This is the accepted manuscript of the article, which has been published in European Urology. 2019, 76(6), 823-830. https://doi.org/10.1016/j.eururo.2019.08.010

Title page

Docetaxel versus surveillance after radical radiotherapy for intermediate-or high-risk prostate cancer - results from the prospective randomized, open-label phase III SPCG 13 trial.

Kellokumpu-Lehtinen P-L[1], Hjälm-Eriksson M[2], Thellenberg-Karlsson C[3], Åström L[4], Franzen L[5], Fransson A-S[6], Leskinen M[7], Zeke M[8], Huttunen T[9], Ginman C[10] on behalf of the Investigators of the Scandinavian Prostate Cancer Study no 13

[1]Tampere University Hospital, Tampere, Finland, [2] Department of Surgery Capio ST: Görans hospital and Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden, [3] Department of Radiation Sciences, Oncology, Umeå University Hospital, Umeå, Sweden, [4]Uppsala University Hospital, Uppsala, Sweden, [5] Sundsvall University Hospital, Sundsvall, Sweden, [6] Gävle Central Hospital, Gävle, Sweden, [7] Seinäjoki Central Hospital, Seinäjoki, Finland, [8] Växjö Central Hospital, Växjö, Sweden, [9]4Pharma, Turku, Finland, [10] Karlstad Central Hospital, Karlstad, Sweden

Send proofs and correspondence to:

Pirkko-Liisa Kellokumpu-Lehtinen, M.D., PhD, Professor

Professor of Radiotherapy and Oncology
Faculty of Medicine and Health Technology, University of Tampere and Tampere University Hospital
P.O. Box 2000
33521 Tampere
Finland

Telephone; +358 50 5951103
Fax; +358 3 31163009
e-mail; pirkko-liisa.kellokumpu-lehtinen@tuni.fi

Key words; Prostate cancer, adjuvant, docetaxel, randomized trial, radical radiotherapy.
Word count of text; 2799 Word count of the abstract; 395

Take Home Message

In a randomized setting, intermediate- or high-risk prostate cancer patients treated with adjuvant chemotherapy with docetaxel following radical radiotherapy and ADT did not show improved biochemical disease-free survival compared to those who underwent radical radiotherapy and ADT alone. More adverse events occurred with the combined treatment, but there were less PSA relapses than were estimated to occur in both groups.

Background*:* Docetaxel combined with androgen deprivation therapy (ADT) has improved patient survival for advanced prostate cancer (PCa).

Objective: This randomized trial evaluated if six courses of docetaxel improved the 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 randomized in this multinational phase III study and received either 6 cycles of adjuvant docetaxel 75 mg/m^2 every 3 weeks 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 a rising PSA $\geq$ 2 ng/ml above the nadir PSA value. Intermediate- or high-risk prostate cancer was defined as T2 with a Gleason score (GS) of 4+3, PSA>10; T2, GS 8-10 any PSA; or any T3.

The patients were followed for 5 years by assessing PSA levels every 3 months for two years and every 6 months thereafter.

Outcome measurements and statistical analysis: The study power was 89% to detect a difference between groups in biochemical disease-free survival (BDFS), 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 years in both treatment groups, and 75% had T3 disease, and 46% had GS 8-10. The median follow-up was 59 months (range 1 to 111 months). 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-year estimated biochemical progression rates were 31% for Arm A and 28% for Arm B. Febrile neutropenia occurred in 16% of the docetaxel patients. 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 9 and 7, respectively, were due to PCa. The Hazard Ratio from Cox multivariate analysis for PSA progression of Arm A (docetaxel) vs Arm B (surveillance) was 1.14 (95% CI 0.79 to 1.64, p=0.5).

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

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

Introduction

Radical prostatectomy or radiotherapy is evidence based treatment options for intermediate- or high-risk localized prostate cancer (PCa) (1,2). However, the risk of biochemical recurrence after surgery or radiotherapy for high-risk disease is approximately 50% at 5 years (3-5). After a recurrence with distant metastases, several new treatment options are available today, including enzalutamide, abiraterone, cabazitaxel, sipuleucil-T, enzalutamide, abiraterone, and radium-223 (6,7). However, metastatic disease eventually leads to death. Higher stage, higher Gleason score (GS) and high prostate specific antigen (PSA) levels correlate to cancer specific and overall survival in long-term follow-ups (5).

In 2004, two randomized trials showed that a docetaxel-based treatment given every third 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 (8-10). In addition, two large prospective randomized trials (CHAARTED and STAMPEDE) have shown survival gain with docetaxel in metastatic hormone naïve prostate cancer combined to androgen deprivation therapy (11-13). In early breast cancer, adjuvant docetaxel-based regimen was accepted as standard of care over ten years ago (14, 15). However, today using gene profiling, like in the TAILORx trial with hormone receptor positive and Her-2 negative breast cancer patients, we could avoid adjuvant chemotherapy in many breast cancer patients (16). The SPCG-group initiated two prospective open labelled, randomized trials to evaluate a possible benefit of docetaxel as an adjuvant treatment after local curative treatment in prostate cancer e.g., SPCG-12 and SPCG-13. In the SPCG-12 trial, the patients were randomized 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 co-workers (17)

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

Patients and methods

The key inclusion criteria in the SPCG trial-13 were the following: men > 18 and ≤75 years of age; WHO/ECOG performance status 0 – 1; histologically proven adenocarcinoma of the prostate within 12 months prior to randomization; one of the following: T2 with Gleason 7 (4+3) and PSA >10 ng/ml to ≤ 70 ng/ml or T2 with Gleason 8-10; PSA ≤ 70 ng/ml or any T3 tumours. According to the NCCN guidelines SPCG-13 patients belong to intermediate- or high-risk group (5). Prior neoadjuvant hormone therapy was mandatory for all the patients, and adequate haematological, liver and kidney function (less than 1.5 x UNL for creatinine, less than 1.5 X UNL for liver laboratory values except bilirubin ≤ 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 five years), previous radiotherapy to pelvic region, previous chemotherapy within five years, systemic corticosteroids within 6 months prior to randomization, unstable cardiovascular disease within 6 months prior to randomization or active untreated infectious disease known allergy to Polysorbate 80, other serious illness or medical condition, symptomatic peripheral neuropathy ≥ CTCAE grade 2 and unable 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 (QoL, measured by FACT-P, 18), safety (using Common Terminology Criteria for Adverse Events (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 randomized after completing RT between the control or six courses of docetaxel. ADT was continued according the protocol. Permuted block randomization within each stratum was used. Stratification factors were centre and T stage (T2 vs T3). Randomization request was recorded on a clinical case report form . It was sent to separate randomization unit by fax to 4Pharma. Thus, the site personnel did not had access to the randomization list. Most patients (N=320, 85%) were enrolled from Sweden. The defined endpoint was PSA relapse, according to the ASTRO-RTOG guidelines (19), with progression of PSA defined $\geq$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 done every three months after finishing RT for two years then every 6 months until PSA progression or end of trial.

Docetaxel 75 mg/m^2 i.v. in 60 minutes was given on day one of each 21-day cycle and started within three months after radiotherapy (**Arm A**). Premedication with corticosteroids was used. No continuous prednisone was prescribed during the docetaxel therapy. **Arm B;** No docetaxel treatment. Neoadjuvant LH-RH analogue 3 months before RT, during RT and 3 months after RT (altogether, there were 3 injections every third month or monthly injections, treatment lasted 9 months). Both groups received 3D conformal radiotherapy or intensity modulated radiotherapy (IMRT) alone or combined to brachytherapy, tumour dose at least 74 Gray.

Statistical calculations

The null hypothesis of 'no difference in the PSA recurrences 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 done using software nQuery Advisor 6.0 and with following assumptions: uniformly distributed inclusion times on the interval [0, 3] years; 70/30 mixture of subjects with T3/T2 prostate cancer 5-year recurrence rates of 70%/36% for T3/T2 patients in surveillance group; a 15%/12% difference in BDFS in favour of docetaxel was assumed for the T3/T2 patients; a two-sided null hypothesis; and a significance level of 5%. With 360 evaluable subjects 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% non-evaluable 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 done and published (20).

Results

Study population and randomization

Altogether 378 patients were included to the study from May 2, 2007 to July 24, 2012, 376 pts were randomized and started the follow-up (Fig 1). Nine patients withdrew consent after randomization, and 3 patients were had protocol violations. The randomization 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, and thus, there were 84% high risk patients in both arms (T3 or PSA over 20). Median radiation dose was 78 Gy in both arms.

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 6 cycles per the protocol. A dose reduction was necessary in 92 (51%) patients, with no difference seen in the outcome (HR 1.15 for patients with dose reduction, 95% CI 0.69 to 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 SAE´s 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).

Analysis of progression

At the five-year follow-up, the rate of progression was declining and we decided to analyze the primary endpoint as planned in protocol per follow-up time using the 31st Dec 2017 as the data cut-off although the number of recurrences were not at the expected level. The end-of-study visit was at 1-104 months from the randomization. At this time-point, of the 375 patients with a follow-up registered, 58 patients in Arm A and 57 in Arm B had reached the endpoint (progression of PSA defined $\geq$2.0 ng/ml above nadir). The median time to progression, death or last follow-up was 60 months in Arm A and 59 in Arm B (61 months for non-progressors in both groups). The risk of progression over time in the two arms was illustrated by a Kaplan-Meier analysis showing no difference between treatment groups (Figure 2) (p=0.6, log-rank test). The 5-year 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 9 and 7, respectively, were due to prostate cancer. The 5-year

estimated death rates were 10% for both treatment groups. In the Cox multivariate analysis with T stage, treatment group and Gleason Score (GS), GS (p=0.001) was a significant predictor of PSA progression. The Hazard Ratio for Arm A (docetaxel) vs Arm B (surveillance) was 1.14 (95% CI 0.79 to 1.64, p=0.5) indicating that there was no overall benefit of using docetaxel. The interaction between GS class (GS over 8/ GS 8 or under) and treatment group was close to significant (p=0.059) and there was a tendency towards treatment benefit in the high-risk (Gleason 9-10) subgroup (n=80) with HR 0.67 (95% CI 0.34 to 1.30, p=0.2) for PSA progression in Arm A (docetaxel) vs Arm B (surveillance) (Figure 3).

Discussion

This is the first published randomized trial of an adjuvant docetaxel treatment after radical radiotherapy compared to surveillance in PCa patients. Our result does not support the use of docetaxel after radical radiotherapy 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 (21). Also improved disease-free survival and reduction in the rate of distant metastasis was observed. Their study included more advanced patients, e.g., locally advanced T4 tumors, and with PSA values up to 150 vs 70 in our study. They had 53% with Gleason score 9-10 and 31% GS 8 (altogether 84% GS 8-10), while only 46% of our patients had GS 8-10. Thus RTOG 0521 patients had more advanced disease (Table 5). However, in our study the interaction between treatment group and Gleason class was almost significant (p=0.059), and the patients in high risk (GS 9-10) had tendency towards benefit (HR 0.67, 95% CI 0.34 to 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 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 to mitoxantrone, which was the comparator to docetaxel in the early trials of mCRPC like 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 in breast cancer (14,15), were 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 (5, 22). We chose a shorter than three years duration of the LH-RH-analogue to avoid permanent castration in these elderly men and still their BDFS and overall survival were very good. Also in the recently published phase III PCa trial the shorter duration of ADT was used after radiotherapy (22). However, long ADT with radiotherapy remains the standard of care.

In an adjuvant study after radiotherapy in high-risk PCa patients with long follow-up and survival as an endpoint (RTOG 9902), no difference was seen in either biochemical failure, distant metastasis free survival or overall survival after a median follow-up of 9.4 years (23). This study used a probably less effective non-taxane triple chemotherapy in combination with ADT after RT. In addition, RTOG 9902 was early closed 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 curative treatment for high-risk disease and most of them after radiation therapy (24). A significant difference in time to biochemical recurrence was found in favor of the combination therapy. The primary treatment was radiotherapy in combination with ADT, and ADT was given for 3 years, 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≤7, while no effect was seen in the GS=8 or higher patients. In both the RTOG 9902 and GETUG 12 studies, the primary

endpoint was biochemical progression, and no conclusion was drawn about metastasis-free or cancer-specific survival (23,24). Updated results of GETUG-12 were presented in ESMO 2018 (25). According to them four cycles of docetaxel-based chemotherapy reduced risk of clinical relapse or death in this long-term follow-up (12 years). 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 randomization, but a positive effect on PSA was observed (12). Both RTOG trials had also much more aggressive tumors (see Table 5, GS distribution) than in our study explaining partly the difference in the outcome. Tosco et al. published recently systematic review of therapeutic combinations with local treatments for high risk localized prostate cancer (26). They identified altogether 77 prospective trials. Multiple of them showed benefit of combining ADT with EBRT compared to EBRT alone and docetaxel showed to increase relapse free survival in GETUG-12, RTOG 0521 and nonmetastatic group in STAMPEDE with EBRT plus ADT and according to the recent results of RTOG 0521 improved overall survival was observed. However, all these trials like 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%) (27) However, the reduction in survival was four percent, 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 (28). 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 (16) should be studied, especially in the neoadjuvant situation before prostatectomy (29) allowing response evaluation more quickly.

The toxicity profile of docetaxel was in line with the previous publications (12-15,17) and no toxic deaths occurred. Even 78% of the patients received all six cycles of docetaxel. However, more effort should be done 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 favor of either treatment arm. The lower limit of 0.79 do not indicate signs of considerable overall benefit of docetaxel over surveillance based on this study. In conclusion, based on our current results there is no evidence that adjuvant docetaxel with ADT after radiotherapy would provide benefit for intermediate- or high-risk prostate cancer patients in general clinical practice. However, whether docetaxel could improve outcomes in high-risk local prostate cancer cannot be ruled-out by this trial and based on the results of RTOG 0521 trial, adjuvant docetaxel should be discussed with patients as a treatment options for high-risk prostate cancer.

Role of the funding source

All data within the database were stored at 4Pharma, Turku, Finland. The corresponding author had full access to the data in the study and had final responsibility for the decision to it submit

for publication. The funder of the study (Sanofi) had no impact on study design, data collection, data analysis, data interpretation or writing of the report. The representatives from the company were regularly updated on how the study was proceeding and participated in the investigators meetings.

Acknowledgements: To all the investigators, study coordinators and nurses within the SPCG-13 participating centers, including the University Hospitals, Karolinska University Hospital, Uppsala University Hospital, Örebro University Hospital, Hospitals, Karlstad, Sundsvall, Eskilstuna, Växjö and Jönköping in Sweden and the University Hospital in Tampere, Hospitals in Lahti and Seinäjoki in Finland.

All the patients, their families and to Sanofi for a generous research grant. This study was partly supported by the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital.

Conflicts of interest

Marie Hjälm-Eriksson is a member of advisory board; Bayer and Sanofi.

Camilla Thellenberg-Karlsson is a member of advisory board; Sanofi, Bayer. Speakers fee Janssen, Astellas

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;199:683-690.

2. Motter N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Par 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: Seminars and Original Investigations 2015;33:163.e7-13.

4 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;71:618–629

5. National Comprehensive Cancer Network guidelines. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (accessed 07, November 2018).

6. 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.

7. 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;50:1617-1627.

8. 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.

9. Tannock IF, de Wit R, Berry WR, et al for the TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502-12

10. 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;14:117-124.

11. Sweeney CJ, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2018;373;737-46.

12. 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.

13. 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 CHAARTEED trial. J Clin Oncol 2018;11;1080-87.

14 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.

15. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;352:2302-13.

16. Sparano JA, Gray RJ, Makover DF et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 2018;379;111-121.

17. 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;73:870-876.

18. Esper P, Mo F, Chodak G, et al. Measuring quality of life in men with prostate cancer using the Functional Assessment of Cancer Therapy–prostate instrument. Urol 1997;50:920-8.

19. Roach M 3rd, Hanks G, Thames H Jr, et al. 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.

20. 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;15:303-307.

21.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;March 12, https://doi.or/10.1200.18.02158.

22. 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;74:432-441.

23. 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.

24. 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.

25. 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.

26.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.

27. Vale C L, Burdett S, Rydzewsk L H M 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.

28. 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;119:3610–18.

29. Montgomery B, Lin DW. Adjuvant chemotherapy for prostate cancer: The long and winding road. Eur Urol 2018;73:877-78.

Table 1. Baseline characteristics in Arm A and Arm B.

Factor	**Adjuvant Docetaxel (Arm A, n=188)**	**Surveillance (Arm B, n=188)**
Age median (IQR)	67 (63-70)	67 (63-71)
PSA median before RT (ng/ml, IQR)	14.6 (8.2-29.0)	14.0 (7.0-26.0)
PSA median after RT (ng/ml, 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

Table 2. Reported number of serious adverse events (SAE) in Arm A and Arm B. Some patients several SAE´s.

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**

Table 3. Docetaxel treatment delivered at each cycle

No. cycles	**Frequency**	**Percent (%)**	**Cumulative Percent (%)**
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	

Table 4. Uni- and multivariate Cox analysis of Hazard Ratio to have progression to end-point PSA≥2.0 ng/ml for prognostic factors and treatment Arm.

Prognostic factor	Univariate analysis n=375 p-value	HR (95% Ci)	Multivariate analysis n=375 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)

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

Trial	**T**	PSA (ng/ml)	**GS**	**ADT**	**CT**	**Results**
GETUG-12	T 1-2 23% T 3-4 67% N+ 29%	>20, 59%	GS ≥ 8, 42%	36 months	DE x 4	12 yr. RFS 49% vs 36% p=0.01
RTOG 9902	T 1-2 66% T 3-4 34%	23 median	GS ≥ 8, 68%	28 months	E+Eto+P x 4	10 yr. OS 65% vs 63%, P=0.8
RTOG 0521	T 1-2 73% T 3-4 27%	15 median	GS 8-10, 84%	28 months	D x 6	4 yr. OS 86% vs 81%, p=0.03
SPCG-13	T 2 25% T 3 75%	14 median	GS 8-10, 46%	9 months	D x 6	5 yr. BDFS 69% vs 70%, p=0.6

CT=chemotherapy, D=docetaxel, E=Estramustine, Eto=etoposide, P= paclitaxel, RFS= recurrence free survival, OS= overall survival, BDFS= biochemical disease-free survival

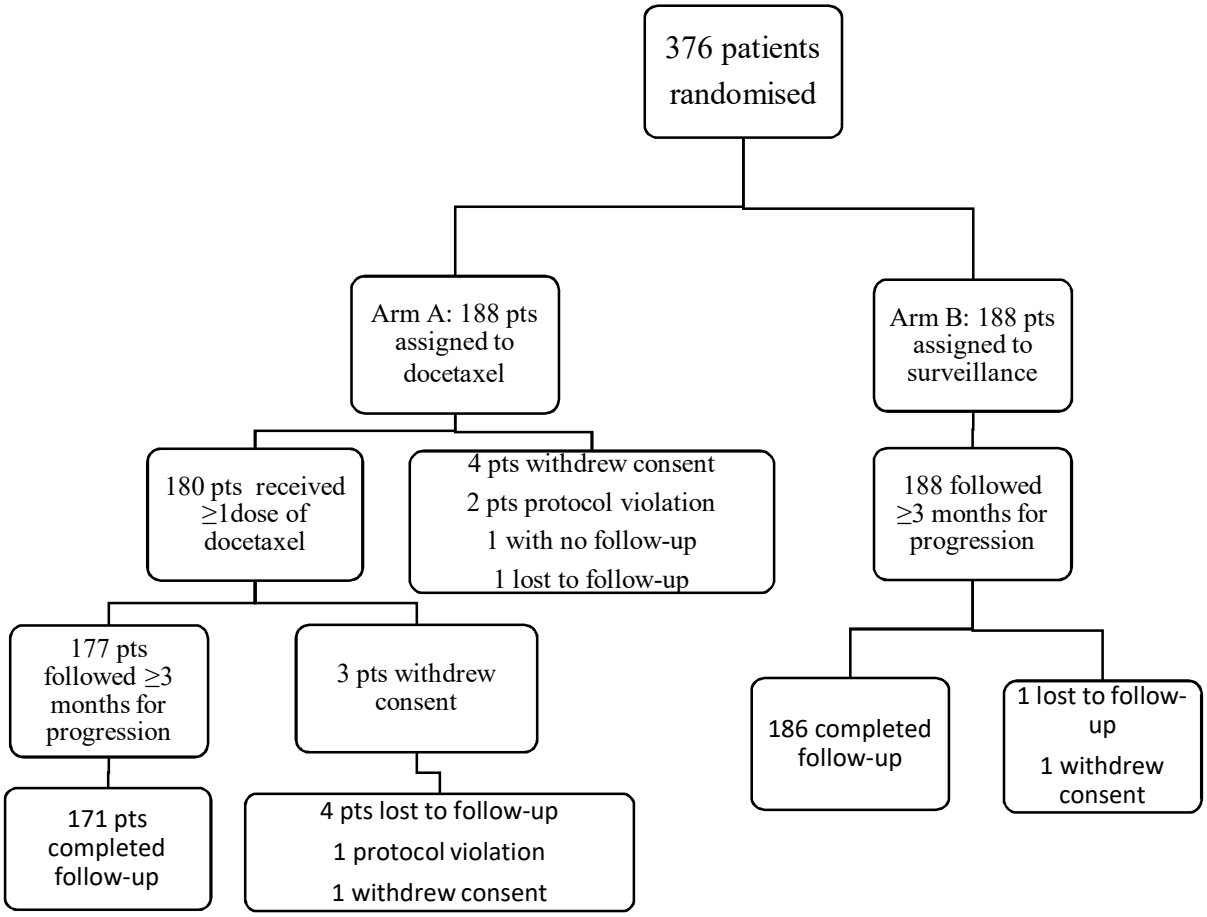

Fig. 1. Trial profile for SPCG13: Arm A adjuvant, Arm B surveillance only.

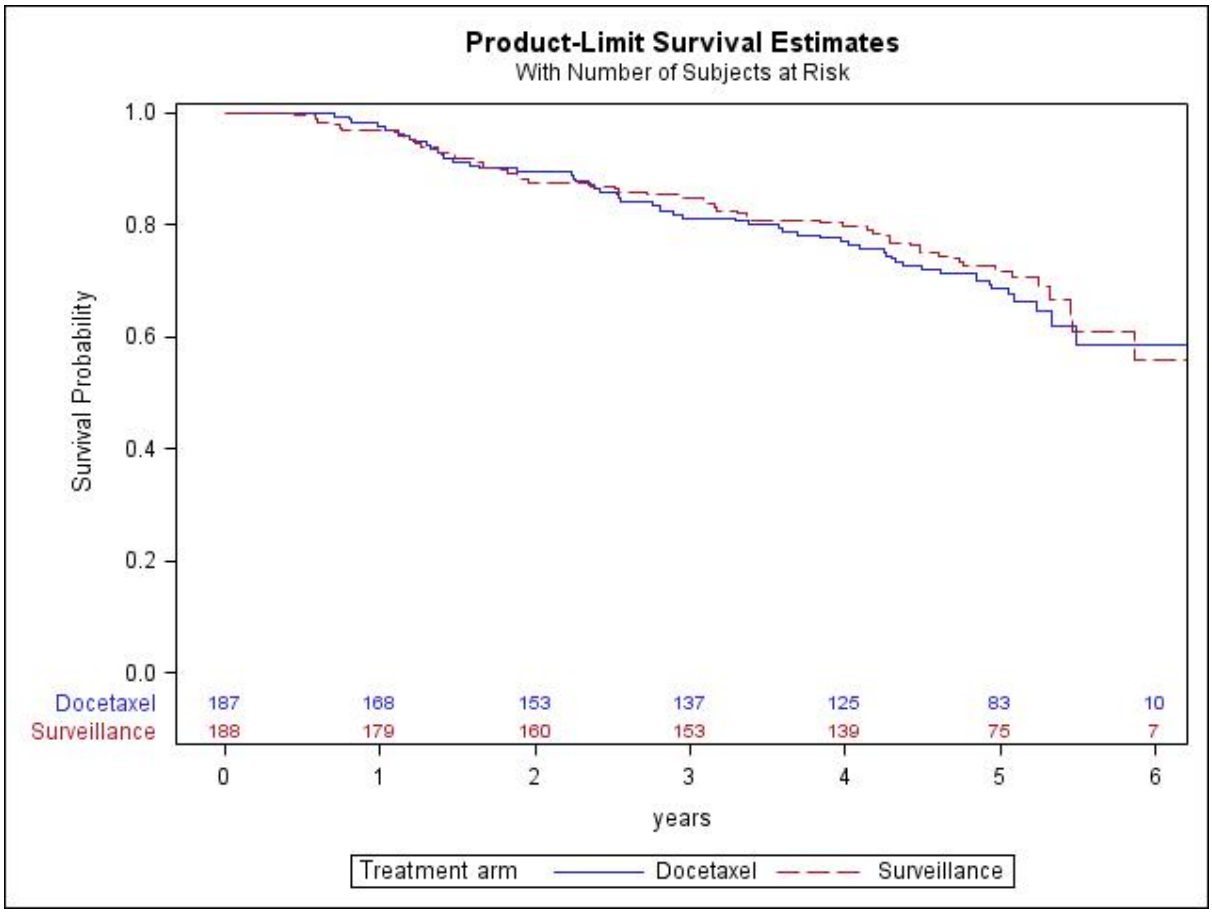

Fig 2. Kaplan-Meier curves of survival free of progression (PSA $\geq$ 2.0ng/ml) by intent to treat (p=0.6).

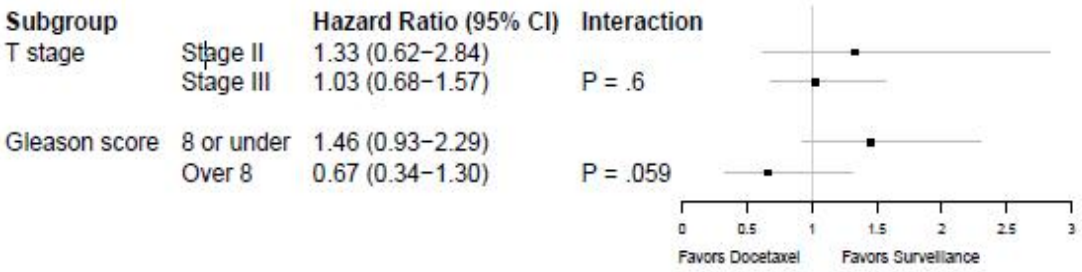

Fig. 3. Forest plot of Hazard Ratio for biochemical progression (PSA ≥ 2.0ng/ml) in subgroups for the variables used in multivariate analysis.