Addition of Docetaxel to Androgen Deprivation Therapy for Patients with Hormone-sensitive Metastatic Prostate Cancer: A Systematic Review and Meta-analysis

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Abstract

Context: Several randomized clinical trials (RCTs) have recently tested the early addition of docetaxel to androgen deprivation therapy (ADT) in hormone-sensitive metastatic prostate cancer (PCa).

Objective: To perform a systematic review and meta-analysis of RCTs evaluating the combination of docetaxel and ADT in hormone-sensitive metastatic PCa. The primary end point was overall survival (OS). Secondary end point was progression-free survival.

Evidence acquisition: A systematic review of PubMed/Medline, Embase, and the proceedings of major international meetings was performed in June 2015 and updated in August 2015. Three trials were selected for inclusion.

Evidence synthesis: Overall, 2951 patients were included in the three trials. Two trials enrolled only metastatic patients; in the third trial, 61% were metastatic. A total of 2262 patients (951 docetaxel and ADT; 1311 ADT alone) were metastatic. Most patients had a good performance status. In metastatic patients, the addition of docetaxel was associated with improved OS (hazard ratio [HR]: 0.73; 95% confidence interval [CI], 0.60–0.90; \( p = 0.002 \)), with nonsignificant heterogeneity among the three trials. Considering the whole study population (2951 patients), the addition of docetaxel was associated with a similar OS improvement (HR: 0.74; 95% CI, 0.61–0.91; \( p = 0.003 \)). Although with limited statistical power, no significant interaction was demonstrated between the addition of docetaxel and the high or low volume of disease (\( p = 0.5 \)). The addition of docetaxel was associated with improvement in progression-free survival (metastatic patients: HR: 0.63; 95% CI, 0.57–0.70; \( p < 0.001 \)).

Conclusions: This meta-analysis shows a significant OS benefit from concomitant administration of docetaxel and ADT in patients with metastatic hormone-sensitive PCa.

Patient summary: We synthesized the evidence available about the early administration of docetaxel in patients starting hormonal treatment for metastatic prostate cancer. Based on the results of this meta-analysis, we believe the combination of chemotherapy and hormonal treatment should be considered in fit patients.

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1. Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer in men and the second leading cause of cancer death in male patients in the United States and Europe [1]. Although localized PCAs may be successfully treated with radical prostatectomy and external-beam radiation, many patients subsequently develop metastatic disease [2]. In the United States, the proportion of PCa patients presenting with advanced stage at first diagnosis is 4–5% for distant disease and 10–12% for regional disease [3]. Androgen deprivation therapy (ADT) by medical or surgical castration is the mainstay of treatment for locally advanced and metastatic PCa because the androgen receptor (AR) pathway plays a key role in the development and progression of PCa cells [4]. Although ADT is able to induce biochemical and clinical response in >90% of patients, after a median of 24–36 mo, patients experience progression to castration-resistant prostate cancer (CRPC), despite persisting low testosterone levels [5].

Until very recently, chemotherapy with docetaxel was the only effective treatment for CRPC patients. The randomized clinical trial (RCT) TAX327 demonstrated that docetaxel plus prednisone prolonged overall survival (OS) compared with mitoxantrone plus prednisone [6]. Another RCT, the SWOG-9916 study, also demonstrated that treatment with docetaxel, estramustine, and dexamethasone increased median OS by 2 mo compared with mitoxantrone and prednisone [7]. Based on these results, docetaxel was the first cytotoxic drug to demonstrate OS improvement in PCa. More recently, several new agents have been introduced in clinical practice. Results from RCTs have demonstrated the efficacy of two new-generation hormonal therapies (abiraterone [8] and enzalutamide [9]), an immunotherapy (sipuleucel-T [10]), a new microtubule-targeting chemotherapy (cabazitaxel [11]), and an α-emitter (radium-223 [12]), all able to prolong OS.

The progression of CRPC is now known to be due to the onset of a number of resistance mechanisms induced by the selective pressure of endocrine therapy [13–18]. Castration is able to induce clonal selection and subsequent growth of androgen-independent cellular clones [19]. Hormone-sensitive PCa should be considered a heterogeneous disease, characterized by the coexistence of both AR-positive and AR-negative tumor cells.

In this biologic context, patients with hormone-sensitive PCa may benefit from chemotherapy in association with endocrine therapy, also targeting AR-negative cells and delaying the development of resistance mechanisms. In the pre-docetaxel era, several RCTs investigated the combination of endocrine therapy with other cytotoxic drugs in hormone-sensitive PCa patients, but none of these studies showed a significant and convincing advantage [20,21]. In the last 2 yr, the results of three clinical trials, Hormone Therapy and Docetaxel or Hormone Therapy Alone in Treating Patients with Metastatic Prostate Cancer (GETUG-AFU 15) [22], Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED-E3805 [23]), and Systematic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy: A Multi-stage Multi-arm Randomized Controlled Trial (STAMPEDE) [24], investigating the combination of docetaxel and ADT in hormone-sensitive disease, were made available to the scientific community.

The aim of this systematic review is to conduct a meta-analysis of RCTs that evaluated the combination of docetaxel with ADT versus ADT alone, in hormone-sensitive metastatic PCa, to assess the impact of this therapeutic option in terms of OS.

2. Evidence acquisition

2.1. Identification of eligible trials

Full protocol of the review is available on request from the corresponding author. The search was performed in June 2015 and updated in August 2015 to identify all RCTs testing the addition of docetaxel to ADT in patients with hormone-naive metastatic PCa. A literature search was performed using PubMed, Embase, Medline, and the Cochrane Library. The following keywords were used: (prostate cancer) AND docetaxel AND (random*). References of the selected articles were also checked to identify further eligible trials. Proceedings of the major international meetings (American Society of Clinical Oncology (ASCO) annual meeting, ASCO Genitourinary symposium, European Society of Medical Oncology, European Association of Urology), were searched from 2010 onward for relevant abstracts. Trials enrolling both patients with metastatic disease and patients without metastases were eligible (details about subgroups were collected as specified). Trials enrolling only patients without metastases [25,26] were excluded. When more than one report of the same trial was available, the most recent information (corresponding to longer follow-up and higher number of events) was considered in the analysis.

2.2. Data collection and study quality

For each eligible trial, the following data were collected, if available:

- Main inclusion criteria: age, performance status, stage, Gleason score, prostate-specific antigen (PSA) at randomization, presence of visceral metastases, volume (high vs low) of metastatic disease, previous treatments
- Details of study treatment: type of ADT allowed, schedule and number of cycles of docetaxel planned in the experimental arm, timing of docetaxel start compared with ADT initiation in the experimental arm, number of docetaxel cycles actually administered (median, range), proportion of patients completing planned docetaxel cycles, proportion of patients needing dose reduction of docetaxel
- Study design: primary end point, study hypothesis
- Patients’ enrollment and follow-up: date of start and date of end of accrual; number of patients assigned to experimental arm (docetaxel and ADT), number of patients assigned to control arm (ADT alone), median follow-up
• OS: number of deaths in each arm, median OS, hazard ratio (HR) with 95% confidence interval (CI), p value, details of subgroup analysis of metastatic patients (for trials enrolling both M0 and M1 patients), details of subgroup analysis in high- and low-volume patients
• Progression-free survival (PFS): number of events in each arm, median PFS, HR with 95% CI, p value, details of subgroup analysis of metastatic patients (for trials enrolling both M0 and M1 patients)

For each study, the quality of randomization was evaluated based on the information available in the publication [22,23] or in the study protocol [24].

2.3. Statistical methods

After data were abstracted, analysis was performed with the Review Manager software (RevMan v.5.3; The Nordic Cochrane Center, Copenhagen, Denmark). In all the trials included, efficacy data were analyzed from all randomly assigned patients on an intention-to-treat basis. Primary end point of the meta-analysis was OS. Secondary end point was biochemical progression-free survival (bPFS). Definition of bPFS was different in the three trials and is reported in Supplementary Table 1.

For both OS and bPFS, the summary measure was HR (with 95% CI). A random-effects model was applied. Statistical heterogeneity among studies was examined using the chi-square test and the I² statistic.

Main analysis was performed considering the three comparisons of docetaxel and ADT versus ADT alone. In one trial [24], a further experimental arm was reported, testing the addition of docetaxel and zoledronic acid to ADT alone. Because the addition of zoledronic acid alone did not show any significant efficacy compared with ADT, we performed an exploratory analysis also adding this comparison to the analysis of docetaxel. However, because that trial used the same control arm for the two comparisons (docetaxel and ADT vs ADT alone, and docetaxel and zoledronic acid and ADT vs ADT alone), the weight of each comparison was reduced according to a correction factor equal to the number of events actually observed in the trial, divided by the number of events taken into account in the analysis (where the control arm was counted twice). This correction resulted in a prudential increase in the width of the CI for the estimated HR of each comparison.

For OS, the subgroup analysis of patients according to disease volume (high vs low volume) was available for two trials [23,27]. In both trials, high-volume disease was defined as the presence of at least four bone lesions and at least one lesion in any bone beyond the spine/pelvis or the presence of visceral metastasis. Patients without these conditions were classified as low volume. No subgroup analysis of PFS according to disease volume was available.

2.4. Role of funding source

There was no funding source for this review. All authors had full access to all the data, and the corresponding author (M.D.M.) had final responsibility for the decision to submit for publication.

3. Evidence synthesis

3.1. Characteristics and quality of the trials

The selection process of trials eligible for the meta-analysis is reported in Supplementary Figure 1. In the search updated in August 2015, 464 of the 466 full-length published papers were excluded, and 2 (GETUG-AFU 15 and CHAARTED-E3805) were found eligible for inclusion [22,23]. Another eligible trial (STAMPEDE) was found searching the proceedings of the major international meetings [24]. An updated report of the already published GETUG-AFU 15 trial, with longer follow-up and a higher number of events for analysis, was available [27].

Table 1 lists the main characteristics of the three available trials. In all the trials, patients assigned to the experimental arm received docetaxel 75 mg/m², for a maximum of six [23,24] or nine cycles [22]. The maximum interval since the ADT start allowed to start docetaxel ranged from 2 to 4 mo. In the GETUG-AFU 15 trial, about half of the patients had started ADT within 15 d of enrollment [22]; in the CHAARTED-E3805 trial, median time from ADT to randomization was slightly >1 mo in both arms [23].

According to the descriptions available in the publication [22,23] or in the study protocol [24], the quality of randomization process was judged adequate in all three trials.

3.2. Patient characteristics

Overall, 2951 patients were included in the three trials in the meta-analysis, 1181 (40%) assigned to docetaxel and ADT, and 1770 (60%) assigned to ADT alone (Table 2). The main characteristics of the 2951 patients are described in Table 2. Patients were enrolled between October 2004 and March 2013. Median age was 63–65 yr, and most patients had a good performance status. Two trials [22,23] enrolled only metastatic patients; in the STAMPEDE trial [24], metastatic patients were 61% of the total study population: overall, there were 2262 metastatic patients (951 docetaxel and ADT; 1311 ADT alone). Patients with metastatic disease at diagnosis were 71% in the GETUG-AFU 15 trial and 73% in the CHAARTED-E3805 trial; in the STAMPEDE trial, 94% of patients had not received previous local therapy. Patients with high-volume disease were 48% in the GETUG-AFU 15 trial and 65% in the CHAARTED-E3805 trial; this information was not available in the STAMPEDE trial.

3.3. Treatment compliance and toxicity

The median number of docetaxel cycles actually administered was eight in the GETUG-AFU 15 [22], six in the CHAARTED-E3805 [23], and six in the STAMPEDE trial [24]. The proportion of patients completing the planned number of cycles was 48% in the GETUG-AFU 15 trial (nine planned cycles), 86% in the CHAARTED-E3805 trial...
(six planned cycles), and 76% in the STAMPEDE trial (six planned cycles). The proportion of patients needing dose reduction was 11% in the GETUG-AFU 15 trial and 26% in the CHAARTED-E3805 trial; this information was not available in the report of the STAMPEDE trial.

Most common adverse events reported with the addition of docetaxel were hematologic toxicity (anemia, thrombocytopenia, and neutropenia), fatigue, gastrointestinal toxicity (nausea, vomiting, constipation, and diarrhea), alopecia, sensory neuropathy, stomatitis/mucositis, nail changes, and peripheral edema. In all three trials, the addition of docetaxel was associated with a higher incidence of febrile neutropenia: 8%, 6%, and 12% in the GETUG-AFU 15, CHAARTED-E3805, and STAMPEDE trials versus 0%, not reported, and 1% with ADT alone in the three trials, respectively.

| Table 1 – Characteristics of the three trials included in the meta-analysis |
|-----------------------------|-----------------------------|-----------------------------|
| **Main inclusion criteria** | GETUG-AFU 15 [22,27]        | CHAARTED-E3805 [23]         |
| Age                         | >18 yr                      | Both <70 and >70 yr were eligible (stratification criteria) | Not specified |
| Performance status          | Karnofsky ≥70               | ECOG 0–2 (2 only if due to PCa) | WHO 0–2 |
| Stage                       | Metastatic prostate cancer (high volume vs low volume assessed retrospectively) | Metastatic prostate cancer (Stratification: high-volume vs low-volume) | PCA if metastatic, node-positive, or ≥2 among: Stage T3/T4 PSA ≥40 ng/ml Gleason 8–10 |
| Previous treatment          | Previous chemotherapy for metastatic disease was not allowed. In the neoadjuvant and adjuvant settings or in the context of isolated PSA increase, previous chemotherapy or ADT, or both, were allowed, with the condition that the treatment had been discontinued at least 12 mo before inclusion in the study | No prior docetaxel was allowed. Adjuvant ADT was allowed, but <24 mo (Stratification: ≤12 vs >12 mo) and interval between end of adjuvant treatment and progression >12 mo | Prior chemotherapy was not allowed. Long-term androgen ablation therapy was not allowed. Short periods of prior androgens to cover tumor flare were allowed. Adjuvant or neoadjuvant hormone therapy had to be completed at least 12 mo before the trial, and duration of therapy had to be no longer than 12 mo |
| Treatment                   | ADT (both arms)             | Medical or surgical castration. Use of a nonsteroidal antiandrogen at the time of initiation of therapy was at the discretion of the investigator | LHRH analogs or LHRH antagonists, or bilateral orchidectomy according to local practice |
| Docetaxel                   | Docetaxel (75 mg/m² IV day 1 every 3 wk); up to 9 cycles. Standard corticosteroids premedication, no daily prednisone | Docetaxel (75 mg/m² IV day 1 every 3 wk); up to 6 cycles. Standard dexamethasone premedication, no daily prednisone | Docetaxel (75 mg/m² IV day 1 every 3 wk); up to 6 cycles. Standard dexamethasone premedication, daily prednisolone 10 mg |
| Timing of treatment         | Docetaxel within 2 mo of ADT start | Docetaxel within 4 mo of ADT start | Randomization within 12 wk of ADT start |
| **Study design**            |                             |                             |                             |
| **Hypothesis**              | Increase in 3-yr OS from 50% to 65% | 33% increase in median OS (from 33 to 44 mo in high volume patients; from 67 to 89 mo in low volume patients) | 25% increase in overall survival |
| **Patient enrollment and follow-up** |                             |                             |                             |
| Accrual start               | October 2004                | July 2006                   | October 2005                |
| Accrual stop                | December 2008               | November 2012               | March 2013                  |
| No. of patients             | ADT alone 193               | 393                         | 1184                        |
| ADT plus docetaxel          | 192                         | 397                         | 592                         |
| ADT plus docetaxel and zoledronic acid | –                            | –                            | 593                         |
| Median follow-up            | 82.9 mo                     | 28.9 mo                     | NA                          |

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; LHRH = luteinizing hormone-releasing hormone; NA = not available; OS = overall survival; PCa = prostate cancer; PSA = prostate-specific antigen; WHO = World Health Organization.

* After amendment. In the initial protocol version, only high-volume patients were eligible.
3.4. Overall survival

Table 3 summarizes the number of events and OS data reported in each trial. Overall, 916 deaths were recorded for the main comparison (docetaxel and ADT vs ADT alone) in metastatic patients. As shown in Figure 1A, the addition of docetaxel to ADT in metastatic patients was associated with a statistically significant OS benefit (HR: 0.73; 95% CI, 0.60–0.90; \( p = 0.002 \)). There was no evidence of statistically significant heterogeneity among the three trials (\( p = 0.15; I^2 = 48\% \)). In the whole study population, including also the minority of nonmetastatic patients (Fig. 1B), the addition of docetaxel to ADT was associated with a similar, statistically significant OS benefit (HR: 0.74; 95% CI, 0.61–0.91; \( p = 0.003 \)). Very similar results were obtained in the exploratory analysis also including the docetaxel and zoledronic acid arm of the STAMPEDE trial: HR 0.74 (95% CI, 0.63–0.88; \( p < 0.001 \)) considering only metastatic
patients (Fig. 1C), HR 0.76 (95% CI, 0.64–0.89; \(p = 0.001\)) in all patients (Fig. 1D).

Subgroup analysis was performed for metastatic patients with high-volume and low-volume disease enrolled in the GETUG-AFU 15 and in the CHAARTED-E3805 trial (Fig. 2). The test for difference of efficacy among the two subgroups did not demonstrate a statistically significant interaction (\(p = 0.5\)). The HR for the addition of docetaxel to ADT was 0.67 (95% CI, 0.51–0.88) in patients with high-volume disease and 0.80 (95% CI, 0.49–1.32) in patients with low-volume disease.

### 3.5. Progression-free survival

As shown in Figure 3A, the addition of docetaxel to ADT in metastatic patients was associated with a statistically significant benefit in PFS (HR: 0.63; 95% CI, 0.57–0.70; \(p < 0.001\)) without significant heterogeneity among the three trials (\(p = 0.7\); \(I^2 = 0\%\)). The same benefit was shown considering the whole study population including the minority of patients without metastases (HR: 0.63; 95% CI, 0.57–0.70; \(p < 0.001\)) (Fig. 3B). Very similar results were obtained in the exploratory analysis including also the docetaxel and zoledronic acid arm of the STAMPEDE trial: HR: 0.63 (95% CI, 0.56–0.70; \(p < 0.001\)) in metastatic patients (Fig. 3C), HR 0.63 (95% CI, 0.57–0.70; \(p < 0.001\)) in all patients (Fig. 3D).

### 3.6. Discussion

This meta-analysis shows that the addition of docetaxel to ADT in patients with metastatic hormone-sensitive PCa is associated with a significant improvement in OS and PFS. A quantitative synthesis of the evidence currently available about this treatment strategy can be really helpful for clinical decisions because three recent phase 3 trials (GETUG-AFU-15 [22,27], CHAARTED-E3805 [23], and STAMPEDE [24]) tested the activity of docetaxel in combination with endocrine therapy in the relatively early setting of hormone-sensitive PCa. To the best of our knowledge, no other trials have been conducted with docetaxel in the same setting, and this meta-analysis represents the synthesis of all the evidence produced to date. Notably, in the GETUG-AFU-15 trial, the first trial to be published, the concomitant administration of docetaxel with ADT versus ADT alone did not show a significant OS benefit [22,27]. On the contrary, the CHAARTED-E3805 trial showed a significant OS improvement for ADT plus docetaxel [23], adding fuel to the scientific debate about the opportunity of this therapeutic option in hormone-sensitive PCa patients. In our meta-analysis that also included the recent results of the “third comer,” the STAMPEDE trial [24], the addition of docetaxel to ADT in metastatic patients was associated with a statistically significant increase in OS, with a moderate nonsignificant heterogeneity among the three RCTs. Of note, the absence of statistical heterogeneity increases the validity of the result, allowing a global, unambiguous interpretation of all the evidence available. Of course, a meta-analysis based on individual patient data (IPD) would represent the best synthesis of evidence, allowing for data checking, updated follow-up compared with publications, calculation and comparison of times to events, and investigation of treatment heterogeneity in subgroups [28]. However, in the absence of an IPD meta-analysis, a meta-analysis based on abstracted data can be considered an acceptable surrogate, allowing a timely synthesis of all the available trials.

The efficacy demonstrated by docetaxel in combination with ADT in hormone-sensitive patients is not surprising, due to its strong biologic basis. Recent evidence shows that one of the mechanisms responsible for progression from...
hormone-sensitive to the castration-resistant phase of disease is the clonal selection and proliferation of preexisting AR-independent cells, able to survive in a low androgen level environment [19]. Therefore it is reasonable to assume that, since its onset, PCa is a heterogeneous disease where AR-positive and AR-negative cells coexist [19,29]. Both these cellular clones are likely involved in progression to castration-resistant disease [19]. Docetaxel administration concurrent to ADT in hormone-sensitive PCa patients allows the inhibition of the growth of the preexisting AR-insensitive clones, killing these cells earlier when they are still a small number and before the development of multiple escape mechanisms.

Preclinical data show that the adaptive response to ADT by PCa cells is mediated by both ligand-dependent AR activation and ligand-independent AR activation and by mechanisms of progression bypassing AR signaling [19,30]. Taxanes are able to interfere with several steps of these resistance mechanisms. Emerging preclinical data demonstrated that taxanes could inhibit the AR signaling pathway [31]. These cytotoxic drugs interfere with polymerization of microtubules, blocking AR nuclear translocation and AR-induced gene expression [31,32]. Therefore docetaxel could act synergistically with endocrine therapy because it impairs AR activity [31,32]. Chemotherapy may also kill cells that escape ADT through activation of AR-independent survival pathways [33].

From a clinical point of view, administering chemotherapy to metastatic PCa patients in an early phase of the disease has several potential advantages. In the

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**Fig. 1** – Forest plots of hazard ratios (HRs) for overall survival from three randomized trials of docetaxel plus androgen deprivation therapy (ADT) compared with ADT alone in patients with advanced hormone-sensitive prostate cancer. Pooled HRs were computed using random-effect models. The bars indicate 95% confidence intervals. (A, B) Comparisons between docetaxel plus ADT and ADT alone: (A) only metastatic patients and (B) all randomized patients. (C, D) A sensitivity analysis including the comparison of docetaxel and zoledronic acid plus ADT versus ADT alone in the STAMPEDE trial: (C) only metastatic patients and (D) all randomized patients.

ADT = androgen deprivation therapy; CI = confidence interval; IV = inverse variance; SE = standard error; Doc + Zol = docetaxel plus zoledronic acid.
hormone-sensitive setting, patients are, on average, in better clinical condition compared with the castration-resistant setting, due to a lower burden of disease. Consequently, they are able to better tolerate chemotherapy and to maintain adequate drug dose intensity. More patients are eligible for chemotherapy, whereas in the castration-resistant setting a relevant number of patients cannot receive chemotherapy due to worsening performance status and clinical conditions.

Our meta-analysis shows an OS improvement that is not only statistically significant but also clinically relevant. The addition of docetaxel to ADT is associated with a 27% reduction in the risk of death of metastatic patients (HR: 0.73), and the reduction in the risk of death is 33% in patients with high-volume disease (HR: 0.67). In absolute terms, this magnitude of benefit is rarely obtained in the setting of advanced solid tumors: the difference in median survival for metastatic hormone-sensitive prostate cancer. Pooled HRs were computed using random-effect models. The bars indicate 95% confidence intervals. Definitions of high- and low-volume disease are provided in text.

ADT = androgen deprivation therapy; CI = confidence interval; IV = inverse variance; SE = standard error.

Particular attention should be given to toxicity associated with combination treatment. In the experimental arm of GETUG-AFU 15 study, four treatment-related deaths were reported (one due to febrile neutropenia, one neutropenia with infection, one multiorgan failure, and one pulmonary embolism), compared with no treatment-related deaths with ADT alone [22]. In the CHAARTED-E3805 trial, only one treatment-related death (sudden death) occurred in the combination arm [23]. Although these numbers, considered overall, are quite reassuring, it is well known that patients enrolled in clinical trials are selected compared with all patients treated in daily clinical practice in terms of age, performance status, and comorbidities. For instance, patients aged >70 yr are a relevant proportion in clinical practice but were quite underrepresented in the three trials. In the CHAARTED trial, subgroup analysis according to age supports docetaxel efficacy also in elderly patients, but they represented only 23% of the total study population [23]. Although a potential explanation is that the age of metastatic presentation of patients eligible for these three trials could be younger than the whole population of...
patients with a new diagnosis of earlier stage PCa, we believe the main reason for the underrepresentation of elderly patients in the trials included in this meta-analysis is the selection bias because patients had to be fit enough to receive chemotherapy with docetaxel [37]. In any case, chemotherapy toxicity is often worse in the real-world population compared with the toxicity reported in clinical trials. Therefore, clinicians must take into account some relevant clinical factors (performance status, comitant diseases) before considering the addition of docetaxel to ADT, to reduce the risk of severe toxicity that could negatively affect quality of life and, in worst cases, survival.

4. Conclusions

In conclusion, our meta-analysis clearly shows a significant impact on OS with the concomitant administration of docetaxel and ADT in patients with metastatic hormone-sensitive PCa. Considering the absence of heterogeneity among the available trials, and the balance between magnitude of efficacy and risk of toxicity, the combination of chemotherapy and hormonal treatment should be reasonably offered to patients with metastatic disease, if judged eligible for chemotherapy. Higher statistical power would be needed to better understand the interaction, if any, between the efficacy of docetaxel and the volume of disease.
Author contributions: Massimo Di Maio 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: Tucci, Di Maio.

Acquisition of data: Tucci, Bertaglia, Vignani, Buttiglieri, Di Maio.

Analysis and interpretation of data: Tucci, Di Maio.

Drafting of the manuscript: Tucci, Bertaglia, Di Maio.

Critical revision of the manuscript for important intellectual content: Tucci, Bertaglia, Vignani, Buttiglieri, Fiori, Porpiglia, Scagliotti, Di Maio.

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Appendix A. Supplementary data

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