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REVIEW

The effect of additional chemotherapy on high-risk prostate cancer: a systematic review and meta-analysis

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Objective: The role of additional chemotherapy in the treatment of high-risk prostate cancer (PCa) remains a controversy. This meta-analysis aimed to investigate the effect of additional chemotherapy on high-risk PCa.

Methods: Randomized controlled trials (RCTs) about additional chemotherapy for high-risk PCa were searched in PubMed, MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. We extracted HRs of overall survival (OS) and progression-free survival (PFS) for each trial and performed the meta-analysis using Review Manager 5.3.

Results: Eight RCTs involving 4,007 patients were included. Data from four trials, which could collect OS, showed that additional chemotherapy could not significantly improve the OS in patients with high-risk PCa (HR: 0.93; 95% CI: 0.79–1.09; P=0.37). However, the pooled analysis suggested significantly longer PFS in high-risk PCa patients treated with additional chemotherapy (HR: 0.81; 95% CI: 0.74–0.90; P<0.0001). The meta-analysis showed additional chemotherapy to androgen-deprivation therapy improved PFS (HR: 0.82; 95% CI: 0.74–0.91; P=0.0002). Greater improvement in PFS was found in high-risk PCa patients treated with additional docetaxel-based chemotherapy (HR: 0.73; 95% CI: 0.64–0.83; P<0.00001). No prolonged PFS was observed in high-risk PCa patients with non-docetaxel-based chemotherapy (HR: 0.97; 95% CI: 0.83–1.14; P=0.74).

Conclusion: Additional chemotherapy, especially docetaxel-based chemotherapy, could significantly improve the PFS in high-risk PCa patients. More evidence about the effect of additional chemotherapy on OS is needed. Further investigations in PCa should also focus on the suitable population for chemotherapy as well as optimal use of chemotherapy.

Keywords: chemotherapy, high-risk, prostate cancer, systematic review, meta-analysis

Introduction

Prostate cancer (PCa) is the most common malignancy in men and the second leading cause of cancer death in male patients in the USA.[1] Although most patients diagnosed with prostate cancer have favorable disease characteristics and can be cured by radical surgery or radiation, those with high-risk features have a high biochemical relapse rate and an increased mortality up to about 30%.[2,3] Boorjian et al evaluated the records of 7,591 patients in Mayo Clinic and found that compared with patients with low-risk PCa, those with high-risk PCa had significantly higher risk of recurrence and cancer-specific mortality.[4]

Although high-risk PCa has been variously defined, the D'Amico classification is widely used at present.[5] Current treatments for high-risk PCa include radical prostatectomy (RP), radiation therapy (RT), external-beam RT, brachytherapy,

androgen-deprivation therapy (ADT), and chemotherapy, alone or in combination.[6] Several studies indicated that RT plus adjuvant ADT could decrease the risk of progression and improve survival,[7–9] but adjuvant ADT alone seemed underpowered to prolong survival in patients with high-risk PCa who received RP.[10,11] In the end, high-risk patients still progressed after receiving radical therapies and adjuvant ADT. So, it is reasonable to apply more aggressive therapies to target the systemic components of the disease. Chemotherapy of docetaxel has been proved to improve clinical outcomes of patients with metastatic castrate-resistant prostate cancer (mCRPC).[12,13] Furthermore, a recent systematic review and meta-analysis demonstrated that addition of docetaxel to standard of care improved survival in patients with metastatic hormone-sensitive PCa.[14] Therefore, the question arose whether patients with high-risk PCa could benefit from additional chemotherapy. Results from the GETUG 12 trial showed that ADT plus docetaxel and estramustine could significantly improve relapse-free survival in patients with high-risk localized PCa.[15] However, the RTOG 9902 trial demonstrated no significant differences in overall survival (OS) or progression-free survival (PFS) with additional chemotherapy to long-term androgen suppression plus RT.[16] Therefore, more evidence on the validity of additional chemotherapy in high-risk PCa is needed.

The aim of this study was to conduct a systematic review and meta-analysis of relevant randomized controlled trials (RCTs) to evaluate the effects of additional chemotherapy in high-risk PCa and guide clinical practice.

Methods
Protocol and registration
We developed a protocol defining search strategy and data synthesis of the review, in accordance with the PRISMA statement. The review was registered on the International Prospective Register of Systematic Reviews (PROSPERO, registration number 42017064354). The protocol is available on https://www.crd.york.ac.uk/PROSPERO/display_record. asp?ID=CRD42017064354.

Search strategy
The search strategy is available in the protocol. EMBASE (1974 to 2018.5) and MEDLINE (1966 to 2018.5) were searched through OvidSP. Further searches were undertaken on the Cochrane Central Register of Controlled Trials (1948 to 2018.5) and PubMed (1950 to 2018.5). The last search was conducted on May 10, 2018. The references of included trials not identified by our electronic searches

were also searched for extra possible studies. There were no limitations to language and publication status.

Inclusion and exclusion criteria
Inclusion criteria: 1) RCTs investigating the effects of additional chemotherapy in high-risk PCa (according to D'Amico criteria) patients;[5] 2) no restrictions in published languages.

Exclusion criteria: 1) patients with evidence of metastases on bone scan, CT scan, or MRI; 2) patients who received chemotherapy previously; 3) RCTs reporting only laboratory findings or without survival outcomes.

Data extraction
Two researchers (JRC and XMZ) assessed the titles and abstracts of the searched studies, respectively. Any disagreements were reconciled by a third researcher (PFS). Full texts of potential eligible studies were screened to identify the final included studies. For each included study, the information collected was as follows: study design, study duration, selection criteria, sample size, characteristics of participants (median age, TNM stage, Gleason score, and median prostate-specific antigen [PSA] concentration), follow-up time, controlled group treatments, chemotherapy (components, dosage, scheduling), outcomes, etc.

Outcomes
The primary outcome, OS, was defined as the time from randomization until death from any cause. The secondary outcomes were PFS and adverse events (AEs). PFS was defined as the time from randomization to biochemical failure, onset of metastases on imaging, proven local relapse, or death from any cause.

Quality assessment
Two reviewers (JRC and XMZ) used RevMan 5.3 software to evaluate the risk of bias of the included studies according to the Cochrane Handbook version 5.1.0 and cross-checked, respectively. The items assessed were as follows: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; and 7) other sources of bias. Disagreements were solved by discussion with a third reviewer (PFS).

Data synthesis
The meta-analysis was conducted using RevMan 5.3 software. For each trial, we extracted HRs and the corresponding 95% CI of the effects of chemotherapy on OS and PFS directly from the trial reports. If not reported, they

would be estimated from Kaplan–Meier curves. If insufficient data were available, supplementary data were sought directly from the trial investigators. We used a fixed-effect model (Mantel–Haenszel) a priori. If significant heterogeneity was found, we assessed the results using a random-effect model. I^2 statistic and chi-squared test were used to assess the heterogeneity among trials and $I^2 > 50\%$ or χ^2 p-value < 0.1 was considered as significant heterogeneity. We also planned subgroup analyses according to 1) whether chemotherapy was combined with ADT; 2) the drugs used for chemotherapy. Publication bias was assessed by Egger's test and funnel plot created using RevMan 5.3 software.

Results
Characteristics of the included trials
A flowchart of the selection process of eligible trials is shown in Figure 1. In total, 4,007 patients in eight RCTs were included in the meta-analysis.[15–22] Of the eight included RCTs, five[15–19] were full articles and the other three[20–22] were abstracts. The main characteristics of the included trials are summarized in Table 1.

The definitions of "high-risk" varied in each trial, but they were basically consistent with D'Amico criteria.[5] In these trials, patients were assigned either to an experimental arm and received additional chemotherapy or to a control arm. As one RCT (TAX-3501) investigated immediate or deferred hormonal therapy after RP with or without chemotherapy, we divided it into two parts as two separate trials for analysis.[18] Patients received chemotherapy consisting of docetaxel in seven trials,[15,17,18,20–22] paclitaxel + estramustine + etoposide (TEE) in RTOG 9902 trial[16] and mitoxantrone in SWOG S9921 trial.[19] Three trials compared RT plus ADT with or without chemotherapy in patients with high-risk PCa.[16,17,20] Four trials investigated the effects of additional chemotherapy to ADT plus RP.[18,19,21] One trial investigated the efficacy of additional chemotherapy to RP only.[22] In GETUG 12 trial, RT
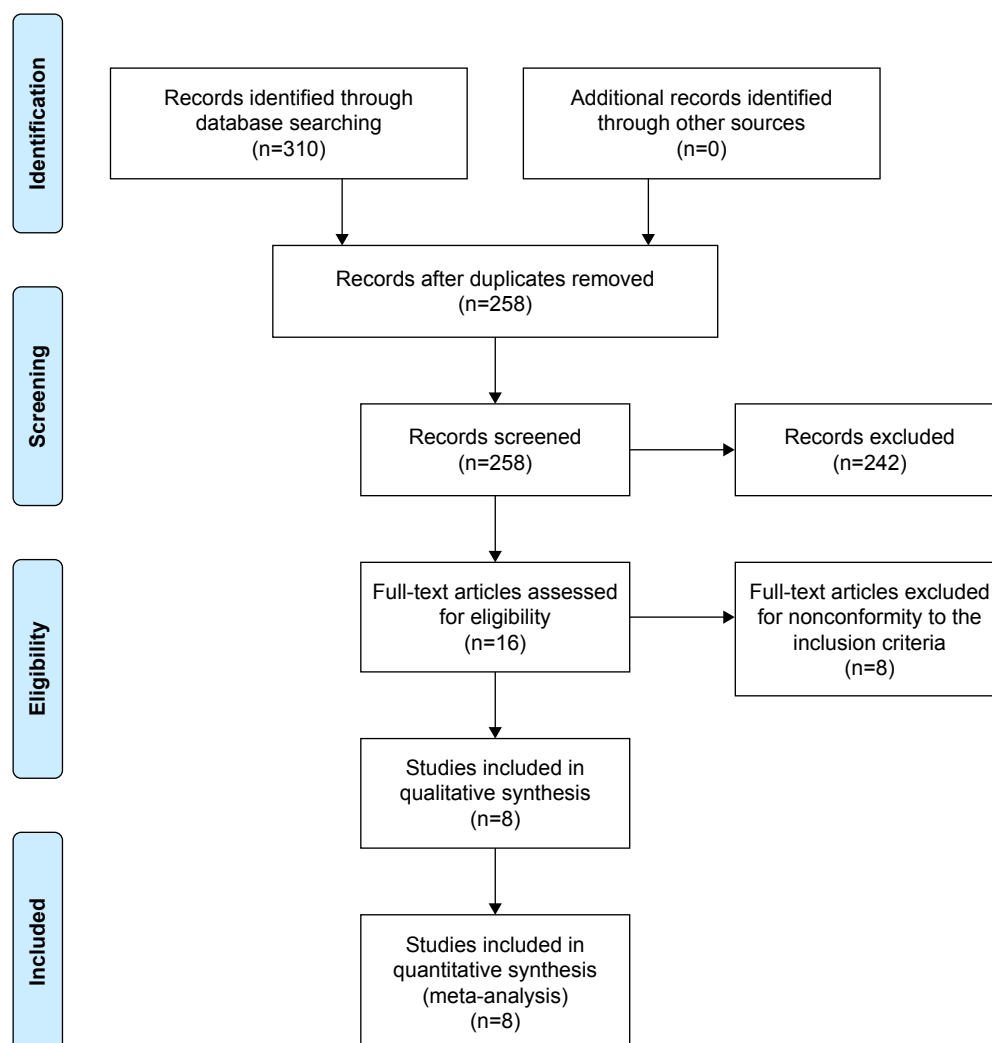

Figure 1 Flowchart of the selection process of eligible trials.

Table 1 Characteristics of the included trials

Trial (year)	Stage	Sample size	Median age (y)	Median PSA (ng/mL)	Gleason score ≥8 (%)	T stage ≥3 (%)	Treatments Experiment	Control	Median follow-up	Outcomes
STAMPEDE 2016	Metastatic, high-risk	690	65	65	71	81.8	ADT + RT + CT (3-weekly docetaxel 75 mg/m² for 6 cycles)	ADT + RT	43 months	OS, FFS, AEs
RTOG 9902 2015	High-risk	397	66	22.6	67.8	34.3	ADT + RT + CT (paclitaxel + estramustine + etoposide every 3 weeks for 4 cycles)	ADT + RT	9.2 years	OS, BF, LP, DM, DFS, AEs
GETUG 12 2015	High-risk	413	63	NR	Treatment: 42 control: 43	Treatment: 68 control: 67	ADT + RP/RT + CT (docetaxel 70 mg/m²+ estramustine every 3 weeks for 4 cycles)	ADT + RP/RT	8.8 years	RFS, MFS, CRFS, OS, PSA response, toxic effects, quality of life
TAX-3501 2013	High-risk	228	61.9 mean	11.74 mean	51.8	NR	ADT + RP + CT (3-weekly docetaxel 75 mg/m² for 6 cycles)	ADT + RP	3.4 years	PFS, safety
SPCG 12 2016	High-risk	459	Treatment: 61.8 control: 62.7	Treatment: 12.2 control: 11.9	Treatment: 37.9 control: 37.1	Treatment: 84 control: 86	RP + CT (3-weekly docetaxel 75 mg/m² for 6 cycles)	RP	NR	PFS, AEs
RTOG 0521 2015	High-risk	562	66	15	84	27	ADT + RT + CT (3-weekly docetaxel 75 mg/m² for 6 cycles)	ADT + RT	66 months	DFS, OS, AEs
SWOG S9921 2018	High-risk	961	60	7.7	52	62	ADT + RP + CT (3-weekly mitoxantrone 12 mg/m² for 6 cycles)	ADT + RP	11.2 years	OS, DFS, toxicity
CSP 553 2016	High-risk	297	NR	NR	NR	NR	ADT + RP + CT (3-weekly docetaxel 75 mg/m² for 6 cycles)	ADT + RP	62.4 months	PFS, AEs

Abbreviations: ADT, androgen deprivation therapy; AEs, adverse events; BF, biochemical failure; CRFS, clinical relapse-free survival; CT, chemotherapy; DFS, disease-free survival; DM, distant metastases; FFS, failure-free survival; LP, local progression; MFS, metastases-free survival; NR, not report; RFS, relapse-free survival; RP, radical prostatectomy; RT, radiation therapy.

Figure 2 The risk of bias of the included trials.

or RP combined ADT were admitted according to the status of lymph nodes, and the effects of additional chemotherapy were also investigated.[15] The TAX 3501 trial was terminated ~21 months after its activation due, in part, to enrollment challenges.[18] The STAMPEDE trial is still recruiting.[17]

Assessment of risk of bias

The risk of bias of the included trials is summarized in Figure 2. Due to inadequate information, seven trials had an unclear risk of bias for allocation concealment.[16,18–22] One trial (GETUG 12) had a high risk of bias for allocation concealment because neither patients nor investigators were

masked to treatment allocation.[15] Eight trials were considered at high risk of bias for blinding because of no masking.[15–20,22] A funnel plot was used to assess the risk of publication bias (Figure S1). An Egger's test P-value of 0.968 indicated that there was no significant publication bias.

The effect of additional chemotherapy on OS

Four trials reported HRs of the effect of additional chemotherapy on OS,[16,17,19,20] of which three compared RT + ADT plus additional chemotherapy with RT + ADT,[16,17,20] and the other trial investigated RP + ADT with or without chemotherapy.[19] The pooled analysis showed that additional chemotherapy could not significantly improve the OS (HR: 0.93; 95% CI: 0.79–1.09; P=0.37) (Figure 3). There was no statistically significant heterogeneity among the four trials (I^2=31%, P=0.23).

The effect of additional chemotherapy on PFS

The data of PFS are available in all the included trials.[15–22] The pooled analysis suggested a significantly longer PFS in high-risk PCa patients treated with additional chemotherapy (HR: 0.81; 95% CI: 0.74–0.90; P<0.0001) (Figure 4). No statistically significant heterogeneity was found among the nine trials (I^2=32%, P=0.16). Eight trials reported the data of PFS and the results showed that additional chemotherapy to radical treatment plus ADT could significantly improve the PFS in high-risk PCa patients (HR: 0.82; 95% CI: 0.74–0.91; P=0.0002) (Figure 4). Two trials used non-docetaxel-based chemotherapy, one used TEE[16] and the other used mitoxantrone.[19] The meta-analysis showed no significantly prolonged PFS in high-risk PCa patients with non-docetaxel-based chemotherapy (HR: 0.97; 95% CI: 0.83–1.14; P=0.74) (Figure 5). Seven trials reported the PFS data in patients treated with docetaxel-based chemotherapy.[15,17,18,20–22] The pooled results indicated that significant improvement in PFS was found in patients who had received docetaxel-based

Study or subgroup	Log (HR)	SE	Weight (%)	HR IV, fixed, 95% CI	HR IV, fixed, 95% CI
RTOG 0521	−0.3567	0.1616	26.8	0.70 (0.51–0.96)	
RTOG 9902	0.0392	0.16	27.3	1.04 (0.76–1.42)	
STAMPEDE	−0.0513	0.2177	14.8	0.95 (0.62–1.46)	
SWOG S9921	0.0583	0.15	31.1	1.06 (0.79–1.42)	
Total (95% CI)			**100**	**0.93 (0.79–1.09)**	

Heterogeneity: χ^2=4.35, df=3 (P=0.23); I^2=31%
Test for overall effect: Z=0.89 (P=0.37)

With chemotherapy   Without chemotherapy
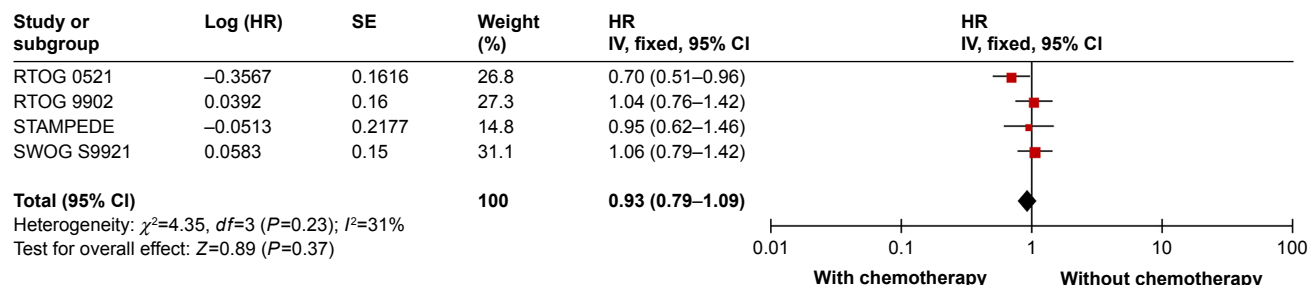
Figure 3 Effects of additional chemotherapy on overall survival.

Study or subgroup	Log (HR)	SE	Weight (%)	HR IV, fixed, 95% CI	HR IV, fixed, 95% CI
RP/RT + ADT + chemotherapy vs RP/RT + ADT					
CSP 553	−0.1985	0.1594	10.0	0.82 (0.60–1.12)	
GETUG 12	−0.3425	0.1396	13.1	0.71 (0.54–0.93)	
RTOG 0521	−0.2744	0.1379	13.4	0.76 (0.58–1.00)	
RTOG 9902	−0.0619	0.1152	19.2	0.94 (0.75–1.18)	
STAMPEDE	−0.5108	0.1468	11.8	0.60 (0.45–0.80)	
SWOG S9921	0.01	0.1189	18.0	1.01 (0.80–1.28)	
TAX-3501 (immediate hormonal therapy)	0.4574	0.6523	0.6	1.58 (0.44–5.67)	
TAX-3501 (deferred hormonal therapy)	−0.3147	0.3331	2.3	0.73 (0.38–1.40)	
Subtotal (95% CI)			**88.4**	**0.82 (0.74–0.91)**	

Heterogeneity: χ^2=11.51, df=7 (P=0.12); I^2=39%
Test for overall effect: Z=3.72 (P=0.0002)

RP/RT + chemotherapy vs RP/RT					
SPCG 12	−0.2705	0.1479	11.6	0.76 (0.57–1.02)	
Subtotal (95% CI)			**11.6**	**0.76 (0.57–1.02)**	

Heterogeneity: not applicable
Test for overall effect: Z=1.83 (P=0.07)

Total (95% CI)			**100**	**0.81 (0.74–0.90)**	

Heterogeneity: χ^2=11.71, df=8 (P=0.16); I^2=32%
Test for overall effect: Z=4.12 (P<0.0001)
Test for subgroup differences: χ^2=0.20, df=1 (P=0.65); I^2=0%

0.01 0.1 1 10 100
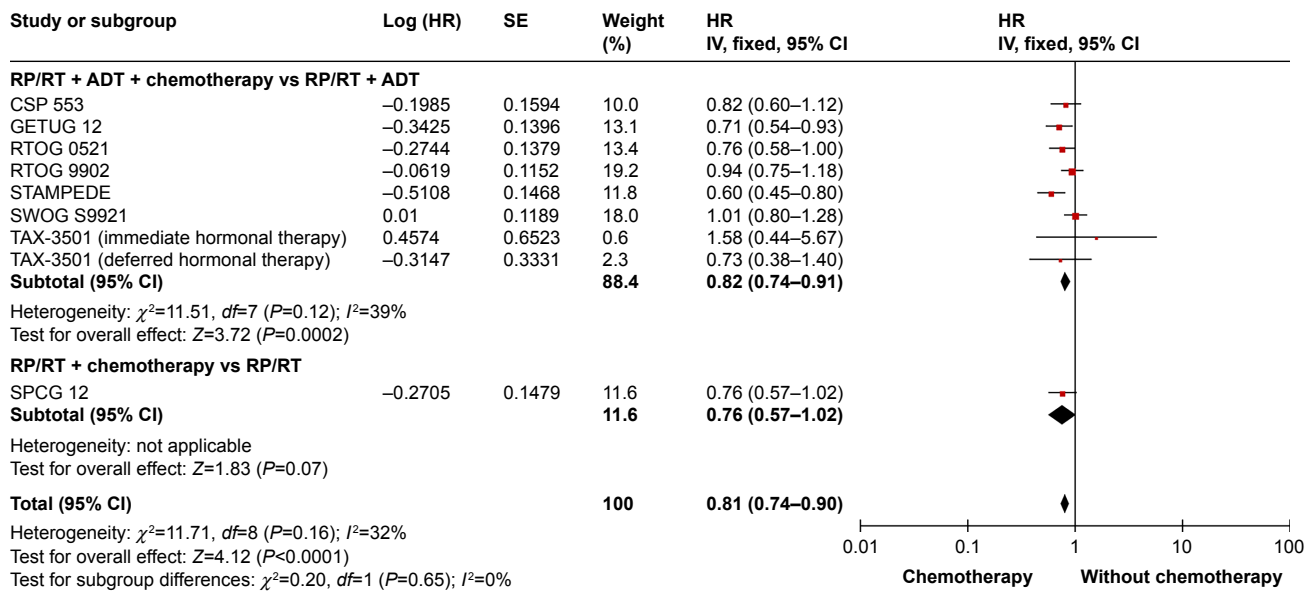Chemotherapy   Without chemotherapy

Figure 4 Effects of additional chemotherapy on PFS (subgroup analysis according to chemotherapy combining with ADT or not).
Abbreviations: ADT, androgen deprivation therapy; PFS, progression-free survival; RP, radical prostatectomy; RT, radiation therapy.

chemotherapy (HR: 0.73; 95% CI: 0.64–0.83; P<0.00001) (Figure 5).

Outcomes of AEs

The most common AEs were neutropenia and febrile neutropenia. In the GETUG 12 trial, no toxicity-related death and grade 3–4 toxicity during the first 3 months were recorded, and the negative impact of chemotherapy on quality of life at 3 months disappeared at 1 year.[23] In the RTOG 9902,[16] the TAX-3501,[18] and the SWOG S9921 trials,[19] patients

with chemotherapy had a higher incidence of ≥ grade 3 AEs than those without chemotherapy. As reported in the STAMPEDE[17] and SPCG 12 trials,[22] the most frequent ≥ grade 3 AE was febrile neutropenia (15% and 17.9%, respectively). Of all patients who received chemotherapy in the RTOG 0521, 65% suffered from ≥ grade 3 AEs definitely or probably related to treatment.[20] In the CSP 553 trial, the most common ≥ grade 3 AEs related or possibly related to chemotherapy included neutropenia in 40%, hyperglycemia in 18%, and fatigue in 5%, with febrile neutropenia in 1.4%.[21]
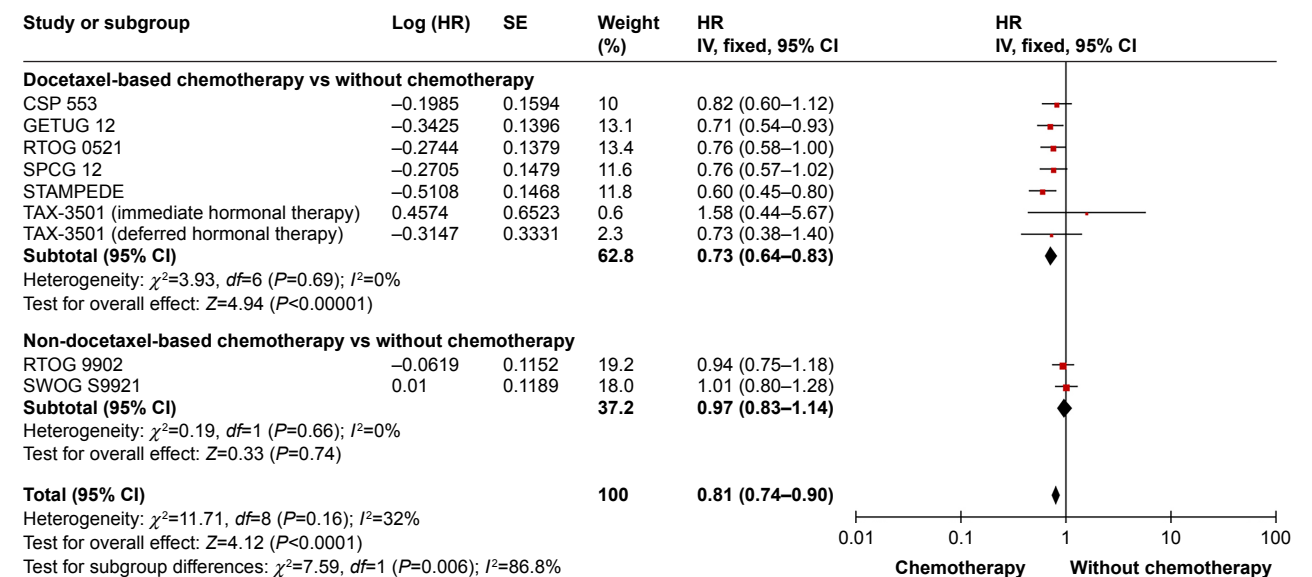
Study or subgroup	Log (HR)	SE	Weight (%)	HR IV, fixed, 95% CI	HR IV, fixed, 95% CI
Docetaxel-based chemotherapy vs without chemotherapy					
CSP 553	−0.1985	0.1594	10	0.82 (0.60–1.12)	
GETUG 12	−0.3425	0.1396	13.1	0.71 (0.54–0.93)	
RTOG 0521	−0.2744	0.1379	13.4	0.76 (0.58–1.00)	
SPCG 12	−0.2705	0.1479	11.6	0.76 (0.57–1.02)	
STAMPEDE	−0.5108	0.1468	11.8	0.60 (0.45–0.80)	
TAX-3501 (immediate hormonal therapy)	0.4574	0.6523	0.6	1.58 (0.44–5.67)	
TAX-3501 (deferred hormonal therapy)	−0.3147	0.3331	2.3	0.73 (0.38–1.40)	
Subtotal (95% CI)			**62.8**	**0.73 (0.64–0.83)**	

Heterogeneity: χ^2=3.93, df=6 (P=0.69); I^2=0%
Test for overall effect: Z=4.94 (P<0.00001)

Non-docetaxel-based chemotherapy vs without chemotherapy					
RTOG 9902	−0.0619	0.1152	19.2	0.94 (0.75–1.18)	
SWOG S9921	0.01	0.1189	18.0	1.01 (0.80–1.28)	
Subtotal (95% CI)			**37.2**	**0.97 (0.83–1.14)**	

Heterogeneity: χ^2=0.19, df=1 (P=0.66); I^2=0%
Test for overall effect: Z=0.33 (P=0.74)

Total (95% CI)			**100**	**0.81 (0.74–0.90)**	

Heterogeneity: χ^2=11.71, df=8 (P=0.16); I^2=32%
Test for overall effect: Z=4.12 (P<0.0001)
Test for subgroup differences: χ^2=7.59, df=1 (P=0.006); I^2=86.8%

0.01 0.1 1 10 100
Chemotherapy   Without chemotherapy

Figure 5 Effects of additional chemotherapy on progression-free survival (subgroup analysis according to the drugs for chemotherapy: docetaxel-based and non-docetaxel-based chemotherapy).

Two patients died of infection/febrile neutropenia and one of acute myelogenous leukemia in the chemotherapy arm in the RTOG 9902 trial.[16]

Discussion

As is known, the development of PCa is dependent on androgen signaling and can be suppressed by ADT at the early stages.[24] Despite the low testosterone concentration controlled by ADT, PCa still progresses. Two potential mechanisms have been proposed to explain this problem, which indicates that the resistance to ADT by PCa cells mainly may be the result of results from abnormal androgen receptor (AR) signaling and proliferation of androgen-independent cells.[25,26] Several studies have reported that taxanes were able to impair the AR activities and interfere with the resistance mechanisms.[27–29] Based on these preclinical data, RCTs investigating the effect of chemotherapy on PCa have emerged recently and verified its efficacy in mCRPC.[12,13] However, the use of chemotherapy in non-metastatic PCa patients remains a matter of debate.[30,31] Non-metastatic PCa patients represent a large, heterogeneous population, whose biological features and disease stages change with cancer. Currently, non-metastatic PCa patients with high-risk features are more likely to develop recurrences and metastases even with ADT. Given the success of chemotherapy in CRPC population, patients with high-risk PCa may also benefit from additional chemotherapy.

To our knowledge, this was the first systematic review and meta-analysis to investigate the effect of additional chemotherapy on patients with high-risk PCa. The meta-analysis showed that additional chemotherapy in high-risk PCa patients had no impact on the OS but could significantly improve PFS.

The pooled HR of 0.93 indicated that additional chemotherapy might have a potential effect on improving the OS, but the result was not statistically significant. Several possible reasons may be responsible for the absence of significant differences in OS. First, the follow-ups in several trials are relatively short; the TAX 3501 trial was terminated early due to slow recruitment and the STAMPEDE trial is still recruiting patients. Thus, the available data for OS are not enough and less mature. Second, OS is affected by crossover treatments during the long follow-up. Patients may receive other active treatments, such as abiraterone and/or enzalutamide beyond progression. Unfortunately, the details of the post-progression treatments were not available in the included trials. Third, the chemotherapy regimens and number of cycles administered may have an effect. Four cycles of TEE were used in the RTOG 9902 trial[16] and six cycles of docetaxel were used in the other three trials.[17,19,20] Recently, a post hoc analysis of the mainsail study by de Morree et al has indicated that the total number of docetaxel cycles delivered was an independent and important contributor to the OS benefit provided by docetaxel chemotherapy and the median OS for patients receiving >7 cycles was significantly longer than for those receiving 5–7 cycles.[32] Therefore, the difference in OS may emerge after increasing the cycles of docetaxel. Furthermore, the definition of "high-risk PCa" is not consistent in the included trials, and the differences in the baseline characteristics of patients, local treatments, and the use of chemotherapy can cause a clinical heterogeneity, which may have an influence on the result.

The pooled analysis demonstrated that significant improvement in PFS was associated with additional chemotherapy in high-risk PCa patients. According to the results of subgroup analyses, ADT combined with additional chemotherapy was superior to ADT alone in high-risk PCa patients who received radical treatments, which may be the result of the synergistic effect of ADT and chemotherapy on AR signaling. Docetaxel-based chemotherapy could significantly improve PFS; however, non-docetaxel-based chemotherapy is not effective in delaying progression. Two reasons may be responsible for this result. First, the TEE regimen used in the RTOG 9902 trial would currently be regarded as obsolete because the systemic therapy options were limited at the time of study design.[16] Second, mitoxanrone used in the SWOG S9921 may not be as effective as docetaxel. The TAX 327 trial has shown that in mCRPC, 3-weekly docetaxel led to superior survival and improved response in terms of pain, serum PSA level, and quality of life, when compared with mitoxantrone.[33] The prolonged PFS in the current study indicated that additional chemotherapy could postpone the progression of high-risk PCa into metastatic diseases or CRPC and then potentially improve the OS. According to the SWOG S9346 trial,[34] longer median OS was found in patients with metastatic hormone-sensitive prostate cancer who did not have PSA-progression within the first 7 months compared with those with PSA-progression (44 vs 10 months). The results of the TAX 327 trial also indicated that among the mCRPC patients receiving 3-weekly docetaxel, those with PSA response had a significantly longer OS.[35] Thus, with the emergence of new trials and data, the improvement in PFS by additional chemotherapy may eventually translate into longer OS.

Not all PCa patients are suitable for additional chemotherapy. To refine individualized treatment strategies, it is necessary to determine the population that can receive

maximal benefit from chemotherapy and those not suitable for additional chemotherapy. The subgroup analyses in the GETUG 12 and the SPCG 12 trials suggested patients with a Gleason score of <8 could gain more benefit from chemotherapy than those with a higher Gleason score, which might result from a differential effect of taxanes on AR trafficking according to Gleason score.[15,22] Another two Phase III trials also reported that patients with a low Gleason score might derive greater benefit from chemotherapy.[36,37] Lin et al found more benefits of chemotherapy in PFS for patients with tumor stage ≥ T3 b.[21] Yu et al reckoned that PCa patients with a short PSA doubling time of <3 months would benefit from early introduction of docetaxel.[30] In the latest advanced prostate cancer consensus conference (APCCC 2017), the panel voted on factors which they consider would render a man "unfit" for docetaxel.[38] Of all, 96% voted for severe hepatic impairment, 82% for neuropathy grade ≥2 and 81% for platelets $<50 \times 10^9$/L and/or neutrophils $<1.0 \times 10^9$/L.

In total, additional chemotherapy was tolerated with life-threating AEs and severe toxicity occurring rarely. Neutropenia and febrile neutropenia were the most common AEs and in the RTOG 9902 trial,[16] two patients were reported to have died of sepsis in the context of neutropenia. Therefore, intensive monitoring should be arranged for patients who are potentially immunocompromised to chemotherapy.[39] Although the overall numbers of AEs in these clinical trials are acceptable, particular attention should be paid when chemotherapy is used in real-world population, especially when multiple therapies are used.

There are some limitations of the review. First, several trials have limited methodological quality and the risk of performance and detection bias is high. Second, the definition of "high-risk PCa" is not consistent in each trial and the baseline characteristics of the patients, the local treatments, drugs, doses, and cycles of chemotherapy varied among trials, which may lead to clinical heterogeneity. Third, the data for OS are not mature and the analyses of OS were restricted by limited number of trials.

Conclusion

The meta-analysis demonstrates that significant improvement in PFS is associated with additional chemotherapy, especially docetaxel-based chemotherapy, in high-risk PCa patients. More trials and reliable data are needed to determine the effects of additional chemotherapy on OS in high-risk PCa population. Further investigations in PCa should also focus on the suitable patients for chemotherapy as well as the optimal use of chemotherapy.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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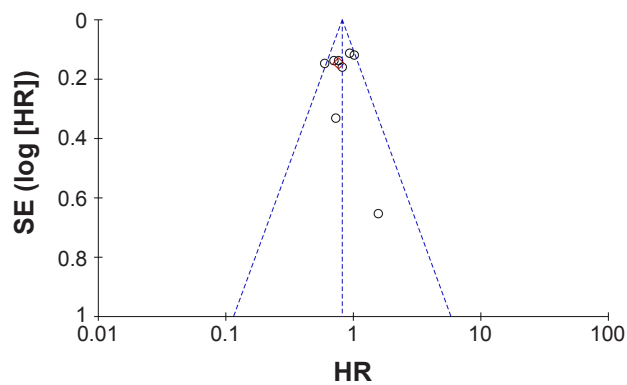
Supplementary material

Figure S1 Funnel plot created by outcome of progression-free survival.