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Platinum Priority – Prostate Cancer

Editorial by Thomas Van den Broeck, Steven Joniau, Wouter Everaerts on pp. 164–165 of this issue

Androgen Deprivation and Radiotherapy with or Without Docetaxel for Localized High-risk Prostate Cancer: Long-term Follow-up from the Randomized NRG Oncology RTOG 0521 Trial

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Abstract

Background: Intensification of therapy may improve outcomes for patients with high-risk localized prostate cancer.

Objective: To provide long-term follow-up data from phase III RTOG 0521, which compared a combination of androgen deprivation therapy (ADT) + external beam radiation therapy (EBRT) + docetaxel with ADT + EBRT.

Design, setting, and participants: High-risk localized prostate cancer patients (>50% of patients had Gleason 9–10 disease) were prospectively randomized to 2 yr of ADT + EBRT or ADT + EBRT + six cycles of docetaxel. A total of 612 patients were accrued, and 563 were eligible and included in the modified intent-to-treat analysis.

Outcome measurements and statistical analysis: The primary endpoint was overall survival (OS). Analyses with Cox proportional hazards were performed as prespecified in the protocol; however, there was evidence of nonproportional hazards. Thus, a post hoc analysis was performed using the restricted mean survival time (RMST). The secondary endpoints included biochemical failure, distant metastasis (DM) as detected by conventional imaging, and disease-free survival (DFS).

Results and limitations: After 10.4 yr of median follow-up among survivors, the hazard ratio (HR) for OS was 0.89 (90% confidence interval [CI] 0.70–1.14; one-sided log-rank $p = 0.22$). Survival at 10 yr was 64% for ADT + EBRT and 69% for ADT + EBRT + docetaxel.

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The RMST at 12 yr was 0.45 yr and not statistically significant (one-sided $p = 0.053$). No differences were detected in the incidence of DFS (HR = 0.92, 95% CI 0.73–1.14), DM (HR = 0.84, 95% CI 0.73–1.14), or prostate-specific antigen recurrence risk (HR = 0.97, 95% CI 0.74–1.29). Two patients had grade 5 toxicity in the chemotherapy arm and zero patients in the control arm.

Conclusions: After a median follow-up of 10.4 yr among surviving patients, no significant differences are observed in clinical outcomes between the experimental and control arms. These data suggest that docetaxel should not be used for high-risk localized prostate cancer. Additional research may be warranted using novel predictive biomarkers.

Patient summary: No significant differences in survival were noted after long-term follow-up for high-risk localized prostate cancer patients in a large prospective trial where patients were treated with androgen deprivation therapy + radiation to the prostate \pm docetaxel.

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1. Introduction

Localized high-risk prostate cancer is typically treated with either surgery or radiation therapy plus androgen deprivation therapy (ADT). Despite the use of these effective therapies, relapses occur, and a number of strategies are currently being employed to improve outcomes. Some data suggest that brachytherapy may improve outcomes when employed concomitantly with external beam radiation therapy (EBRT) and ADT [1]. New data indicate that hormonal treatment intensification with abiraterone plus prednisone adds value for very-high-risk (or pelvic lymph node-positive) patients being treated with ADT plus EBRT [2]. Of note, studies to date with high-risk patients have not incorporated newer forms of imaging, such as prostate-specific membrane antigen (PSMA) positron emission tomography (PET). PSMA PET would be expected to upstage many of these “localized” patients compared with conventional imaging.

Docetaxel adds value to androgen deprivation in those with metastatic hormone-sensitive prostate cancer. Data from the STAMPEDE and CHAARTED trials indicate that men with high-volume hormone-sensitive metastatic prostate cancer benefit from the addition of docetaxel to androgen deprivation [3,4]. For men with low-volume metastatic prostate cancer, data regarding docetaxel benefits are more controversial [3,4].

In this report, we provide long-term follow-up for localized high-risk patients treated in the NRG Oncology/RTOG 0521 prospective randomized trial using EBRT + ADT compared with those treated with EBRT + ADT + docetaxel. The initial report of these trial results were published previously with a median follow-up among survivors of 6.1 yr [5]. An overall survival (OS) benefit was reported in the initial analysis (hazard ratio [HR] 0.69, 90% confidence interval [CI] 0.49–0.97). Herein, the OS data are updated to include a median follow-up of 10.4 yr.

2. Patients and methods

The primary endpoint was OS. The secondary endpoints were death from prostate cancer, biochemical failure (BF) using the Phoenix definition [6], distant metastasis (DM) as detected by conventional imaging, death from prostate cancer (PM), and disease-free survival (DFS), defined as the occurrence of BF, local or distant failure, or death from any cause.

OS and DFS were estimated by the Kaplan-Meier [7] method and compared between treatment arms using a log-rank test. Cox [8] proportional hazard models were fit to determine the HR. For BF, DM, and PM, cumulative incidence curves were generated by treating death, local failure, or distant failure as a competing risk (BF), or death alone as the competing risk (DM and PM). Treatment effects for these endpoints were evaluated by the cause-specific log-rank test and HR [9]. For this report, a post hoc comparison of the restricted mean survival time (RMST) [10] at 12 yr was also performed due to the detection of nonproportional hazards for OS [11]. As specified in the protocol, all statistical tests were two sided, and statistical significance was defined as $p < 0.05$, with the exception of OS, where a one-sided test was used per study design.

3. Results

Of 612 accrued patients, 563 were eligible and included in the analysis (modified intention to treat). The median follow-up among survivors was 10.4 yr. See the CONSORT diagram for clarity (Fig. 1). Characteristics of the patients at the time of trial entry have previously been described [5]. Four risk groups were enrolled into the trial. A total of 53% of patients were in risk group 1 (Gleason 9–10 cancers), 21% in risk group 2 (Gleason 8, prostate-specific antigen [PSA] <20 , $T \geq 2$), 10% in risk group 3 (Gleason 8, PSA >20), and 16% in group 4 (Gleason 7, PSA >20). It is noteworthy that the majority of patients had Gleason 9–10 cancers.

OS curves are shown in Figure 2. The 10-yr OS rates were 64% (95% CI 58–70%) for ADT + EBRT and 69% (95% CI 63–75%) for ADT + EBRT + docetaxel (HR = 0.89, 90% CI 0.70–1.14, one-sided log-rank $p = 0.22$). However, there was evidence of nonproportional hazards (Grambsch-Therneau test [12], $p = 0.016$). The survival curves diverged between approximately 4 and 8 yr, and then converged after 10–11 yr. The difference in the RMST at 12 yr was not statistically significant (difference = 0.45 yr, 90% CI –0.01 to 0.91, one-sided $p = 0.053$). Deaths were centrally reviewed for causality, and a total of 190 deaths were observed across the two arms, 100 in patients treated with ADT + EBRT and 90 in patients treated with ADT + EBRT + docetaxel. A total of two deaths were attributed to protocol therapy. Prostate cancer deaths totaled 76:46 in the conventional arm and 30 in the experimental arm. Deaths from other causes totaled 108 and were exactly balanced between the two arms (54 in each). See Table 1 for further details.

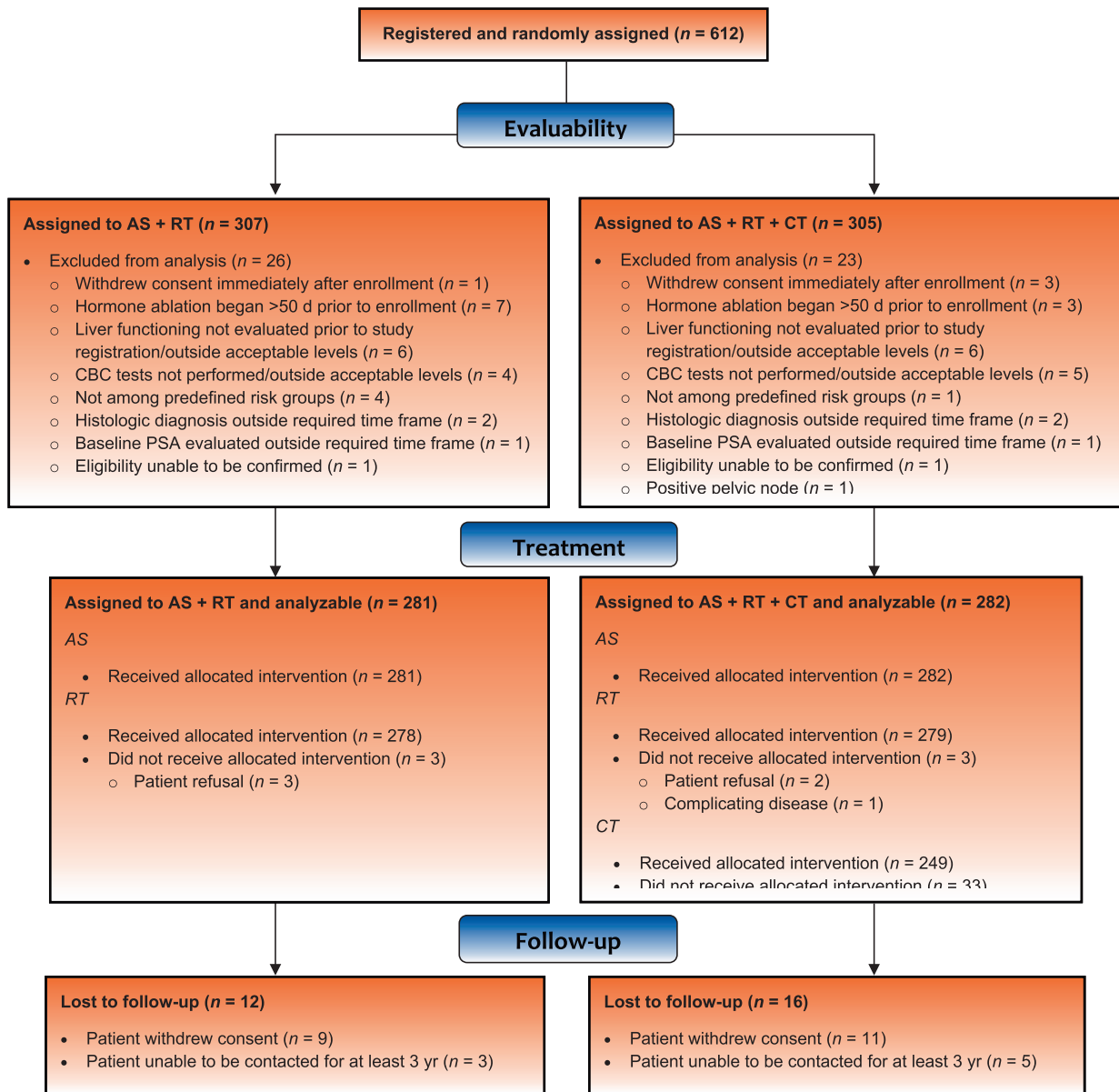


Fig. 1 – CONSORT flow diagram. AS = androgen suppression; CBC = complete blood count; CT = chemotherapy; PSA = prostate-specific antigen; RT = radiotherapy.

DFS curves are shown in [Figure 3A](#). The curves are not significantly different (HR = 0.92, 95% CI 0.73–1.14, two-sided log-rank $p = 0.44$). The cumulative incidence curves for DM, PSA recurrence, and PM are given in [Figures 3B–D](#). The cumulative incidence of DMs was not significant (HR = 0.84, 95% CI 0.58–1.22, two-sided log-rank $p = 0.59$). PSA recurrence rates were similar between the two arms (HR = 0.97, 95% CI 0.74–1.29, log-rank $p = 0.61$). Prostate cancer mortality was lower in the docetaxel arm, but not statistically significant (HR = 0.65, 95% CI 0.41–1.03, two-sided log-rank $p = 0.079$). At 10 yr of follow-up, the PSA recurrence risk was 36.0% for ADT + EBRT and 36.3% for ADT + EBRT + docetaxel.

There were no new related grade 5 toxicities. Toxicities remain essentially the same as documented in the prior report.

4. Discussion

While the original publication reported a survival benefit of docetaxel after a median follow-up of 5.7 yr, with the longer follow-up (a median follow-up of 10.4 yr) in this report, the data no longer provide a compelling case for the use of docetaxel for patients with high-risk clinically localized prostate cancer when combined with EBRT and ADT. With a longer follow-up, the survival curves have converged, although the difference in the RMST at 12 yr is nearly statistically significant ($p = 0.053$). Even if the RMST is taken at face value, the impact of these findings is not sufficient in magnitude to be clinically significant. We also note the two treatment-related deaths. While this is low percentage-wise, for adjuvant treatment it is quite relevant.

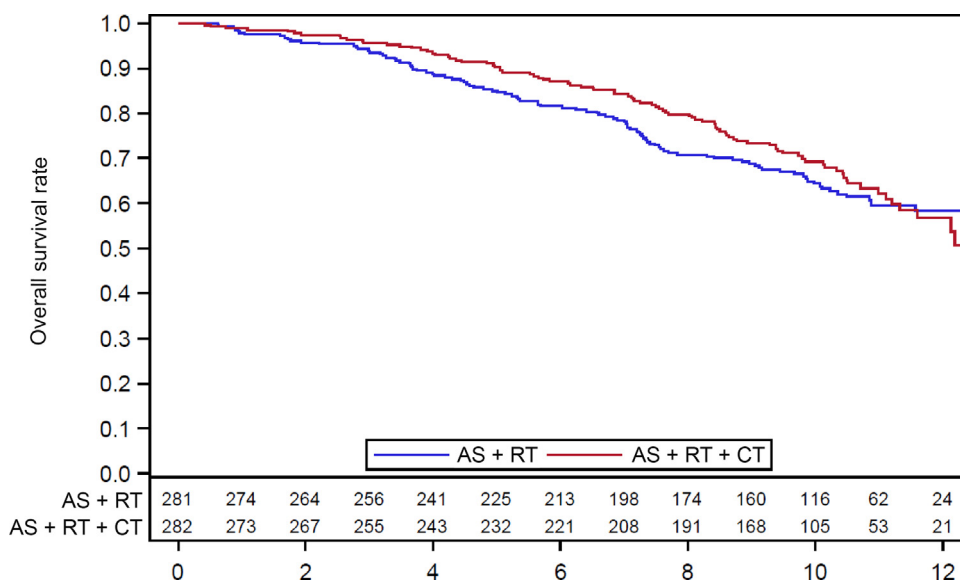


Fig. 2 – Overall survival. AS = androgen suppression; CT = chemotherapy; RT = radiotherapy.

These findings are not necessarily surprising given the failure of docetaxel to provide clinical benefit in various prostate cancer studies examining nonmetastatic disease. The trials conducted with adjuvant docetaxel given in combination with local therapies include the STAMPEDE, GETUG-12 trial, SPCG-12, SPCG-13, VA-553, CALGB 90203, the “Boston study,” and RTOG 0521 trials. The STAMPEDE trial was complex as local therapies were not administered to all patients and follow-up was short (median 6.5 yr) [13]. In the STAMPEDE M0 cohort, 62% were planned for EBRT, with the actual reported use in 57% for those treated with ADT + docetaxel versus 63% for those treated with the ADT alone. The HR for OS for those treated with ADT + docetaxel versus ADT alone was 0.88 (95% CI 0.64–1.21) [13]. Of note, additional STAMPEDE data demonstrate the importance of radiation in survival of patients with low-volume metastatic disease, emphasizing the importance of local treatments [14]. For the GETUG-12 trial, ADT + docetaxel/estrabutine was added to EBRT for high-risk localized disease [15]. After a median follow-up of 12 yr, metastasis-free survival trended favorably in the chemotherapy arm, but OS data were not distinct between the arms. SPCG-12 evaluated “high-risk” men after radical prostatectomy who were randomized between surveillance and docetaxel [16]. After 57 mo of follow-up, no benefit was seen after chemotherapy as measured by biochemical relapse-free survival or RMST. For SPCG-13, ADT and EBRT + docetaxel were compared with ADT + EBRT [17]. No differences were noted in biochemical progression-free survival. OS data were immature, but no benefit was seen. VA protocol 553 was reported despite failing to achieve recruitment goals [18]. A total of 298 patients were randomized after radical prostatectomy for high-risk prostate cancer. No benefit was seen for progression-free survival in this underpowered trial. In CALGB 90203, neoadjuvant ADT + docetaxel + radical prostatectomy versus radical prostatectomy alone was evaluated in 788 patients [19]. After 6.1 yr of median

follow-up, the primary endpoint (3-yr biochemical progression-free survival) was not met, but OS (as a secondary endpoint) was improved (HR = 0.61, 95% CI 0.40–0.94). The CALGB 90203 study OS benefit may have been due to hormonal therapy and cannot be attributed directly to taxane chemotherapy. In the “Boston trial” with long-term follow-up (median follow-up 10.2 yr), 350 men with unfavorable-risk prostate cancer received ADT + docetaxel + EBRT versus ADT + EBRT [20]. The RMST was not improved with docetaxel. Taken together, no study of docetaxel monotherapy in nonmetastatic prostate cancer has reported long-term OS benefit. The CALGB 90203 study OS benefit may have been due to hormonal therapy.

Two large trials have looked at nondocetaxel chemotherapy that are relevant here. The RTOG 9902 trial looked at EBRT + ADT ± a regimen of paclitaxel, oral etoposide, and estrabutine chemotherapy, and after 9.2 yr found no effect on survival [21]. The SWOG 9921 trial looked at ADT ± mitoxantrone after radical prostatectomy and found no effect on survival with the addition of mitoxantrone [22].

The data here, after 10.4 yr of follow-up, demonstrate that prostate cancer death is a relatively rare event despite the selection at the time of trial entry for “high-risk” patients (see Table 1). Most patients died from non-prostate cancer causes, and the rate of prostate cancer deaths

Table 1 – Centrally reviewed cause of death

Centrally reviewed cause of death	AS + RT (n = 100), n (%)	AS + RT + CT (n = 90), n (%)
Death due to cancer under study	46 (46.0)	30 (33.3)
Death due to protocol treatment	0 (0.0)	2 (2.2)
Death due to other cause	37 (37.0)	44 (48.9)
Death due to second primary	17 (17.0)	10 (11.1)
Unknown cause of death	0 (0.0)	4 (4.4)

AS = androgen suppression; CT = chemotherapy; RT = radiotherapy.

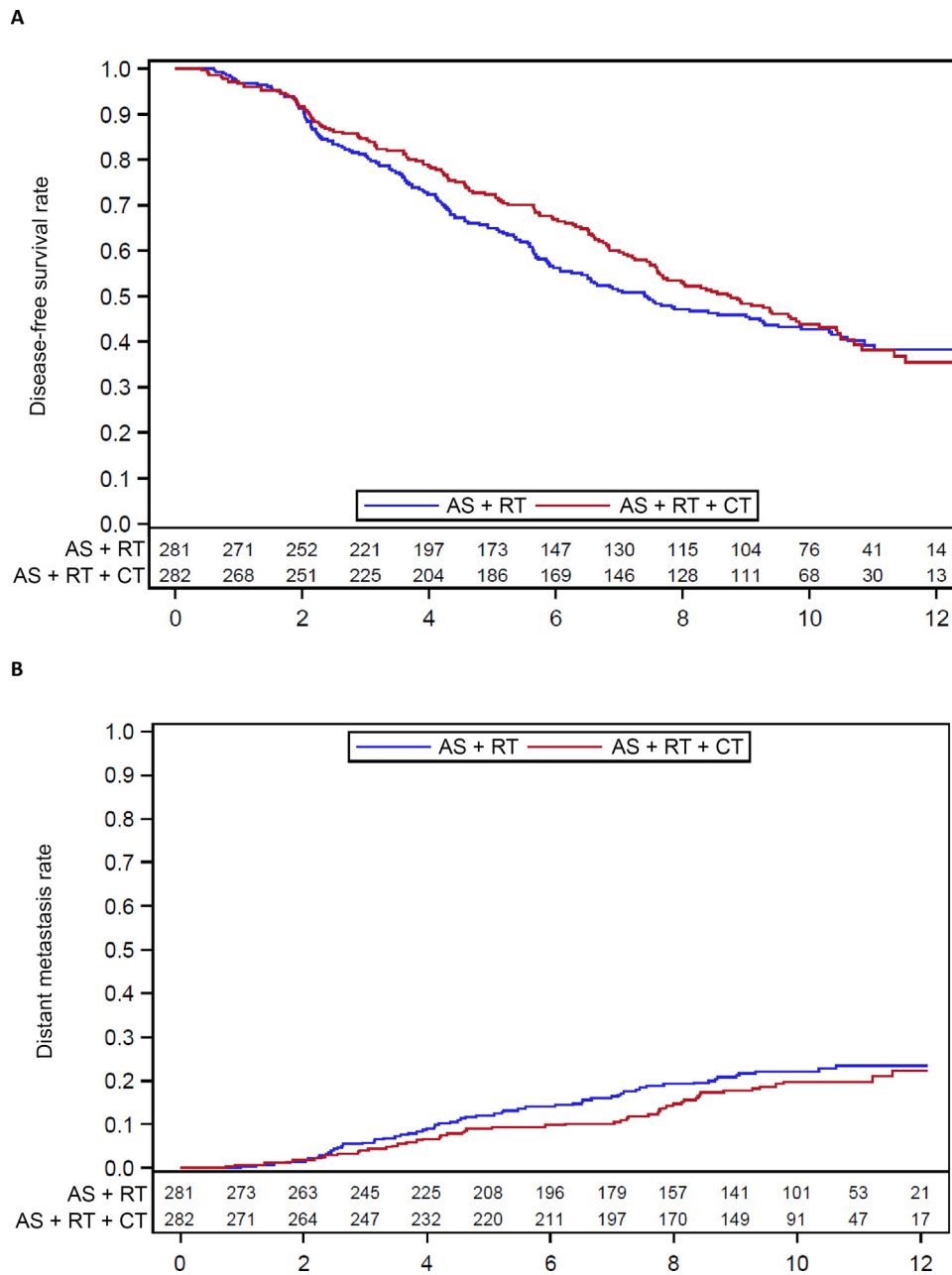


Fig. 3 – Disease-free survival and cumulative incidence curves for DM, PSA recurrence, and PC death: (A) disease-free survival, (B) distant metastasis (cumulative incidence), (C) biochemical failure as first event (cumulative incidence), and (D) prostate cancer mortality (cumulative incidence). AS = androgen suppression; CT = chemotherapy; DM = distant metastasis; PC = prostate cancer; PSA = prostate-specific antigen; RT = radiotherapy.

remains relatively flat from 6 to 12 yr after randomization in both arms. These data indicate one of two possibilities that either conventional therapy is quite effective in most high-risk localized patients or high-risk disease is less deadly than expected. The definitions of high risk used in RTOG 0521 are somewhat distinct from those used in the more recent STAMPEDE trial [2] using ADT + abiraterone + EBRT as compared with ADT + EBRT. In the STAMPEDE trial, patients were enrolled only if they had pelvic nodal metastatic disease (excluded here) or two of the following three characteristics: PSA >40 ng/ml, stage T3/T4, and Gleason 8–10. Of note, 38% of these STAMPEDE patients had

TXN1M0 disease. Thus, the STAMPEDE and RTOG 0521 patient populations are not analogous.

The use of PSMA PET to stage the high-risk localized prostate cancer patients of yesteryear will only result in a better prognosis for those staged as nonmetastatic in the future. In these RTOG 0521 studies in the control group, the cumulative incidence of distance metastases at 10 yr was 22% in the control arm. The incidence of DMs was 16% in the RTOG 9902 trial in the control arm. Taken together, the introduction of PSMA PET imaging in the future is likely to diminish the rate of metastatic events for high-risk localized prostate cancer.

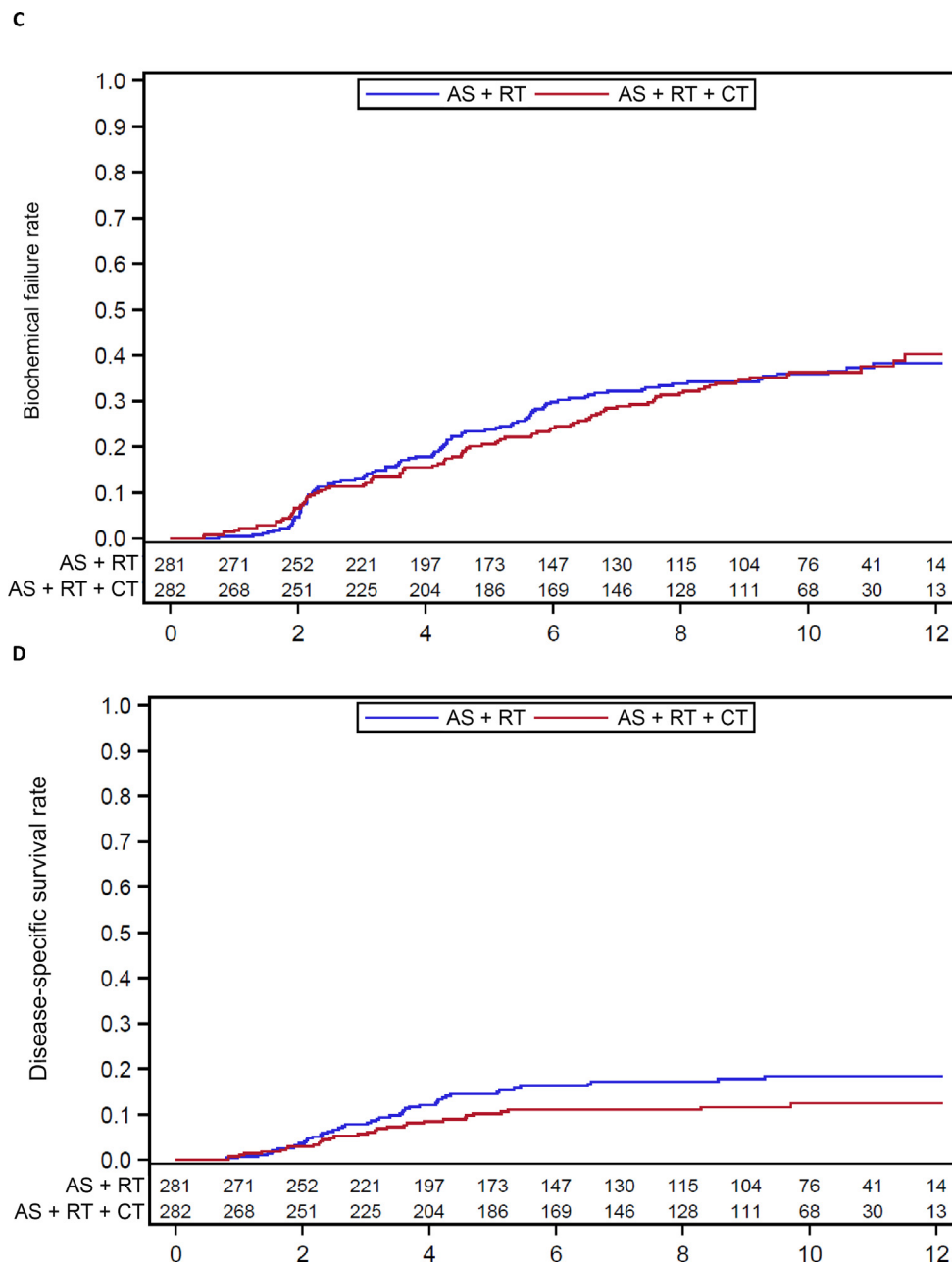


Fig. 3 (continued)

Limitations include the fact that 49 patients were excluded from the modified intent-to-treat analysis. In addition, 28 patients were lost to long-term follow-up. The RMST analysis was not protocol specified. Only conventional imaging was used in the selection and follow-up of patients.

5. Conclusions

The goals of prostate cancer treatment remain to improve survival rates and decrease treatment-associated morbidity. Treatment intensification will benefit most of those patients who are at the highest risk for disease progression with conventional therapies. The potential for further intensification to add to conventional therapeutic outcomes in this setting

will be difficult without more precise identification of a higher-risk cohort. Given that PSMA PET and other advanced imaging modalities will become more common in staging going forward, and the challenge of identifying higher-risk localized patients will depend on genomic classifiers (or other new strategies) in conjunction with advanced imaging modalities to risk stratify patients more precisely [23]. The use of artificial intelligence (machine learning) will also potentially play a significant role given the recent demonstration that such techniques may be used to predict who is most likely to benefit from ADT [24]. Machine learning may help predict benefit from docetaxel as well, but studies on this issue are yet to be reported. As more precise identification of the highest-risk patients will

be appropriate in defining patients who will benefit from treatment intensification strategies, deintensification of therapy is appropriate for those who may be overtreated with current approaches. Protocols such as NRG 009 are assessing genomic classifiers in risk stratification [25].

Author contributions: Oliver Sartor 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: Amin, Feng, Garzotto, Gomella, Michalski, Rosenthal, Sartor.

Acquisition of data: Balogh, Hannan, Horwitz, Jones, Karrison, Purdy, Reaume, Rosenthal, Sandler, Sartor, Williams.

Analysis and interpretation of data: Balogh, Feng, Gomella, Hannan, Horwitz, Karrison, Michalski, Pervez, Reaume, Rodgers, Rodrigues, Rosenthal, Sartor, Souhami.

Drafting of the manuscript: Amin, Balogh, Feng, Garzotto, Gomella, Hannan, Horwitz, Jones, Karrison, Michalski, Pervez, Purdy, Reaume, Rodgers, Rodrigues, Rosenthal, Sandler, Sartor, Souhami, Williams.

Critical revision of the manuscript for important intellectual content: Amin, Balogh, Feng, Garzotto, Gomella, Hannan, Horwitz, Jones, Karrison, Michalski, Pervez, Purdy, Reaume, Rodgers, Rodrigues, Rosenthal, Sandler, Sartor, Souhami, Williams.

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Peer Review Summary

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