative incidences of all-cause mortality (black lines), other-cause mortality (blue lines), and prostate cancer-specific mortality (red lines) in a competing risk model stratified according to clinical tumour stage (localised [A], locally advanced [B]) presented for randomised groups (bicalutamide [dotted lines], placebo [full lines]). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to bicalutamide was 9.7 years (95% CI: 9.0–10.4) compared to 10.1 years (95% CI: 9.3–10.8) for patients managed on placebo ($p = 0.87$), Fig. 1.

The expected survival for the entire study population and the Kaplan–Meier estimated survival curves stratified according to disease stage and randomisation are depicted in Fig. 2. In patients with localised disease survival favoured randomisation to the placebo arm (HR = 1.19 (95% CI: 1.00–1.43), $p = 0.056$). The median survival for patients with localised disease randomised to bicalutamide was 10.1 years (95% CI: 9.2–10.9) compared to 11.8 years (95% CI: 10.9–12.6) in

the placebo arm, a difference driven by a higher cumulative incidence of death from other causes, Fig. 3A. The slope for cumulative other cause mortality separated following 1 year of observation.

In contrast, bicalutamide significantly improved OS and reduced the risk of death by 23% relative to the placebo arm in patient with locally advanced disease (HR = 0.77 (95% CI: 0.63–0.94, $p = 0.01$), Fig. 2. The median survival in the bicalutamide arm was 9.1 years (95% CI: 8.1–10.1) compared to 7.3 years (95% CI: 6.4–8.2) in the placebo arm. The survival benefit of bicalutamide in patients with locally advanced PCa was present throughout the study period. The PCa-specific mortality was almost immediately lower in the bicalutamide arm with the greatest difference observed between 5 and 10 years following randomisation, Fig. 3B. The cumulative other cause mortality was lower in the bicalutamide group following 3 years of observation and from there on the incidence was almost parallel between the two study arms.

According to the modified NCCN risk categories survival non-significantly favoured randomisation to placebo in patients with low- (HR 1.53 (95% CI: 0.81–2.90)) and intermediate-risk PCa (HR 1.07 (95% CI: 0.83–1.38)), Supplementary Table 2. In patients with high-risk PCa there was a non-significant survival benefit of bicalutamide (HR 0.87 (95% CI: 0.73–1.04)).

In multivariate Cox proportional hazard model, including only patients managed on WW as their standard of care ($n = 991$) there were interactions between baseline PSA and randomised treatment ($p = 0.07$), baseline PSA and locally advanced PCa ($p = 0.007$), and between locally advanced PCa and randomised treatment ($p = 0.07$). OS depended on age, WHO grade, baseline PSA, clinical stage, and randomised treatment (Table 3). The impact of baseline PSA was apparent in patients with localised disease and a relatively high PSA of more than 28 ng/mL at randomisation, in whom a survival gain of bicalutamide was present, Fig. 4A. The survival gain of adding bicalutamide to standard care in patients with locally advanced PCa was practically present regardless of baseline PSA, Fig. 4B.

4. Discussion

Consistent with the second and third analyses of the SPCG-6 study with 5.3 and 7.1 year follow-up, respectively, the addition of bicalutamide to standard care

Table 3
Association between baseline variables and overall survival in patients managed on watchful waiting. Multivariate Cox proportional hazard regression model.

Variable	HR	95% CI	*p*
Age[a]	1.57	1.31–1.87	<0.0001
WHO histological grade			
Well differentiated	1 (ref)		
Moderate differentiated	1.26	1.07–1.48	0.004
Poorly differentiated	1.92	1.50–2.44	<0.0001
Baseline PSA[b]			
Localised PCa			
Placebo	1.13	1.05–1.22	0.001
Bicalutamide	1.03	0.95–1.12	0.64
Locally advanced PCa			
Placebo	1.29	1.18–1.42	<0.0001
Bicalutamide	1.18	1.08–1.30	0.0005
Localised versus locally advanced PCa			
Baseline PSA 5 ng/mL			
Placebo	0.77	0.57–1.05	0.09
Bicalutamide	1.02	0.75–1.38	0.90
Baseline PSA 20 ng/mL			
Placebo	0.59	0.47–0.73	<0.0001
Bicalutamide	0.77	0.62–0.97	0.022
Bicalutamide versus placebo			
Localised PCa			
Baseline PSA 10 ng/mL	1.15	0.94–1.40	0.17
Baseline PSA 30 ng/mL	1.00	0.80–1.24	0.99
Locally advanced PCa			
Baseline PSA 10 ng/mL	0.87	0.66–1.14	0.31
Baseline PSA 30 ng/mL	0.76	0.60–0.95	0.015

Abbreviations: PCa, prostate cancer; PSA, prostate-specific antigen.
[a] For every 10 year increase in age.
[b] For every doubling of prostate-specific antigen (PSA) at randomisation.

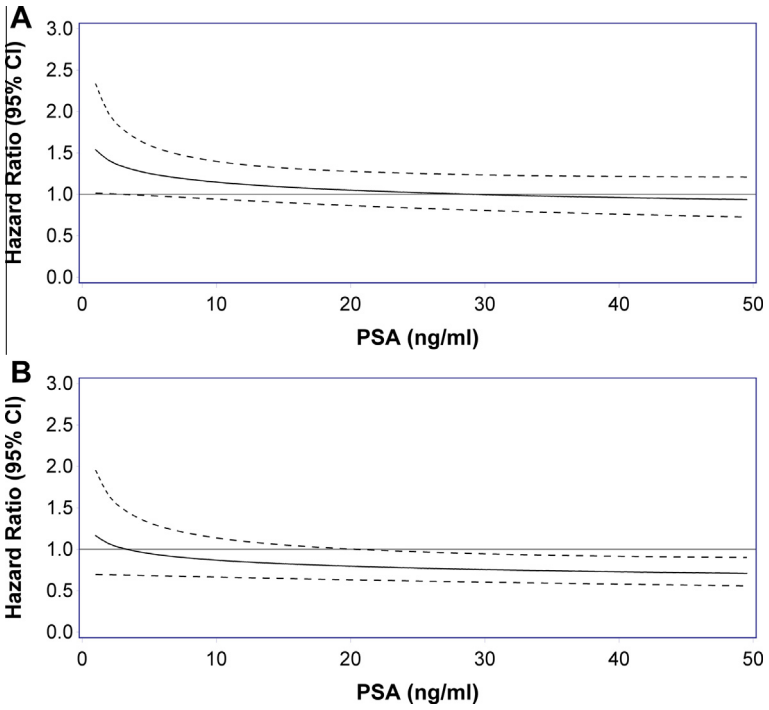

Fig. 4. Hazard ratio (bicalutamide:placebo) for risk of all cause mortality as a function of baseline prostate-specific antigen (PSA) in multivariate analysis including only patients managed on watchful waiting as standard care before randomisation ($n = 991$) for (A) patients with localised disease and (B) patients with locally advanced disease. *X*-axis truncated at PSA 50 ng/mL.

did not improve OS in the overall population of patients with non-metastatic PCa [7,8]. However, when stratified by clinical stage, the addition of bicalutamide significantly improved OS in patients with locally advanced PCa, while survival in localised PCa favoured the placebo arm. Besides disease stage, HR for OS decreased with higher baseline PSA – indicating an increased benefit of immediate bicalutamide.

The background and rationale for the SPCG-6 study and the entire EPC programme dates back to the nineties, where two open-label, prospective randomised studies compared bicalutamide 150 mg monotherapy to castration (LHRH agonist/bilateral orchiectomy) in patients with advanced PCa. A pooled analysis of M1 patients demonstrated a statistically significant median survival gain of 42 weeks of castration compared to bicalutamide monotherapy [12]. However, no significant survival difference was found in M0 patients with locally advanced disease and PSA greater than 20 ng/mL – although statistical equivalence was not demonstrated [13]. At the time these results were interpreted as a strong indication for a similar efficacy of bicalutamide monotherapy compared to conventional androgen deprivation therapy (ADT) in patients with limited tumour burden (i.e. locally advanced PCa), a perception recently supported in a Cochrane review (OS HR 1.00 [95% CI: 0.79–1.26]) [14]. Because of a favourable toxicity profile and quality of life advantages over castration-based ADT, bicalutamide 150 mg monotherapy was therefore regarded as a rational approach to endocrine therapy in early and non-metastatic PCa.

In essence, the SPCG-6 is a study of early androgen receptor inhibitor monotherapy versus delayed endocrine treatment. More than 80% of the study participants were managed on WW as their standard care and the majority of all included patients required subsequent endocrine therapy following allocated therapy, Table 2. The median time to initiation of ADT or open-label bicalutamide in the placebo arm was 3.8 years.

Early versus deferred endocrine treatment strategies have been investigated in a number of prospective, randomised trials [6,15–20]. Immediate therapy can delay objective disease progression of PCa regardless of the clinical stage [6,15–20]; However, this initial clinical benefit has not materialised into an improved PCa-specific survival in patients with localised PCa managed on WW or following curative intended therapy in patients without lymph node metastasis [6,15,16]. In contrast, early hormonal therapy has been demonstrated to improve both OS and PCa-specific survival in patients with locally advanced PCa or lymph node metastasis [17–20]. The Medical Research Council Prostate Cancer Working Party Investigators Group found an OS benefit of early ADT in 938 newly diagnosed patients with cT2–4 with or without metastasis compared to deferred ADT [17]. The survival benefit was primarily driven by a difference in PCa-specific mortality

in the group of patients with locally advanced disease. Messing et al. randomised 98 patients with pN1 disease following radical prostatectomy to either immediate ADT or ADT delayed until clinical disease recurrence – not including rising PSA [18]. Although the study was terminated prematurely, it demonstrated a significant benefit in favour of immediate castration in all study end-points: PFS, OS, and PCa-specific survival. A similar study, the EORTC trial 30846 – designed as a non-inferiority study – found no significant survival difference between 234 patients with cT2–3 and lymph node metastases randomised to early or delayed castration [19]. The study failed to show non-inferiority for deferred therapy and a hazard ratio of 1.22 (95% CI: 0.92–1.62) pointed in the same direction as in the Messing study. [18]. The EORTC trial 30891 randomised 985 patients with cT1–4, non-metastatic PCa patients unsuitable for curatively intended treatment and found an OS benefit of immediate castration compared to deferred therapy [20]. Finally, two meta-analyses of randomised trials have shown a PCa-specific and OS benefit of adding ADT to external beam radiotherapy with curative intent [21,22]. These studies advocate in favour early castration-based therapy in patients with locally advanced or lymph node positive PCa.

The present study, albeit its post hoc analysis according to disease stage, supports this perception by demonstrating that early androgen receptor inhibition in locally advanced PCa improve OS. Interestingly, the survival benefit in these patients was maintained throughout the study period with almost 15 year follow-up, Fig. 2. Surprisingly, the survival difference was caused by a 6% difference in other cause mortality while the PCa-specific mortality was almost identical between the two arms (48.2% compared to 49.6%), Table 2. These findings are in contrast to the third analysis of the SPCG-6 study, at 7.1 year follow-up, where the survival difference in patients with locally advanced PCa was driven by a lower PCa-specific mortality (25.5% compared to 34.8%) [8]. Fig. 3B depicts that the greatest difference in PCa-specific mortality was observed between 5 and 10 years of observation. On the other hand, our current findings concur with the EORCT trial 30891, where the survival benefit of immediate ADT was caused by a lower other cause mortality [20]. Similar to the authors of the EORTC 30891 analysis we can only speculate about the reason for this somewhat unsuspected observation. As the overall study is negative it is plausible that these findings are caused by chance. However, post-study patient management, cardio-prophylaxis etc. have not been registered and any possible differences between the two study arms are unknown. The SPCG-6 study was un-blinded following the second analysis of the EPC programme with 5.4 year follow-up [10]. Patients randomised to the active arm could potentially have been followed more closely since at the time when SPCG-6 was conducted there were some debate about possible cardiovascular toxicity of bicalutamide [23,24] This concern has since been refuted [25–27]. Still, a more intensive surveillance of bicalutamide treated patients could theoretically lower the risk of other cause mortality. Another explanation that cannot be excluded is a misclassification of the cause of death, i.e. thirty percent of patients in the initial placebo arm never received endocrine therapy and may have been less likely to be classified as PCa deaths.

Diagnostic techniques and histopathological evaluation have changed compared to the standard procedures in Scandinavia in the period 1995–1998. In an attempt to evaluate bicalutamide according to a contemporary risk classification we stratified patients according to a modification of the NCCN guideline [11]. In neither of the NCCN risk categories a survival difference between the allocated therapies was found, Supplementary Table 2. The positive effect of bicalutamide observed in locally advanced PCa, was most likely diluted in patients with high-risk NCCN by including patients with localised PCa and PSAs between 20 and 30 ng/mL and excluding patients with T4 or lymph node metastases from the analyses.

The toxicity profile of bicalutamide is different to castration. Patients treated with bicalutamide may experience breast pain (73.7%) and gynaecomastia (68.8%) [6] adverse events rarely seen in castrated patients [14]. However, androgen receptor inhibitors have a more favourable profile with regard to hot flashes and erectile dysfunction [6,12–14]. The different toxicity profiles of androgen receptor inhibition and castration have previously been discussed [28].

A limitation to the present study is the incomplete survival follow-up, as information could not be obtained in 28.6% of the patients alive at the last update August 2008. However, because of randomisation we consider the risk of a systematic sampling bias to be limited. The histopathological grading was primarily reported as WHO grade traditionally used in Scandinavia at the time of the study. Previous studies in Scandinavia have unsuccessfully tried to transform WHO grades into Gleason scores [29], thus no attempts was made to reclassify the diagnostic tissue according to the Gleason score. Finally, the initiation of open label bicalutamide and ADT was not determined per protocol but initiated at each physician's discretion and no attempts was made to update these data since the last EPC analysis [6].

The current study presents the physician with data on the optimal timing of androgen receptor inhibitor therapy in patients with non-metastatic PCa either unfit for or unwilling to undergo curative therapy. Patients with localised PCa who are managed on active surveillance or WW should be followed with serial PSA measurements and clinical prostate evaluations in order to

initiate androgen receptor inhibition when they, according to T-category and PSA, can expect a survival benefit hereof. Further, patients with locally advanced PCa who either refuse to undergo curatively intended radiotherapy or are deemed unsuitable for curative intervention can achieve a survival benefit from immediately initiation of bicalutamide.

Finally, our study may provide useful information on what may constitute an optimal study population for new trials investigating the efficacy of endocrine therapy in early non-metastatic PCa.

5. Conclusion

Throughout the almost 15 year follow-up period the addition of early bicalutamide to standard of care resulted in a significant OS benefit in patients with locally advanced PCa. In contrast, patients with localised PCa derived no survival benefit from early bicalutamide. The optimal timing for initiating bicalutamide in non-metastatic PCa patients is dependent on disease stage and baseline PSA.

6. Funding

The study was financially supported by grants from IMK Almene fonden.

7. Contributions

The corresponding author (FBT) 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. PI is the principal investigator of the study and was responsible for planning of the study. FBT, KB, J-EJ, AA and TLT performed survival updates. The data analysis was made by FBT and IJC. The interpretation of data was made by FBT, KB, IJC and PI. FBT and PI performed the literature search. All authors were involved in the writing, revision (FBT, KB, PI) or review (IJC, J-EJ, AA, TLT) of the manuscript. PI was responsible for funding.

Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2015.03.021.

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