

Article

A Multimodal Artificial Intelligence Model to Guide Use of Whole-Pelvic Radiation Therapy in Patients with Localized Prostate Cancer: Exploratory Analysis of RTOG 9413

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Simple Summary

Whole-pelvic radiotherapy may improve outcomes for some patients with localized prostate cancer, but identifying who is most likely to benefit remains challenging. In this study, we evaluated whether a multimodal artificial intelligence model that combines information from biopsy tissue images and clinical characteristics could identify patients with different outcome patterns following whole-pelvic versus prostate-only radiotherapy. Using data from a randomized clinical trial, we found that patients classified as high risk by the model showed larger numerical differences in biochemical failure rates with whole-pelvic radiotherapy, although the formal statistical interaction test was not significant. These findings should be considered exploratory and hypothesis-generating. Nevertheless, these findings support further investigation of artificial intelligence-based risk assessment as a tool for risk stratification and hypothesis generation in future prospective clinical trials.



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Abstract

Background/Objectives: This study explored whether a multimodal artificial intelligence (MMAI) model integrating digitized histopathology and clinical features can identify prostate cancer patients who may benefit from neoadjuvant hormonal therapy (NHT) and whole-pelvic radiotherapy (WPRT). **Methods:** This secondary analysis of NRG/RTOG 9413 included NHT-treated patients with digitized biopsy slides and clinical data who were not part of the MMAI model optimization. A previously validated MMAI model estimated long-term risk, and Fine-Gray models evaluated interactions between MMAI-derived scores and the radiation field (WPRT vs. prostate-only RT [PORT]) for biochemical failure (BF), chosen over progression-free survival because of extended follow-up and distant

metastasis (DM), with subgroup analyses by predefined MMAI strata. **Results:** Among 81 eligible patients, the MMAI-by-treatment interaction for BF did not confirm a differential effect ($p = 0.30$). Therefore, subgroup findings should be interpreted as descriptive and hypothesis-generating. Nevertheless, the magnitude effect of WPRT was numerically greater in the MMAI high-risk subgroup (5-yr: 41% vs. 79%; 10-yr: 47% vs. 79%; aHR 0.35 [0.14–0.86]) than in the low–intermediate group (5-yr: 18% vs. 33%; 10-yr: 44% vs. 57%; aHR 0.66 [0.29–1.48]). **Conclusions:** Although no statistically significant treatment-by-MMAI interaction was demonstrated, these findings are hypothesis-generating and support further investigation of MMAI approaches for guiding WPRT in NRG/RTOG 0534, 0924, GETUG-01, and POP-RT trials.

Keywords: artificial intelligence; prostatic neoplasms; radiotherapy

1. Introduction

External-beam radiotherapy (EBRT) with hormonal therapy (HT) is a standard of care for intermediate- and high-risk prostate cancer [1–8]. Still, the role of whole-pelvic RT (WPRT) remains debated, especially regarding which patients are likely to benefit. RTOG 9413 demonstrated a progression-free survival (PFS) benefit with WPRT versus prostate-only RT (PORT) [9], with long-term follow-up confirming durable benefit among patients receiving neoadjuvant-HT (NHT) [10]. However, GETUG-01 did not show a PFS improvement with WPRT [11,12]. Recent data highlight the importance of patient selection, including high-risk disease [13] and younger age [14]. Current risk stratification tools lack precision in identifying who benefits from WPRT [15,16]. Multimodal artificial intelligence (MMAI) algorithms may help by integrating clinical variables and digitized histopathology [17]. While these models have been validated in predicting clinical outcomes [18–22], their potential role in informing treatment selection—particularly for WPRT—remains unexplored.

In this study, leveraging patient-level data from RTOG 9413, we applied a previously validated MMAI prognostic model to explore whether MMAI-derived risk groups exhibit distinct patterns of biochemical or metastatic outcomes following NHT with WPRT versus PORT. This secondary analysis is intended to provide insights that may motivate validation in trials such as POP-RT, GETUG-01, NRG/RTOG 0534, and 0924.

2. Materials and Methods

2.1. Study Cohort

This retrospective analysis included consenting patients enrolled in the NRG/RTOG 9413 trial, which compared WPRT versus PORT and NHT versus adjuvant-HT in localized prostate cancer. Details of the trial design have been previously described [9,10,23,24].

The current analytic cohort excluded patients used in the MMAI model development (v1.2) [25]. This cohort corresponds to the internal validation group used in MMAI model development and was further reduced to patients receiving NHT; the subgroup guided the design of NRG/RTOG 0924 [26,27].

2.2. Data Acquisition

Digitized H&E-stained biopsy slides and clinical data were obtained for a subset of NRG/RTOG 9413 patients with pretreatment biopsy images, complete clinical data, and no prior use in model optimization. Slides were scanned at 20× magnification and underwent centralized quality assurance.

2.3. Application of the MMAI Model

We applied a validated MMAI prognostic model integrating biopsy histopathology with clinical data (PSA, age, and clinical T-stage) to generate a prognostic risk score [17,20,25]. This model was trained and validated across multiple randomized trials and demonstrated superior prediction performance for distant metastasis (DM) and biochemical failure (BF) compared to conventional tools. The model combined convolutional neural network-extracted image features with clinical variables through a fully connected neural network. The model combined image-derived features from biopsy histopathology with clinical variables using a neural network.

2.4. Statistical Analysis

The endpoints of interest were BF and DM, analyzed using time-to-event methods. BF was selected over the trial's original PFS endpoint due to the extended duration of follow-up, during which PFS events increasingly reflected non-cancer-related deaths [10], limiting its utility in assessing prostate cancer-specific outcomes. BF was chosen for its clearer signal of disease control and treatment effect, while DM was included because it is the endpoint toward which the MMAI model was initially developed.

To explore whether BF or DM differed by MMAI between WPRT and PORT, Fine-Gray models with interaction terms between treatment and MMAI were used. Correspondingly, estimated treatment effects were adjusted for biomarker interaction (adjusted hazard ratio, aHR), and 95% confidence intervals (CIs) were reported. Subgroup summaries were generated within MMAI risk strata (low–intermediate vs. high) using previously validated thresholds (low risk: <0.273; intermediate risk: 0.273–0.499; and high risk: >0.499). Cumulative incidence functions accounting for competing risks (defined as death without an event) were used to provide BF and DM risk estimates for the MMAI subgroups and comparisons between treatment groups (WPRT vs. PORT) based on Gray's test were treated as descriptive and not intended for inference.

All tests were two-sided at a 0.05 significance level, without multiplicity adjustments. Given the exploratory design, findings should be considered hypothesis-generating.

3. Results

Eighty-one patients were included in this analysis (Figure 1; Table 1). BF rates were lower with WPRT (5-year: 28% vs. 55%; 10-year: 45% vs. 67%; aHR 0.49 [0.27–0.89]). The treatment-by-MMAI interaction was not statistically significant (interaction $p = 0.30$), indicating no evidence of treatment effect heterogeneity in this cohort. Accordingly, all subgroup findings should be interpreted as descriptive and hypothesis-generating. Nevertheless, exploratory subgroup estimates showed numerically larger risk differences between WPRT and PORT among patients classified as MMAI high-risk (5-year: 41% vs. 79%; 10-year: 47% vs. 79%; exploratory-aHR 0.35 [0.14–0.86]) than among those in the low–intermediate group (5-year: 18% vs. 33%; 10-year: 44% vs. 57%; exploratory-aHR 0.66 [0.29–1.48]) (Figure 2). For DM, no apparent differences were observed between WPRT and PORT (5-year: 8% vs. 15%; 10-year: 19% vs. 20%; exploratory-aHR 0.62 [0.26–1.48]). The interaction between the MMAI category and the radiation field on DM was assessed (interaction $p = 0.82$). WPRT vs. PORT treatment effects were aHR 0.56 [0.14–2.25] for MMAI low–intermediate subgroup vs. aHR 0.69 [0.22–2.16] for MMAI high subgroup (Figure 2). Because baseline PSA differed numerically between treatment groups, a sensitivity analysis was performed by adding PSA as a continuous covariate to the interaction models. For BF, the treatment-by-MMAI interaction estimate remained similar and was modestly strengthened after PSA adjustment (primary model: sHR 0.52, $p = 0.30$; PSA-adjusted model: sHR 0.45, $p = 0.20$). For DM, results were essentially unchanged (primary

model: sHR 1.22, $p = 0.82$; PSA-adjusted model: sHR 1.20, $p = 0.85$). Exploratory NCCN risk group analyses are presented in Supplementary Table S1. These analyses yielded unstable estimates because only 13 patients were classified as NCCN intermediate-risk and events were sparse.

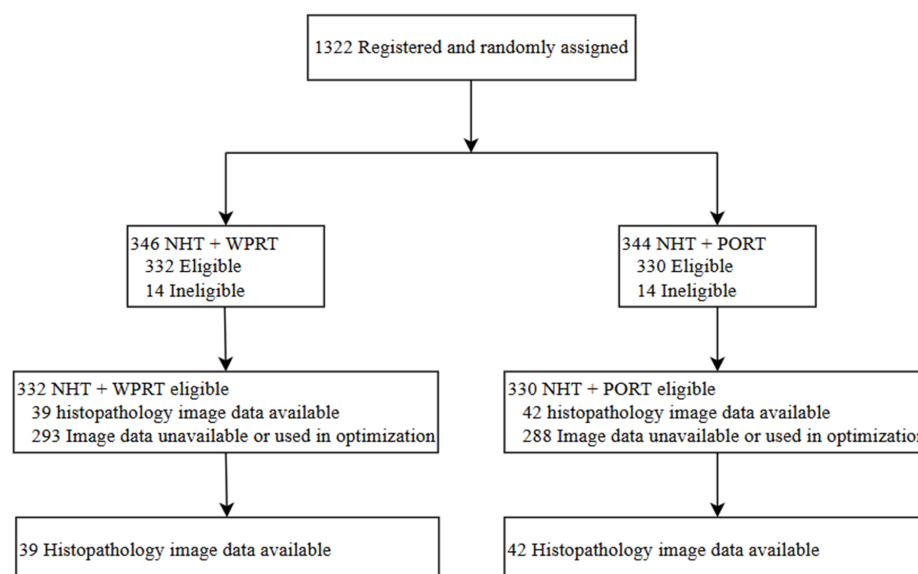


Figure 1. CONSORT diagram. Abbreviations: NHT, neoadjuvant hormonal therapy; PORT, prostate only radiotherapy; WPRT, whole-pelvic radiotherapy.

Table 1. Baseline characteristics of patients who received neoadjuvant hormonal therapy, stratified by radiation treatment volume.

Characteristic	Overall (N = 81)	PORT (N = 42)	WPRT (N = 39)	p-Value
Age, years, median (IQR)	70 (66–74)	70 (66–74)	70 (65–74)	
Race, No. (%)				0.6
African American	23 (28%)	13 (31%)	10 (26%)	
White	4 (4.9%)	1 (2.4%)	3 (7.7%)	
Other	54 (67%)	28 (67%)	26 (67%)	
PSA at baseline, median (IQR)	25.3 (11.8–38.3)	27.0 (16.8–40.2)	15.4 (9.8–33.7)	
Clinical Gleason Score, No. (%)				0.7
≤6	20 (25%)	9 (21%)	11 (28%)	
7 (3 + 4)	27 (33%)	14 (33%)	13 (33%)	
7 (4 + 3)	14 (17%)	9 (21%)	5 (13%)	
8	12 (15%)	5 (12%)	7 (18%)	
9–10	8 (9.9%)	5 (12%)	3 (7.7%)	
Clinical T Stage, No. (%)				0.4
T1c–T2a	17 (21%)	11 (26%)	6 (15%)	
T2b–c	36 (44%)	20 (48%)	16 (41%)	
T3/T3a	13 (16%)	5 (12%)	8 (21%)	
T3b–T4	15 (19%)	6 (14%)	9 (23%)	
Clinical N stage, No. (%)				0.6
N0	4 (4.9%)	3 (7.1%)	1 (2.6%)	
Nx	77 (95%)	39 (93%)	38 (97%)	

Table 1. Cont.

Characteristic	Overall (N = 81)	PORT (N = 42)	WPRT (N = 39)	p-Value
NCCN risk group, No. (%)				0.7
Intermediate	13 (16%)	6 (14%)	7 (18%)	
High	68 (84%)	36 (86%)	32 (82%)	
Follow-up, years, median (IQR)	14.5 (6.0, 17.0)	14.8 (8.5–18.3)	14.5 (4.9–17.0)	0.6

Abbreviations: PORT, prostate-only radiation therapy; WPRT, whole-pelvic radiation therapy; PSA, prostate specific antigen; NCCN, National Comprehensive Cancer Network.

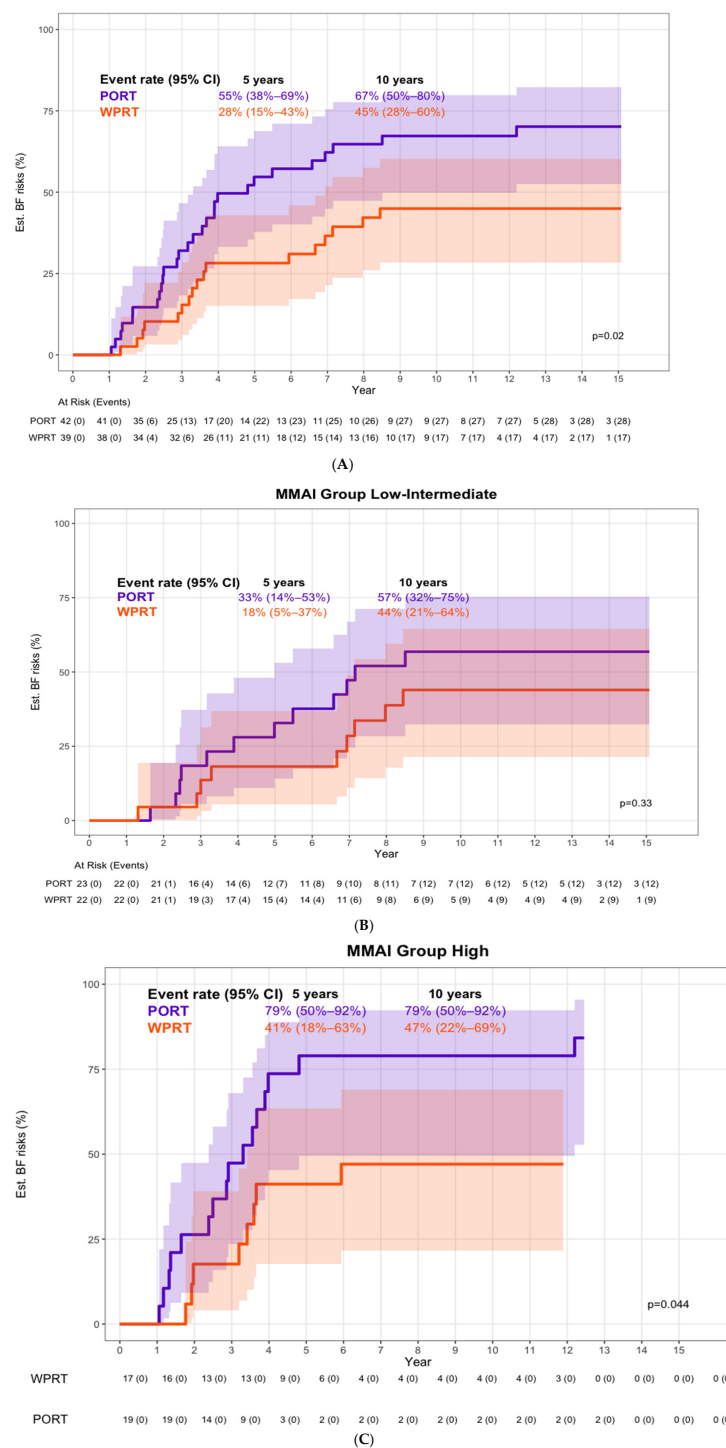


Figure 2. Cont.

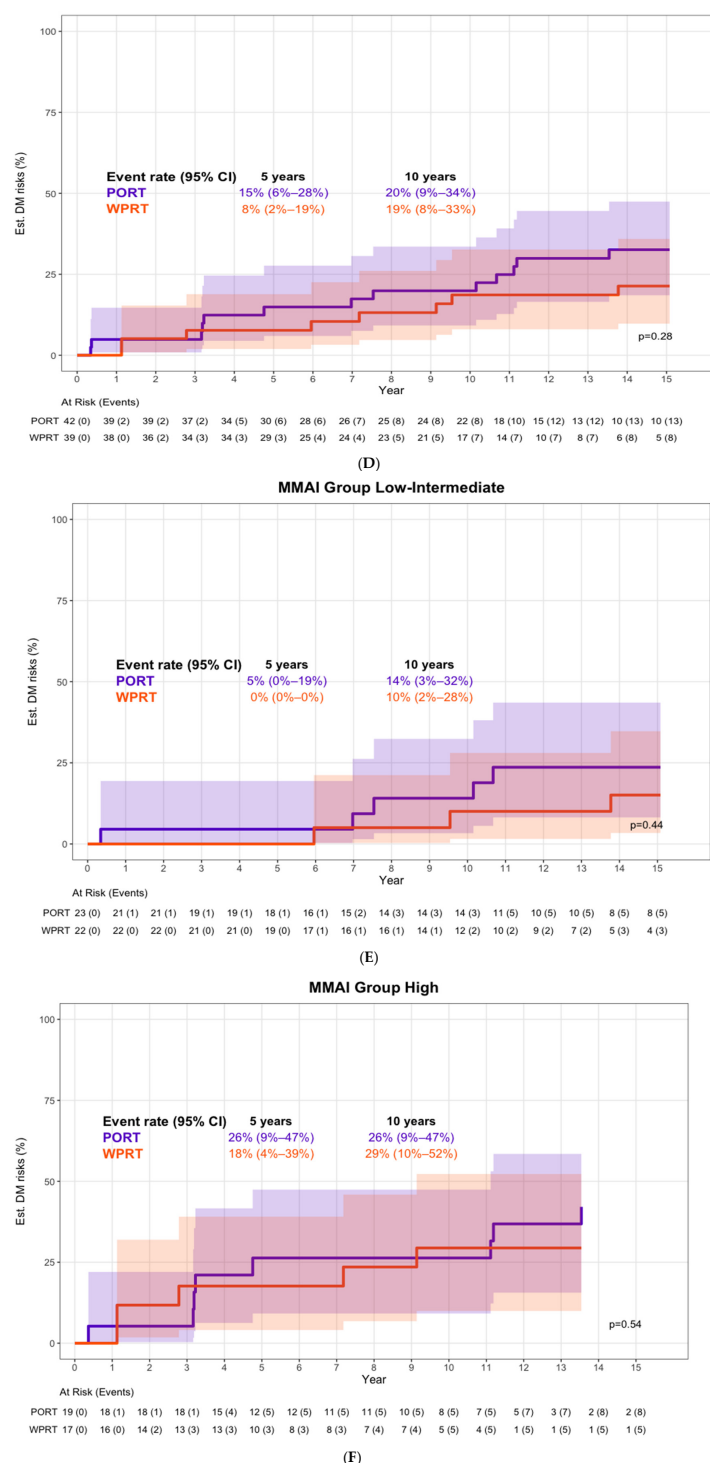


Figure 2. Cumulative incidence estimates and 95% confidence bands of biochemical failure (A–C) and distant metastasis (D–F) among patients who received neoadjuvant hormonal therapy by MMAI risk classification and radiation treatment volume. Shaded areas represent the 95% confidence bands around each cumulative incidence curve.

4. Discussion

This exploratory analysis of NRG/RTOG 9413 examined whether MMAI-derived risk groups showed differing treatment effect patterns for WPRT versus PORT. Numerically larger BF differences were observed among MMAI high-risk patients than in the low-intermediate group, whereas DM estimates were similar across strata. However, the treatment-by-MMAI interaction was not statistically significant; therefore, these findings

should be interpreted as descriptive and hypothesis-generating. Further retrospective evaluation in larger randomized datasets will be needed to determine whether these exploratory patterns are reproducible.

Despite validation of prior nodal risk models [28], more sensitive, biologically driven methods are needed to guide WPRT. The clinical relevance of these findings lies in the potential of MMAI risk classification to meet this unmet need, offering an efficient tool to personalize treatment decisions and inform future validation efforts.

These findings arrive at a time when the optimal use of WPRT remains uncertain, with randomized trials yielding inconsistent results. RTOG 9413 demonstrated a PFS benefit with WPRT [9,10], while GETUG-01 did not [11,12], and POP-RT showed BF benefits but lacks long-term data [13]. Recent observational work also suggests benefit in biologically selected subgroups [14]. Our analysis extends these insights by applying a validated MMAI framework.

Importantly, these findings should be considered within the context of contemporary PSMA-PET staging. Although PSMA-PET has substantially improved detection of nodal and distant metastases compared with conventional imaging, its sensitivity for microscopic pelvic nodal disease remains imperfect. Surgical validation studies have demonstrated that a meaningful proportion of patients with negative PSMA-PET findings harbor occult pathologic nodal metastases [29–31]. In this setting, tissue-based MMAI approaches may provide information complementary to imaging by capturing biologic features associated with aggressive disease and patterns of disease progression that are not constrained by imaging resolution. Rather than replacing PSMA-PET, MMAI may ultimately provide complementary information, with PSMA-PET identifying radiographically detectable disease and MMAI providing additional biologic risk stratification. Future studies should evaluate whether integrating MMAI with PSMA-PET improves risk stratification and further refines the study of WPRT in randomized clinical trial datasets.

NRG/RTOG 0534 and 0924 trials provide opportunities to assess whether MMAI can refine patient selection for WPRT and serve as a biomarker to guide treatment intensification. Additional validation opportunities may emerge from ongoing pelvic nodal radiotherapy trials, including PIVOTALboost and PEARLS. Future efforts should include prospective validation in larger randomized datasets adequately powered to test interactions. Using the observed interaction effect as a planning assumption, approximately 500 patients (corresponding to roughly 275 BF events) may be required to achieve 80% power for treatment-by-MMAI interaction testing.

Several limitations warrant consideration. This was a retrospective analysis, and treatment was not stratified by MMAI risk. Only a small subset ($n = 81$) of the original NHT cohort was available because many patients were used for original model optimization or lacked biopsy slides. Additionally, staging was based on pre-PSMA PET imaging, which may limit its applicability to modern practice. Moreover, while BF is a clinically relevant endpoint, its long-term association with prostate cancer-specific and overall mortality remains variable, particularly in the contemporary era of salvage therapies [32,33]. Nonetheless, BF occurred frequently enough in this cohort to permit more stable descriptive estimation of outcome patterns. In contrast, events for DM, PCSM, or OS were too sparse to support reliable subgroup summaries. Similarly, exploratory interaction analyses using NCCN risk groups yielded unstable estimates because only 13 patients were classified as NCCN intermediate-risk and events were sparse, resulting in clinically implausible treatment effect estimates that should be interpreted with caution (Supplementary Table S1). Given the limited sample size, all treatment effect estimates, particularly within MMAI risk strata, should be interpreted cautiously, and no confirmatory conclusions regarding treatment effect heterogeneity can be drawn.

BF was selected over the trial's original primary endpoint of PFS because the extended follow-up of RTOG 9413—now exceeding two decades—led many progression events to be driven by non-cancer-related deaths rather than PSA progression, and neither the original trial nor the subset analyzed here was powered to assess DM or OS. As a result, PFS has become increasingly difficult to interpret as a cancer-specific measure of treatment efficacy. BF, by contrast, offers a more direct signal of disease control and treatment effect, consistent with its use in recent trials such as POP-RT and NRG/RTOG 0924.

5. Conclusions

This study observed a stronger association between WPRT and reduced BF among MMAI high-risk patients than among low- and intermediate-risk patients. Because no significant treatment-by-MMAI interaction was observed, these findings should be considered exploratory and hypothesis-generating. MMAI may offer a potential avenue for exploring personalized treatment selection beyond conventional risk stratification. These results motivate further adequately powered validation to support the broader integration of digital pathology-based AI tools in future clinical trial design.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/doi/s1>: Table S1: Exploratory NCCN risk group analyses, neoadjuvant ADT cohort (n = 81). (A) NCCN by radiation field interaction effect; (B) Subgroup-specific treatment effects (WPRT vs. PORT) within each NCCN risk group to aid clinical interpretation of the interaction effect.

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Institutional Review Board Statement: The NRG/RTOG 9413 trial was registered at ClinicalTrials.gov (NCT00769548) and approved by the Ethics Committee of NRG (protocol code: 20027; date of approval: 29 September 2021).

Informed Consent Statement: Written informed consent was obtained from all patients enrolled in the original RTOG 9413 clinical trial. This secondary analysis was conducted using de-identified data.

Data Availability Statement: All data will be made available in accordance with the National Clinical Trials Network Data Archive policies and procedures.

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Abbreviations

The following abbreviations are used in this manuscript:

ADT	Androgen deprivation therapy
aHR	Adjusted hazard ratio
BF	Biochemical failure
CI	Confidence interval
DM	Distant metastasis
EBRT	External-beam radiotherapy
H&E	Hematoxylin and eosin
HT	Hormonal therapy
IQR	Interquartile range
MMAI	Multimodal artificial intelligence
NCCN	National Comprehensive Cancer Network
NHT	Neoadjuvant hormonal therapy
OS	Overall survival
PCSM	Prostate cancer-specific mortality

PFS	Progression-free survival
POP-RT	Prostate-Only Versus Whole-Pelvic Radiation Therapy trial
PORT	Prostate-only radiotherapy
PSA	Prostate-specific antigen
PSMA PET	Prostate-specific membrane antigen positron emission tomography
RT	Radiotherapy
WPRT	Whole-pelvic radiotherapy

References

1. Jones, C.U.; Hunt, D.; McGowan, D.G.; Amin, M.B.; Chetner, M.P.; Bruner, D.W.; Leibenhaut, M.H.; Husain, S.M.; Rotman, M.; Souhami, L.; et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N. Engl. J. Med.* **2011**, *365*, 107–118. [\[CrossRef\]](#)
2. Pisansky, T.M.; Hunt, D.; Gomella, L.G.; Amin, M.B.; Balogh, A.G.; Chinn, D.M.; Seider, M.J.; Duclos, M.; Rosenthal, S.A.; Bauman, G.S.; et al. Duration of androgen suppression before radiotherapy for localized prostate cancer: Radiation therapy oncology group randomized clinical trial 9910. *J. Clin. Oncol.* **2015**, *33*, 332–339. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Eastham, J.A.; Aufferberg, G.B.; Barocas, D.A.; Chou, R.; Crispino, T.; Davis, J.W.; Eggener, S.; Horwitz, E.M.; Kane, C.J.; Kirkby, E.; et al. Clinically Localized Prostate Cancer: AUA/ASTRO Guideline, Part I: Introduction, Risk Assessment, Staging, and Risk-Based Management. *J. Urol.* **2022**, *208*, 10–18. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Eastham, J.A.; Aufferberg, G.B.; Barocas, D.A.; Chou, R.; Crispino, T.; Davis, J.W.; Eggener, S.; Horwitz, E.M.; Kane, C.J.; Kirkby, E.; et al. Clinically Localized Prostate Cancer: AUA/ASTRO Guideline, Part II: Principles of Active Surveillance, Principles of Surgery, and Follow-Up. *J. Urol.* **2022**, *208*, 19–25. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Bekelman, J.E.; Rumble, R.B.; Freedland, S.J. Clinically Localized Prostate Cancer: ASCO Clinical Practice Guideline Endorsement of an AUA/ASTRO/SUO Guideline Summary. *J. Oncol. Pract.* **2018**, *14*, 618–624. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Spratt, D.E.; Srinivas, S.; Adra, N.; Ahmed, B.; An, Y.; Bitting, R.; Chapin, B.; Cheng, H.H.; Cho, S.Y.; D’Amico, A.V.; et al. Prostate Cancer, Version 3.2026, NCCN Clinical Practice Guidelines In Oncology. *J. Natl. Compr. Cancer Netw.* **2025**, *23*, 469–493. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Parker, C.; Castro, E.; Fizazi, K.; Heidenreich, A.; Ost, P.; Procopio, G.; Tombal, B.; Gillessen, S. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **2020**, *31*, 1119–1134. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Cornford, P.; van den Bergh, R.C.N.; Briers, E.; Van den Broeck, T.; Brunckhorst, O.; Darraugh, J.; Eberli, D.; De Meerleer, G.; De Santis, M.; Farolfi, A.; et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer-2024 Update. Part I: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur. Urol.* **2024**, *86*, 148–163. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Roach, M., 3rd; DeSilvio, M.; Lawton, C.; Uhl, V.; Machtay, M.; Seider, M.J.; Rotman, M.; Jones, C.; Asbell, S.O.; Valicenti, R.K.; et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J. Clin. Oncol.* **2003**, *21*, 1904–1911. [\[CrossRef\]](#) [\[PubMed\]](#)
10. Roach, M.; Moughan, J.; Lawton, C.A.F.; Dicker, A.P.; Zeitzer, K.L.; Gore, E.M.; Kwok, Y.; Seider, M.J.; Hsu, I.C.; Hartford, A.C.; et al. Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): Long-term results of a randomised, phase 3 trial. *Lancet Oncol.* **2018**, *19*, 1504–1515. [\[CrossRef\]](#) [\[PubMed\]](#)
11. Pommier, P.; Chabaud, S.; Lagrange, J.L.; Richaud, P.; Lesaunier, F.; Le Prise, E.; Wagner, J.P.; Hay, M.H.; Beckendorf, V.; Suchaud, J.P.; et al. Is There a Role for Pelvic Irradiation in Localized Prostate Adenocarcinoma? Preliminary Results of GETUG-01. *J. Clin. Oncol.* **2007**, *25*, 5366–5373. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Pommier, P.; Chabaud, S.; Lagrange, J.L.; Richaud, P.; Le Prise, E.; Wagner, J.P.; Azria, D.; Beckendorf, V.; Suchaud, J.P.; Bernier, V.; et al. Is There a Role for Pelvic Irradiation in Localized Prostate Adenocarcinoma? Update of the Long-Term Survival Results of the GETUG-01 Randomized Study. *Int. J. Radiat. Oncol. Biol. Phys.* **2016**, *96*, 759–769. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Murthy, V.; Maitre, P.; Kannan, S.; Panigrahi, G.; Krishnatry, R.; Bakshi, G.; Prakash, G.; Pal, M.; Menon, S.; Phurailatpam, R.; et al. Prostate-Only Versus Whole-Pelvic Radiation Therapy in High-Risk and Very High-Risk Prostate Cancer (POP-RT): Outcomes From Phase III Randomized Controlled Trial. *J. Clin. Oncol.* **2021**, *39*, 1234–1242. [\[CrossRef\]](#) [\[PubMed\]](#)
14. Sayan, M.; Chen, M.H.; Loffredo, M.; McMahon, E.; Moningi, S.; Orio, P.F.; Nguyen, P.L.; D’Amico, A.V. Elective Pelvic Lymph Node Radiation Therapy and the Risk of Death in Patients With Unfavorable-Risk Prostate Cancer: A Postrandomization Analysis. *J. Clin. Oncol.* **2024**, *42*, 2558–2564. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Partin, A.W.; Yoo, J.; Carter, H.B.; Pearson, J.D.; Chan, D.W.; Epstein, J.I.; Walsh, P.C. The Use of Prostate Specific Antigen, Clinical Stage and Gleason Score to Predict Pathological Stage in Men with Localized Prostate Cancer. *J. Urol.* **1993**, *150*, 110–114. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Chilukuri, S.; Sayan, M.; Pra, A.D.; Murthy, V. Elective Regional Nodal Irradiation in Prostate Cancer. *Semin Radiat. Oncol.* **2025**, *35*, 374–384. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Esteva, A.; Feng, J.; van der Wal, D.; Huang, S.C.; Simko, J.P.; DeVries, S.; Chen, E.; Schaeffer, E.M.; Morgan, T.M.; Sun, Y.; et al. Prostate cancer therapy personalization via multi-modal deep learning on randomized phase III clinical trials. *npj Digit. Med.* **2022**, *5*, 71. [\[CrossRef\]](#) [\[PubMed\]](#)

18. Spratt, D.E.; Tang, S.; Sun, Y.; Huang, H.C.; Chen, E.; Mohamad, O.; Armstrong, A.J.; Tward, J.D.; Nguyen, P.L.; Lang, J.M.; et al. Artificial Intelligence Predictive Model for Hormone Therapy Use in Prostate Cancer. *NEJM Evid.* **2023**, *2*, EVIDoA2300023. [\[CrossRef\]](#) [\[PubMed\]](#)
19. Roach, M.; Zhang, J.; Mohamad, O.; Wal, D.v.d.; Simko, J.P.; DeVries, S.; Huang, H.-C.; Joun, S.; Schaeffer, E.M.; Morgan, T.M.; et al. Assessing Algorithmic Fairness With a Multimodal Artificial Intelligence Model in Men of African and Non-African Origin on NRG Oncology Prostate Cancer Phase III Trials. *JCO Clin. Cancer Inform.* **2025**, *9*, e2400284. [\[CrossRef\]](#) [\[PubMed\]](#)
20. Parker, C.T.A.; Mendes, L.; Liu, V.Y.T.; Grist, E.; Joun, S.; Yamashita, R.; Mitani, A.; Chen, E.; Parry, M.A.; Sachdeva, A.; et al. External validation of a digital pathology-based multimodal artificial intelligence-derived prognostic model in patients with advanced prostate cancer starting long-term androgen deprivation therapy: A post-hoc ancillary biomarker study of four phase 3 randomised controlled trials of the STAMPEDE platform protocol. *Lancet Digit. Health* **2025**, *7*, 100885. [\[CrossRef\]](#) [\[PubMed\]](#)
21. Armstrong, A.J.; Liu, V.Y.T.; Selvaraju, R.R.; Chen, E.; Simko, J.P.; DeVries, S.; Sartor, O.; Sandler, H.M.; Mohamad, O.; Huang, H.C.; et al. Development and Validation of an Artificial Intelligence Digital Pathology Biomarker to Predict Benefit of Long-Term Hormonal Therapy and Radiotherapy in Men With High-Risk Prostate Cancer Across Multiple Phase III Trials. *J. Clin. Oncol.* **2025**, *43*, 3494–3504. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Morgan, T.M.; Ren, Y.; Tang, S.; Zwerink, W.; Chen, E.; Mitani, A.; Huang, H.C.; Simko, J.P.; DeVries, S.; Pollack, A.; et al. Development and Validation of a Multimodal Artificial Intelligence-derived Digital Pathology-based Biomarker Predicting Metastasis Among Patients with Biochemical Recurrence After Radical Prostatectomy in NRG/RTOG Trials. *Eur. Urol.* **2025**, *in press*. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Lawton, C.A.F.; Lin, X.; Hanks, G.E.; Lepor, H.; Grignon, D.J.; Brereton, H.D.; Bedi, M.; Rosenthal, S.A.; Zeitzer, K.L.; Venkatesan, V.M.; et al. Duration of Androgen Deprivation in Locally Advanced Prostate Cancer: Long-Term Update of NRG Oncology RTOG 9202. *Int. J. Radiat. Oncol. Biol. Phys.* **2017**, *98*, 296–303. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Lawton, C.A.; DeSilvio, M.; Roach, M., 3rd; Uhl, V.; Kirsch, R.; Seider, M.; Rotman, M.; Jones, C.; Asbell, S.; Valicenti, R.; et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: Updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int. J. Radiat. Oncol. Biol. Phys.* **2007**, *69*, 646–655. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Gerrard, P.; Zhang, J.; Yamashita, R.; Huang, H.-C.; Nag, S.; Nhek, S.; Kish, J.M.; Cole, A.; Silberman, N.; Royce, T.J.; et al. Analytical Validation of a Clinical Grade Prognostic and Classification Artificial Intelligence Laboratory Test for Men with Prostate Cancer. *AI Precis. Oncol.* **2024**, *1*, 119–126. [\[CrossRef\]](#)
26. National Cancer Institute; NRG Oncology. *Androgen Deprivation Therapy and High Dose Radiotherapy with or Without Whole-Pelvic Radiotherapy in Unfavorable Intermediate or Favorable High Risk Prostate Cancer: A Phase III Randomized Trial*; National Cancer: Philadelphia, PA, USA; NRG Oncology: Philadelphia, PA, USA, 2011.
27. Roach, M.I.; Karrison, T.; Chung, H.; Chang, A.J.; Gomella, L.G.; Hsu, I.-C.; Morton, G.; Wallace, R.E.; Movsas, B.; Bruner, D.W.; et al. Androgen Deprivation Therapy (ADT) and High Dose Definitive Radiotherapy (RT) + / – Whole Pelvic RT in Patients with Unfavorable Intermediate or Favorable High-Risk Prostate Cancer: Early Results of a Phase III Randomized Trial, NRG/RTOG 0924. In Proceedings of the ASTRO Annual Meeting, San Francisco, CA, USA, 28–30 September 2025.
28. Abdollah, F.; Cozzarini, C.; Suardi, N.; Gallina, A.; Capitanio, U.; Bianchi, M.; Tutolo, M.; Salonia, A.; La Macchia, M.; Di Muzio, N.; et al. Indications for pelvic nodal treatment in prostate cancer should change. Validation of the Roach formula in a large extended nodal dissection series. *Int. J. Radiat. Oncol. Biol. Phys.* **2012**, *83*, 624–629. [\[CrossRef\]](#) [\[PubMed\]](#)
29. Yaxley, J.W.; Raveenthiran, S.; Nouhaud, F.X.; Samartunga, H.; Yaxley, A.J.; Coughlin, G.; Delahunt, B.; Egevad, L.; McEwan, L.; Wong, D. Outcomes of Primary Lymph Node Staging of Intermediate and High Risk Prostate Cancer with (68)Ga-PSMA Positron Emission Tomography/Computerized Tomography Compared to Histological Correlation of Pelvic Lymph Node Pathology. *J. Urol.* **2019**, *201*, 815–820. [\[CrossRef\]](#) [\[PubMed\]](#)
30. Ozen, A.; Sarikaya, Z.; Gur, C.; Ozboru, D.; Canat, H.L. Pelvic Lymph Node Staging With PSMA PET in Prostate Cancer: Surgical Validation With Implications for Radiotherapy Planning. *Prostate* **2026**, *86*, 648–654. [\[CrossRef\]](#) [\[PubMed\]](#)
31. Pickersgill, N.A.; Yu, R.; Vertosick, E.A.; Fletcher, S.A.; Liso, N.; Kluckert, J.; Akin, O.; Ehdaie, B.; Laudone, V.P.; Eastham, J.A.; et al. Diagnostic and prognostic utility of PSMA-PET/CT in node-metastatic prostate cancer. *BJU Int.* **2026**, *Online ahead of print*. [\[CrossRef\]](#)
32. Dignam, J.J.; Hamstra, D.A.; Lepor, H.; Grignon, D.; Brereton, H.; Currey, A.; Rosenthal, S.; Zeitzer, K.L.; Venkatesan, V.M.; Horwitz, E.M.; et al. Time Interval to Biochemical Failure as a Surrogate End Point in Locally Advanced Prostate Cancer: Analysis of Randomized Trial NRG/RTOG 9202. *J. Clin. Oncol.* **2019**, *37*, 213–221. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Valle, L.F.; Lehrer, E.J.; Markovic, D.; Elashoff, D.; Levin-Epstein, R.; Karnes, R.J.; Reiter, R.E.; Rettig, M.; Calais, J.; Nickols, N.G.; et al. A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER). *Eur. Urol.* **2021**, *80*, 280–292. [\[CrossRef\]](#) [\[PubMed\]](#)

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