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Platinum Priority – Review – Prostate Cancer

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Local Failure Events in Prostate Cancer Treated with Radiotherapy: A Pooled Analysis of 18 Randomized Trials from the Meta-analysis of Randomized Trials in Cancer of the Prostate Consortium (LEVIATHAN)

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Abstract

Context: The prognostic importance of local failure after definitive radiotherapy (RT) in National Comprehensive Cancer Network intermediate- and high-risk prostate cancer (PCa) patients remains unclear.
Objective: To evaluate the prognostic impact of local failure and the kinetics of distant metastasis following RT.
Evidence acquisition: A pooled analysis was performed on individual patient data of 12 533 PCa (6288 high-risk and 6245 intermediate-risk) patients enrolled in 18 randomized trials (conducted between 1985 and 2015) within the Meta-analysis of Randomized Trials in Cancer of the Prostate Consortium. Multivariable Cox proportional hazard (PH) models were developed to evaluate the relationship between overall survival (OS), PCa-specific survival (PCSS), distant metastasis-free survival (DMFS), and local failure as a time-dependent covariate. Markov PH models were developed to evaluate the impact of specific transition states.
Evidence synthesis: The median follow-up was 11 yr. There were 795 (13%) local failure events and 1288 (21%) distant metastases for high-risk patients and 449 (7.2%) and 451 (7.2%) for intermediate-risk patients, respectively. For both groups, 81% of distant metastases developed from a clinically relapse-free state (cRF state). Local failure was significantly associated with OS (hazard ratio [HR] 1.17, 95% confidence interval [CI] 1.06–1.30), PCSS (HR 2.02, 95% CI 1.75–2.33), and DMFS (HR 1.94, 95% CI 1.75–2.15, $p < 0.01$ for all) in high-risk patients. Local failure was also significantly associated with DMFS (HR 1.57, 95% CI 1.36–1.81) but not with OS in intermediate-risk patients. Patients without local failure had a significantly lower HR of transitioning to a PCa-specific death state than those who had local failure (HR 0.32, 95% CI 0.21–0.50, $p < 0.001$). At later time points, more distant metastases emerged after a local failure event for both groups.
Conclusions: Local failure is an independent prognosticator of OS, PCSS, and DMFS in high-risk and of DMFS in intermediate-risk PCa. Distant metastasis predominantly developed from the cRF state, underscoring the importance of addressing occult microscopic disease. However a "second wave" of distant metastases occurs subsequent to local failure events, and optimization of local control may reduce the risk of distant metastasis.
Patient summary: Among men receiving definitive radiation therapy for high- and intermediate-risk prostate cancer, about 10% experience local recurrence, and they are at significantly increased risks of further disease progression. About 80% of patients who develop distant metastasis do not have a detectable local recurrence preceding it.

1. Introduction

Distant metastasis-free survival (DMFS) has been demonstrated to be a strong surrogate endpoint for overall survival (OS) for localized prostate cancer (PCa) [1,2]. Recent evidence derived from prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) suggests that occult distant metastases at presentation may be the true driver of PCa natural history, especially for patients with National Comprehensive Cancer Network (NCCN) high-risk disease [3,4]. This is especially relevant for assessing the prognostic impact of local failure and the clinical importance of local treatment intensification strategies such as radiotherapy (RT) dose escalation. At the core of dose escalation is the hypothesis that local failure eventually "seeds" distant metastases, leading to a "second wave" of distant metastases (the first wave being undiagnosed occult metastatic disease at presentation) [5,6]. However, data in this domain are not entirely consistent. Retrospective studies as well as post hoc analyses of randomized trials have shown that increased local control is associated with increased DMFS as well as PCa-specific survival (PCSS) [5,7–11]. However, only two randomized controlled trials (RCTs) among many have suggested a distant metastasis benefit from dose escalation and none identified a PCSS or OS benefit [12,13]. In contrast, while androgen deprivation therapy (ADT) may have radiosensitizing effects that improve local control, it also has cytostatic and cytotoxic effects on occult microscopic disease and has been shown in multiple randomized trials to improve not only DMFS, but PCSS and OS as well [14–19]. As each form of treatment intensification has quality of life implications, it is critical to develop a unified framework that takes into account the temporal relationship of local failure and distant metastasis (ie, first and second "waves" of distant metastasis), and how different treatment strategies (ie, dose escalation and ADT) impact the development of distant metastasis and other clinical outcomes. It is hypothesized that a first wave of distant metastasis stems from the emergence of occult micrometastatic disease that

was present at the time of initial treatment, which may be followed by a subsequent second wave of distant metastasis representing "seeding" from a preceding local failure event. The magnitude of the first wave distant metastasis may be smaller in intermediate-risk patients than in high-risk patients given a lower burden of occult metastasis at initial treatment. In this study, we leveraged the Meta-analysis of Randomized Trials in Cancer of the Prostate (MARCAP) Consortium to analyze individual patient data from 18 RCTs of definitive RT of varying RT dose levels and ADT durations that included local failure as a prespecified endpoint to explore the prognostic impact of local failure events and the kinetics of distant metastasis after RT in intermediate- and high-risk PCa.

2. Evidence acquisition

The current study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement regarding the process of identifying eligible trials to be included in the pooled analysis (Fig. 1) [20]. Individual patient data for 18 RCTs were obtained from the MARCAP Consortium. Although a minority of the trials permitted node-positive patients, all patients included in this analysis had clinically node-negative disease. For trials that included ADT, only those with short-term ADT (STADT) and long-term ADT (LTADT) were included. STADT was defined as 3–9 mo of ADT and LTADT was defined as 18–36 mo. Trials with nonstandard ADT duration (eg, life-long ADT) and nonstandard ADT agents (eg, bicalutamide monotherapy) were excluded (Fig. 1). Intention-to-treat data were used. Trials included in the analysis are listed in Table 1, and trial-specific definitions of local failure and distant metastasis are listed in Supplementary Table 1. All time-to-event outcome variables were measured from the date of randomization to the reported occurrence of the event of interest. If a specific event was not reported during the follow-up period, the patient was considered censored for that particular event. The reverse Kaplan-Meier (KM) method was used to assess the length and completeness of the follow-up. Multivariable Cox proportional hazard (PH) models were developed to evaluate the relationship between OS, PCSS, DMFS, and local failure (as a time-dependent covariate), while adjusting for the following variables: initial

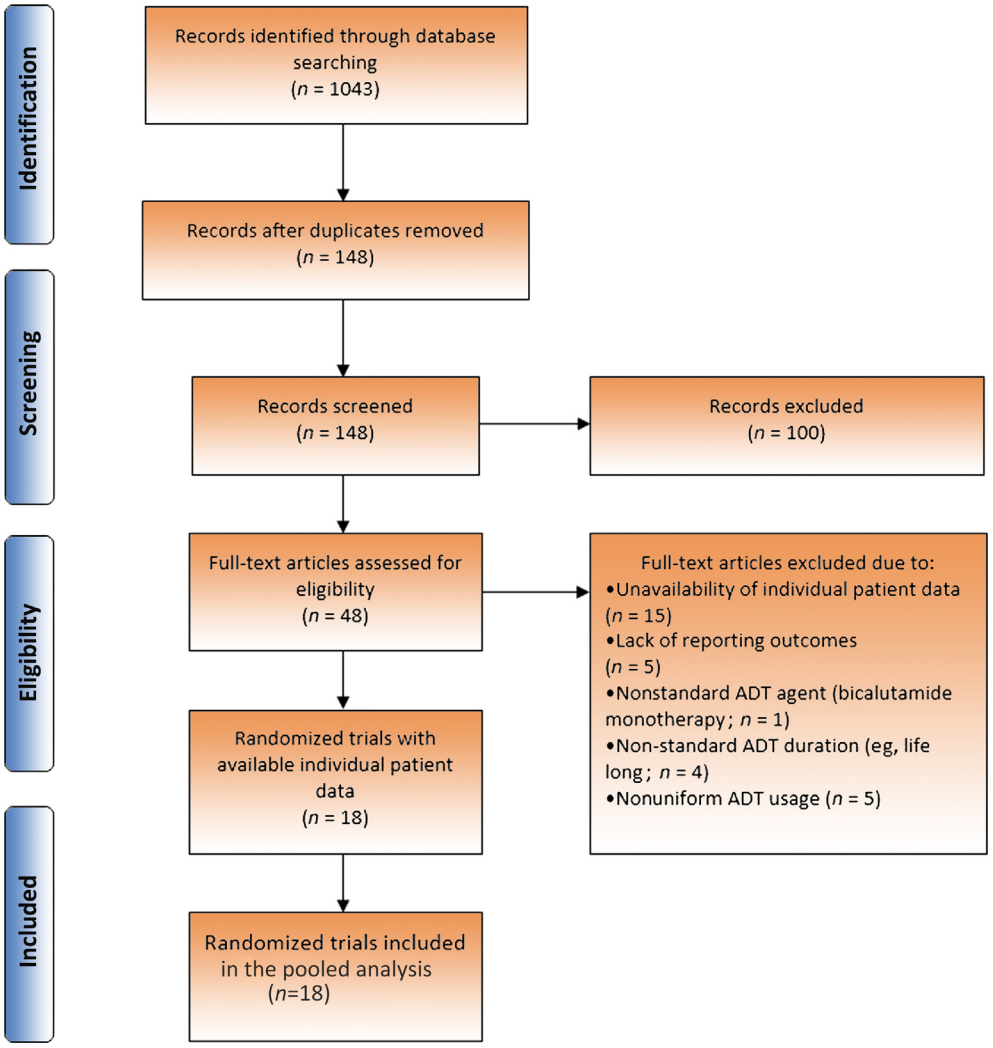

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart. ADT = androgen deprivation therapy.

Table 1 – Summary of trials included in study (by treatment categories)

Trial name	Trial recruitment year	Radiation dose (Gy)	ADT duration (mo)	Median age (yr)	No. of intermediate-risk patients	No. of high-risk patients	Median follow-up (yr)
Low-dose RT alone							
RTOG 8610	1987–1991	65–70	NA	72	2	50	6.7
EORTC 22863	1987–1995	70	NA	69	1	87	5.0
RTOG 9408	1994–2001	66.6	NA	72	435	91	9.4
TROG 96.01	1996–2000	66	NA	68	68	148	10
CKTO 9610	1997–2003	68	NA	69	84	111	8.5
EORTC 22991	2001–2008	70	NA	68	46	33	12
RTOG 0126	2002–2008	70.2	NA	71	751	0	8.4
Subtotal					1387	520	
High-dose RT alone							
CKTO 9610	1997–2003	78	NA	69	84	105	8.4
PCS III	2000–2010	76	NA	72	192	0	11
EORTC 22991	2001–2008	74 or 78	NA	71	166	62	11
RTOG 0126	2002–2008	79.2	NA	71	748	0	8.2
Subtotal					1190	167	
Low-dose RT + short-term ADT							
RTOG 8610	1987–1991	65–70	4	70	3	48	8.8
RTOG 9202	1992–1995	65–70	4	70	42	456	8.9
RTOG 9408	1994–2001	66.6	4	71	420	94	10
RTOG 9413	1995–1999	70.2	4	70	208	993	8.9
TROG 96.01	1996–2000	66	6	69	148	284	11
ICORG 97-01	1997–2001	70	4 or 8	67	42	135	10
EORTC 22961	1997–2001	70	6	70	30	307	5.9
CKTO 9610	1997–2003	68	6	69	1	30	6.8
MRC RT01	1998–2001	64	3–6	68	141	147	9.2
RTOG 9910	2000–2004	70.2	4 or 9	71	1057	353	8.7
PCS III	2000–2010	70	6	71	193	0	11
EORTC 22991	2001–2008	70	6	70	44	35	11
TROG RADAR	2003–2007	66 or 70	6	70	124	154	11
Subtotal					2453	3036	
Low-dose RT + long-term ADT							
EORTC 22863	1987–1995	70	36	71	2	86	7.5
RTOG 9202	1992–1995	65–70	24	70	50	487	9.6
EORTC 22961	1997–2001	70	36	69	33	297	6.1
CKTO 9610	1997–2003	68	36	66	5	28	8.0
RTOG 9902	2000–2004	70.2	24	65	0	239	10
PCS IV	2000–2008	70	18 or 36	71	0	617	11
TROG RADAR	2003–2007	66 or 70	18	69	111	158	11
Subtotal					201	1912	
High-dose RT + short-term ADT							
CKTO 9610	1997–2003	78	6	68	5	20	5.1
MRC RT01	1998–2001	74	3–6	67	129	157	9.2
PCS III	2000–2010	76	6	71	195	0	11
Ottawa 0101	2002–2012	76	6	70	394	0	10
TROG RADAR	2003–2007	74 or 46 Gy/ 23 fx plus HDR-BT boost	6	68	60	186	10
EORTC 22991	2001–2008	74 or 78	6	72	175	56	11
Subtotal					958	419	
High-dose RT + long-term ADT							
CKTO 9610	1997–2003	78	36	67	3	36	8.3
TROG RADAR	2003–2007	74 or 46 Gy/ 23 fx plus HDR-BT boost	18	68	53	198	10
Subtotal					56	234	
Total					6245	6288	

ADT = androgen deprivation therapy; fx = fraction; HDR-BT = high-dose-rate brachytherapy; RT = radiation therapy.

prostate-specific antigen (iPSA; continuous variable; per 10 ng/mL), Gleason score (GS; 6, 7, and 8–10; GS 6 as reference), treatment category (low-dose RT only, low-dose RT + STADT, low-dose RT + LTADT, high-dose RT only, high-dose RT + STADT, and high-dose RT + LTADT; low-dose RT as reference [Cox PH model], or RT, STADT, and LTADT; RT as reference [Markov model]), T stage (T1–2 and T3–4; T1–2 as reference), age (continuous variable; per 10 yr), and time from midpoint year of the trial (continuous variable). These variables were chosen because of availability and prior data suggesting that these were of prognostic importance. RT doses of $\geq$74 Gy were considered "high dose" (presuming an α/β of 3.0). Patients without clinically diagnosed extracapsular extension or seminal vesicle invasion were classified as having T1-T2 disease.

Fine and Gray competing risk regression was performed for PCa-specific mortality (PCSM) and distant metastasis with all-cause mortality death as the competing event; in these analyses, local failure was a time-independent covariate. The hazard function for the development of distant metastasis over time was estimated via kernel-based methods in subgroups of patients based on local failure status and ADT duration, to provide an overview as an exploratory analysis. Furthermore, within each treatment category, hazard rates for distant metastasis over 2-yr intervals were calculated using the life-table method for patients with and without local failure as a time-independent covariate. The hypothesis of first and second waves of distant metastasis was evaluated based on the hazard rate of distant metastasis as well as the event rate of different transition states to

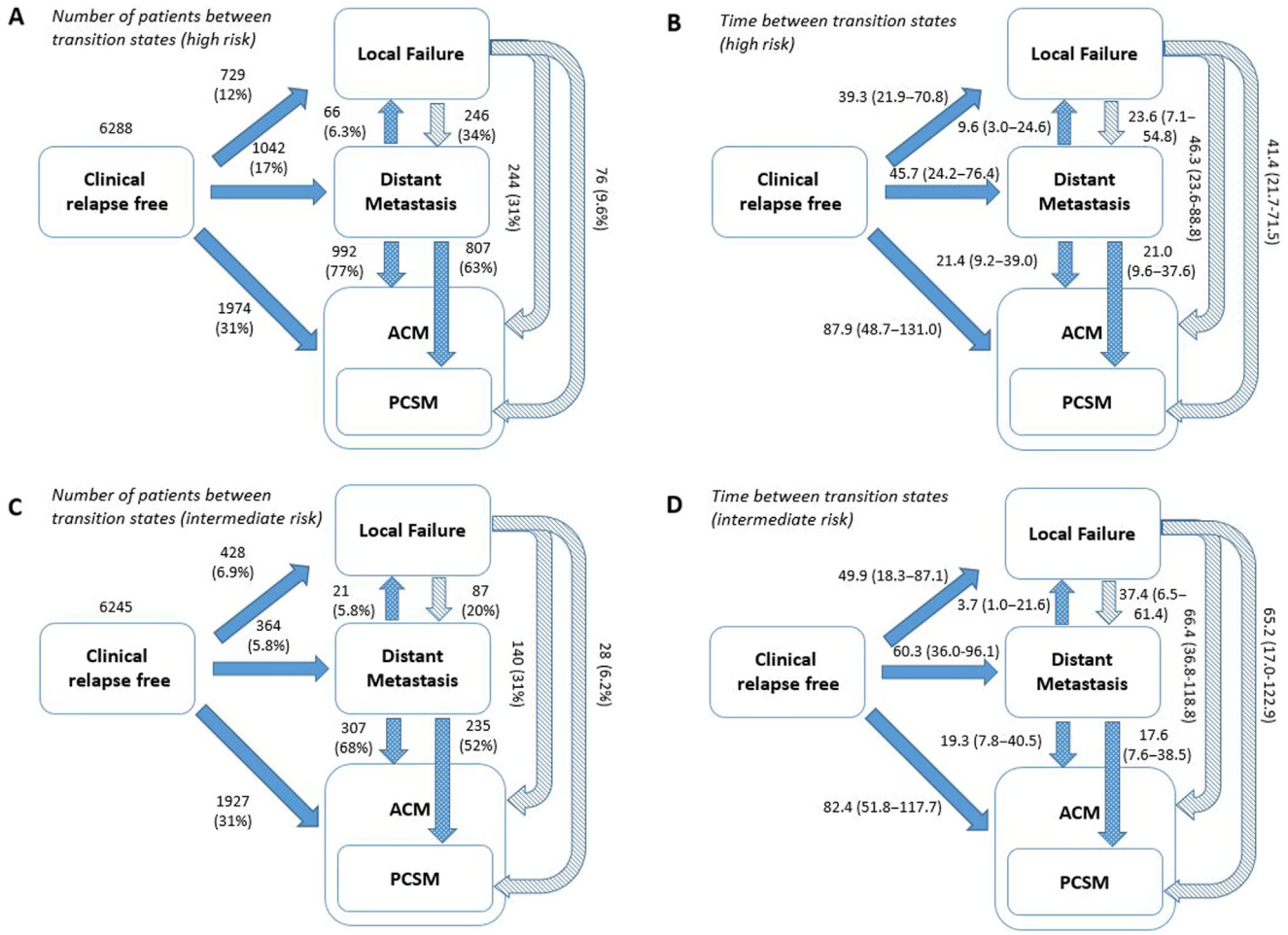

Fig. 2 – Crude rates of events and transition time between disease states in the four-state model. The four states are clinical relapse-free state, local failure state, distant metastasis state, and death state (all-cause mortality and prostate cancer–specific mortality). (A and B) NCCN high-risk patients, and (C and D) NCCN intermediate-risk patients. Figures 2A and 2C) show the number of patients in each transition state, with percentage in parenthesis. Percentage was calculated with the number of patients in the beginning state as the denominator (eg, for distant metastasis to PCSM transition, the denominator was the number of patients with distant metastasis [ie, 1288 for NCCN high risk]). Arrows with the same fill patterns (solid, dotted, or hashed) share the same denominator. Figures 2B and 2D show the median transition time between disease states in months with interquartile range in parenthesis; overall cohort of patients are same as in Figures 2A and 2C). Each transition time in Figures 2B and 2D was calculated based on different subcohorts of patients. ACM = all-cause mortality; NCCN = National Comprehensive Cancer Network; PCSM = prostate cancer–specific mortality.

distant metastasis over time in local failure and local control patients.

We developed a four-state model to simultaneously analyze multiple events occurring during the natural history of PCa (Fig. 2). The model consists of a clinical relapse-free survival state (cRF state, which may or may not include biochemical recurrence), a local failure state, a distant metastasis state, and a death state. Patients who did not have a PCSM event were censored for PCSS. Markov PH models for the four-state model were developed to assess the effects of the aforementioned covariates on PCSS and OS along with the effect of a transition from the cRF state versus local failure state to the death state. This model was not stratified by NCCN risk groups. The potential heterogeneity between trials was accounted for by including random effects in Cox PH and Markov PH models. The PH assumption was examined via the diagnostic plot method. The chi-square test of independence (or Fisher's exact test when applicable) was used to assess the association of the rate of transition between disease states with certain treatment subgroups. The Mann-Whitney *U* test was used to compare the median time to a specific transition state between patients of different risk levels or treatment categories. The level of significance was set to be 0.05. All analyses were carried out via R version 3.6.0/4.1.2 (R Foundation for Statical Computing, Vienna, Austria) [21] with packages *survival* [22,23], *muhaz* [24], *KMsurv* [25], *crrSC* [26], *cmprsk* [27], *coxme* [28], *mstate* [29,30], *dplyr* [31] and *ggplot2* [32], *devtools* [33], *ggforestplot* [34], and *gridExtra* [35].

3. Evidence synthesis

3.1. Results

A total of 12 533 patients (6288 high risk and 6245 intermediate risk) were included in the analysis from 18 randomized trials, recruited from 1987 to 2012 (Supplementary Table 1). The median follow-up was 11 yr overall, 12 yr for high-risk patients, and 11 yr for intermediate-risk

patients, using the reverse KM method. The numbers of events of local failure, distant metastasis, PCSM, and all-cause mortality were 795, 1288, 1034, and 3210, respectively, for patients with high-risk PCa; these numbers were 449, 451, 353, and 2374, respectively, for patients with intermediate-risk PCa.

We first evaluated the crude rates of events and transit time between states in the four-state model (Fig. 2). For high-risk patients, 39% of distant metastasis events occurred within 2 yr after RT; 81% (n = 1042) of distant metastases developed from a cRF state, with a median interval of 46 (interquartile range [IQR] 24–76) mo. In contrast, 19% (n = 246) of distant metastases developed after local failure, with a median interval of 24 (IQR 7–55) mo after local failure. With respect to local failure, 92% (n = 729) of events occurred from a cRF state with a corresponding median interval of 39 (IQR 22–71) mo after initial treatment. Among patients who developed distant metastasis, 63% (n = 807) died of PCa. The median interval from distant metastasis to death was 21 (IQR 10–38) mo. For intermediate-risk patients, 13% of distant metastasis events occurred within 2 yr after RT; 81% (n = 364) of distant metastases developed from a cRF state, with a median interval of 60 (IQR 36–96) mo. In contrast, 19% (n = 87) of distant metastases developed after local failure, with a median interval of 37 (IQR 7–61) mo after local failure. Regarding local failure, 95% (n = 428) of events occurred from a cRF state with a corresponding median interval of 50 (IQR 18–87) mo after initial treatment. For patients who developed distant metastasis, 52% (n = 235) died of PCa. The median interval from distant metastasis to death was 18 (IQR 8–39) mo. Rates and transit times between four states within each treatment group are shown in Supplementary Figs. 1 and 2.

Next, we assessed the impact of local failure on the development of distant metastasis and other clinical endpoints. In high-risk patients, local failure, as a time-dependent variable, was significantly associated with a greater hazard of distant metastasis or death (as a composite endpoint, hazard ratio [HR] of 1.94 [95% confidence interval {CI} 1.75–2.15], p < 0.001; Fig. 3A) in the Cox PH model adjusted for iPSA, GS, treatment categories, T stage, age, and time from midpoint year of the trial. Local failure was also significantly associated with PCSS and OS (HRs 2.02 [95% CI 1.75–2.33], p < 0.001 and 1.17 [95% CI 1.06–1.30], p < 0.01; Fig. 3B and 3C). In intermediate-risk patients, local failure was significantly associated with a greater hazard of distant metastasis or death (HR 1.57 [95% CI 1.36–1.81], p < 0.001), but not OS (HR 0.93 [95% CI 0.81–1.08], p = 0.35; Fig. 3D and 3E). The model fit was

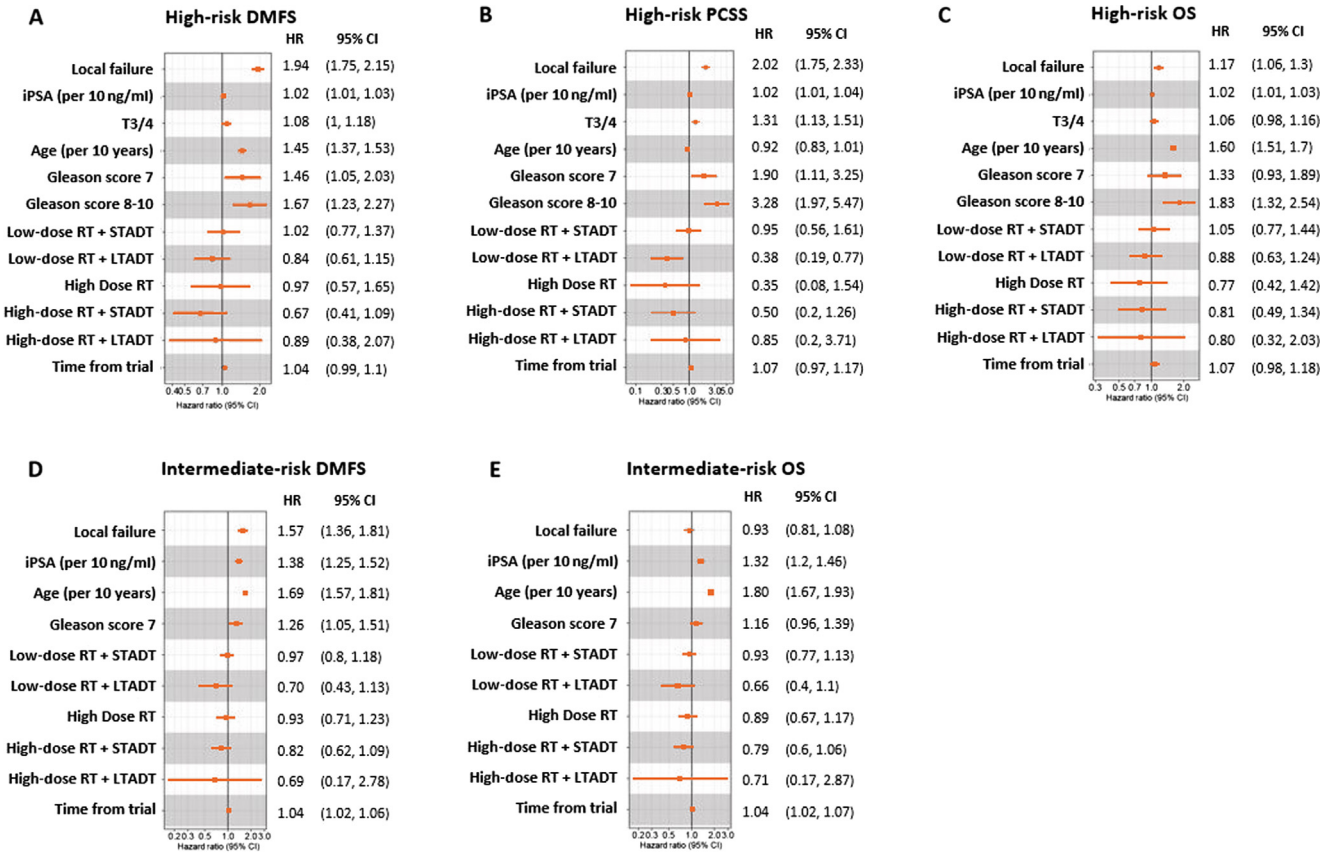

Fig. 3 – Forest plots of Cox proportional hazard model with local failure as a time-dependent variable. (A) DMFS, (B) PCSS, and (C) OS for NCCN high-risk patients, and (D) DMFS and (E) OS for NCCN intermediate-risk patients. T1/2, Gleason score 6, and low-dose RT only were used as the reference for their respective categories. The interactions between the Gleason score and treatment strategies were found to be insignificant and not reported in the forest plots. See the text for definition of low/high-dose RT and STADT/LTADT. CI = confidence interval; DMFS = distant metastasis-free survival; HR = hazard ratio; iPSA = initial prostate-specific antigen; LTADT long-term androgen deprivation therapy; NCCN = National Comprehensive Cancer Network; OS = overall survival; PCSS = prostate cancer–specific survival; RT = radiation therapy; STADT = short-term androgen deprivation therapy.

not attainable for the PCSS endpoint. In the Fine and Gray competing risk regression with all-cause mortality death as the competing event and local failure as a time-independent covariate, local failure was significantly associated with PCSS (subdistribution HR [sHR] 2.15 [95% CI 1.84–2.5], $p < 0.001$) and distant metastasis (sHR 1.77 [95% CI 1.46–2.14], $p < 0.001$) in high-risk patients (Supplementary Fig. 3A and 3B). In intermediate-risk patients, local failure was also significantly associated with a greater hazard of PCSS (sHR 3.34 [95% CI 2.52–4.44], $p < 0.001$) and distant metastasis (sHR 3.63 [95% CI 2.93–4.49], $p < 0.001$; Supplementary Fig. 3C and 3D). In the Markov model derived from the four-state model adjusting for the GS, iPSA, T stage, treatment category, age, and time from midpoint year of the trial, patients who did not have local failure had a significantly lower hazard of PCSM than those who had local failure (HR 0.32 [95% CI 0.21–0.5], $p < 0.001$; Fig. 4A), but not of all-cause mortality (HR 1.07 [95% CI 0.88–1.31], $p = 0.5$; Fig. 4B). Patients who developed distant metastasis had a significantly greater hazard of PCSM (HR 12.85 [95% CI 8.67–19.03], $p < 0.001$) and all-cause mortality (HR 4.81 [95% CI 3.85–6.01], $p < 0.001$) than those who developed only local failure (Fig. 4A and 4B). Crude event rates by 2-yr intervals are shown for each transition for patients with high- and intermediate-risk disease (Supplementary Figs. 4 and 5).

When stratified by local failure status, estimated by kernel-based methods, high-risk patients with local failure seem to have a higher risk of distant metastasis numerically, with a steep increase within the first 10 yr after RT, while those without local failure had an initial peak around year 3, with a gradual decline for the rest of the study period (Fig. 5A). Patients with intermediate-risk disease followed a similar trend, although the hazard rate was generally lower, and patients without local failure maintained a steady hazard rate without a discernable initial peak (Fig. 5B). Similar temporal changes were observed in the hazard rate of distant metastasis over 2-yr intervals using the life-table method (Supplementary Figs. 6 and 7). In addition, the percentage of distant metastasis events occurring from a cRF state declined over time, while the proportion occurring after a local failure event increased steadily among both high- and intermediate-risk patients (Fig. 5C and 5D). In high-risk patients, 91% and 9% of distant metastasis originated from a cRF state and a local failure state, respectively, during 0–2 yr after RT; these changed to 66% and 34%, respectively, when assessing distant metastasis events developing between 8 and 10 yr after RT. In intermediate-risk patients, 92% and 8% of distant metastasis originated from a cRF state and a local failure state, respectively, during 0–2 yr after RT, and 73% and 27%, respectively, between 8 and 10 years after RT. Similar trends were seen when stratified by treatment categories (Supplementary Figs. 8 and 9).

Finally, we examined the effect of ADT and RT dose on various transition states. ADT significantly reduced the incidence (24% vs 16%, $p < 0.0001$) and delayed the onset of distant metastasis from a cRF state (27.1 vs 48.5 mo, $p < 0.0001$) in high-risk patients. However, ADT did not significantly reduce the rates of distant metastasis from the

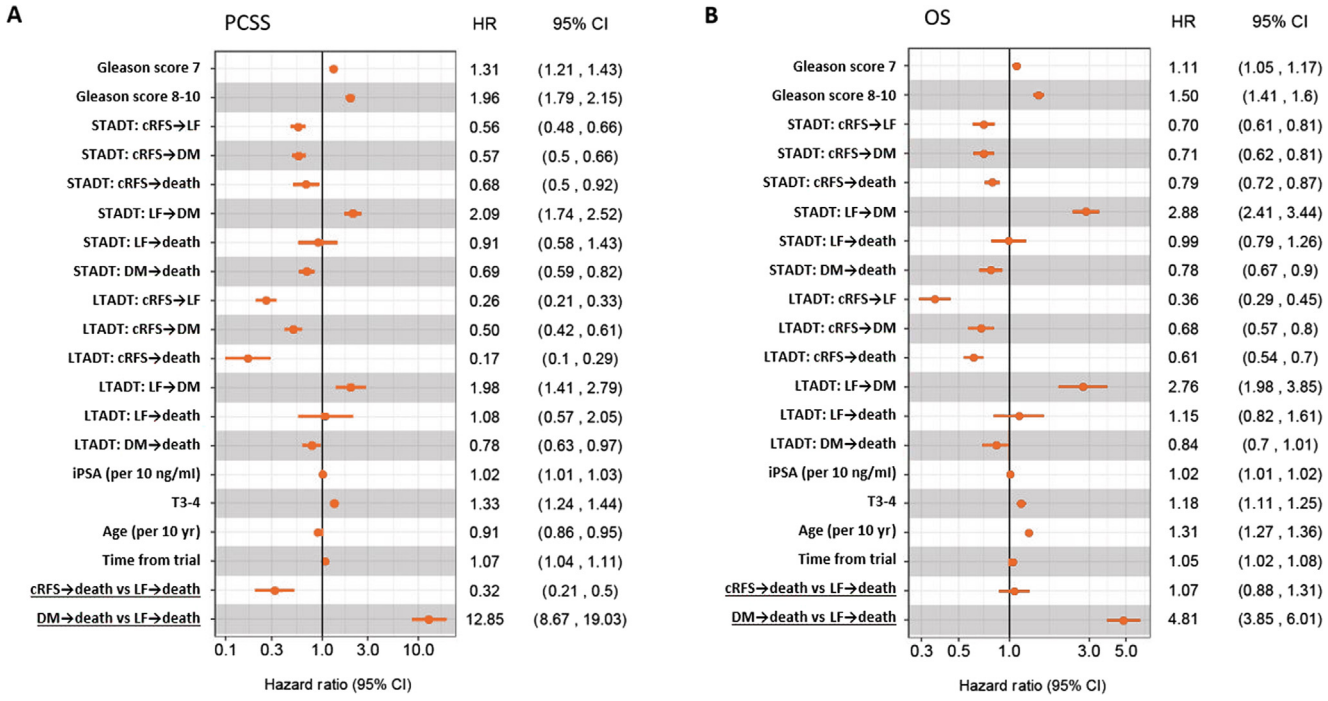

Fig. 4 – Forest plots of the Markov model for prostate cancer–specific survival and overall survival in the four-state model. T1/2 and Gleason score 6 were used as the reference for their respective categories. ADT: transition state indicates that the effect is specific on the respective transition. For example, "STADT: cRFS → LF" denotes the effect of STADT specifically on the transition between the cRF state and LF state. For those without appended transition states, a homogeneous effect of the covariate across transitions was assumed. CI = confidence interval; cRFS/cRF state = clinical relapse-free state; DM = distant metastasis; HR = hazard ratio; iPSA = initial prostate-specific antigen; LF = local failure; LTADT = long-term androgen deprivation therapy; OS = overall survival; PCSS = prostate cancer–specific survival; STADT = short-term androgen deprivation therapy.

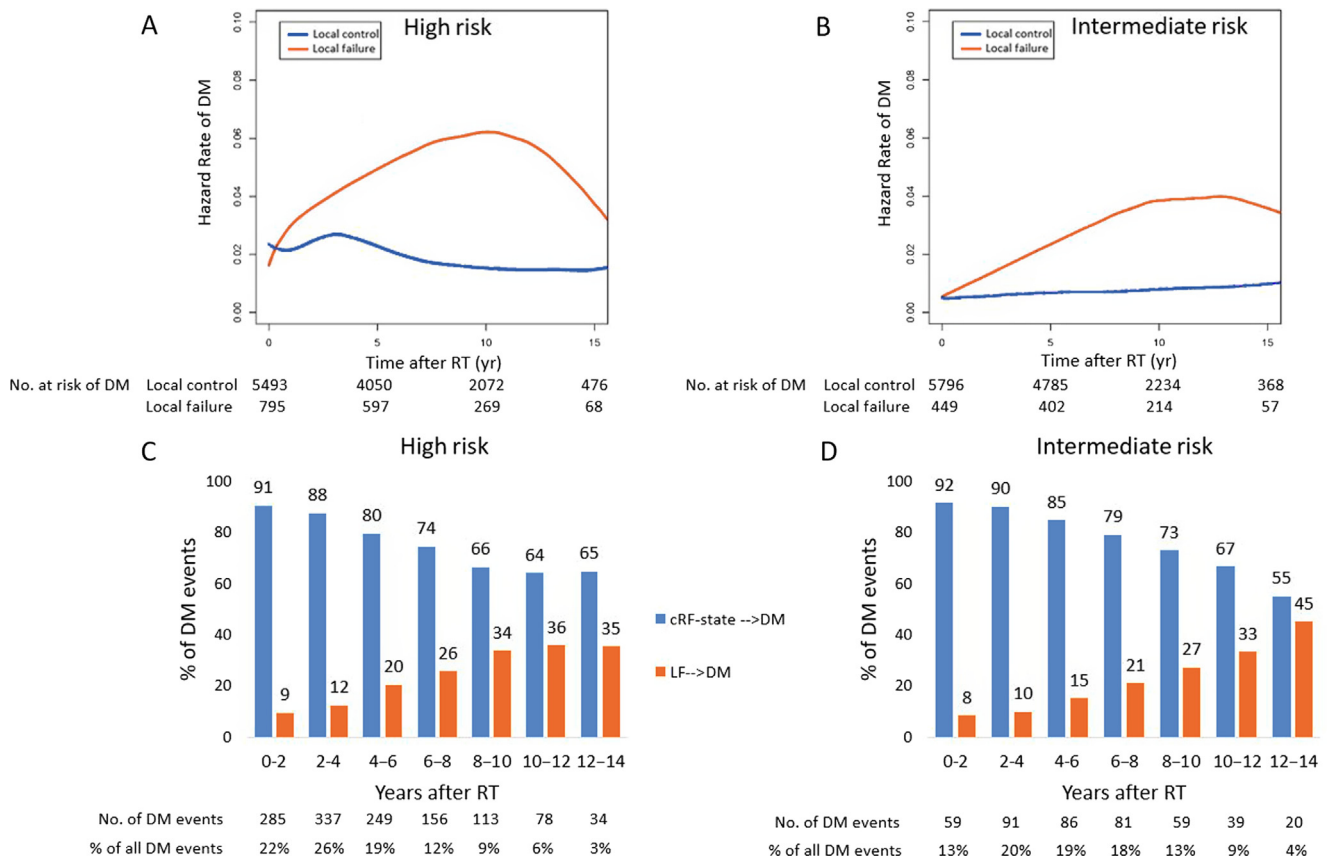

Fig. 5 – Hazard rate of distant metastasis over time and percentage of distant metastasis from a clinically relapse-free state versus a local failure state during different time periods in NCCN high- and intermediate-risk patients stratified by local failure status. Hazard rates of distant metastasis over time using kernel-based methods are shown in NCCN (A) high-risk and (B) intermediate-risk patients. Tables below the graphs indicate the number of patients who were still at a risk of distant metastasis event at different time points. Percentages of distant metastasis from a clinically relapse-free state versus a local failure state during different time periods are shown in NCCN (C) high-risk and (D) intermediate-risk patients. The percentage of distant metastasis events denotes the proportion of distant metastasis during the specified 2-yr interval after RT that was preceded by a cRF state versus an LF state. For example, for high-risk patients at 4–6 yr after RT, 80% of metastatic events arose from a cRF state and 20% from an LF state. The number of distant metastasis events below the graphs indicate the number of distant metastasis events developed in specific intervals. For example, 337 distant metastasis events developed between 2 and 4 yr after RT. Note that in Figures 5C and 5D), the percentages of all distant metastasis events below the graphs do not add up to 100% as a small percentage of patients developed distant metastases beyond 14 yr after RT. cRF state = clinically relapse-free state; DM = distant metastasis; LF = local failure; NCCN = National Comprehensive Cancer Network; RT = radiation therapy.

cRF state (6.4% vs 5.4%, $p = 0.13$) or delay the time from the cRF state to distant metastasis for intermediate-risk patients (60.3 vs 61.8 mo, $p = 0.24$). ADT significantly decreased the local failure rate from a cRF state in both high-risk (11% vs 20%, $p < 0.0001$) and intermediate-risk (6.2% vs 7.8%, $p = 0.017$) patients. Compared with low-dose RT, high-dose RT significantly decreased the local failure rate from a cRF state in high-risk (12% vs 8.0% for low- vs high-dose group, $p = 0.0007$) and intermediate-risk (8.6% vs 3.7%, $p < 0.0001$) patients. The proportions of distant metastasis developed after local failure in regard to the total number of distant metastasis events were significantly reduced with high-dose RT for both high-risk (12% vs 20%, $p = 0.0035$) and intermediate-risk (13% vs 22%, $p = 0.019$) PCa patients. The hazard rate of distant metastasis over time in patients treated with RT only, RT + STADT, and RT + LTADT in high- and intermediate-risk patients is shown in Supplementary Fig. 10. Two waves of distant metastases were seen in high-risk patients treated without ADT; the first wave was reduced, while the second wave was delayed by STADT; only delayed first wave was seen in patients treated with LTADT with no discernable second wave.

3.2. Discussion

In this individual patient-level pooled analysis of 18 randomized trials, we demonstrate that the vast majority of distant metastasis events (>80%) occur in patients who are clinically relapse free. Local failure events, however, portend a poor prognosis in both patients with high-risk disease (for whom it is associated with OS, PCSS, and DMFS) and those with intermediate-risk disease (for whom it is associated with DMFS). We also identified a biphasic pattern of distant metastasis development wherein an initial large first wave of distant metastases was followed years later by a smaller second wave occurring subsequent to the time when the majority of local failure events occurred. The proportion of distant metastasis events arising from a cRF state decreased steadily, while the proportion occurring after a local failure event increased over time. Finally, we

demonstrated that the upfront use of ADT in patients with high-risk disease decreased distant metastasis development irrespective of whether the distant metastases originated from the cRF state or the local failure state, while dose escalation reduced only the development of local failure from the cRF state.

These data provide a framework for understanding the patterns of clinical relapse in high- and intermediate-risk PCa, and how different treatment intensification strategies might alter these relapse patterns. The major mode of distant metastasis development is from a cRF state, likely representing the emergence of occult micrometastatic disease that was present at the time of initial treatment. This can be suppressed with the use of upfront ADT and/or androgen receptor signaling inhibitors such as abiraterone [36,37]. A smaller proportion of distant metastasis events—albeit one that grows with time—emerges after a local failure event has occurred. This proportion can be minimized with the use of both upfront ADT and higher-dose RT; together these would be expected to improve local control. Local failure events, when these occur, are associated with a worse prognosis. Mechanistically, this might be either because they directly seed subsequent distant metastasis events or because cancers that relapse locally may simply be more aggressive and thus also more likely to metastasize. In support of the former possibility is the distinct temporal pattern of distant metastasis development among patients with and without local failure, as well as the increasing rate of distant metastasis over time in patients with local failure. Interestingly, we also observed that a minority of local failure events developed after distant metastases (8.3% and 4.7% of local failure events in high- and intermediate-risk patients, respectively; Fig. 2A and 2C), raising the possibility that distant metastasis may seed a second wave of local failure, as observed in a whole-genome sequencing study [38]. A schematic depiction of transitions over time for patients with high-risk disease, as well as potential effects of ADT use and RT dose escalation, is shown in Supplementary Fig. 11. The peak distant metastasis rate was within 2–4 yr of RT completion, with most events arising from a cRF state. The smaller-amplitude second wave was seen approximately 6–10 yr after RT completion, and coincided with the rise in distant metastases in patients with local failure and increase in local failure to distant metastasis transitions. The true amplitude of the second wave may be underestimated here given relatively short follow-up time of certain trials. The first wave was reduced in amplitude and delayed by the addition of ADT, with LTADT having more dramatic effect than STADT. The second wave was also delayed by STADT, while no discernable second wave was observed with LTADT (Supplementary Fig. 10). For patients with intermediate-risk disease, no first wave of distant metastasis was seen, likely due to a lower prevalence of occult metastatic disease at presentation substantiated by studies using PSMA PET/CT [39]. Occult metastatic disease exists in a measurable proportion of unfavorable intermediate-risk patients, given early rise in distant metastasis rates within the first 12 mo after STADT seen in RTOG 9408 [40], which is diluted out by minimal occult metastatic disease in the favorable intermediate-risk patients [40], explaining the absence of first wave seen in the combined cohort in the current study. While a second wave was not noticeably present in intermediate-risk patients, a late-onset increase in local failure to distant metastasis transition events and an increase in the proportion of distant metastasis events arising from the local failure state over time were still observed, consistent with the concept of distant seeding from local failure events. As would be expected with this framework, dose escalation alone without ADT is unlikely to robustly augment DMFS as the predominant mode of distant metastasis is from the cRF state, and not from local failure. On the contrary, ADT prevents the development of distant metastasis by inhibiting both the cRF state to distant metastasis transition and the cRF state to local failure transition. This is consistent with the observation that ADT has both a cytostatic and a cytotoxic effect [41,42], and synergizes with RT for optimal PCa cell killing [43,44]. The effect of ADT on the cRF state to distant metastasis transition in patients with intermediate-risk disease was not significant, although the low event rate likely impacted the power to detect a significant difference, and multiple other lines of evidence suggest that upfront ADT certainly limits the development of distant metastasis events in patients with intermediate-risk disease [19,40]. Emerging strategies, such as focal microboosts, may be associated with lower rates of regional failure, although a significant change in distant metastatic failure has not been reported [45].

The present study has several limitations. First, despite pooling across multiple trials, some treatment subgroups remained small in size, potentially limiting the statistical power of subgroup analysis and generalizability. For example, only 10% of high-risk patients received high-dose RT plus ADT. Second, heterogeneity between trials is also a limitation for a pooled analysis in general, including the current study. We have attempted to mitigate this by using random effects in our modeling [46]. Third, there was heterogeneity in the definition of local failure and distant metastasis across trials (Supplemental Table 1). Some trials did not specify the definition, while some were reliant on digital rectal examination to determine the local failure status. Certain trials (eg, RTOG 9902) included regional lymph node involvement in the definition of local failure. Nonuniform definition of local failure and PSA-driven imaging also likely impacted the reliability of cRF-state determination in certain cases. However, trials with nonconventional definitions remained a minority. Fourth, incorporating post-treatment prostate biopsy [47,48] and/or advanced imaging such as multiparametric magnetic resonance imaging and PSMA PET/CT at different stages would likely alter the proportion of patients labeled as having local failure or distant metastasis events. Not all patients underwent ascertainment of local failure at the time of recurrence. Therefore, the local failure rate in our study is most likely underestimated. RTOG 9408 showed a 2-yr post-RT repeat prostate biopsy positive rate of 20–39% in a patient population of mixed-risk groups treated with or without ADT [49]; this is considerably higher than the 13% local failure rate in high-risk patients in the current study, although the RT dose used in RTOG 9408 was low (66.6 Gy in 37 fractions) and

positive biopsies may represent inactive tumor cells with severe treatment effect. For example, for PSMA PET/CT, when used at initial staging, the first wave of distant metastases may diminish in amplitude as more patients with occult metastatic disease would have been detected and excluded from the study; when used at local failure, more distant metastases would be detected concurrently, reducing the rate of local failure to distant metastasis transition while increasing the rate of the cRF state to distant metastasis transition. Potentially, this may augment the outcomes of our models and their implications on the impact of treatment modification (dose escalation, focal boost, and ADT) on distant metastasis and PCSS outcomes. Fifth, we could not distinguish local disease that had a complete response initially after RT but subsequently recurred (true local recurrence) from local disease that never achieved a complete response (locally persistent disease), and the latter may be more biologically aggressive and may exhibit a different clinical phenotype including the propensity for distant metastasis. We were also unable to definitely distinguish a local recurrence stemming from the original prostate tumor or a new primary, especially for a delayed presumed local recurrence; however, the incidence of a new primary in the prostate is likely low. Additionally, there was no uniform salvage therapy standard when local failure or distant metastasis events were discovered, and therefore heterogeneous management practices could not be accounted for. Systemic salvage therapy evolved rapidly during the follow-up periods of most trials included; thus, the transition of distant metastasis to PCSM is skewed toward earlier trials when systemic therapy was less effective. Finally, more effective systemic salvage therapies have been developed over the years, leading to a prolongation between distant metastasis and PCSM, as well as an improvement in PCSM and OS. The population studied may not be fully representative of contemporary outcomes/survival. It is uncertain whether the impact of local failure on PCSM and OS may be reduced with these more effective therapies.

4. Conclusions

This patient-level pooled analysis from 18 RCTs provides high-level evidence that local failure is an independent prognosticator of OS, PCSS, and DMFS in high-risk PCa and of DMFS in intermediate-risk PCa. With the caveat that local failure and distant metastasis may be underestimated in these trials, the predominant mode of distant metastasis development is from a cRF state for both high- and intermediate-risk PCa, likely from occult metastatic disease at presentation, underscoring the importance of accurate upfront staging and systemic therapy. This source of distant metastasis constitutes the first wave of distant metastases in high-risk patients, which occurred within the first 4 yr after the completion of RT. This is inconspicuous in intermediate-risk patients, likely due to a much smaller burden of occult metastatic disease. However, particularly at late time points, an increasing proportion of distant metastasis events originated after the diagnosis of local failure, constituting a second wave of distant metastasis events in both patients with high- and intermediate-risk disease. This suggests that in order for a regional/systemic therapy to improve long-term outcome, local control needs to be also optimized to minimize the second wave and vice versa. Finally, ADT reduces the development of distant metastases from a cRF state and indirectly from a local failure state by reducing local failure, while higher-dose RT impacted only the local failure rate, consistent with the observation that ADT has a more significant impact on DMFS irrespective of the RT dose than RT dose escalation.

***Author contributions*:** Amar U. Kishan 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: Ma, Kishan, Chu, Spratt.
Acquisition of data: All authors.
Analysis and interpretation of data: Ma, Kishan, Chu.
Drafting of the manuscript: Ma, Kishan, Chu.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Ma, Kishan, Chu.
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