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Prostate Cancer

Docetaxel Versus Surveillance After Radical Radiotherapy for Intermediate- or High-risk Prostate Cancer—Results from the Prospective, Randomised, Open-label Phase III SPCG-13 Trial

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on behalf of the Investigators of the Scandinavian Prostate Cancer Study No. 13

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Abstract

Background: Docetaxel combined with androgen deprivation therapy (ADT) has improved patient survival for advanced prostate cancer (PCa).
Objective: This randomised trial aimed to evaluate whether six courses of docetaxel improved biochemical disease–free survival (BDFS) after radical radiotherapy (RT) for intermediate- or high-risk PCa patients.
Design, setting, and participants: A total of 376 patients were randomised in this multinational phase III study, and received either six cycles of adjuvant docetaxel 75 mg/m^2 every 3 wk without continuous prednisone (arm A, $n = 188$) or surveillance (arm B, $n = 188$) after RT (NTC006653848). Neoadjuvant/adjuvant ADT was mandatory for all the patients. The primary endpoint was rising prostate-specific antigen (PSA) $\geq$2 ng/ml above the nadir PSA value. Intermediate- or high-risk PCa was defined as T2 with a Gleason score (GS) of 4 + 3, PSA $>$ 10; T2, GS 8–10, $\leq$ 70 ng/ml; or any T3. The patients were followed for 5 yr by assessing PSA levels every 3 mo for 2 yr and every 6 mo thereafter.
Outcome measurements and statistical analysis: The study power was 89% to detect a difference in BDFS between groups, and the sample size calculation accounted for the T2/T3 distribution, where a 12%/15% difference in BDFS was assumed for the T2/T3 patients.
Results and limitations: All six cycles were completed in 147 (78%) of the patients in arm A. The median age was 67 yr in both treatment groups, 75% had T3 disease, and 47% had GS 8–10. The median follow-up was 59 mo (range 1–111 mo). The primary endpoint was observed for 58 patients in arm A (docetaxel) and for 57 patients in arm B (surveillance). The Kaplan-Meier analysis showed no difference in the BDFS curves ($p = 0.6$) between the treatment groups. The 5-yr estimated biochemical progression rates were 31% for arm A and 28% for arm B. Febrile neutropenia occurred in 16% of the docetaxel patients.

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No deaths were related to the docetaxel treatment. There were 43 deaths during the trial, including 20 in arm A and 23 in arm B, of which nine and seven, respectively, were due to PCa. The hazard ratio from Cox multivariate analysis for PSA progression of arm A (docetaxel) versus arm B (surveillance) was 1.14 (95% confidence interval 0.79–1.64, $p = 0.5$).

Conclusions: Adjuvant docetaxel without prednisone did not improve BDFS after radical RT with ADT for intermediate- or high-risk PCa.

Patient summary: We compared six cycles of adjuvant docetaxel given after radical external radiotherapy plus androgen deprivation therapy to surveillance in intermediate- and high-risk localised prostate cancer. We found no overall benefit in this setting.

1. Introduction

Radical prostatectomy or radiotherapy (RT) is an evidence-based treatment option for intermediate- or high-risk localised prostate cancer (PCa) [1,2]. However, the risk of biochemical recurrence after surgery or RT for high-risk disease is approximately 50% at 5 yr [2–4]. After a recurrence with distant metastases, several new treatment options are available today, including enzalutamide, abiraterone, cabazitaxel, sipuleucil-T, enzalutamide, abiraterone, and radium-223 [5,6]. However, metastatic disease eventually leads to death. A higher stage, a higher Gleason score (GS), and high prostate-specific antigen (PSA) levels correlate with cancer-specific and overall survival in long-term follow-ups [4].

In 2004, two randomised trials showed that a docetaxel-based treatment given every 3rd week prolonged survival in metastatic castrate–resistant prostate cancer (mCRPC), and later, a biweekly dosing of docetaxel was shown to be better tolerated and gave a survival gain in our study [7–9]. In addition, two large prospective randomised trials (CHAARTED and STAMPEDE) have shown survival gain in metastatic hormone-naïve PCa with docetaxel combined with androgen deprivation therapy (ADT) [10–12]. In early breast cancer, adjuvant docetaxel-based regimen was accepted as standard of care over 10 yr ago [13,14]. However, today using gene profiling, similar to the TAILORx trial with hormone receptor–positive and Her-2–negative breast cancer patients, we could avoid adjuvant chemotherapy in many breast cancer patients [15]. The SPCG group initiated two prospective open-labelled, randomised trials to evaluate a possible benefit of docetaxel as an adjuvant treatment after a local curative treatment for PCa, for example, SPCG-12 and SPCG-13. In the SPCG-12 trial, the patients were randomised to receive six cycles of docetaxel without ADT or surveillance after radical prostatectomy. However, docetaxel was not beneficial in our SPCG-12 trial, as recently published by Ahlgren and coworkers [16].

The aim of this SPCG-13 trial was to evaluate whether docetaxel combined with neo/adjuvant hormonal therapy improved biochemical disease–free survival (BDFS) after radical RT for high- or intermediate-risk PCa patients.

2. Patients and methods

The key inclusion criteria in the SPCG-13 trial were the following: men >18 and ≤ 75 yr of age; World Health Organization/Eastern Cooperative Oncology Group performance status 0–1; histologically proven adenocarcinoma of the prostate within 12 mo prior to randomisation; and one of the following: T2 with Gleason 7 (4 + 3) and PSA >10–≤ 70 ng/ml, or T2 with Gleason 8–10; PSA ≤ 70 ng/ml; or any T3 tumours. According to the National Comprehensive Cancer Network guidelines, SPCG-13 patients belong to intermediate- or high-risk group [4]. Prior neoadjuvant hormone therapy was mandatory for all the patients, and adequate haematological, liver, and kidney function ($<1.5 \times$ upper normal limit [UNL] for creatinine and $<1.5 \times$ UNl for liver laboratory values, except for bilirubin $\leq$ UNL) was required. The key exclusion criteria were metastatic disease, pathologically or clinically node positive cancer, a history of previous malignant disease (exceptions were made for basal cell carcinoma and squamous cell carcinoma of the skin and curatively treated malignant disease, which had been disease free for the past 5 yr), previous RT to pelvic region, previous chemotherapy within 5 yr, systemic corticosteroids within 6 mo prior to randomisation, unstable cardiovascular disease within 6 mo prior to randomisation or active untreated infectious disease, known allergy to polysorbate 80, other serious illness or medical condition, symptomatic peripheral neuropathy greater than Common Terminology Criteria for Adverse Events (CTCAE) grade 2, and inability to cooperate. All the patients gave written informed consent. The ethics committee approved the trial. The trial identifier was NTC006653848 (www.clinicaltrial.gov).

The primary endpoint of the trial was PSA progression. The secondary endpoints were PSA doubling time, quality of life (measured by FACT-P [17]), safety (using CTCAE version 3·0; http://ctep.cancer.gov), metastases-free survival, and overall survival.

Between May 2007 and August 2012, a total of 378 patients satisfying the inclusion and exclusion criteria were randomised after completing RT between the control or six courses of docetaxel. ADT was continued according to the protocol. Permuted block randomisation within each stratum was used. Stratification factors were centre and T stage (T2 vs T3). Randomisation request was recorded on a clinical case report form. It was sent to a separate randomisation unit (4Pharma) by fax. Thus, the site personnel did not have access to the randomisation list. Most patients ($N = 320$, 85%) were enrolled from Sweden. The defined endpoint was PSA relapse, according to the ASTRO-RTOG guidelines [18], with progression of PSA

defined as ≥2.0 ng/ml above nadir, with censoring at the last PSA measurement, and discontinuations during PSA follow-up (including deaths from other causes) censored at the time of death/discontinuation. PSA measurements were performed every 3 mo after finishing RT for 2 yr and then every 6 mo until PSA progression or end of trial. Docetaxel 75 mg/m^2 intravenously in 60 min was given on day 1 of each 21-d cycle and started within 3 mo after RT (arm A). Premedication with corticosteroids was used. No continuous prednisone was prescribed during the docetaxel therapy. Arm B received no docetaxel treatment; a neoadjuvant luteinising hormone–releasing hormone (LH–RH) analogue was used 3 mo before RT, during RT, and 3 mo after RT (altogether, there were three injections every 3rd month or monthly injections, treatment lasted 9 mo). Both groups received three-dimensional conformal RT or intensity-modulated radiotherapy alone or in combination with brachytherapy (tumour dose at least 74 Gy).

2.1. Statistical calculations

The null hypothesis of "no difference in the PSA recurrence experience between the treatment groups" was tested against the corresponding nondirectional alternative hypothesis using the log-rank test. Since the recurrence times were assumed to follow mixing distributions, the sample size and the power for the study were estimated through simulation with specific hazard rates for each of the periods with different recurrence rates.

The calculations were performed using software nQuery Advisor 6.0 and with the following assumptions: uniformly distributed inclusion times on the interval (0, 3) yr; 70/30 mixture of T3/T2 PCa patients with 5-yr recurrence rates of 70%/36% in the surveillance group; assumption of a 15%/12% difference in BDFS in favour of docetaxel for T3/T2 patients; a two-sided null hypothesis; and a significance level of 5%. With 360 evaluable patients evenly distributed between the treatment groups, the study had a power of 89% to show the anticipated difference between the treatment groups. The planned number of patients to be recruited was 378, assuming a 5% nonevaluable inclusion.

The Cox proportional hazards model was used in order to conduct the multivariate analysis of the prognostic factors. Survival was estimated with Kaplan-Meier method, and BDFS between groups was compared with the log-rank test.

According to the protocol, a separate safety interim analysis was performed and published [19].

3. Results

3.1. Study population and randomisation

Altogether 378 patients were included in the study from 2 May 2007 to 24 July 2012; 376 patients were randomised and started the follow-up (Fig. 1). Nine patients withdrew consent after randomisation and three had protocol violations. The randomisation was successful, with comparable risk factors in both arms (Table 1). This high- or intermediate-risk cohort was enrolled with 75% T3 and 47% GS 8–10 (21% GS 9–10), and the median PSA was 14; thus, there were 84% high-risk patients in both arms (T3 or PSA over 20). The median radiation dose was 78 Gy in both arms.

3.2. Arm A

A total of 180 (96%) of the 188 patients in arm A received at least one dose of docetaxel, and 147 (78%) of them received all six cycles as per the protocol. A dose reduction was

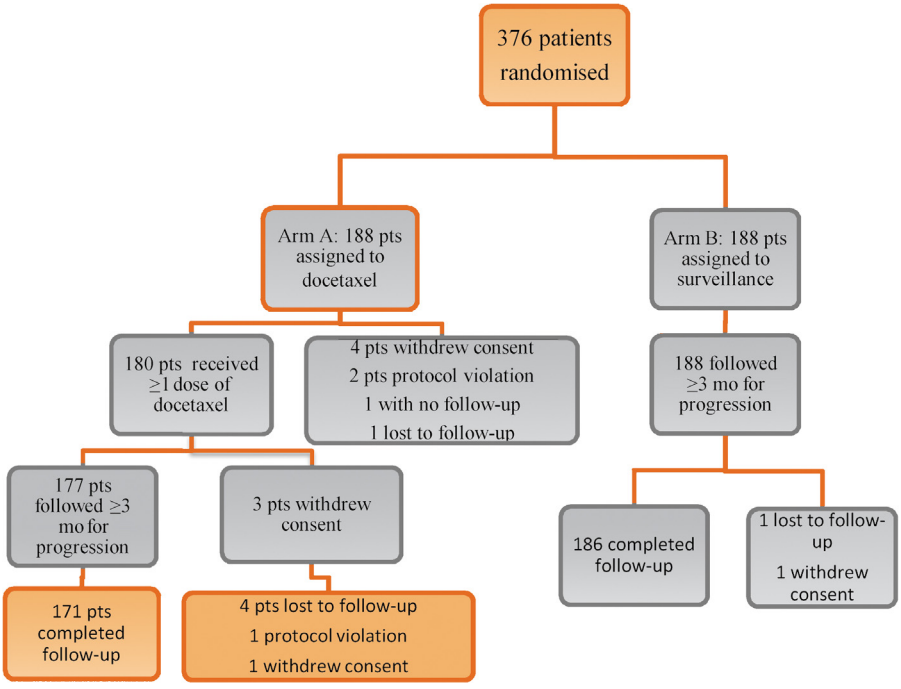

Fig. 1 – Trial profile for SPCG-13: arm A, adjuvant; arm B, surveillance only. pts: patients.

Table 1 – Baseline characteristics in arms A and B.

Factor	Adjuvant docetaxel (arm A, *n* = 188)	Surveillance (arm B, *n* = 188)
Age (yr), median (IQR)	67 (63–70)	67 (63–71)
PSA before RT (ng/ml), median (IQR)	14.6 (8.2–29.0)	14.0 (7.0–26.0)
PSA after RT (ng/ml), median (IQR)	0.50 (0.15–2.80)	0.57 (0.12–1.75)
T-stage T2/T3 (%)	26/74	24/76
Gleason ≤7/8/9–10 (%)	56/26/18	51/25/24
WHO status 0/1 (%)	93/7	95/5

IQR = interquartile range; PSA = prostate-specific antigen; RT = radiotherapy; WHO = World Health Organization.

necessary in 92 (51%) patients, with no difference seen in the outcome (hazard ratio [HR] 1.15 for patients with dose reduction, 95% confidence interval [CI] 0.69–1.93, $p = 0.6$, in exploratory univariate Cox model for PSA progression in docetaxel-treated patients). Neutropenia grade 3–4 was observed in 79 (44%) patients who received at least one docetaxel infusion. Twenty-nine episodes of febrile neutropenia were reported (16%). No docetaxel-related deaths were reported. Other serious adverse events that were more common in arm A were cardiovascular disease and thromboembolism (Table 2). However, 78% of patients in arm A received all the six cycles of docetaxel (Table 3).

3.3. *Analysis of progression*

At the 5-yr follow-up, the rate of progression was declining and we decided to analyse the primary endpoint as planned in protocol per follow-up time using the 31 December 2017 as the data cut-off, although the number of recurrences was not at the expected level. The end-of-study visit was at 1–104 mo from the randomisation. At this time point, of the 375 patients with a follow-up registered, 58 in arm A and 57 in arm B had reached the endpoint (progression of PSA defined as ≥2.0 ng/ml above nadir). The median time to progression, death, or last follow-up was 60 mo in arm A and 59 in arm B (61 mo for nonprogressors in both groups). The risk of progression over time in the two arms was illustrated by a Kaplan–Meier analysis, showing no difference between the treatment groups ($p = 0.6$, log-rank test; Fig. 2). The 5-yr estimated biochemical progression rates were 31% for arm A and 28% for arm B. There were 43 deaths during the trial, including 20 in arm A (docetaxel) and 23 in arm B (surveillance), of which nine and seven, respectively, were due to PCa. The 5-yr estimated death rate was 10% for both treatment groups. In the Cox multivariate analysis with T stage, treatment group, and GS, GS ($p = 0.001$) was a significant predictor of PSA progression (Table 4). The HR for arm A (docetaxel) versus arm B (surveillance) was 1.14 (95% CI 0.79–1.64, $p = 0.5$), indicating that there was no overall benefit of using docetaxel. The interaction between GS class (GS >8/GS ≤8) and treatment group was close to significant ($p = 0.059$), and there was a tendency towards a treatment benefit in the high-risk (Gleason 9–10) subgroup ($n = 80$) with HR 0.67 (95% CI 0.34–1.30, $p = 0.2$) for PSA progression in arm A (docetaxel) versus arm B (surveillance; Fig. 3).

Table 3 – Docetaxel treatment delivered at each cycle.

No. of cycles	Frequency	Percentage (%)	Cumulative percentage (%)
0	8	4	4
1	12	6	11
2	6	3	14
3	5	3	16
4	5	3	19
5	5	3	23
6	**147**	**78**	100
Total	188	100	

4. Discussion

This is the first published randomised trial of an adjuvant docetaxel treatment after radical RT compared with

Table 2 – Reported number of serious adverse events (SAEs) in arms A and B (some patients several SAEs).

Type of SAE	Arm A (docetaxel)*N* = 188	Arm B (surveillance)*N* = 188	Total
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

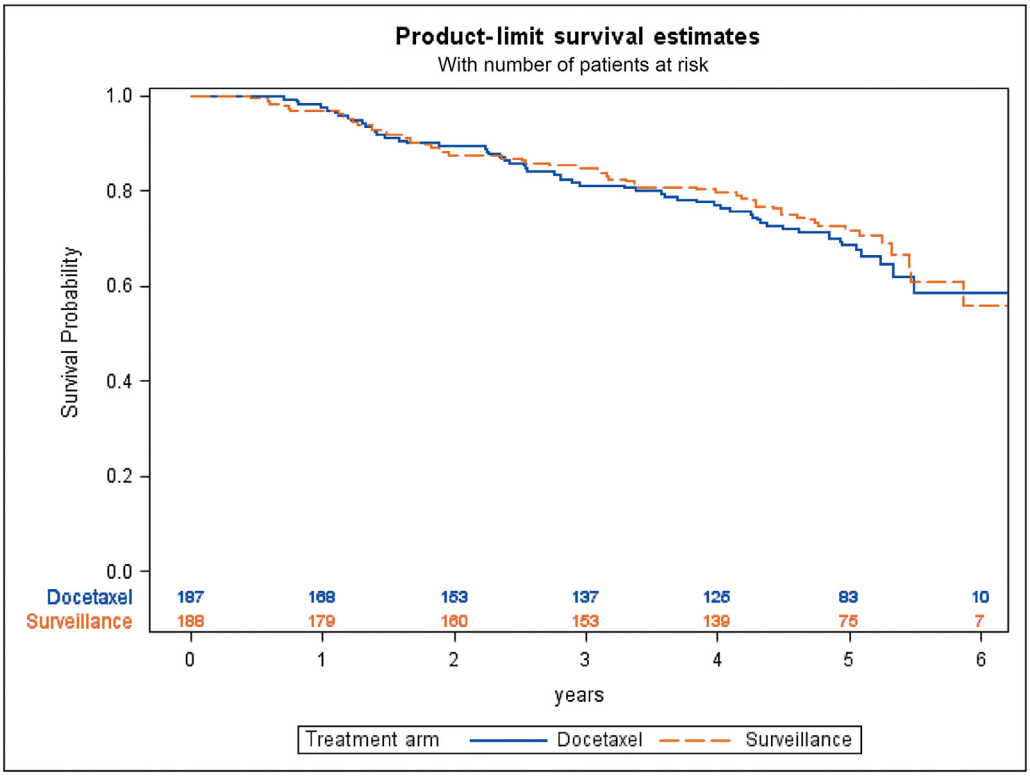

Fig. 2 – Kaplan-Meier curves of survival free of progression (PSA ≥ 2.0 ng/ml) by intent to treat (p = 0.6). PSA = prostate-specific antigen.

Table 4 – Uni- and multivariate Cox analysis of hazard ratio to have progression to endpoint PSA ≥ 2.0 ng/ml for prognostic factors and treatment arm.

Prognostic factor	Univariate analysis (n = 375)		Multivariate analysis n = 375	
	p value	HR (95% CI)	p value	HR (95% CI)
T stage T2 vs T3	1.0	0.99 (0.65–1.53)	0.18	0.73 (0.46–1.15)
Gleason sum (linear effect of 1 unit *)	<0.001	1.47 (1.22–1.78)	0.001	1.52 (1.22–1.88)
Arm A vs arm B	0.6	1.09 (0.76–1.58)	0.5	1.14 (0.79–1.64)

CI = confidence interval; HR = hazard ratio.

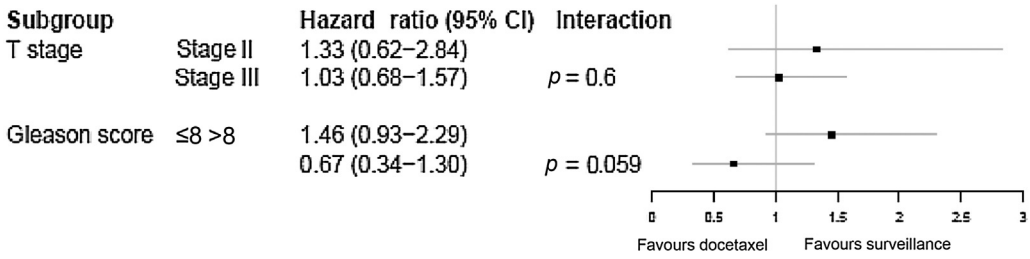

Fig. 3 – Forest plot of hazard ratio for biochemical progression (PSA ≥ 2.0 ng/ml) in subgroups for the variables used in multivariate analysis. CI = confidence interval; PSA = prostate-specific antigen.

surveillance in PCa patients. Our result does not support the use of docetaxel after radical RT for intermediate- or high-risk PCa. This study used neoadjuvant/adjuvant ADT combined with RT, and still no beneficial effect of docetaxel in BDFS was observed. A recent publication of RTOG 0521 showed a significant overall survival gain with docetaxel [20]. In addition, improved disease-free survival and reduction in the rate of distant metastasis were observed. The study included more advanced patients, for example, locally advanced T4 tumours and with PSA values up to 150 versus 70 in our study. Among the patients in that study, 53% had GS 9–10 and 31% GS 8 (altogether 84% GS 8–10), while only 47% of our patients had GS 8–10. Thus, RTOG 0521 patients had more advanced disease (Table 5).

Table 5 – Summary of adjuvant trials in prostate cancer using docetaxel combined with ADT and radical radiotherapy.

Trial	T	PSA (ng/ml)	GS	ADT (mo)	CT	Results
GETUG-12	T1–2, 23% T3–4, 67% N+, 29%	>20, 59%	GS ≥ 8, 42%	36	DE × 4	12 yr RFS, 49% vs 36%; $p = 0.01$
RTOG 9902	T1–2, 66% T3–4, 34%	23 median	GS ≥ 8, 68%	28	E + Eto + P × 4	10 yr OS, 65% vs 63%; $p = 0.8$
RTOG 0521	T1–2, 73% T3–4, 27%	15 median	GS 8–10, 84%	28	D × 6	4 yr OS, 86% vs 81%; $p = 0.03$
SPCG-13	T2, 25% T3, 75%	14 median	GS 8–10, 47%	9	D × 6	5 yr BDFS, 69% vs 72%; $p = 0.6$

ADT = androgen deprivation therapy; BDFS = biochemical disease–free survival; CT = chemotherapy; D = docetaxel; E = estramustine; Eto = etoposide; GS = Gleason score; P = paclitaxel; PSA = prostate-specific antigen; RFS = recurrence-free survival; OS = overall survival.

However, in our study, the interaction between treatment group and Gleason class was almost significant ($p = 0.059$), and the patients in the high-risk group (GS 9–10) had a tendency towards achieving a benefit (HR 0.67, 95% CI 0.34–1.30, $p = 0.2$) from adjuvant docetaxel. RTOG 0521 used also prednisone with docetaxel. We did not use prednisone either in SPCG-12 or in SPCG-13 trial in order to avoid the known side effects of prednisone. The practice to use it with docetaxel comes from the trials of advanced PCa, where cortisone is also used to palliate symptoms. Thus, it was combined with mitoxantrone, which was compared with docetaxel in the early trials of mCRPC, such as in TAX 327. In addition, our treatment protocol with docetaxel and ADT was different from the sequential treatment protocols, which are used in adjuvant studies on breast cancer [13,14], where docetaxel was given before hormonal treatment.

In several studies, combining ADT with RT has been beneficial, and included in RT guidelines of high- and intermediate-risk PCa [4,21]. We chose the duration of the LH-RH analogue to be shorter than 3 yr to avoid permanent castration in these elderly men, and still their BDFS and overall survival were very good. Moreover, in the recently published phase III PCa trial, the shorter duration of ADT was used after RT [21]. However, long-duration ADT with RT remains the standard of care.

In an adjuvant study after RT in high-risk PCa patients with long follow-up and survival as an endpoint (RTOG 9902), no difference was seen in biochemical failure, distant metastasis-free survival, or overall survival after a median follow-up of 9.4 yr [22]. This study used a probably less effective nontaxane triple chemotherapy in combination with ADT after RT. In addition, RTOG 9902 was closed early due to the toxicity of chemotherapy and slow patient accrual. In the GETUG-12 trial, docetaxel and estramustine phosphate, in combination with ADT, were compared with ADT alone after a curative treatment for high-risk disease and most of them after RT [23]. A significant difference in time to biochemical recurrence was found in favour of the combination therapy. The primary treatment was RT in combination with ADT, and ADT was given for 3 yr, and the progression was defined by PSA > 2.0 ng/ml above nadir as in our study. The difference in the outcome in the GETUG-12 study was seen in patients with a GS of ≤7, while no effect was seen in the GS = 8 or higher patients. In both RTOG 9902 and GETUG-12 studies, the primary endpoint was biochemical progression, and no conclusion was drawn about metastasis-free or cancer-specific survival [22,23]. Updated results of GETUG-12 were presented in ESMO 2018 [24]. According to these results, four cycles of docetaxel-based chemotherapy reduced the risk of clinical relapse or death in the long-term follow-up (12 yr). In the recently published STAMPEDE trial, there was no survival benefit from docetaxel combined with ADT compared with ADT alone for patients with locally advanced disease without proven metastasis at randomisation, but a positive effect on PSA was observed [11]. Both RTOG trials also had much more aggressive tumours (see Table 5, GS distribution) than in our study explaining partly the difference in the outcome. Tosco et al [25] recently published a systematic review of therapeutic combinations with local treatments for high-risk localised PCa. They identified altogether 77 prospective trials. Many of these trials showed a benefit of combining ADT with external beam radiotherapy (EBRT) compared with EBRT alone; docetaxel showed to increase relapse-free survival with EBRT plus ADT in GETUG-12, RTOG 0521, and the nonmetastatic group in STAMPEDE; and according to the recent results of RTOG 0521, improved overall survival was observed. However, all these trials, similar to ours, should have longer follow-up time.

In a recent meta-analysis of the results from clinical trials on the use of docetaxel plus ADT in hormone-naive nonmetastatic locally advanced PCa, the gain in failure-free survival was highly significant (8%) [26]. However, the reduction in survival was 4%, which was not significant. In the SPCG-12 radical prostatectomy trial, no ADT and no daily prednisone were used, and likewise, as in our study, there was no benefit of six cycles of docetaxel. Similar findings were observed in the TAX 3501 radical prostatectomy study for the arm with the sequential docetaxel and hormonal treatment, but the number of patients and events was very low [27]. Thus, it seems that the beneficial effect of docetaxel in early PCa is not dependent on the docetaxel-ADT interaction. New therapeutic approaches and molecular profiling as in TAILORx trial [15] should be studied, especially in the neoadjuvant situation before prostatectomy [28], allowing response evaluation more quickly.

The toxicity profile of docetaxel was in line with the previous publications [11–14,16], and no toxic deaths occurred. Of the patients, 78% received all six cycles of docetaxel. However, more efforts should be made to avoid toxicity in this elderly patient population.

The limitations of our study include having a heterogeneous risk profile in our study population, and that the primary endpoint is BDFS and not survival. However, the inclusion criteria were designed based on a 50% risk of relapse by nomograms. The trial might have been underpowered to detect subgroup differences. There were far fewer relapses than expected, lowering the planned statistical power of the study, even though most of our patients belonged to the high-risk group, and we will continue the follow-up of our patients.

In the main analysis for biochemical progression, the confidence interval of HR (docetaxel vs surveillance) spreads from 0.79 to 1.64, indicating that there is no clear difference in favour of either treatment arm. The lower limit of 0.79 does not indicate signs of considerable overall benefit of docetaxel over surveillance based on this study.

5. Conclusions

In conclusion, based on our current results, there is no evidence that adjuvant docetaxel with ADT after RT would provide a benefit for intermediate- or high-risk PCa patients in general clinical practice. However, based on the results of this trial, the possibility that docetaxel could improve outcomes in high-risk local PCa cannot be ruled out, and based on the results of RTOG 0521 trial, adjuvant docetaxel should be discussed with patients as a treatment option for high-risk PCa.

Author contributions: Pirkko-Liisa Kellokumpu-Lehtinen 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: Kellokumpu-Lehtinen, Ginman, Hjälm-Eriksson, Huttunen, Thellenberg-Karlsson.
Acquisition of data: Kellokumpu-Lehtinen, Hjälm-Eriksson, Thellenberg-Karlsson, Åström, Franzen, Fransson, Leskinen, Zeke, Ginman.
Analysis and interpretation of data: Huttunen, Kellokumpu-Lehtinen.
Drafting of the manuscript: Kellokumpu-Lehtinen, Hjälm-Eriksson, Thellenberg-Karlsson, Åström, Franzen, Fransson, Leskinen, Zeke, Huttunen, Ginman.
Critical revision of the manuscript for important intellectual content: Kellokumpu-Lehtinen, Huttunen.
Statistical analysis: Huttunen.
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References

[1] Sandra MG, Cadeddu JA, Kirby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. J Urol 2018;199:683–90.
[2] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis and local treatment with curative intent. Eur Urol 2017;71:618–29.
[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] National Comprehensive Cancer Network. National comprehensive Cancer network guidelines. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
[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 2018;73:178–211.
[6] Fitzpatrick JM, Bellmunt J, Fizazi, et al. Optimal management of metastatic castration-resistant prostate cancer: highlights from a European expert consensus panel. Eur J Cancer 2014;50:1617–27.
[7] 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.
[8] 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.
[9] Kellokumpu-Lehtinen P-L, Harmenberg U, Joensuu T, et al. 2-weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial. Lancet Oncol 2013;14:117–24.
[10] Sweeney CJ, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2018;373:737–46.
[11] James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line hormonal therapy (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387:1163–77.
[12] Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018;11:1080–7.
[13] Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006;354:809–20.

[14] Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;352:2302–13.
[15] Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 2018;379:111–21.
[16] Ahlgren G, Flodgren P, Tammela T, et al. Docetaxel versus surveillance after radical prostatectomy for high risk prostate cancer: results from the prospective randomized, open-label phase 3 Scandinavian prostate cancer group 12 trial. Eur Urol 2018;73:870–6.
[17] 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. Urol 1997;50:920–8.
[18] Roach 3rd M, Hanks G, Thames Jr H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of RTOG-ASTRO Phoenix consensus Conference. In J Rad Oncol Biol Phys 2006;65:965–74.
[19] Kellokumpu-Lehtinen PL, Hjälm-Eriksson M, Thellenberg-Karlsson C, et al. Toxicity in patients receiving adjuvant docetaxel + hormonal treatment after radical radiotherapy for intermediate or high-risk prostate cancer: a preplanned safety report of the SPCG-13 trial. Prostate Cancer Prostatic Dis 2012;15:303–7.
[20] Rosenthal SA, Hu C, Sartor O, et al. Effect of chemotherapy with docetaxel with androgen suppression and radiotherapy for localized high-risk prostate cancer: the randomized phase III NRG Oncology RTOG 0521 trial. J Clin Oncol 2019;37:1159–68.
[21] Nabid A, Carrier N, Martin AG, et al. Duration of androgen deprivation therapy in high-risk prostate cancer: a randomized phase III trial. Eur Urol 2018;74:432–41.
[22] 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.
[23] 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.
[24] Fizazi K, Carmel A, Florence J, et al. Updated results of GETUG-12, a phase 3 trial of docetaxel-based chemotherapy in high-risk localized prostate cancer, with a 12-year follow up. ESMO 2018 Congress. Ann Oncol 2018;29(suppl_8), viii271–302.
[25] Tosco L, Briganti A, D'amico AV, et al. Systematic review of systemic therapies and therapeutic combinations with local treatment for high risk localized prostate cancer. Eur Urol 2019;75:44–60.
[26] 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.
[27] 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;119:3610–3618.
[28] Montgomery B, Lin DW. Adjuvant chemotherapy for prostate cancer: the long and winding road. Eur Urol 2018;73:877–8.