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ORIGINAL ARTICLE

Predicting dose response to prostate cancer radiotherapy: validation of a radiation signature in the randomized phase III NRG/RTOG 0126 and SAKK 09/10 trials

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Background: The SAKK 09/10 trial randomized biochemically recurrent prostate cancer patients to salvage radiation 64 Gy versus 70 Gy, and the NRG/RTOG 0126 randomized intermediate-risk prostate cancer patients to definitive radiation 70.2 Gy versus 79.2 Gy. We investigated a previously developed Post-Operative Radiation Therapy Outcomes Score (PORTOS) to identify preferential benefit from radiation dose escalation (DE).

Materials and methods: PORTOS was evaluated in patients enrolled in SAKK 09/10 and NRG/RTOG 0126 with available tissue that passed quality control ($n = 226, 215$). PORTOS was evaluated in the published post-operative groups in SAKK 09/10 and in tertiles in NRG/RTOG 0126 as cut-offs had not been established for biopsy samples and definitive radiation patients. Clinical and molecular correlates in a real-world dataset of 42 407 prostatectomy and 31 107 biopsy samples were also analyzed.

Results: In SAKK 09/10, the biomarker-treatment interaction was statistically significant between PORTOS (lower versus higher) and treatment arm for clinical progression-free survival. Only patients in the higher PORTOS group benefited from DE. In NRG/RTOG 0126, in patients with a lower tertile PORTOS, there was no difference in Phoenix biochemical failure (BF). However, for patients in the average and higher tertile PORTOS range, there was a significant benefit for DE for Phoenix BF. An interaction test indicated a significant difference in benefit for DE between higher and lower PORTOS groups. PORTOS was not strongly associated with clinicopathological variables in either trial or the large real-world dataset. In the latter, PORTOS was modestly associated with hypoxia signatures and strongly associated with immune signatures and subtypes.

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Conclusion: In the SAKK 09/10 and RTOG 0126 randomized controlled trials, we demonstrated that PORTOS can potentially identify a subset of patients who benefit from DE, a subgroup that cannot be identified using clinicopathological or prognostic variables. These results suggest that PORTOS could be used clinically as a predictor of radiation response.

Key words: prostate cancer, radiation dose response, biomarkers

INTRODUCTION

Localized prostate cancer is commonly treated surgically with radical prostatectomy (RP). Prostate-specific antigen (PSA) is expected to become undetectable after RP. However, surgery is sometimes unsuccessful, and biochemical recurrence (BCR) occurs with a detectable and rising postoperative PSA. Salvage radiation (SRT) is commonly initiated at this point as it represents the only potentially curative option for these patients. SRT doses in landmark SRT randomized trials have ranged from 64.8 to 70.2 Gy.[1-3] The SAKK 09/10 trial was an international, multicenter, phase III, randomized clinical trial (RCT) designed to conclusively establish a standard SRT dose. Men with BCR without macroscopic disease after RP were randomized to 64 Gy versus 70 Gy to the prostate bed without hormonal therapy.[4] The SAKK trial was negative for significant differences in oncologic endpoints between arms. Another smaller single-institution randomized trial that included both adjuvant (33%) and SRT (67%) also found no difference in 66 Gy versus 72 Gy.[5] Interestingly, these RCTs demonstrated the limitations of earlier meta-analyses of retrospective non-randomized studies showing a benefit from dose escalation (DE).[6]

The Decipher genomic classifier (GC) score was previously evaluated in the SAKK 09/10 trial and found to be prognostic, but not predictive for the benefit of DE.[7] No clear subgroup could be identified that preferentially benefited from DE-SRT. The Post-Operative Radiation Therapy Outcomes Score (PORTOS) had been previously developed on the same platform[8] before the publication of the SAKK trial, and we hypothesized that PORTOS might be able to identify a subset of patients who could still benefit from radiation DE.

Definitive radiotherapy (RT) is the other primary treatment modality for localized prostate cancer. The ProtecT trial established the equivalency in clinical outcomes compared with RP.[9] The radiation course historically consisted of a conventionally fractionated dose of around 70 Gy. Numerous randomized controlled trials established an improvement in biochemical control with DE to around 80 Gy.[10] Based on these data, DE has become the new standard of care for conventionally fractionated radiation. However, large meta-analyses have failed to demonstrate a metastasis-free survival or overall survival (OS) benefit.[10]

If PORTOS predicts radiosensitivity/resistance in the postoperative setting, we hypothesized that we could apply it to predict which patients may benefit from DE in the definitive setting. We therefore sought to investigate PORTOS in NRG/RTOG 0126,[11] a phase III RCT in men with primarily intermediate-risk localized prostate cancer randomized to 79.2 Gy versus 70.2 Gy. This trial showed an improvement in biochemical control and distant metastasis (DM) with DE, but not OS, at the cost of increased toxicity. Finally, we also investigated associations between PORTOS and clinicopathological and genomic variables in a large-scale, real-world clinical dataset of both prostatectomy and biopsy samples.

MATERIALS AND METHODS

SAKK 09/10

The SAKK 09/10 randomized phase III trial tested whether dose-escalated SRT is superior to conventional dose SRT with respect to freedom from biochemical progression.[4] More details on study exclusion and inclusion criteria are available at ClinicalTrials.gov (NCT01272050), and details on the translational research project investigating genomic markers and ethical approval have been previously described.[7] Genomic signatures were generated using the whole transcriptome Decipher assay (Veracyte, Inc., San Francisco, CA). Of the original 350 patients enrolled in the trial, 233 had tissue available for genomic analysis, and 226 passed quality control and were included in the final analysis as reported previously, and this subset was representative of the overall trial.[7]

NRG/RTOG 0126

The NRG/RTOG 0126 randomized phase III trial tested whether dose-escalated definitive radiation (79.2 Gy) was superior to conventional dose definitive radiation (70.2 Gy). The primary endpoints were biochemical failure (BF) by the American Society for Therapeutic Radiology and Oncology American Society for Radiation Oncology (ASTRO) and Phoenix criteria. More details on study inclusion and exclusion criteria are available at ClinicalTrials.gov (NCT00033631). Details on the translational research project investigating genomic markers and ethical approval have been previously described.[12] Genomic signatures were generated using the whole transcriptome Decipher assay (Veracyte, Inc.). Only 215 patients had tissue available and passed quality control for inclusion in the final analysis as reported previously, and this subset was representative of the overall trial.[12] All patients in the final analysis had intermediate-risk prostate cancer as per the modern National Comprehensive Cancer Network (NCCN) risk groups.[12]

Decipher GRID

Prospectively obtained transcriptomic data from RP and biopsy specimens were obtained from the Genomic Resource for Intelligent Discovery (GRID) database (NCT02609269), a large-scale, real-world clinical dataset from clinical use of the Decipher assay.[13-16] A total of 42 407 RP specimens (tested between February 2016 and February 2022) and 31 107 intermediate-risk prostate cancer (mirroring the NRG/RTOG 0126 population) biopsy specimens were included (tested between May 2016 and February 2022) to investigate associations between PORTOS and clinicopathological and genomic variables in a large-scale, real-world clinical dataset. These patients' data were de-identified in accordance with the Safe Harbor method described in the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule 45 CFR 164.514(b) and (c) (Veracyte, Inc.) before analysis.

PORTOS calculation

PORTOS was derived on the same clinical-grade microarray platform as the Decipher GC. The PORTOS was, therefore, calculated exactly as previously published.[8] A previously locked cut-off for RP samples was applied to categorize higher (>0) versus lower (≤ 0) PORTOS in the SAKK 09/10 trial, as it was a similar post-operative patient cohort. Patients with a high PORTOS were previously predicted to derive the most benefit from post-operative radiation. Thus, we hypothesized that they would potentially derive the most benefit from RT DE. As previously observed,[12,17] the age of the RTOG 0126 specimens and subsequent RNA degradation resulted in artificially depressed expression levels.[18] To account for this, we leveraged the GRID biopsy samples described in the previous section to apply a quantile mapping procedure[19] of the genes used in the calculation of PORTOS. Again, the score was calculated as previously published. The previously published score cut-offs were established in the post-prostatectomy setting. However, the best cut-offs using biopsy samples and in patients receiving definitive RT may differ. Therefore, we instead chose to investigate PORTOS in tertiles, balancing subgroup size with granular information across the range of PORTOS.

Statistical methods—SAKK 09/10

Descriptive statistics were provided for 226 patients from the SAKK 09/10 trial, including median and interquartile range (IQR) for continuous variables, and frequency and proportion for categorical variables. Comparisons between PORTOS subgroups (lower versus higher) were conducted using Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. The primary endpoint of this study was time to clinical progression-free survival (CPFS) as defined in the original trial protocol (time to the first local, regional, or distant recurrence). The objective of this study was to evaluate the potential of PORTOS as a predictor for the benefit of RT DE on CPFS. Freedom from biochemical progression (FFBP) was the secondary endpoint in this study as defined in the original trial protocol (time to biochemical progression, clinical progression, or death due to clinical progression).

To assess the effect of DE on CPFS (or FFBP) according to PORTOS subgroups, Kaplan–Meier curves of CPFS were plotted for each PORTOS subgroup by treatment arm (64 Gy versus 70 Gy). The association between DE and CPFS was investigated within each PORTOS subgroup using univariable Cox proportional hazards models. Additional Cox proportional hazards models with an interaction term between treatment arm and PORTOS were fit to determine the statistical significance of differences in the effect of DE on CPFS by PORTOS (both PORTOS subgroups and PORTOS). These models were also used to predict CPFS at 5 years to visualize interaction effects.

Statistical methods—NRG/RTOG 0126

Descriptive statistics were provided for 215 patients from the NRG/RTOG 0126 randomized phase III trial, including median and IQR for continuous variables, and frequency and proportion for categorical variables. Comparisons between PORTOS subgroups, divided into three equal tertiles (lower, average, and higher), were conducted using Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. The primary endpoints of this study were time to BF as per the Phoenix and ASTRO criteria. The objective of this study was to evaluate PORTOS' potential as a predictor for the benefit of definitive radiation DE on BF. DM and receipt of salvage therapy were also considered as the secondary endpoints in this study.

Univariable analysis (UVA) of Fine–Gray models, treating death without events as a competing risk, was conducted for all endpoints. Cumulative incidence curves were plotted for each PORTOS subgroup by randomization arms (79.2 Gy versus 70.2 Gy) to evaluate the effect of definitive radiation DE. UVAs were conducted to investigate the association between definitive radiation DE and endpoints within each PORTOS tertile and to compare PORTOS' performance with other clinicopathological variables.

Statistical methods—general

Standardized mean differences (SMDs) were utilized to evaluate the relationship between PORTOS and clinicopathological variables in the real-world clinical datasets. Interaction testing was used to assess PORTOS as a predictive biomarker.[20] All statistical tests were two-sided, with P values <0.05 considered statistically significant. Analyses were conducted using R, version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PORTOS in SAKK 09/10

In total, 226 patients from the SAKK 09/10 trial had evaluable PORTOS. Of these, 189 (83.6%) had a lower PORTOS and 37 (16.4%) had a higher PORTOS. There were no significant differences in clinicopathological variables

between the PORTOS lower versus higher groups (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.01.017). Importantly, the randomization of arm A (64 Gy) versus arm B (70 Gy) was similar within the lower and higher PORTOS groups.

We next examined PORTOS for both prognostic and potential treatment arm interaction for the CPFS endpoint. PORTOS was not prognostic overall for CPFS [hazard ratio (HR) 1.24, 95% confidence interval (CI) 0.66-2.33, $P = 0.50$]. Regarding the predictive value for DE, in patients with a lower PORTOS, there was a slightly worse CPFS in the DE arm (HR 1.78, 95% CI 1.02-3.11, $P = 0.04$; Figure 1A). In contrast, there was a significant benefit to DE in the higher PORTOS group (HR 0.19, 95% CI 0.05-0.70, $P = 0.01$; Figure 1B). In patients with a lower PORTOS, the 5-year CPFS was 82% in the 64-Gy arm versus 72% in the 70-Gy arm, which reversed in patients with a higher PORTOS, with a CPFS of 49% in the 64-Gy arm versus 94% in the 70-Gy arm. The interaction between PORTOS (lower versus higher) and treatment arm was statistically significant ($P = 0.003$). The results were similar for FFBP (Supplementary Figures S1 and S2, available at https://doi.org/10.1016/j.annonc.2025.01.017). Additional trial endpoints are shown for reference in Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2025.01.017.

We also plotted the relationship between PORTOS as a continuous score and the 5-year CPFS and FFBP in both treatment arms to better illustrate this point. We can clearly see in the interaction plot that the curves cross, with a lower PORTOS favoring 64 Gy and a higher PORTOS favoring 70 Gy (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.01.017). We next evaluated other clinicopathological variables and compared them with PORTOS in predicting the benefit of DE (Figure 2). No other clinicopathological variables were significant in identifying patients who benefited from DE (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.01.017). In total, these data suggest that PORTOS is predictive of benefit from DE in this population, identifying a subset of patients who have improved outcomes from 70 Gy versus 64 Gy SRT that could not be determined solely from clinicopathological variables.

PORTOS in NRG/RTOG 0126

In total, 215 intermediate-risk prostate cancer patients from the NRG/RTOG 0126 trial had evaluable PORTOS. Since the post-operative cut-offs for high versus low PORTOS likely do not apply to the definitive setting, we instead divided patients into three equal tertiles for lower, average, and higher PORTOS. We first examined associations of PORTOS and clinicopathological variables (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.01.017). There were no associations that were both statistically significant and consistently ordered (i.e. increasing or decreasing consistently from PORTOS low to medium to high).

We next examined PORTOS for prognosis as well as potentially identifying patients who benefit from definitive DE for BF endpoints. We primarily focused on the Phoenix definition as the more contemporary and clinically used definition for BF,[21] but the historical ASTRO definition is reported as it was part of the original protocol. PORTOS was not prognostic overall for either endpoint (BF ASTRO $P = 0.15$; BF Phoenix $P = 0.23$). Regarding the predictive value for DE (Figure 3), in patients with a lower PORTOS, there was no difference in BF [Phoenix subdistribution HR (sHR) 1.03, 95% CI 0.45-2.36, $P = 0,94$; ASTRO sHR 1.14, 95% CI 0,54-2.40, $P = 0.73$]. However, for patients with an average PORTOS, there was a significant benefit for DE for BF as per

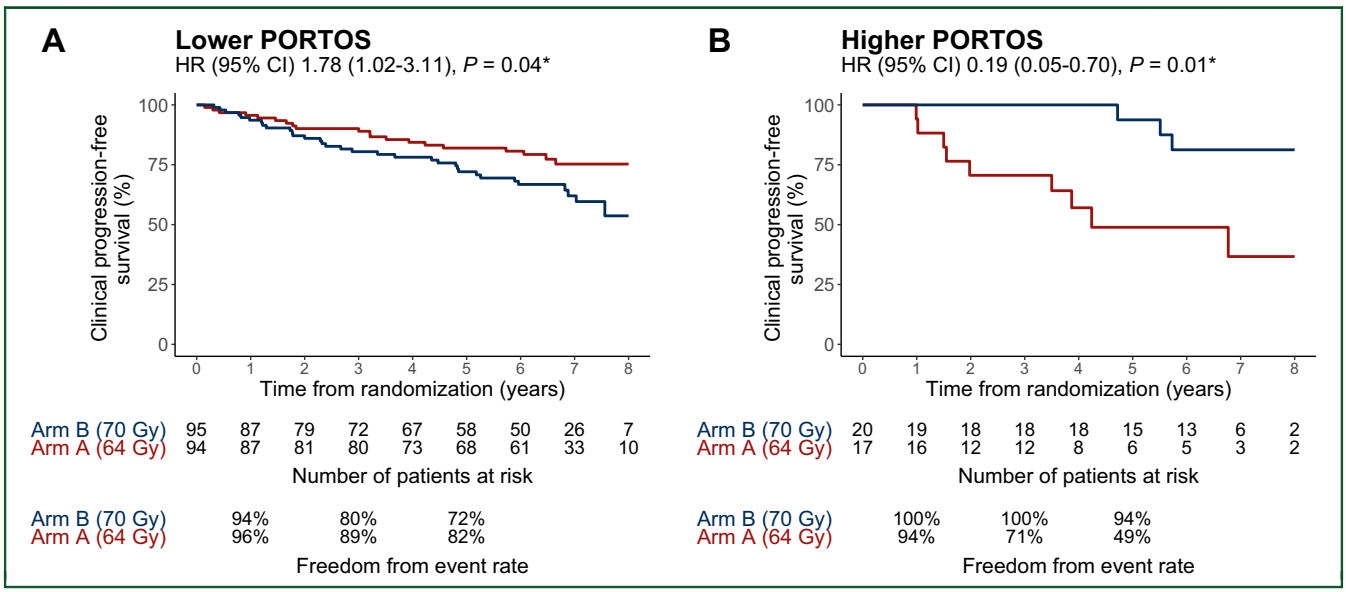

Figure 1. PORTOS clinical outcomes in SAKK 09/10. (A) CPFS Kaplan–Meier curves of patients with a lower PORTOS in SAKK 09/10. (B) CPFS Kaplan–Meier curves of patients with a higher PORTOS in SAKK 09/10.
CPPS, clinical progression-free survival; CI, confidence interval; HR, hazard ratio; PORTOS, Post-Operative Radiation Therapy Outcomes Score.
*$P < 0.05$.

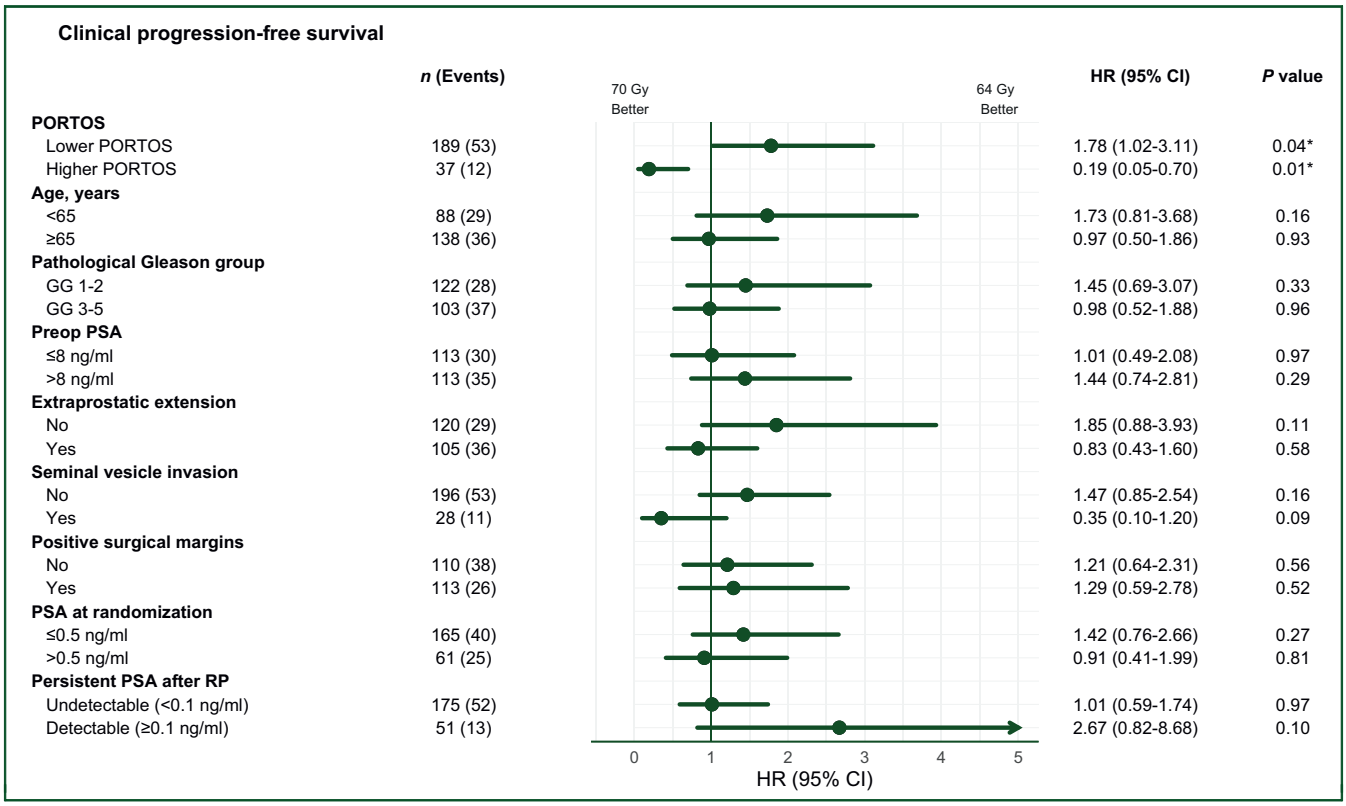

Figure 2. Forest plot of treatment effects within PORTOS and clinicopathologically defined strata for the clinical progression-free survival benefit of 70 Gy versus 64 Gy in SAKK 09/10 with significance derived from univariable Cox regression models.

CI, confidence interval; GG, grade group; HR, hazard ratio; PORTOS, Post-Operative Radiation Therapy Outcomes Score; PSA, prostate-specific antigen; RP, radical prostatectomy.

*$P < 0.05$.

the Phoenix criteria (sHR 0.45, 95% CI 0.22-0.90, $P = 0.02$), though not for BF as per the ASTRO criteria (sHR 0.60, 95% CI 0.32-1.14, $P = 0.12$). For patients with a higher PORTOS, this benefit was even more pronounced for a BF benefit (Phoenix sHR 0.30, 95% CI 0.12-0.75, $P = 0.009$; ASTRO sHR 0.46, 95% CI 0.23-0.92, $P = 0.03$), with interaction tests indicating a significant difference in benefit for DE between higher and lower PORTOS tertiles for BF Phoenix ($P = 0.048$; $P = 0.09$ for ASTRO; Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2025.01.017). These results indicate that patients with a higher PORTOS appear to be benefitting the most from DE RT, with less benefit in the lower tertile of PORTOS.

We also examined the secondary endpoints of DM and receipt of salvage therapy. Like BF, in patients with a lower PORTOS, there was no difference in DM (sHR 1.73, 95% CI 0.16-18.43, $P = 0.65$). For patients with an average PORTOS, there was not a statistically significant benefit for DE for DM (sHR 0.14, 95% CI 0.02-1.11, $P = 0.06$). In patients with a high PORTOS, there were no DM events in the dose-escalated arm, only in the standard dose arm, and thus a model did not converge (Supplementary Figure S5A, available at https://doi.org/10.1016/j.annonc.2025.01.017). For receipt of salvage therapy (Supplementary Figure S5B, available at https://doi.org/10.1016/j.annonc.2025.01.017), both lower (sHR 0.91, 95% CI 0.37-2.21, $P = 0.83$) and average (sHR 0.73, 95% CI 0.30-1.77, $P = 0.48$) PORTOS groups did not show a difference, but the higher PORTOS group demonstrated a significant benefit for DE (sHR 0.12, 95% CI 0.03-0.53, $P = 0.005$), with interaction tests indicating a significant difference in benefit for DE between higher and lower PORTOS tertiles ($P = 0.026$). Additional trial endpoints are shown for reference in Supplementary Figure S6, available at https://doi.org/10.1016/j.annonc.2025.01.017.

We next evaluated other clinicopathological variables and compared them to PORTOS in predicting the benefit of DE. No other clinicopathological variables were consistently significant across both Phoenix and ASTRO BF in identifying patients who benefited from DE (Figure 4, Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.01.017). In total, these data suggest that PORTOS is predictive of benefit from DE in this population, identifying a subset of patients who have improved outcomes from 79.2 Gy versus 70.2 Gy definitive radiation that could not be determined solely from clinicopathological variables.

Evaluation of PORTOS in real-world clinical datasets

We next evaluated the association of PORTOS with clinicopathological and molecular variables in a real-world clinical dataset from clinical testing with the Decipher platform (GRID cohort). This included 42 407 prostate cancer patients treated with RP and 31 107 intermediate-risk prostate cancer patients (mirroring the RTOG 0126 population) with pre-treatment biopsy testing. Because of the

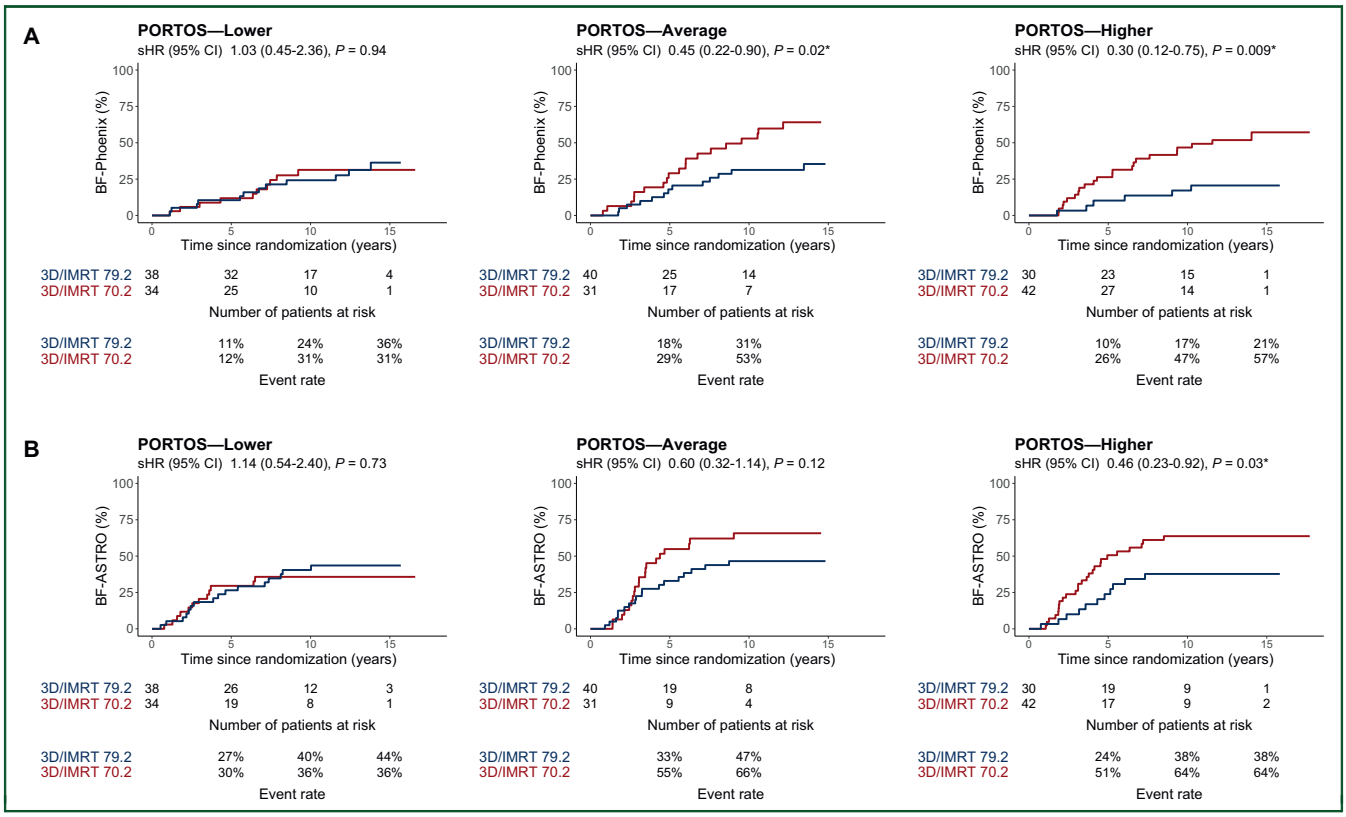

Figure 3. PORTOS clinical outcomes in NRG/RTOG 0126. Cumulative incidence curves for BF as per (A) Phoenix and (B) ASTRO criteria comparing 79.2 Gy versus 70.2 Gy stratified by PORTOS tertile in NRG/RTOG 0126.
3D/IMRT, three-dimensional/intensity-modulated radiotherapy; ASTRO, American Society for Radiation Oncology and Oncology; BF, biochemical failure; CI, confidence interval; PORTOS, Post-Operative Radiation Therapy Outcomes Score; sHR, subdistribution hazard ratio.
*$P < 0.05$.

size of the dataset, nearly all *P* values are highly statistically significant. Therefore, we report SMDs to evaluate and compare effect sizes. SMD values can approximately be interpreted as >0.2, >0.5, and >0.8 corresponding to small, medium, and large differences.[22] We first examined the association of PORTOS and other known clinicopathological and genomic variables across this extremely large dataset. In the GRID RP cohort, there were only very weak associations between PORTOS and Gleason grade group (GG; SMD = 0.16), the Decipher GC (SMD = 0.19), seminal vesicle invasion (SMD = 0.18), and lymph node involvement (SMD = 0.21). The remaining SMDs for preoperative PSA, extracapsular extension, and margins were all <0.1 (Supplementary Figure S7, available at https://doi.org/10.1016/j.annonc.2025.01.017). In the GRID biopsy cohort, there was an weak association of PORTOS with race (SMD = 0.18). However, PSA, clinical T stage, Gleason GG, and NCCN risk group all had SMDs <0.1 (Supplementary Figure S7, available at https://doi.org/10.1016/j.annonc.2025.01.017). These results suggest that PORTOS is conveying independent information from these clinicopathological and genomic variables.

We next evaluated the association of PORTOS with other biological pathways (Figure 5). In both the GRID RP and biopsy cohorts, PORTOS had a weak association with the expression of DNA damage response gene signature (Supplementary Figure S8, available at https://doi.org/10.1016/j.annonc.2025.01.017; RP SMD = 0.33, biopsy SMD = 0.16). Hypoxic tumors are known to be more radiation resistant,[23,24] and concordantly, there was a modest association with high PORTOS (which derives a benefit from DE) and a hypoxia signature (RP SMD = 0.56, biopsy SMD = 0.29). Interestingly, the strongest association was with an immune signature (RP SMD = 1.13, biopsy SMD = 0.83). Furthermore, when comparing with published subtypes of localized prostate cancer, there was a very strong enrichment of basal-immune (BI) tumors in the PORTOS-high samples (RP SMD = 1.00, biopsy SMD = 0.85). These findings shed light on the underlying biological mechanisms underpinning the observed effects of PORTOS.

DISCUSSION

In the SAKK 09/10 RCT, we have demonstrated that PORTOS is able to identify a subset of patients who benefit from SRT DE from 64 Gy to 70 Gy. In the NRG/RTOG 0126 RCT, we have also demonstrated that PORTOS is able to identify a subset of patients who benefit more from definitive RT DE from 70.2 Gy to 79.2 Gy. These subgroups cannot be identified using only clinicopathological variables. Since DE comes at the cost of increased risk of toxicity, PORTOS might identify patients who do not require DE and could be particularly helpful in situations where dose constraints are

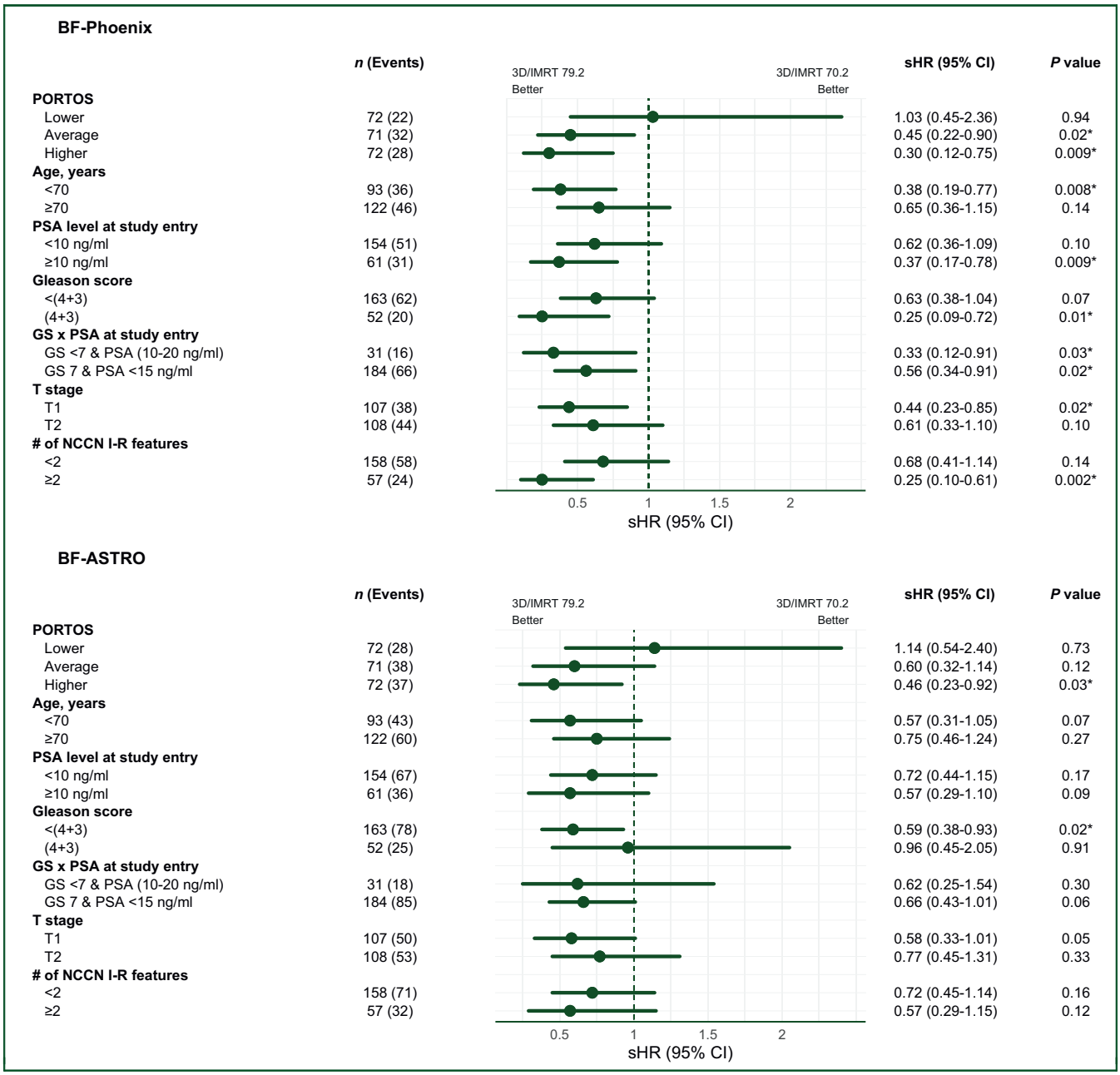

Figure 4. Forest plot of treatment effects for BF as per Phoenix and ASTRO criteria within strata defined by PORTOS and clinicopathological variables in NRG/RTOG 0126 with significance derived from univariable Fine and Gray models.

3D/IMRT, three-dimensional intensity-modulated radiotherapy; ASTRO, American Society for Therapeutic Radiology and Oncology; BF, biochemical failure; CI, confidence interval; GS, Gleason score; I-R, intermediate-risk; PORTOS, Post-Operative Radiation Therapy Outcomes Score; PSA, prostate-specific antigen; sHR, subdistribution hazard ratio.

*$P < 0.05$.

proving difficult to meet, or even to stop treatment early in patients who are tolerating treatment poorly. However, it should be noted that neither trial was designed to test this hypothesis specifically.

Our analysis of a large real-world cohort of molecularly profiled samples sheds further light into the biological underpinnings of PORTOS. Intriguingly, while PORTOS was not associated with tumor-intrinsic pathological variables, it did have a stronger association with gene expression pathways involving the tumor microenvironment. The link between hypoxia and radiation resistance is known[23,24] and PORTOS-high tumors had modestly higher expression of a hypoxia signature. Perhaps more pronounced was the association with immune signatures and, particularly, the BI subtype. A luminal—basal axis has been extensively described in prostate cancer,[25-27] and these were further refined into four specific subtypes in localized prostate cancer[15]: luminal differentiated, luminal proliferating, BI, and basal neuroendocrine. The BI subtype was extremely over-enriched in the PORTOS-high samples and, interestingly, has been shown to predict a benefit for adjuvant radiation in other studies.[15] The interaction between the

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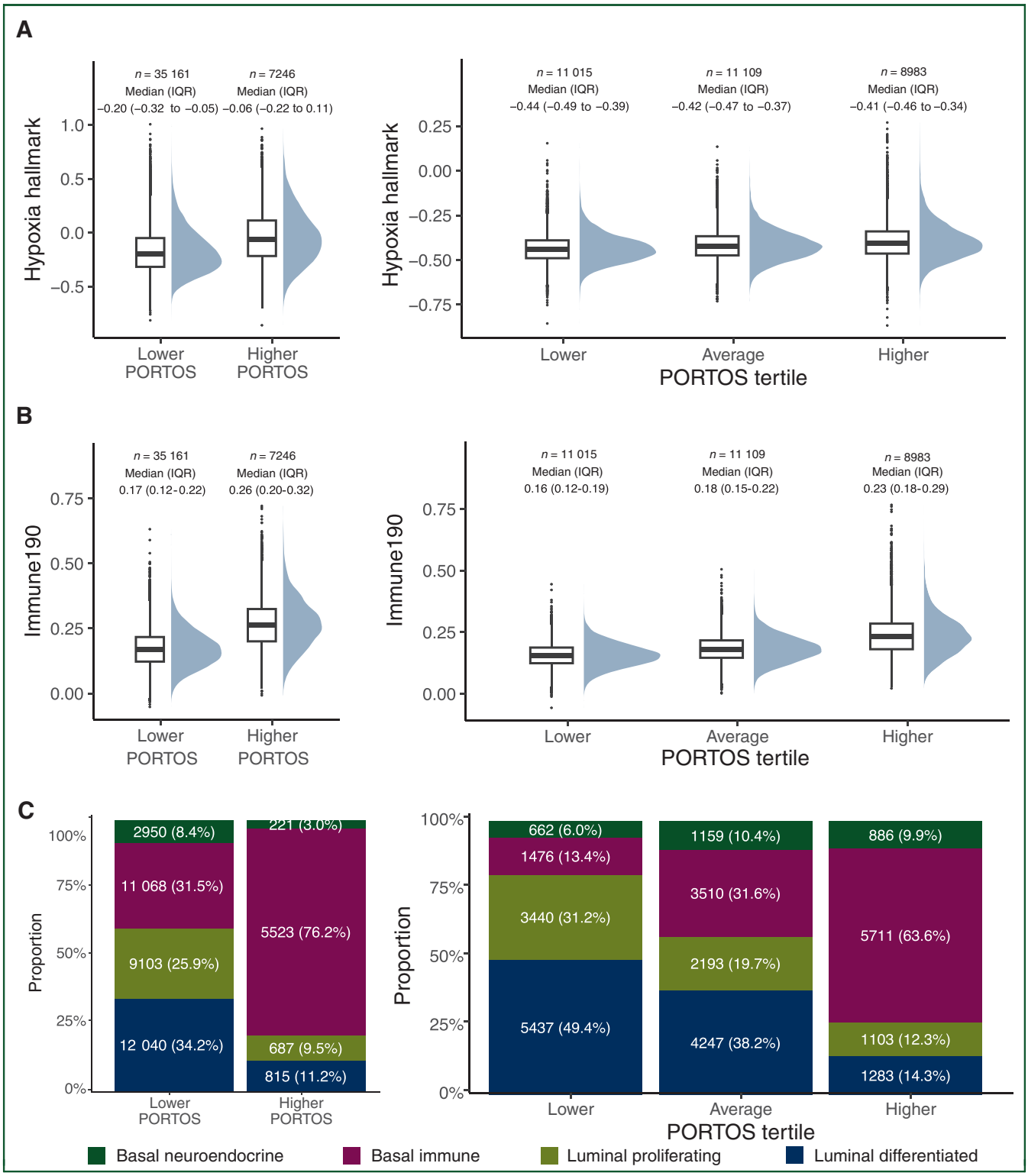

Figure 5. Biological pathways associated with PORTOS. (A) Hypoxia, (B) immune (Immune190) scores, and (C) molecular subtypes in real-world commercial Decipher (left) RP and (right) NCCN intermediate-risk biopsy samples grouped by PORTOS (same as SAKK 09/10 and RTOG 0126).
IQR, interquartile range; NCCN, National Comprehensive Cancer Network; PORTOS, Post-Operative Radiation Therapy Outcomes Score; RP, radical prostatectomy.

immune system and radiation in prostate cancer is complex[28] and this study highlights the potential interplay with PORTOS and radiation dose. These intriguing results require mechanistic studies to further elucidate these relationships.

The results of PORTOS in SAKK 09/10 provide a valuable tool for guiding optimal radiation dose decisions in the salvage setting. Considering the limited evidence from randomized trials demonstrating the superiority of DE for

biochemically recurrent patients, there has been a notable shift in practice toward dose de-escalation to the prostate bed. Therefore, PORTOS could help clinicians with tailored guidance for RT prescriptions. Clinical and dosimetric factors can also influence radiation dose decisions, but there are many situations where clinical equipoise exists. Notably, compared with PORTOS-low patients, those with high PORTOS derive a superior benefit when treated with higher doses to the prostate bed, underscoring the utility of PORTOS in facilitating more personalized treatment strategies.

Definitive DE in prostate cancer has also progressed beyond 80 Gy. Further DE using simultaneous integrated boost (SIB) has been evaluated in randomized trials, such as the FLAME trial, which demonstrated improved biochemical control rates.[29] Patients predicted to benefit from DE by PORTOS, especially those with the highest scores, may also benefit from further DE using SIB, as they have tumors which benefit from higher radiation doses. In intermediate-risk patients receiving brachytherapy, external beam radiation therapy (EBRT) boost is another method of DE. In NRG/RTOG 0232, no overall benefit was identified for combination EBRT and brachytherapy compared with brachytherapy alone,[30] but there was a trend suggesting that a subset of patients might benefit. Investigation of PORTOS in the context of these additional modalities could help establish additional clinical scenarios where PORTOS may be useful in identifying the best candidates for definitive RT DE.

The SAKK 09/10 trial did not use elective nodal irradiation (ENI) or androgen deprivation therapy (ADT). Both of these modalities have been shown to have a clinical benefit when combined with prostate bed salvage radiotherapy.[1,2,31] This is something that will be examined in the forthcoming biomarker analysis of the NRG/RTOG 0534 SPPORT trial testing the use of ADT and ENI. It is important also to mention that the SAKK 09/10 trial did not include patients with evidence of macroscopic local recurrence, as retrospective data suggest that higher doses may be more beneficial for these patients.[32] Patients in the NRG/RTOG 0126 trial were also not treated with ADT, which would be considered as standard of care today for patients with NCCN unfavorable intermediate-risk prostate cancer. However, these patients made up the minority of patients in our study. Both these SAKK and NRG/RTOG RCTs were also conducted before the widespread adoption of prostate-specific membrane antigen positron emission tomography scans. Future studies are being planned which can help clarify the role of PORTOS for post-operative and definitive radiation, including prospective trials randomizing RT dose based on PORTOS. This is especially important given the smaller sample sizes in these current studies, and also to further validate PORTOS in biopsy samples where we needed to use tertiles instead of the original RP groups. To our knowledge, PORTOS is the only radiation response biomarker in prostate cancer validated in RCTs in both post-operative and definitive clinical settings. Thus, we propose renaming PORTOS to the PrOstate cancer Radiation Therapy Outcomes Score.

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