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Docetaxel Versus Surveillance After Radical Prostatectomy for High-risk Prostate Cancer: Results from the Prospective Randomised, Open-label Phase 3 Scandinavian Prostate Cancer Group 12 Trial

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on behalf of the Investigators of the Scandinavian Prostate Cancer Study Number 12

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Abstract

Background: Adjuvant chemotherapy is standard treatment for other solid tumours, but to date has not proven effective in prostate cancer.
Objective: o evaluate whether six cycles of docetaxel alone improve biochemical disease-free survival after radical prostatectomy for high-risk prostate cancer.
Design, setting, and participants: Open-label, randomised multinational phase 3 trial. Enrolment of 459 patients after prostatectomy. Inclusion criteria: high-risk pT2 margin positive or pT3a Gleason score $\geq$4+3, pT3b, or lymph node positive disease Gleason score $\geq$3 + 4. Patients assigned (1:1) to either six cycles of adjuvant docetaxel 75 mg/m^2 every 3 wk without daily prednisone (Arm A) or surveillance (Arm B) until endpoint was reached. Primary endpoint was prostate-specific antigen progression $\geq$0.5 ng/ml.
Intervention: Docetaxel treatment after prostatectomy.
Results and limitations: Median time to progression, death, or last follow-up was 56.8 mo. Primary endpoint was reached in 190/459 patients—the risk of progression at 5 yr being 41% (45% in Arm A and 38% in Arm B). There was evidence of nonproportional hazards in Kaplan-Meier analysis, so we used the difference in restricted mean survival time as the primary estimate of effect. Restricted mean survival time to endpoint was 43 mo in Arm A versus 46 mo in Arm B (p = 0.06), a nonsignificant difference of 3.2 mo (95% confidence interval: 6.7 to –1.5 mo). A total of 116 serious adverse events were recorded in Arm A and 41 in Arm B with no treatment-related deaths. Not all patients received docetaxel by protocol. The endpoint is biochemical progression and some patients received radiation treatment before the endpoint.
Conclusions: Docetaxel without hormonal therapy did not significantly improve biochemical disease-free survival after radical prostatectomy.
Patient summary: In this randomised trial, we tested whether chemotherapy after surgery for high-risk prostate cancer decreases the risk of a rising prostate-specific antigen. We found no benefit from docetaxel given after radical prostatectomy.

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1. Introduction

Prostate cancer is common in Western Europe and more than 25 000 new cases are discovered in the Nordic countries each year [1]. It is also a leading cause of death from cancer in men [2]. The risk of biochemical recurrence (BCR) after surgery for high-risk disease is approximately 50% at 5 yr and the earlier the recurrence, the higher the risk of dying from prostate cancer [3]. Cure is not possible if distant metastases occur. If lymph node metastases are present at surgery, the risk of BCR is 69%, and increases with higher pathological stage, higher GS, and positive margins, all factors that correlate to cancer-specific and overall survival with long-term follow-up [4].

A recent report concludes that docetaxel is not a recommended treatment in locally advanced hormone-naive disease in patients with a BCR [5]. In 2004, two randomised trials showed that docetaxel-based treatment prolong survival in metastatic castrate-resistant prostate cancer [6,7]. In breast cancer, disease-free survival increased from 68% to 75% with the use of adjuvant docetaxel-based regimen which was accepted as the standard treatment [8]. In view of the data from adjuvant treatment of breast cancer, we initiated this trial to evaluate whether six cycles of docetaxel alone could improve progression-free survival (PFS) after radical prostatectomy for high-risk patients.

2. Patients and methods

2.1. Study design

This open-label Scandinavian Prostate Cancer Group phase 3 study enrolled patients from 25 hospitals in Denmark, Finland, Iceland, Norway, and Sweden. Inclusion criteria were based on high-risk features in the pathology report after radical prostatectomy based on a $\geq$50% risk of progression by nomogram: pT2 margin positive or pT3a if Gleason score (GS) $\geq$4 + 3 or pT3b/any lymph node positive disease if GS $\geq$3 + 4. Prostate-specific antigen (PSA) nadir after surgery should be $<$0.5 ng/ml, and a bone scan with no evidence of metastases was required before randomisation. Key exclusion criteria were proven skeletal metastases, other malignancies within 5 yr, and previous hormonal or chemotherapy for prostate cancer. Indication for and extension of lymph node dissection was decided by local practice but was recommended if PSA was $>$10 ng/ml. A total of 396 patients were planned for recruitment, which was planned to be completed over 3 yr. All patients provided written informed consent and were randomised to receive either six cycles of docetaxel without hormonal treatment or continuous corticosteroids (Arm A) or surveillance (Arm B) with follow-up until the endpoint was reached. Patients were randomised online with a central computer at the Oncology Centre in Umeå, Sweden and stratified for centre and pT-stage. The study was approved by the Ethical Review Board at Lund University, Lund, Sweden and subsequently in all the Nordic countries.

2.2. Intervention in experimental arm

Patients in Arm A were to start the treatment within 12 wk after radical prostatectomy. The dose of docetaxel (Taxotere; Sanofi-Aventis, Dublin, Ireland) was 75 mg/m^2 given intravenously on day one every 21 d. Dexamethasone, 8 mg per os or equivalent was given at 12 h and 1 h before injection and every 12 h for 48 h after injection. Antiemetic medication was used per local practice. Treatment did not include continuous prednisone or hormonal treatment. Patients who developed leukopenia grade 4 (white blood count $< 1.0 \times 10^9$/l) or neutropenia grade 4 (absolute neutrophil count [ANC] $< 0.5 \times 10^9$/l) during therapy were recommended the addition of granulocyte-colony stimulating factor (G-CSF) during the next and subsequent docetaxel cycles after recovery (grade $<$ 2) with no dose reduction of docetaxel. If leukopenia grade 4 or neutropenia grade 4 recurred during combined docetaxel/G-CSF treatment, the dose of docetaxel was reduced by 20% in the remaining cycles.

Patients who developed febrile neutropenia (ANC $< 1.0 \times 10^9$/l and fever $>$38.5°C) or infection (documented infection with ANC $< 1.0 \times 10^9$/l) during treatment were recommended a 20% dose reduction of docetaxel with the addition of G-CSF during remaining cycles. If a further episode of febrile neutropenia or infection occurred, the patient was taken off therapy. Laboratory tests were performed within 3 d before each chemotherapy cycle. As a safety precaution, haemoglobin, leukocytes, neutrophils, and platelets were controlled on day eight ($\pm$ 1 d) in each cycle of chemotherapy. Physical examination was carried out at least prior to every second treatment.

Side effects, signs, and symptoms were assessed at the start of every cycle using Common Terminology Criteria for Adverse Events (version 3.0; www.ctep.cancer.gov). Patients completed a validated quality of life questionnaire, Functional Assessment of Cancer Therapy-Prostate [9], at baseline, at the end of chemotherapy, and then annually after randomisation for 5 yr.

2.3. Outcome measures

Primary endpoint was defined as a rising PSA $\geq$0.5 ng/ml. A reduction of BCR of 15% in the experimental arm was considered clinically relevant. In both arms, no further treatment should be given until the primary endpoint was reached. All patients were monitored for 5 yr with PSA every 3 mo, in a planned trial duration of 8 yr. If the primary endpoint was reached a bone scan was recommended and repeated annually if symptoms occurred or PSA increased above 10 ng/ml. Secondary endpoints were PSA doubling time at recurrence, quality of life, metastasis-free survival, cancer-specific survival, and overall survival.

2.4. Statistical analysis

The study was designed to show a 15% difference with a power of 90% and a two-sided significance level of 5% using

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the log-rank test. All patients were monitored until the 60-mo visit and were censored thereafter. The database was completed and locked in December 2015. The analysis was involved intention to treat. Our results showed evidence of non-proportional hazards in the initial Kaplan-Meier (KM) analysis, so we used the difference in restricted mean survival time (RMST) as the primary estimate of effect. The analysis was adjusted for GS, pT-stage, surgical margin, lymph node status, and PSA at baseline. Differences between the arms were tested using the delta method. A Forrest-plot with odds ratios compared the risk of progression within subgroups in the two arms. The probability of progression-free survival in subgroups in a posthoc analysis was estimated with a KM analysis and differences between the arms were tested with the log-rank test. A p value < 0.05 was considered significant. SPSS version 24 (SPSS Inc., Chicago, IL, USA) and Stata version 14 with smtp2 (flexible parametric) software (Stata Corp. LLC, College Station, TX, USA), was used for statistical calculations. This trial is registered with ClinicalTrials.gov, number NCT00376792.

3. Results

3.1. Study population and randomisation

After an independent review of the events in Arm B, the recommendation was to increase the number of patients to retain the power in the study. In total, we allocated 459 patients to the study from October 2005 to May 2010. Nine patients withdrew consent after randomisation, and six patients were found to be protocol violations. These 15 patients had been randomised to arm A and censored before the first follow-up. Four of them received one to two doses of docetaxel (Fig. 1). The randomisation was successful with comparable risk factors in both arms (Table 1). A high-risk cohort was enrolled with 39% pT3b and 39% GS 8–10. Of the 309 patients (67%) with a lymph node dissection, 55 (18%) had metastases.

3.2. Treatment in Arm A

Overall, 219 (95%) of the 230 patients in Arm A received at least one dose of docetaxel, and 182 (79%) received all six cycles per protocol. A dose reduction was necessary in 80 patients without any difference in outcome (not shown, $p > 0.9$). Neutropenia grade 3–4 was observed in 60/218 patients (30%), who received at least one docetaxel infusion. Forty-three episodes of febrile neutropenia were reported in 40 of the 219 patients (18%). No docetaxel-related deaths were reported. Other serious adverse events that were more common in Arm A were cardiovascular disease and thromboembolism (Table 2).

3.3. Analysis of progression

At 5-yr follow-up, the risk of progression had declined, and it was decided to analyse the primary endpoint even though we did not reach 50% progression in the control arm. Time to progression, death, or last follow-up was 57 mo (median). The end-of-study visit was at 58–68 mo from randomisation. At this time-point, 190 of the 459 patients had

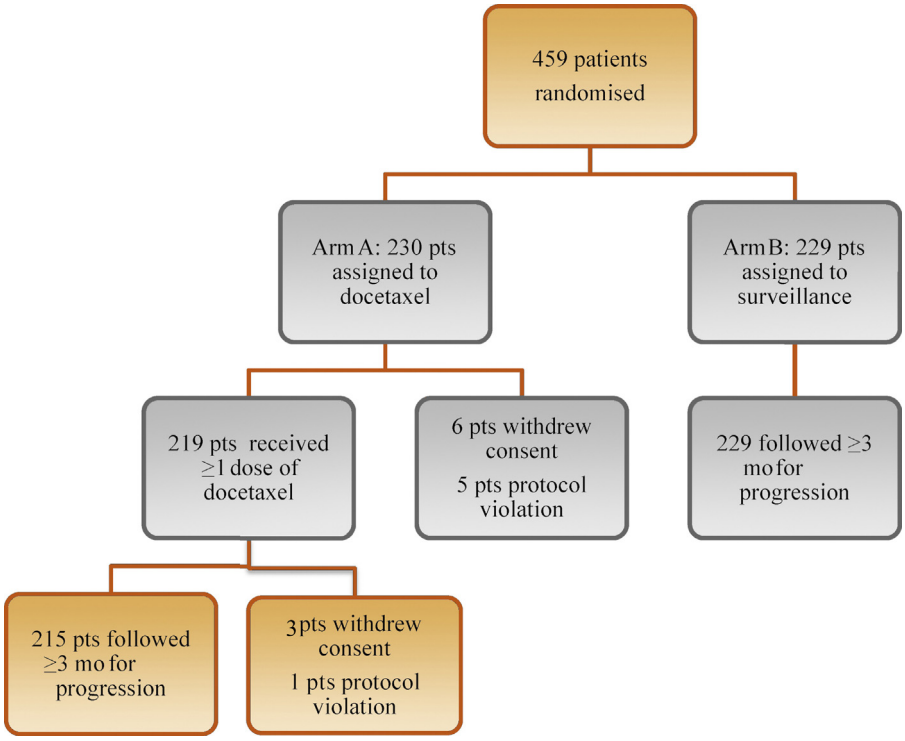

Fig. 1 – Trial profile for Scandinavian Prostate Cancer Group 12: Arm A adjuvant docetaxel, Arm B surveillance only. pts = patients.

Table 1 – Baseline characteristics in Arm A (docetaxel) and Arm B (surveillance) after radical prostatectomy (RP)

Parameter	Arm A (n = 230)	Arm B (n = 229)
Age median, yr (quartiles)	62 (58–66)	63 (60–67)
PSA before RP median (quartiles)	9.5 (6.6–15.0)	9.4 (6.5–15.4)
PSA baseline median (quartiles)	0.1 (0.1–0.2)	0.1 (0.1–0.2)
≤0.2 ng/ml (%)	188 (82)	190 (83)
>0.2 ng/ml (%)	38 (17)	38 (17)
Missing (%)	4 (1.7)	1 (0.4)
Pathological stage		
pT2, n (%)	35 (15)	34 (15)
pT3a, n (%)	104 (45)	102 (45)
pT3b, n (%)	90 (39)	93 (41)
Missing (%)	1 (0.4)	0 (0)
Gleason score		
3 + 4, n (%)	27 (12)	35 (15)
4 + 3, n (%)	115 (50)	109 (48)
8–10, n (%)	86 (37)	85 (37)
Missing (%)	2 (0.9)	0
Surgical margin		
neg, n (%)	95 (41)	90 (39)
Pos, n (%)	133 (58)	139 (61)
Missing, n (%)	2 (0.9)	0
Lymph node dissection		
pos (%)	27 (12)	28 (12)
Neg (%)	133 (58)	120 (52)
Not done	70 (30)	81 (35)

Neg = negative; pos = positive; PSA = prostate-specific antigen; RP = radical prostatectomy.

Table 2 – Reported number of serious adverse events (SAEs) in Arm A (docetaxel) and Arm B (surveillance) after radical prostatectomy (some patients had several SAEs)

Type of SAE	Arm A (n = 219)	Arm B (n = 229)	Total (n = 447)
Febrile neutropenia	43	0	43
Infection no neutropenia	12	2	14
Toxic/allergic reaction	2	0	2
Prostate cancer (death)	6	3	9
Other cancer	9	5	14
Other surgery	7	17	24
Cardiovascular disease	16	8	24
Chest pain (observation)	4	1	5
Thromboembolism	5	1	6
Benign bowel disease	5	1	6
Gastric ulcer	2	0	2
Other	5	3	8
Total	116	41	157

progression to PSA >0.5 ng/ml, the risk of progression at 5 yr being 41% (45% in Arm A and 38% in Arm B). In the KM analysis, we observed a nonproportional hazard over time, where the curve of Arm A crossed the curve of Arm B at 15 mo from randomisation (Fig. 2). Therefore, we used the difference in RMST as the primary estimate of effect from treatment. There was no significant difference between Arm A and B in time to BCR PSA >0.5 ng/ml. RMST to reach endpoint was 43 mo in Arm A versus 46 mo in Arm B (p = 0.06), a nonsignificant difference of 3.2 mo (95% confidence interval: 6.7 to −1.5 mo). To explore if the outcome differed between subgroups, we used a forest plot with odds ratios for progression in Arm A versus Arm B (Fig. 3). Patients with GS ≤7 (p = 0.02) and a positive surgical margin (p = 0.02) were favoured by surveillance, while those with a PSA ≤0.2 ng/ml did not reach significance (p = 0.08). In a posthoc KM analysis, with separate curves for baseline PSA ≤0.2 ng/ml and >0.2 ng/ml, we found proportional hazards. The outcome favoured surveillance if baseline PSA ≤0.2 ng/ml (p = 0.02). Nineteen patients died, 11 in Arm A and eight in Arm B. Of these, six patients died from prostate cancer in Arm A and three in Arm B.

3.4. *Treatments given before endpoint*

The protocol did not allow hormonal treatment or local radiotherapy before endpoint was reached as this could influence the primary endpoint. Overall, 47 patients (19 in Arm A/28 in Arm B) received salvage radiation and 5 (4 in Arm A/1 in Arm B) received hormonal treatment before endpoint. Nineteen of these 52 patients had progression beyond endpoint during follow-up despite salvage treatment. The outcome analysis was the same regardless of whether these patients were included in the analysis or not (not shown).

4. Discussion

This is the first time data are presented from a randomised trial on docetaxel treatment after radical prostatectomy compared with surveillance in prostate cancer patients. Our result does not support the use of adjuvant docetaxel as single treatment after surgery for high-risk prostate cancer. This study is the only randomised trial with docetaxel treatment without androgen deprivation therapy or continuous corticosteroids. Our treatment protocol with docetaxel alone was designed from the sequential treatment used in adjuvant studies in breast cancer, where docetaxel is given before hormonal treatment [10]. This can be questioned, as xenograft models suggest that concurrent chemo-hormonal therapy is superior to either sequential option when the next treatment is given at tumour progression [11].

In a previous adjuvant study on high-risk prostate cancer patients with long follow-up and survival as endpoint (RTOG 9902), no difference was seen in either progression-free survival, distant metastasis-free survival, or overall survival after a median follow-up of 9.4 yr [12]. This study used paclitaxel in a triple chemotherapy combination with androgen deprivation therapy after radiation therapy. In a more recent protocol (RTOG 0521), a minor survival benefit has been found with adjuvant docetaxel given after radiotherapy as reported in an abstract only [13]. In the GETUG 12 trial, docetaxel and estramustine phosphate in combination with androgen deprivation therapy were compared with androgen deprivation therapy alone after curative treatment for high-risk disease, most of them after radiation therapy [14]. A significant difference in time to BCR was found in favour of the combination therapy. There are several differences compared to our study. The primary

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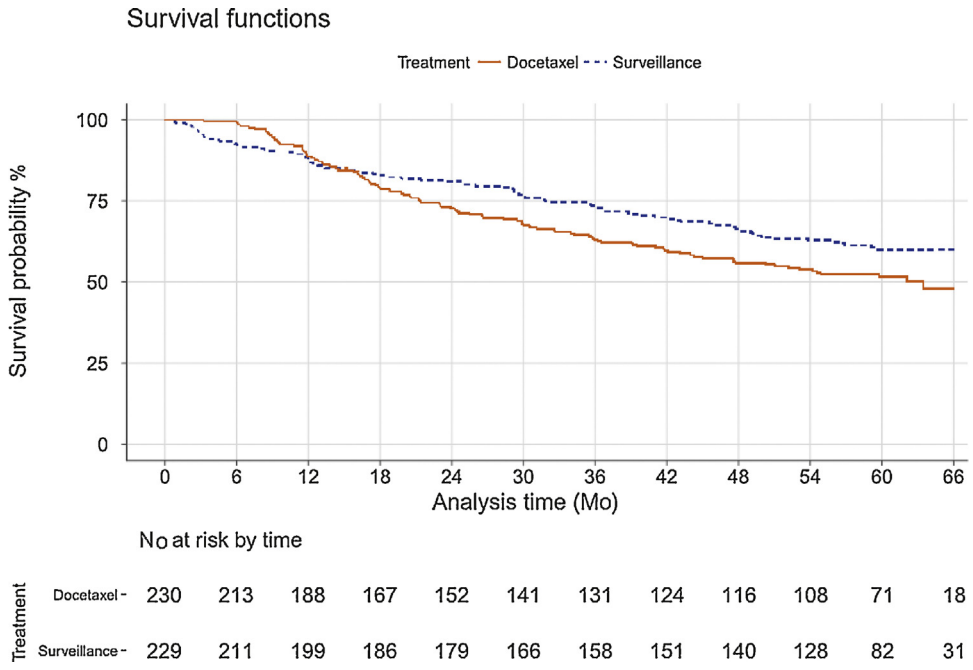

Fig. 2 – Kaplan-Meier curves of survival free of progression (prostate-specific antigen > 0.5 ng/ml) by intention to treat in Arm A (docetaxel) and Arm B (surveillance; $p = 0.06$).

treatment was mainly radiotherapy instead of surgery, hormonal treatment was given for 3 yr and progression was defined by PSA >2.0 ng/ml above nadir. The difference in outcome in the GETUG study is seen in patients with a GS ≤7, while no effect was seen in GS 8 or higher. In our study, we found no effect of docetaxel on progression-free survival as single therapy in patients with a GS ≤7, an observation that may support a synergistic effect between docetaxel and androgen deprivation therapy. In both studies, the primary endpoint is biochemical progression and no conclusion can yet be drawn about metastasis-free or cancer-specific survival. In the recently published Stampede trial, there was a survival benefit of docetaxel combined with androgen deprivation therapy compared with androgen deprivation therapy alone, but not in the subgroup analysis of those with locally advanced disease without proven metastasis at randomisation [15].

In a recent meta-analysis of the results from clinical trials on the use of docetaxel in hormone naive nonmetastatic locally advanced prostate cancer, the absolute reduction in progression-free survival was found to be 8% which was highly significant [16]. However, the reduction in survival was 4% and was not significant. In the TAX 3501 study, no conclusion could be made from the arm with sequential docetaxel and hormonal treatment, as the number of patients and events were low [17].

In the initial KM analysis, we found nonproportional hazards for BCR over time in the docetaxel arm of our study. Consequently, we used the difference in RMST as the primary estimate of the effect of docetaxel treatment. In the subgroup analysis, Gleason score and a positive surgical margin were favoured by surveillance. Most of our study cohort had PSA ≤0.2 ng/ml after surgery. When patients with a PSA above 0.2 after surgery were excluded from the analysis, there was a significant favour for surveillance. One major limitation is that we included patients with measurable PSA after surgery, which makes the interpretation of the result difficult, especially as we did not stratify for this parameter.

Other limitations are a heterogeneous risk profile in the study population and that almost one-third of the patients did not have a lymph node dissection. However, the inclusion criteria were designed based on a 50% risk of relapse by nomograms, and at the time, lymph node dissection was not standard treatment. The primary endpoint in our study is BCR and not survival. We consider time to BCR a clinically relevant endpoint after radical prostatectomy for high-risk prostate cancer. In previous studies, metastasis-free survival correlates with a short PSA doubling time and higher GS in patients with BCR, the median time to metastasis being 4 yr for a patient with a GS 8–10 without additional treatment [18]. Another limitation is that 52 patients received radiotherapy or hormonal therapy before endpoint was reached. The outcome analysis when those patients were excluded or classified as failures, did not alter the result.

In a recent study of 600 patients below the age of 60 yr at surgery, cancer-specific mortality was found to be low after radical prostatectomy for high-risk prostate cancer, approximately 20% at 20 yr [19]. Adjuvant hormonal and/or radiotherapy was given to a minority of these patients. So far, only nine patients have died from the disease within the observation period in our study, with six of them in the docetaxel treatment arm. These results do not support the use of adjuvant or early salvage chemotherapy after surgery.

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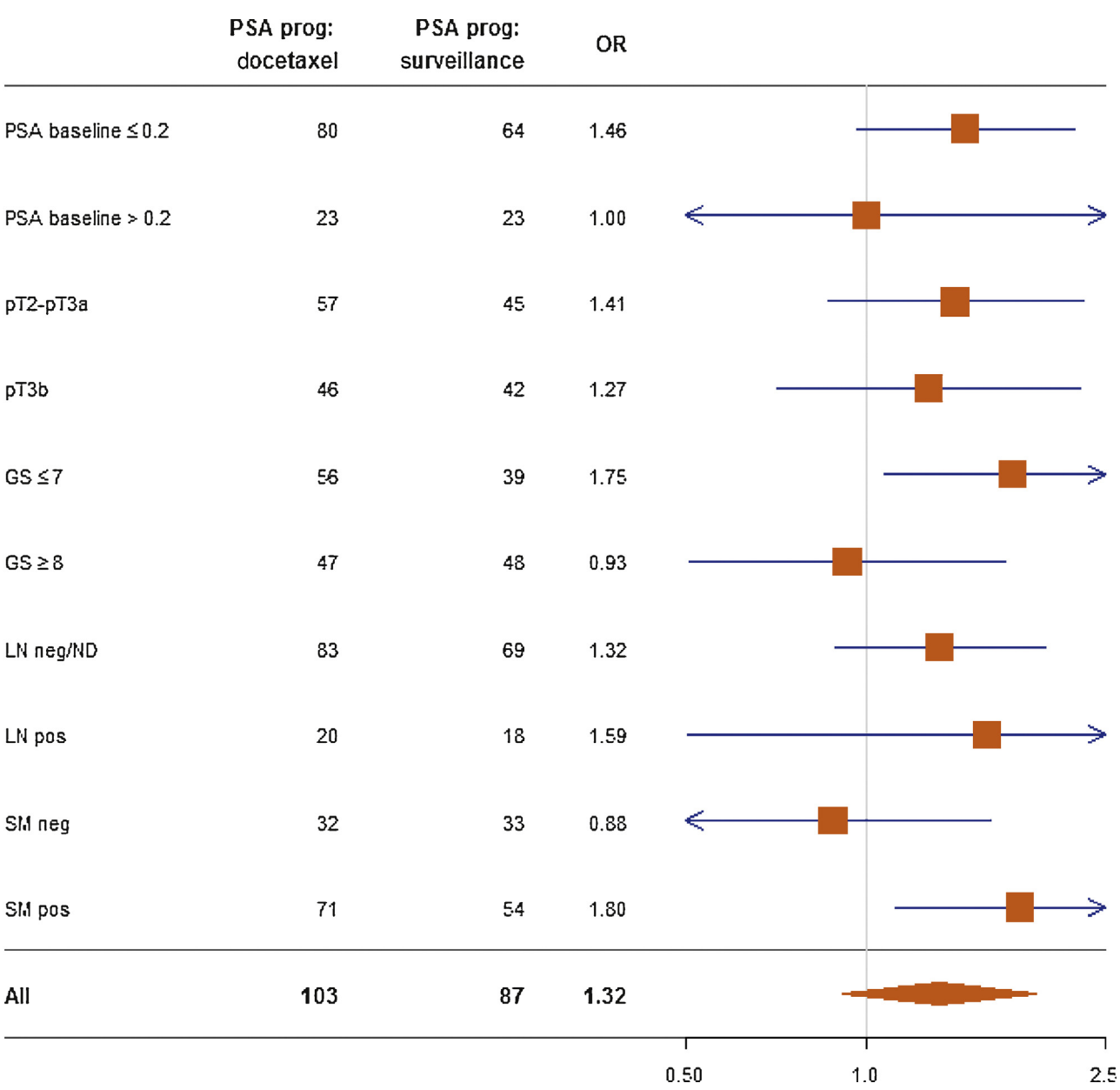

Fig. 3 – Forest plot of odds ratio (OR) with 95% confidence interval for progression to prostate-specific antigen (PSA) >0.5 ng/ml in different risk factors. An OR < 1.0 favours Arm A (n = 230) and an OR >1.0 favours Arm B (n = 229) in each specific subgroup. The subgroups Gleason score (GS) ≤7 (p = 0.02) and positive surgical margin (p = 0.02) was favoured by surveillance.
LN = lymph node; ND = not determined; neg = negative; pos = positive; prog = progression; SM = surgical margin.

5. Conclusions

In conclusion, docetaxel alone cannot be recommended after surgery for high-risk prostate cancer.

Author contributions: Göran M. Ahlgren 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: Ahlgren, Tammela, Kellokumpu-Lehtinen, Borre, Angelsen, Iversen, Sengelov.
Acquisition of data: Ahlgren, Flodgren, Tammela, Kellokumpu-Lehtinen, Borre, Angelsen, Iversen, Sverrisdottir, Jonsson, Sengelov.
Analysis and interpretation of data: Ahlgren, Flodgren, Tammela, Kellokumpu-Lehtinen, Borre, Angelsen, Iversen, Sverrisdottir, Sengelov.
Drafting of the manuscript: Ahlgren, Flodgren.
Critical revision of the manuscript for important intellectual content: Ahlgren, Flodgren, Tammela, Kellokumpu-Lehtinen, Borre, Angelsen, Iversen, Sverrisdottir, Sengelov.
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References

[1] NORDCAN. The NORDCAN project. http://www-dep.iarc.fr/NORDCAN/English/frame.asp.
[2] Wong MCS, Goggins WG, Wang HHX, et al. Global incidence and mortality for prostate cancer: Analysis of temporal patterns and trends in 36 countries. Eur Urol 2016;70:862–74.
[3] Briganti A, Karnes RJ, Gandaglia G, et al. Natural history of surgically treated high-risk prostate cancer. Urol Oncol 2015;33, 163.e7–13.
[4] Moschini M, Sharma V, Zattoni F, et al. Risk stratification of pN+ prostate cancer after prostatectomy from a large single institutional series with long term follow-up. J Urol 2016;195:1774–9.
[5] Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: the report of the Advanced Prostate Cancer Consensus Conference APCCC 2017. Eur Urol. In press. https://doi.org/10.1016/j.eururo.2017.06.002.
[6] Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004;351:1513–20.
[7] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.
[8] Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;352:2302–13.
[9] Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology 1997;50:920–8.
[10] Castiglione-Gertsch M, O'Neill A, Price K, et al. Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative cancer: a randomized trial. J Natl Cancer Inst 2003;95:1833–46.
[11] Eigl BJC, Eggener SE, Baybik J, et al. Timing is everything: preclinical evidence supporting simultaneous rather than sequential chemohormonal therapy for prostate cancer. Clin Cancer Res 2005;11:4905–11.
[12] Rosenthal SA, Hunt D, Sartor AO, et al. A phase 3 trial of 2 years of androgen suppression and radiation therapy with or without adjuvant chemotherapy for high-risk prostate cancer: Final results of radiation therapy oncology group phase 3 randomized trial NRG Oncology RTOG 9902. Int J Radiat Oncol Biol Phys 2015;93:294–302.
[13] Sandler HM, Hu C, Rosenthal SA, et al. A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521). Proc Am Soc Clin Oncol 2015;33(Suppl), abstr 502.
[14] Fizazi K, Faivre L, Lesaunier F, et al. Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): a phase 3 randomised controlled trial. Lancet Oncol 2015;16:787–94.
[15] James ND, Sydes MR, Clark NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet Oncol 2016;387:1163–77.
[16] Vale CL, Burdett S, Rydzewsk LHM, et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. Lancet Oncol 2016;17:243–56.
[17] Schweizer MT, Huang P, Kattan MW, et al. Adjuvant leuprolide with or without docetaxel in patients with high-risk prostate cancer after radical prostatectomy (TAX-3501). Cancer 2013;119:3610–8.
[18] Antonarakis ES, Feng Z, Trock BJ, et al. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. BJU Int 2012;109:32–9.
[19] Dell'Oglio P, Karnes RJ, Joniau S, et al. Very long-term survival patterns of young patients treated with radical prostatectomy for high-risk prostate cancer. Urol Oncol 2016;34:234.e13–9.

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