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Radiotherapy- Versus Surgery-based Treatment Strategy in High-risk Prostate Cancer

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Abstract

Background and objective: Optimal management for high-risk prostate cancer is unclear. Using individual patient data from two contemporaneous North American cooperative group phase 3 randomized controlled trials (RCTs), we compared the outcomes of high-risk prostate cancer patients treated with radiotherapy-based and radical prostatectomy (RP)-based treatment strategies.

Methods: Data were collected from newly diagnosed high-risk prostate cancer patients enrolled in NRG/RTOG 0521 who received radiotherapy-based treatment (2005–2009), and those enrolled in CALGB 90203 who received surgery-based treatment (2006–2015). Patients received radiotherapy plus 24 mo of androgen deprivation therapy (ADT) ± six cycles of adjuvant docetaxel versus RP with personalized postoperative therapy ± neoadjuvant six cycles of docetaxel and 18–24 wk of ADT. The primary objective was to compare the cumulative incidence of distant metastasis considering death as a competing event using the inverse probability of treatment weighting (IPTW).

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Key findings and limitations: Overall, 1290 patients (radiotherapy $n = 557$, RP $n = 733$) were included with similar follow-up (median 6.4 [interquartile range {IQR}: 5.6–6.9] yr and 6.4 [IQR: 4.7–8.5] yr, respectively). Patients who received surgery had generally more favorable prognostic features and were younger relative to those who received radiotherapy. After IPTW, the cumulative incidence of distant metastasis was significantly lower in patients who underwent radiotherapy-based compared with RP-based treatment (8-yr distant metastasis: 15% [95% confidence interval {CI} 9.3–21] vs 22% [95% CI 18–26]; adjusted subdistribution hazard ratio [sHR] 0.58 [95% CI 0.42–0.81]; $p = 0.001$). We did not find any significant difference in the incidence of deaths after distant metastasis (adjusted sHR 0.98 [95% CI 0.61–1.58]) between the two groups.

Conclusions and clinical implications: High-risk prostate cancer patients enrolled in RCTs had a significantly lower incidence of distant metastasis with a radiotherapy-based treatment strategy than with an RP-based treatment strategy, while the risk of deaths after distant metastasis was similar in the two groups.

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ADVANCING PRACTICE

What does this study add?

We used individual patient data from two contemporaneous North American phase 3 randomized controlled trials: NRG/ RTOG 0521 and CALGB 90203. Using inverse probability of treatment weighting, we found that a radiotherapy-based treatment approach was associated with a significantly lower risk of distant metastasis than a surgery-based approach. However, there was no significant difference in the risk of cancer-specific mortality between the two treatment strategies.

Clinical Relevance

This study provides critical insights into the management of high-risk prostate cancer by demonstrating that radiotherapy-based treatment strategies may significantly reduce the incidence of distant metastasis compared to surgery-based approaches. These findings are relevant for clinicians as it highlights the necessity of personalized postoperative therapy and the potential benefits of systemic treatment intensification, thereby enhancing the overall treatment paradigm for high-risk prostate cancer patients. Randomization data remains awaited (as the SPCG-15 will provide) given the selection biases inherent to such treatment comparisons. Associate Editor: Guillaume Ploussard.

Patient Summary

When treated with radiotherapy plus 24 mo of androgen deprivation therapy, patients with high-risk prostate cancer appeared to have a lower incidence of distant spread than those who were treated with guideline concordant radical prostatectomy followed by personalized postoperative therapy. However, the risk of deaths after distant spread was similar between these two strategies.

1. Introduction

High-risk prostate cancer accounts for most deaths among men who are diagnosed with localized disease [1]. Guidelines support the use of radiotherapy (RT) plus long-term androgen deprivation therapy (LT-ADT) or radical prostatectomy (RP) with lymphadenectomy and personalized use of postoperative therapy for the treatment of high-risk prostate cancer [2–11]. These treatment pathways differ in multiple ways beyond the local therapy itself, including patient selection, concomitant use of systemic therapy, definitions of biochemical recurrence (BCR), and utilization of adjuvant and salvage therapy.

In absence of level 1 evidence comparing an RT- versus RP-based strategy for high-risk prostate cancer, several

comparative effectiveness studies have been reported with discordant results [12–18]. These studies have variable data quality from retrospective institutional studies or population-based registries, loss of follow-up, missing data, nonstandardized treatment, limited data on the use and duration of ADT with RT, and a selection bias that limits the confidence in these findings [19–21]. Data collected under controlled circumstances in the context of multicentric randomized controlled trials (RCTs) have superior quality and completeness, and higher compliance rates with a priori standardized treatment and follow-up.

We hypothesized that the use of individual patient data (IPD) from RCTs could potentially mitigate some of the above limitations noted in prior retrospective studies and add clarity in evaluation of the optimal therapeutic strategy

for high-risk prostate cancer. Herein, we performed the first IPD analysis, to our knowledge, of two contemporaneous RCTs to compare the outcomes of patients with high-risk prostate cancer treated with an RT- versus RP-based approach.

2. Patients and methods

A systematic literature search was performed using MEDLINE (1966–2022), Embase (1982–2022), trial registries (Cochrane Central Register of Controlled Trials and [ClinicalTrials.gov](https://clinicaltrials.gov)), and major urology and oncology conference proceedings (1990–2022) to retrieve multicentric cooperative group RCTs in which National Comprehensive Cancer Network (NCCN)-defined high-risk prostate cancer patients (clinical tumor stage T3–T4, prostate-specific antigen [PSA] >20 ng/ml, and/or Gleason score 8–10) were treated with a standard-of-care arm of an RT- or RP-based regimen. To further reduce the potential bias, we limited our search to trials that evaluated similar experimental treatments. The identified trials were then screened for those with both contemporaneous enrollment and enrollment in the same country. Two RCTs were identified that met the inclusion criteria. After data sharing agreements had been approved, IPD were collected from the NRG/Radiation Therapy Oncology Group (RTOG) 0521 and Cancer and Leukemia Group B (CALGB) 90203 (Alliance) randomized phase 3 trials [22,23].

2.1. Treatment groups

2.1.1. RT cohort

The RT cohort for the present study comprised patients in NRG/RTOG 0521 (NCT00288080) enrolled between December 2005 and August 2009. This was a multicentric phase 3 RCT that included patients with a Gleason score of 9–10, or a Gleason score of 7–8 and PSA >20 ng/ml with any T stage, or a Gleason score of 8 and PSA <20 ng/ml with T stage \geq cT2. The maximum allowed PSA level was 150 ng/ml [23]. Patients were assigned randomly to 24 mo of LT-ADT with RT (72–75.6 Gy) including elective nodal RT with or without six cycles of docetaxel and prednisone. Docetaxel (75 mg/m² body surface area every 3 wk) was administered concurrently with ADT beginning 28 d after the completion of RT. Patients were followed with PSA at 4 and 7 mo after ADT initiation and then every 3 mo until the end of year 2, every 6 mo until year 5, and annually thereafter.

2.1.2. RP cohort

The RP cohort for this study comprised patients in the CALGB 90203 trial (NCT00430183). This was a multicentric phase 3 RCT that enrolled patients (between December 2006 and October 2015) with cT1–3a, PSA \leq 100 ng/ml, no radiographic evidence of metastases, and either Gleason score 8–10 or Kattan preoperative nomogram-based probability of <60% biochemical progression-free survival at 5 yr after RP [22,24]. Patients were randomized to RP with either extended lymph node dissection alone or six cycles of neoadjuvant docetaxel (75 mg/m² body surface area every 3 wk) with ADT for 18–24 wk (neoadjuvant chemohormonal therapy). Patients with positive surgical margins

could receive, at the discretion of the treating physician, adjuvant RT to the prostatic fossa and/or whole pelvis with up to 4 mo of concomitant ADT. Salvage treatment was allowed prior to BCR, which usually consisted of postoperative RT with or without ADT. After RP, PSA levels were checked every 3 mo for 3 yr, then every 6 mo for 3 yr, and annually thereafter.

2.2. Objectives

The primary objective of the present study was to compare the risk of distant metastasis (DM) between treatment groups considering deaths as competing events. The secondary objectives included the cumulative incidence of BCR considering PSA progression (as defined in the respective trial) or the onset of salvage therapy prior to reaching BCR as events of interest. Additional endpoints included progression considering BCR and/or DM as an event. Death from any cause was considered as a competing event for these endpoints. We also compared the cumulative incidence of prostate cancer-specific (PCSM) and other-cause (OCM) mortality.

To harmonize trial definitions, PCSM was examined using two different definitions. The primary definition of PCSM (PCSM1) was death after progression, and the secondary definition was death after DM (PCSM2). Owing to the expected higher OCM in RT patients due to the established selection bias, OCM was evaluated to understand the extent of this bias. OCM was also defined and reported separately using two definitions. The primary definition of OCM (OCM1) was death without progression, and the secondary definition was death without DM (OCM2). Patients who were event free were censored on the last date of follow-up or the date of last follow-up with known disease status.

2.3. Statistical analyses

Primary analyses included the entire cohort of patients in both trials who received the intended primary treatment without missing data for key variables (PSA, T stage, and biopsy Gleason score). To minimize differences in measured covariable differences in each cohort, inverse probability of treatment weighting (IPTW) was performed to compare groups. To apply IPTW, a multivariable logistic regression model was applied to estimate the propensity scores. The covariables included age, biopsy Gleason score, race, baseline PSA, and tumor stage.

Multivariable Fine and Gray's regression models without and with IPTW were applied for DM to estimate adjusted subdistribution hazard ratios (sHRs) with 95% confidence intervals (CIs). Proportionality assumptions were verified using the Grambsch-Therneau test. To determine the consistency of the treatment effect, comparisons were performed across subgroups based on age (<60, 60–70, and >70 yr), Gleason score (<8, 8, and 9–10), PSA (<10, 10–20, and >20 ng/ml), and T stage (T1–T2 and T3–T4); across risk groups based on the NCCN high-risk and very-high-risk definitions based on the Systemic Therapy for Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial (at least two of the following risk factors:

T stage T3-T4, Gleason score 8–10, and PSA \geq 40 ng/ml); and across randomly assigned treatment arms [25]. Similar methods were undertaken for all the secondary endpoints. The inverse probability of treatment-weighted restricted mean time lost (RMTL) up to a truncation time point of 8 yr since random assignment was estimated for all endpoints. In the presence of a competing risk, the RMTL is the area under the cause-specific cumulative incidence function and is robust to violation of proportionality assumption [26].

Sensitivity analyses were performed to assess the robustness of our primary findings. Given that the RP cohort had generally more favorable baseline prognostic features, we restricted the comparison to patients who met the inclusion criteria for both trials, which excluded the more favorable prognostic risk patients in the CALGB trial not eligible for the NRG/RTOG 0521 trial. A two-sided p value of <0.05 was considered statistically significant, although we have primarily focused on point estimate and CIs instead of p values given the exploratory nature of our analyses. All statistical analyses were performed using R version 4.4.1 (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient and study characteristics

Fig. 1 demonstrates the CONSORT diagram for the patients included in this study. In the RT cohort, six patients were excluded from NRG/RTOG 0521 due to not receiving RT, leaving 557 patients (278 received RT + LT-ADT and 279 received RT + LT-ADT with docetaxel). In the RP cohort, 55

patients were excluded from CALGB 90203, of whom 50 did not undergo RP and five were missing baseline PSA data, leaving 733 patients for analyses. In the RP-alone cohort ($n = 367$), 75 (20%) had adjuvant RT and 179 (49%) had additional treatment. Overall, 39 (11%) patients had both adjuvant RT and additional treatment. In the cohort receiving neoadjuvant chemohormonal therapy followed by RP ($n = 366$), 57 (16%) had adjuvant RT and 143 (39%) had additional treatment. Overall, 20 patients had both adjuvant RT and additional treatment.

Patients in the RT cohort were significantly older than patients in the RP cohort (median age 66 yr [interquartile range {IQR}: 57–67] vs 63 yr [IQR: 60–72]; Table 1). Approximately 50% had Gleason 9–10 prostate cancer in both treatment cohorts. A higher proportion of patients within the RT cohort had cT3-T4 (27% vs 17%), and median baseline PSA was higher in the RT cohort (15 vs 10 ng/ml). Median follow-up was similar between the RT and RP cohorts (6.4 yr [IQR: 5.6–6.9] and 6.4 yr [IQR: 4.7–8.5], respectively).

The distribution of propensity scores and weights for the full cohort, and balance of covariates before and after IPTW are summarized in Supplementary Figs. 2–6 and Supplementary Table 1. The effective sample size was, respectively, 589 and 433 in the two cohorts.

3.2. Primary objective

RT cohort patients had a significantly lower cumulative incidence of DM than RP cohort patients across all tested analytical methods, with consistent findings on subgroup and sensitivity analyses (Fig. 2 and 3). The IPTW-based

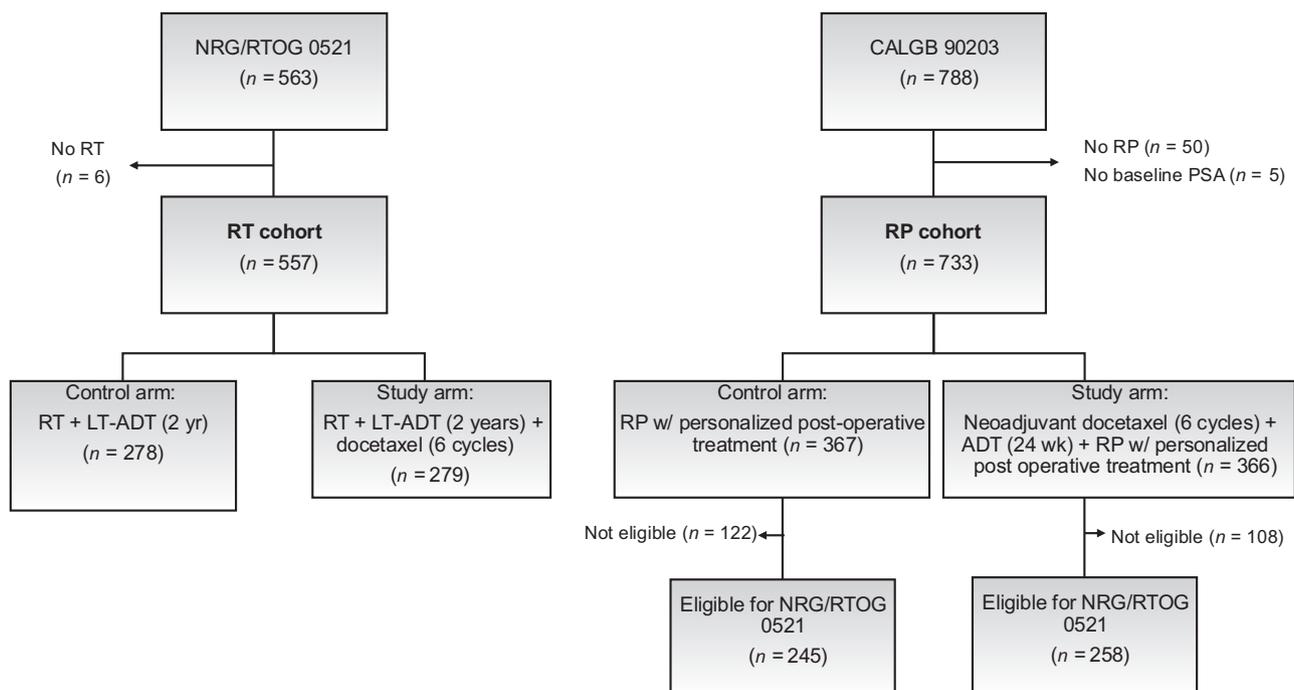


Fig. 1 – CONSORT Diagram. LT-ADT = long-term androgen deprivation therapy; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy; w/ = with.

Table 1 – Baseline characteristics of the study cohort

	Cohort with RP-based treatment (n = 733)	Cohort with RT-based treatment (n = 557)	p value
Age			<0.001
Median (IQR)	63 (57–67)	66 (60–72)	
Range	33–84	46–83	
<60 yr, n (%)	270 (37)	132 (24)	
60–70 yr, n (%)	394 (54)	252 (45)	
>70 yr, n (%)	69 (9)	173 (31)	
Race, n (%)			0.33
White	626 (85)	487 (87)	
Non-White	107 (15)	70 (13)	
Biopsy Gleason score, n (%)			0.03
6–7	93 (13)	89 (16)	
8	279 (38)	176 (32)	
9–10	361 (49)	292 (52)	
Clinical tumor stage, n (%)			<0.001
T1–T2	606 (83)	405 (73)	
T3–T4	127 (17)	152 (27)	
Baseline PSA			<0.001
Median (IQR)	10 (6.0–20)	15 (7.0–34)	
<10 ng/ml, n (%)	371 (51)	202 (36)	
10–20 ng/ml, n (%)	175 (24)	119 (21)	
>20 ng/ml, n (%)	187 (25)	236 (43)	
Risk groups, n (%)			<0.001
High (NCCN)	578 (79)	379 (66)	
Very high (STAMPEDE) ^a	155 (21)	178 (34)	

IQR = Interquartile range; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy; STAMPEDE = Systemic Therapy for Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.

^a The definition of very high risk was used from STAMPEDE (two or more of the following risk factors: cT3–4, Gleason 8–10, and PSA >40 ng/ml). N1 patients were not included in this definition.

cumulative incidences of DM in the RP and RT cohorts at 8 yr were 22% (95% CI 18–26) and 15% (95% CI 9.3–21), respectively ($p = 0.004$; Fig. 2A). On multivariable competing risk regression without IPTW, the RT cohort had a significantly lower risk of DM than the RP cohort (sHR 0.57, 95% CI 0.42–0.79; $p < 0.001$), which was consistent across subgroups (Fig. 3). The results were similar on multivariable competing risk regression with IPTW (adjusted sHR 0.58, 95% CI 0.42–0.81; $p = 0.001$; Fig. 4).

When restricting the analysis to patients eligible for both trials ($n = 1060$; Fig. 1), the baseline characteristics before and after matching are summarized in Supplementary Table 2, and Supplementary Figs. 7 and 8. The cumulative incidence of DM was significantly lower in the RT group on multivariable competing risk regression with IPTW (adjusted sHR 0.60, 95% CI 0.43–0.84; Supplementary Fig. 9).

3.3. Subgroup analyses

To compare the current standard-of-care treatments, the control arms of both trials (RP with personalized postoperative treatment vs RT + LT-ADT) were assessed (Fig. 2B). At 8 yr, the IPTW-based cumulative incidence of DM was 18% (95% CI 11–23) in the RT plus long-term ADT cohort and 24% (95% CI 18–30) in the RP plus personalized postoperative treatment cohort, with significant difference in the risk on a multivariable analysis with IPTW (adjusted sHR 0.62, 95% CI 0.40–0.96). Likewise, when comparing the docetaxel arms (ie, study arms), patients treated with RT plus long-

term ADT plus docetaxel had significantly lower rates of DM (an 8-yr IPTW-based DM rate of 13% [95% CI 2.4–22]) relative to 20% [95% CI 14–25] in the cohorts receiving neoadjuvant chemohormonal therapy plus RP with personalized postoperative treatment; Fig. 2C). RT-treated patients had a significantly lower risk of DM on the multivariable analysis with IPTW (adjusted sHR 0.48, 95% CI 0.28–0.82).

To compare the maximal surgical strategy (neoadjuvant chemohormonal therapy plus RP with selective postoperative treatment) with the standard-of-care RT plus LT-ADT arm, we performed a cross-arm comparison of the control arm of the NRG/RTOG 0521 trial (ie, RT + LT-ADT arm) versus the study arm of the CALGB trial (ie, neoadjuvant chemohormonal therapy and RP with personalized postoperative RT). The 8-yr IPTW-based rates of DM were 18% (95% CI 11–23) versus 20% (95% CI 14–25; Fig. 2D), with no significant difference on the multivariable analysis with IPTW (adjusted sHR 0.96, 95% CI 0.61–1.49).

3.4. Secondary objectives

The findings related to the secondary objectives are shown in Fig. 4. In the overall cohort, BCR rates were significantly lower in the RT cohort (8-yr IPTW-based incidence rates: 32% [95% CI 26–36] vs 68% [95% CI 64–72]; IPTW adjusted sHR 0.24, 95% CI 0.20–0.30). Similarly, the cumulative incidence of progression was significantly lower in RT-treated patients (8-yr IPTW-based incidence rates: 35% [95% CI 29–40] vs 74% [95% CI 69–78]; IPTW adjusted sHR 0.24, 95% CI 0.20–0.30). However, definitions of BCR are different in the post-RP versus post-RT setting.

No significant differences were noted for either definition of PCSM between groups. Death after progression (IPTW adjusted sHR 0.85, 95% CI 0.54–1.32) and death after DM (IPTW adjusted sHR 0.98, 95% CI 0.68–1.58) were not significantly different between the RT and RP cohorts.

Patients who received RT treatment had significantly higher and early differences in OCM with varying effect sizes based on the definition used. For example, the risk of death without progression was significantly higher in the RT group (8-yr IPTW-based cumulative incidence 11% [95% CI: 7.5–14] vs 1.8% [95% CI: 0.5–3.1]; IPTW adjusted sHR 4.99, 95% CI 2.77–9.02), as was the risk of death without DM (14% [95% CI 9.3–18] vs 6.0% [95% CI 3.3–8.6]; IPTW adjusted sHR 2.28, 95% CI 1.35–3.84). The cumulative incidence curves for the secondary endpoints and RMTL-based findings for the subgroups have been summarized in Supplementary Figs. 10–15 and Supplementary Tables 3–5.

4. Discussion

To our knowledge, we report for the first time a comparison of IPD from two phase 3 RCTs with contemporaneous enrollment to determine the clinical outcome differences between common treatment approaches for men with high-risk prostate cancer. Our results indicate that the use of an RT-based approach renders a significantly lower risk of DM than an RP-based approach. This observation was true for IPTW cumulative incidence, RMTL, multivariable analyses without and with IPTW (doubly robust), and sensi-

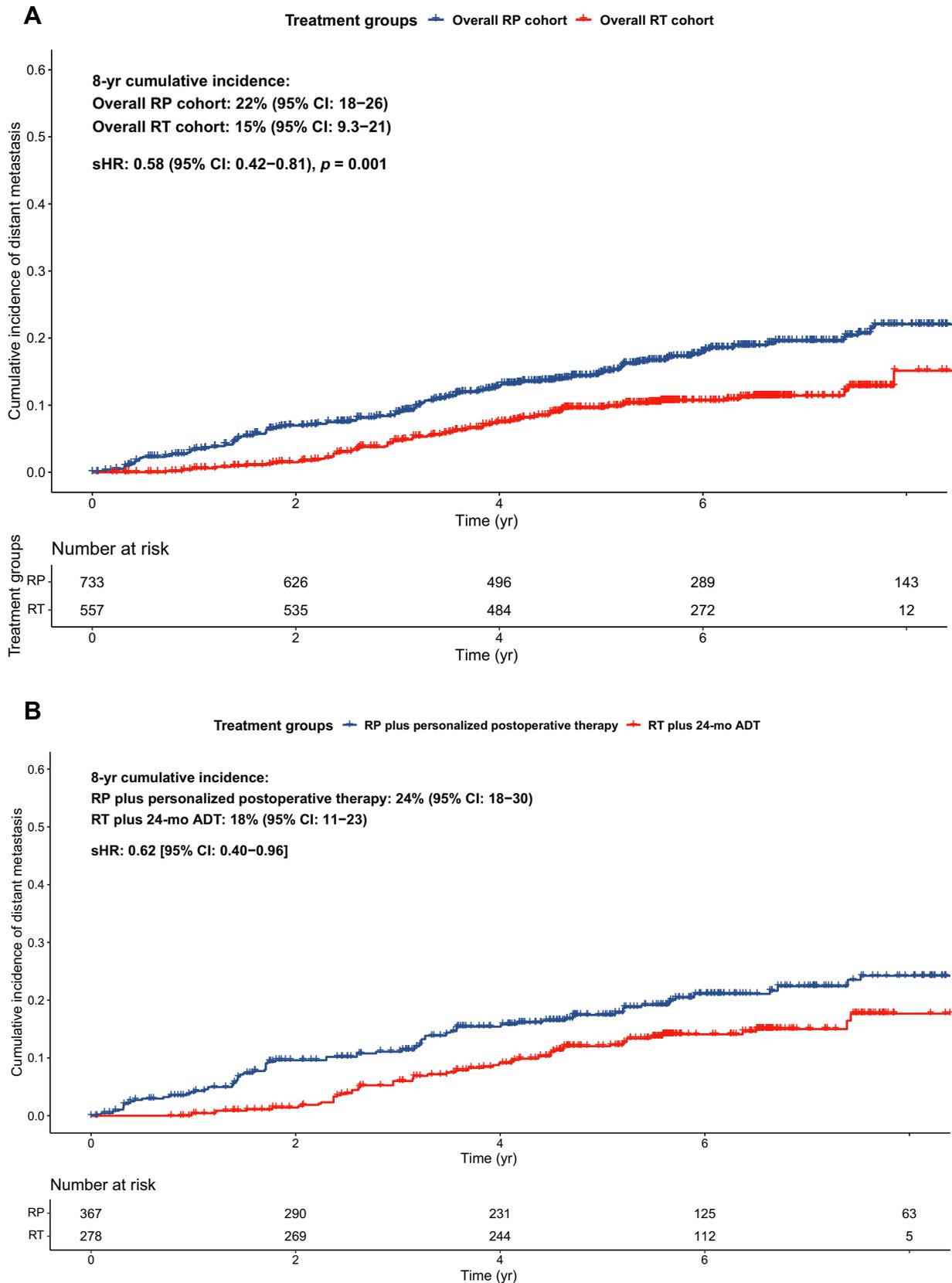


Fig. 2 – Cumulative incidence of distant metastasis with inverse probability of treatment weighting (IPTW) in the (A) RP and RT cohorts from the overall study population, (B) standard-of-care arms of RP plus personalized postoperative treatment versus RT plus long-term ADT for 24 mo, (C) experimental arms of neoadjuvant chemohormonal therapy plus RP plus personalized postoperative treatment versus RT plus long-term ADT plus adjuvant docetaxel, and (D) cohorts with neoadjuvant chemohormonal therapy plus RP plus personalized postoperative treatment versus RT plus long-term ADT. ADT = androgen deprivation therapy; CI = confidence interval; RP = radical prostatectomy; RT = radiotherapy; SHR = subdistribution hazard ratio.

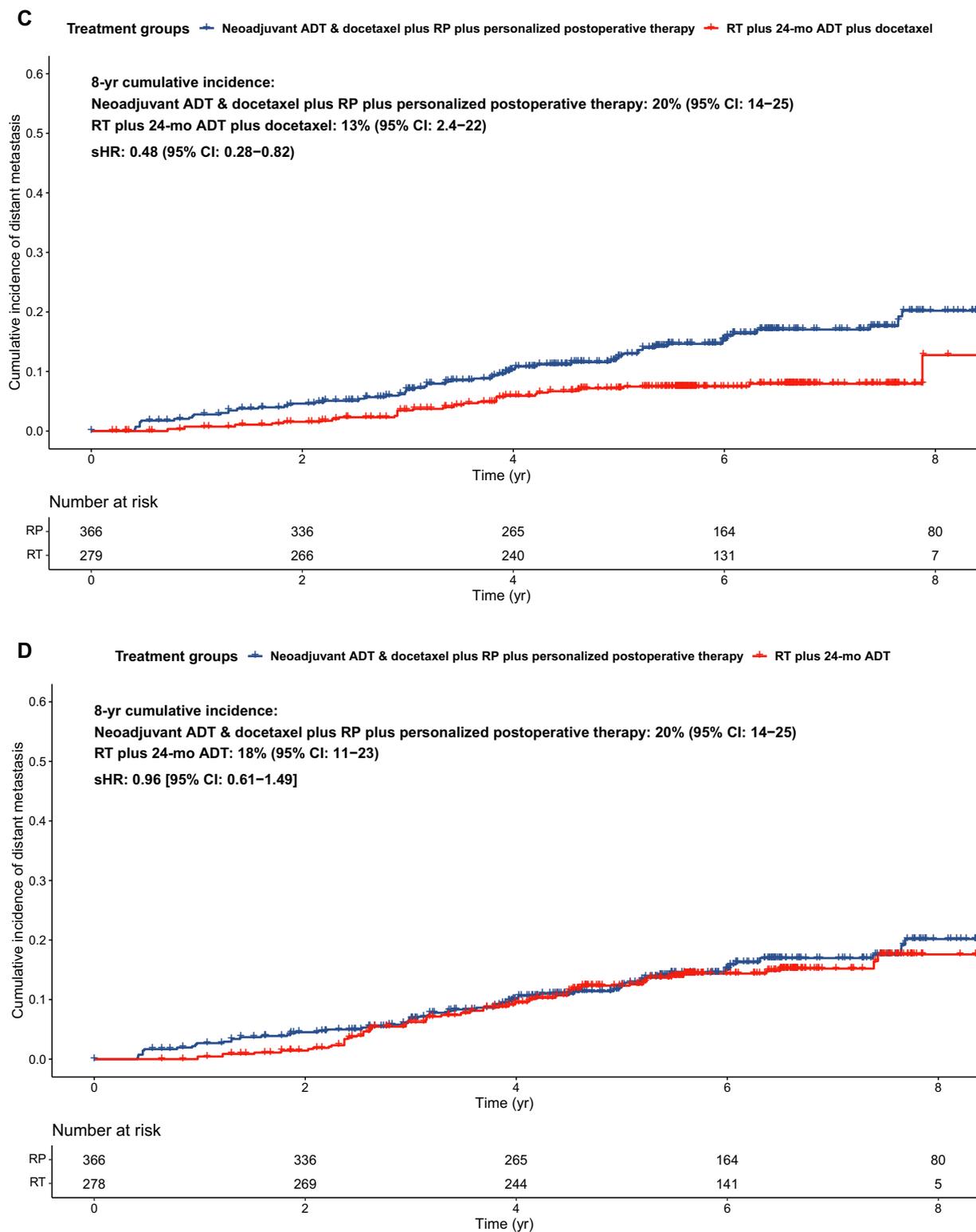


Fig. 2 (continued)

tivity analyses and when explored across subgroups. These findings warrant discussion on the potential drivers of this observation.

The difference in the treatment groups should be viewed beyond the local therapy solely and explained in the context of multimodality treatment. LT-ADT is combined with RT in

high-risk prostate cancer due to an overall survival benefit relative to RT alone or RT plus short-term ADT (ST-ADT) [3]. However, analogous trials of ST-ADT versus LT-ADT have not been performed in RP-treated patients, and trials of RP ± ADT were often conducted for favorable-risk disease and thus did not confer meaningful benefits [27]. Therefore,

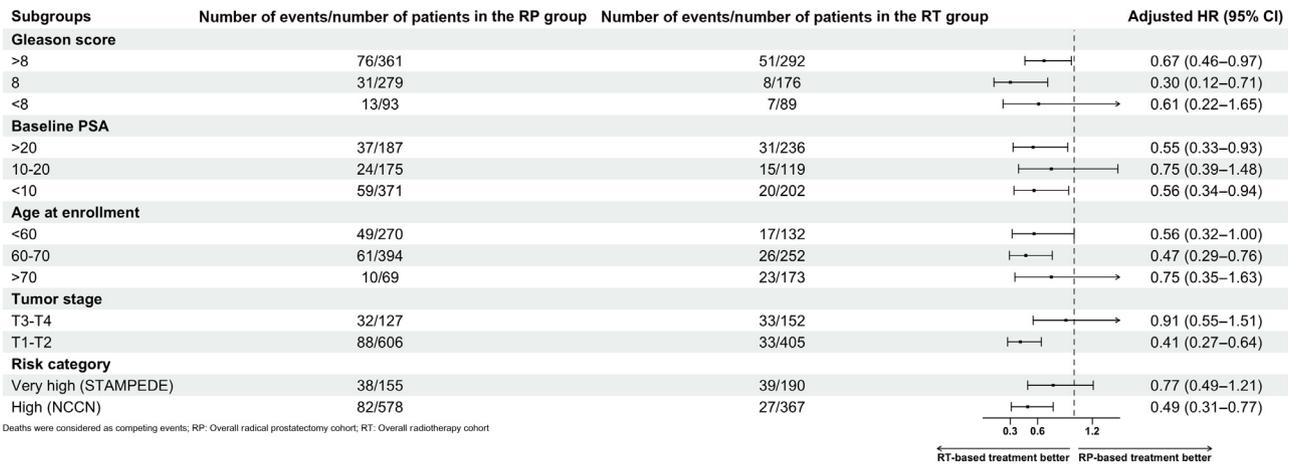


Fig. 3 – Forest plot summarizing the consistency of subdistribution hazard ratio for distant metastasis (RT relative to RP) across subgroups. CI = confidence interval; HR = hazard ratio; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy; STAMPEDE = Systemic Therapy for Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.

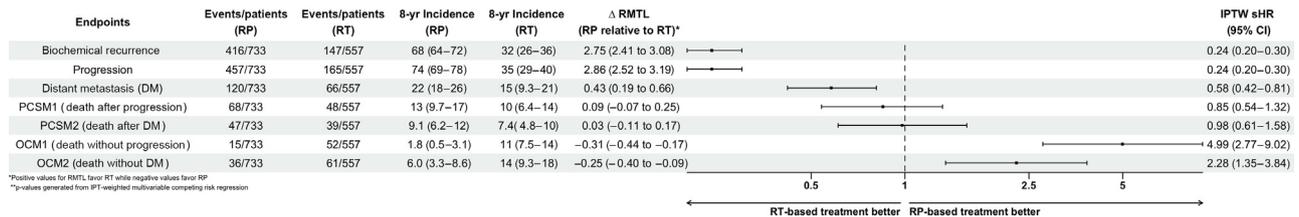


Fig. 4 – Forest plot of outcomes between RT- and RP-treated patients on IPTW adjusted multivariable competing risk regression. DM = distant metastasis; IPT = inverse probability of treatment; IPTW = inverse probability of treatment weighting; PCSM1 = primary definition of prostate cancer-specific mortality (death after progression); PCSM2 = secondary definition of prostate cancer-specific mortality (death after distant metastasis); RMTL = restricted mean time lost; RP = radical prostatectomy; RT = radiotherapy; sHR = subdistribution hazard ratio.

the use of LT-ADT in the RT cohort almost certainly impacted the emergence of DM [28]. Further, we noted that the use of triplet or quadruplet therapy (ADT, chemotherapy, RP, and postoperative RT) in the CALGB trial could confer a similar risk of DM to RT + LT-ADT. This supports the importance of systemic treatment intensification regardless of the local therapy modality, given the overall patterns of failure in high-risk prostate cancer [29].

The median follow-up duration was modest and possibly precluded any observed differences in a second wave of metastatic progression [29,30]. The follow-up could also explain why the risk of PCSM was low and similar between the two cohorts. Additionally, similar PCSM in the two groups potentially alludes to optimal salvage therapies in patients after RP. Thus, systemic treatment with RP with postoperative RT may be associated with a similar risk of PCSM to treatment with RT plus LT-ADT. However, the toxicity and cost implications of such triplet or quadruplet therapy are unclear, and at present, this is not recommended by national guidelines [31].

The importance of DM as an endpoint lies in its correlation with eventual PCSM, quality of life, and implications to treatments that carry considerable financial and potential quality of life impact [32–35]. Over the past decade, the treatment of metastatic prostate cancer has witnessed significant advancement. However, these treatments are often

lifelong and have their own morbidity with significant impact on quality of life, as noted from several RCTs [36,37]. While we had no information on patient-reported outcomes in the present study, there are thematic quality of life differences after RP or RT, such as greater erectile dysfunction and urinary incontinence after RP, and greater decline in bowel function and urinary irritative symptoms after RT [38]. Unfortunately, we have a paucity of data on the quality of life of men receiving RT + LT-ADT or RP with postoperative RT ± ADT.

In the control arm of the CALGB trial, 23% received adjuvant RT and 49% received salvage therapy, with modestly lower rates in the study arm. In high-risk patients, the use of an RP-based approach most likely warrants the use of multimodality therapy [39]. However, in the CALGB trial, approximately one-fourth of patients did not receive postoperative RT, which might have contributed to the inferior outcomes. However, in real-world high-risk prostate cancer patients, the rates of utilization of adjuvant RT (~10%) and salvage RT (~30%) after RP are considerably lower than in the CALGB trial [40–42]. Thus, methods to increase the use of postoperative RT may be relevant to optimize outcomes for patients electing to undergo RP.

A key limitation of our analysis is the lack of detailed data on salvage ADT administration. While the CALGB trial allowed for postoperative RT with or without ADT, we could

not ascertain which patients received ADT or for how long. Therefore, SPCG-15, an ongoing RCT of RT versus RP for patients with high-risk prostate cancer will be invaluable to understand the risks and benefits of each therapeutic approach comprehensively. The standard-of-care arm in the trial is the RT + LT-ADT arm, while the RP arm is considered the experimental arm given that the use of RP has been supported mostly by observational studies [43]. Baseline characteristics of the currently enrolled patients are more favorable than those of the present study. For example, 28% of patients in SPCG-15 have grade group 5 disease, whereas 50% had grade group 5 disease in the present study [43]. Thus, SPCG-15 may end up having an overall lower event rate due to enrollment of a more favorable population of patients.

The impact of prognostic risk and the differences between treatment modalities have been assessed retrospectively. Beesley et al [44] studied the outcomes for either RP- or RT-based treatments for localized prostate cancer and captured extensive data on baseline covariates. Using a myriad of statistical methods, they showed no differences in DM (termed clinical failure in their study) for patients with Gleason score <8 between the RP and RT groups, consistent with the results of the randomized ProtecT trial [45,46]. However, RT had predicted superiority over RP for patients with Gleason 8–10 disease, which is consistent with our findings.

Despite the use of two contemporaneous North American phase 3 trials with similar follow-up and similar experimental questions, there were multiple measured differences in baseline covariate distribution between the two cohorts before matching, which alludes to likely imbalances in unmeasured confounders as well. These unmeasured confounders cannot be accounted for in the available statistical models, and the effect of such residual unmeasured confounding is evident given the early differences in deaths without progression or DM between the two cohorts. With a 15-yr follow-up, the ProtecT trial did not show any increased risk of OCM from RT + ST-ADT as compared with RP [45]; it is unlikely that early differences in OCM observed in our study would be driven by RT-related mortality. This is further supported by the fact that most patients in the CALGB trial also received postoperative RT. Similarly, this difference is also unlikely driven by LT-ADT as trials of ST-ADT versus LT-ADT have not demonstrated any significant increase in OCM from ADT prolongation [47].

Since the conduct of PUNCH and RTOG 0521, the standard-of-care for very-high-risk disease has evolved to include the addition of abiraterone acetate/prednisone to RT + LT-ADT based on metastasis-free survival and overall survival benefits over RT + LT-ADT alone [25]. The use of androgen receptor pathway inhibitors perioperatively with RP (PROTEUS; NCT03767244) or with salvage RT (NRG GU008; NCT04134260) is being investigated in clinical trials and not recommended as a standard approach at present. Thus, the existing standard-of-care approaches with an RT-based regimen may have a further impact on our

observations given that about one-third of patients in our RT cohort had a very high risk.

While previous retrospective institutional and registry-based studies have summarized the outcomes of RP versus RT in prostate cancer population, our study leverages some of the advantages of using IPD from randomized trials, including upfront inclusion criteria, standardized treatment, prescheduled follow-up visits, and minimal missing data. However, our study is subject to several limitations other than what has been discussed already. These impact our study, similar to any nonrandomized observational study. Despite the use of IPTW, we could not rule out the effects of unmeasured confounders and unaccounted mediators. OCM and PCSM are liable to an attribution bias. As in every large RCT in high-risk prostate cancer, serial imaging at predefined intervals was not mandated, and instead was driven mostly by biochemical or clinical indications. In addition to the difference in ADT duration, our findings could also be subject to a bias from the underlying imbalance in the follow-up visits in the two trials. Furthermore, our findings might not be extrapolated fully to the modern era given the evolving risk stratification methods and staging workup, such as prostate-specific membrane antigen positron emission tomography. Toxicity data could not be harmonized due to differences in data collection methods, which thus limits our ability to compare toxicity. Finally, DM, while clinically meaningful, is only one measure of treatment outcome.

5. Conclusions

In this comparison using IPD from two contemporaneously enrolled phase 3 RCTs, we found that an RT-based strategy had a significantly lower risk of DM than an RP-based approach for men with newly diagnosed high-risk prostate cancer. The risk of deaths after DM or progression was similar across the two treatment strategies.

Author contributions: Soumyajit Roy, Yilun Sun, and Daniel E. Spratt had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Roy, Spratt.

Acquisition of data: Roy, Spratt, Eastham, Gleave, Morris, Michalski, Sandler, Sartor.

Analysis and interpretation of data: Roy, Sun, Spratt, Halabi, Wallis, Kishan.

Drafting of the manuscript: Roy, Spratt, Morgan, Wallis, Sun, Berlin, Nagar. *Critical revision of the manuscript for important intellectual content:* All authors.

Statistical analysis: Sun, Halabi, Roy, Spratt.

Obtaining funding: Roy.

Administrative, technical, or material support: Spratt, Gleave, Morgan, Wallis, Nagar, Morris, Michalski, Roach III, Beltran, Zaorsky.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.euo.2025.06.009>.

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