Advances in Radiation Oncology (2026) **11**, 102022

advances in radiation oncology

www.advancesradonc.org

Scientific Article

The Association of p27 With Prostate Cancer Outcomes: A Secondary Analysis of NRG/RTOG 8610 and 9202

Krishnan R. Patel, MD, MHS,[a,*] Stephanie L. Pugh, PhD,[b,c] Jeffry P. Simko, MD, PhD,[d] Anthony Zietman, MD,[e] Michelangelo Fiorentino, MD,[f] David Paul D'Souza, MD,[g] Seth Rosenthal, MD,[h] Adam Currey, MD,[i] Adam Dicker, MD, PhD,[j] Bradley J. Stish, MD,[k] Eric M. Horwitz, MD,[l] Tyler P. Robin, MD, PhD,[m] Michael Dominello, DO,[n] Christopher Peters, MD,[o] Kwang Choi, MD,[p] Jason A. Efstathiou, MD,[q] Samir Narayan, MD,[r] George Daniel Grass, MD, PhD,[s] Zaker H. Rana, MD,[t] Phuoc T. Tran, MD, PhD,[u] Massimo Loda, MD,[v] and Paul L. Nguyen, MD[w]

[a]Radiation Oncology Branch, National Cancer Institute, National Institutes of Health (NIH), Bethesda, Maryland; [b]NRG Oncology Statistics and Data Management Center, Philadelphia, Pennsylvania; [c]American College of Radiology, Philadelphia, Pennsylvania; [d]UCSF Medical Center-Mount Zion, San Francisco, California; [e]Massachusetts General Hospital Cancer Center, Boston, Massachusetts; [f]University of Bologna, Bologna, Italy; [g]Verspeeten Family Cancer Centre, London Health Sciences Centre & Western University, London, Ontario, Canada; [h]Sutter Cancer Centers Radiation Oncology Services-Roseville, Roseville, California; [i]The Medical College of Wisconsin and Zablocki VAMC, Milwaukee, Wisconsin; [j]Thomas Jefferson University, Philadelphia, Pennsylvania; [k]Mayo Clinic, Rochester, Minnesota; [l]Fox Chase Cancer Center and the Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania; [m]University of Colorado, Aurora, Colorado; [n]Wayne State University/Karmanos Cancer Institute, Detroit, Michigan; [o]NROC, Dunmore, Pennsylvania; [p]University Hospital at Downstate, Brooklyn, New York; [q]Massachusetts General Hospital/Mass General Brigham, Boston, Massachusetts; [r]Michigan Cancer Research Consortium - Trinity Health Ann Arbor Hospital, Ann Arbor, Michigan; [s]H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida; [t]University of Maryland School of Medicine, Baltimore, Maryland; [u]Department of Genitourinary Radiation Oncology, Division of Radiation Oncology, MD Anderson Cancer Center, Houston, Texas; [v]NYP/Weill Cornell Medical Center, New York, New York; and [w]Brigham and Women's Hospital, Boston, Massachusetts

Received 12 January 2026; accepted 24 February 2026

Sources of support: Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number UG1CA189867 (NCORP), U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), U24CA196067 (NRG Specimen Bank), R01 CA240582-01, and CTEP. This research was supported in part by the Intramural Research Program of the National Institutes of Health (NIH) (Z99 CA999999). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This research was supported by the National Institutes of Health (NIH). In accordance with the NIH Public Access Policy, the final peer-reviewed manuscript will be submitted to PubMed Central on acceptance for publication and made publicly available immediately on publication.

The data from this study may be made available on reasonable request.

*Corresponding author: Krishnan R. Patel, MD, MHS; Email: Krishnan.R.Patel.MD@gmail.com

https://doi.org/10.1016/j.adro.2026.102022

Purpose: The cyclin-dependent kinase inhibitor p27 is a well-profiled modulator of cell cycle progression. Low nuclear p27 levels have been demonstrated to have a negative prognostic impact on outcomes in patients undergoing prostatectomy. The prognostic value of p27 after radiation therapy (RT) for prostate cancer is unknown.

Methods and materials: Levels of p27 were evaluated in pre-RT prostate biopsy samples from 2 randomized, phase 3 trials, NRG/RTOG 8610 and 9202, which treated patients with RT with or without androgen deprivation therapy (ADT). Nuclear p27 was analyzed using immunohistochemistry and quantified using automated imaging analysis. The association of p27 as both a continuous and categorical measure (≤ median vs > median) with clinical outcome was estimated using both univariable (UVA) and multivariable Cox proportional hazards models. The primary clinical outcome measure was overall survival, and secondary measures were disease-specific survival (DSS), disease-free survival, distant metastases, and biochemical failure.

Results: In the analytical cohort (n = 361), no association of p27 with overall survival was observed on UVA. The only statistically significant association observed on UVA was between categorical p27 high levels and DSS (hazard ratio [HR] 1.57 [95% CI, 1.01-2.43], P = .044) in the combined cohort. However, a similar association was not observed with DSS when analyzing continuous p27 (P = .09). On multivariable analyses, no statistically significant association was observed between p27 and any evaluated clinical outcome measure (all P > .05).

Conclusions: This study produced insufficient evidence to conclude that nuclear p27 level is prognostic of outcome in patients undergoing RT ± ADT. The observed trend was opposite in direction to the prior observations in the postprostatectomy literature, which served as a basis for this study. Given this, these data generate the hypothesis that the negative prognostic value of low nuclear p27 level in patients undergoing prostatectomy may be obviated by the receipt of RT ± ADT. Although this does appear congruent with known mechanistic differences between the two treatments, further studies are required to confirm this finding.

Introduction

Prostate cancer is a heterogeneous condition with a wide spectrum of prognoses. Some patients with low-grade, favorable risk features will have excellent outcomes on surveillance alone,[1] whereas others with more aggressive disease features will require radical therapy[2] with or without systemic intensification[3-5] to optimize survival.

Treatment recommendations are often formulated based on an estimation of prognosis, where treatment intensity is proportional to an estimate of disease aggressiveness. Thus, prognostic tools often serve as a basis for clinical decision making. Several prognostic methods have been proposed including those using anatomic staging alone[6] or anatomic staging with the integration of biomarkers such as prostate-specific antigen (PSA),[7] molecular diagnostics,[8] or pathology assessment.[9]

The development of prognostic, molecular biomarkers is an evolving field, and both exploratory[10] and hypothesis-driven[11] biomarkers have been profiled. One such biomarker is the measured expression of p27, a cyclin-dependent kinase inhibitor (CDKi), which enforces cell cycle checkpoints (Fig. 1).[11-17] Prior studies investigating this biomarker have shown low p27 levels to be prognostic in patients managed with radical prostatectomy.[18-21] It, however, remains unknown whether all predictors of oncologic outcomes after curative local therapy are similar between men who undergo primary management with either surgery or radiation therapy (RT).

Here, we test the hypothesis that low p27 can predict adverse cancer-related outcomes in 2 phase 3 trials, NRG/RTOG 8610[22] and 9202,[23] which treated patients with curative radiation therapy either alone or with androgen deprivation therapy (ADT), to inform future biomarker development.

Methods and Materials

Approval and data source

This project was approved by the Cancer Therapy Evaluation Program Core Correlatives Science Committee at the National Cancer Institute to access archived biopsy specimens from patients treated on NRG Oncology/RTOG 8610 and 9202[22,23] as well as an institutional review board.

p27 quantitation

Specimen review was conducted by the RTOG Biobank pathologist to ensure the presence of tumor for each available sample. For samples with adequate tissue, p27 immunohistochemistry (IHC) staining was performed to quantify nuclear p27 expression. Staining was performed with a purified mouse anti-p27[Kip1] antibody (#610242 BD Biosciences). Each sample was measured via an automated imaging analysis platform, the Ariol system (Leica Biosystems). The Ariol system is an automated software platform that was used to quantify IHC staining with a continuous score from 0 (no expression) to 1 (high expression). Briefly, this system works by evaluating the proportion of cells with a higher signal than an internal control. Any tumor cell expressing levels equal to or higher than the internal positive control on the slides is deemed positive. Once the threshold is estimated from

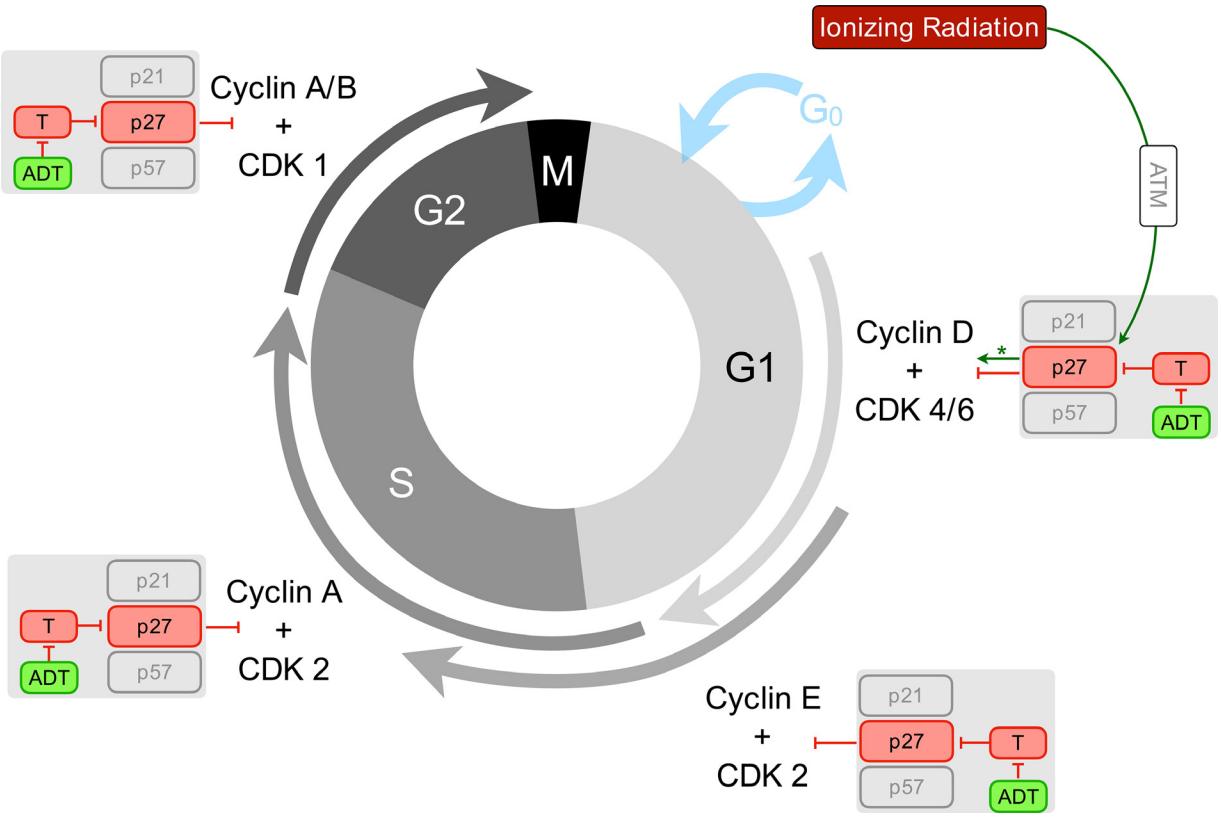

Figure 1 The role of nuclear p27 in the cell cycle. In this schematic, the inhibitory role of p27 on cell cycle progression is highlighted.[12] Each element with a usual inhibitory effect on the cell cycle is depicted in red and those with a stimulatory effect in green. The role of androgen receptor modulation with testosterone (T) and androgen deprivation therapy (ADT) as a regulator of p27 is also shown as relevant to the current study.[13,14] Ionizing radiation has been reported to stabilize p27 via ATM-mediated phosphorylation serving to mediate G1 cell cycle arrest.[15] Although p27 generally serves to negatively regulate cyclin-dependent kinase, they are also promoters/stabilizers of cyclin D-CDK 4/6 complexes, and in the absence of this CDKi, the cell cycle is inhibited.[16,17] This dual role of p27 is denoted by an asterisk (*).
Abbreviations: ADT, androgen deprivation therapy; ATM, Ataxia-Telangiectasia Mutated; CDK, cyclin-dependent kinase; CDKi, cyclin-dependent kinase inhibitor; G1, G1 phase; G2, G2 phase; M, mitosis; S, Synthesis phase; T, testosterone.

the internal control, the automated counts are determined as the proportion of p27-positive tumor cells over the total number of tumor cells. The positive control for each slide was lymphocytes in G0, which do not cycle.

Protocol-specified treatment

Both NRG/RTOG 8610[22] and 9202[23] were randomized phase 3 trials examining the benefit of the addition or protraction of ADT with radiation therapy in patients with higher-risk localized or node-positive prostate cancer. On both trials, RT was delivered via a 2-phase approach with 44 to 50 Gy to the pelvic lymphatics followed by a boost to 65 to 72 Gy to the prostate. In NRG/RTOG 8610, participants were randomized between RT alone (*RT alone*) and 4 months (*RT + 4*) of ADT, and in NRG/RTOG 9202, participants were randomized between 4 (*RT + 4*) with or without an additional 24 months (*RT + 28*) of ADT.

Endpoints

The primary endpoint of this study was overall survival (OS) indexed from the date of randomization. Secondary endpoints included disease-specific survival (DSS), the time from randomization until death because of prostate cancer (OS), disease-free survival (DFS), the time from randomization until disease progression or death, distant metastases (DM), biochemical failure (BF), and the time to biochemical failure or salvage therapy by the Phoenix criteria.[24] Patients without an event were censored at their last known follow-up time.

Statistical analysis

The biomarker, p27, was associated with various clinical outcomes using Cox proportional hazards models.[25]

For endpoints with competing risks, the cause-specific model was produced by censoring the competing risk. The primary analysis was conducted in the overall analytical cohort. Univariate analyses (UVAs) were conducted separately by study as well. UVAs conducted in the overall analytical cohort included adjustment for trial. Multivariable analyses were constructed accounting for trial treatment arm, age, Gleason score, race, and Karnofsky Performance Status in addition to p27 level. The level of p27 was analyzed both as a continuous and categorical variable, where the categorical variable was generated using the median p27 IHC level as the cut point. Baseline characteristics were compared using *t*-tests, or the Wilcoxon rank sum test for non-normality, for continuous data, and χ^2 tests, or Fisher's exact test in the presence of small cell counts, for categorical data. All hypothesis testing was 2-sided with an α threshold of 0.05, and no adjustment for multiple testing was used because of the exploratory nature of these analyses.

Results

Baseline characteristics

The analytical cohort consisted of 361 patients ($n_{NRG/RTOG\ 8610}$ = 38; $n_{NRG/RTOG\ 9202}$ = 323) as shown in Fig. 2. The median age was 70 years (quartile [Q]1-Q3: 66-74) (Table 1). The median PSA for those with PSA available was 21.3 ng/mL (Q1-Q3: 11.2-40.7). The majority of tumors were Gleason score ≥7, and these tumors were overrepresented in patients with a p27 score available as opposed to those with other grades (68.0% vs 55.8%) (Table E1). The median p27 IHC level or score of the analytical cohort was 0.36 (Q1-Q3: 0.13-0.58). The number of events identified and observed for each endpoint is reported in Table E2.

Univariable analysis

On UVA, p27 was not significantly associated with OS, DSS, DFS, DM, or BF when analyzed as a continuous variable (Table 2). When analyzed as a categorical variable, high p27 score was associated with a significantly worse OS in NRG/RTOG 8610 (HR, 2.20 [95% CI, 1.04-4.69], P = .040) but not in NRG/RTOG 9202 (HR, 1.09 [95% CI, 0.86-1.39], P = .47) or the combined study cohort (HR, 1.19 [95% CI, 0.94-1.49], P = .14). A high categorical p27 score was associated with significantly worse DSS in the combined analysis (HR, 1.57 [95% CI, 1.01-2.43], P = .044) but not by individual study. There were no significant associations between categorical p27 score and DFS, DM, or BF. Survival outcomes by p27 category (< vs ≥ median p27) are provided in Figure E1.

Multivariable analysis

On multivariable analyses, no evidence of a statistically significant effect of continuous p27 score was observed for the primary endpoint, OS ($HR_{adjusted}$, 1.31 [95% CI, 0.82-2.10], P = .26). Similarly, a nonsignificant positive association was observed with the remaining oncologic endpoints analyzed: DSS ($HR_{adjusted}$, 2.24 [95% CI,

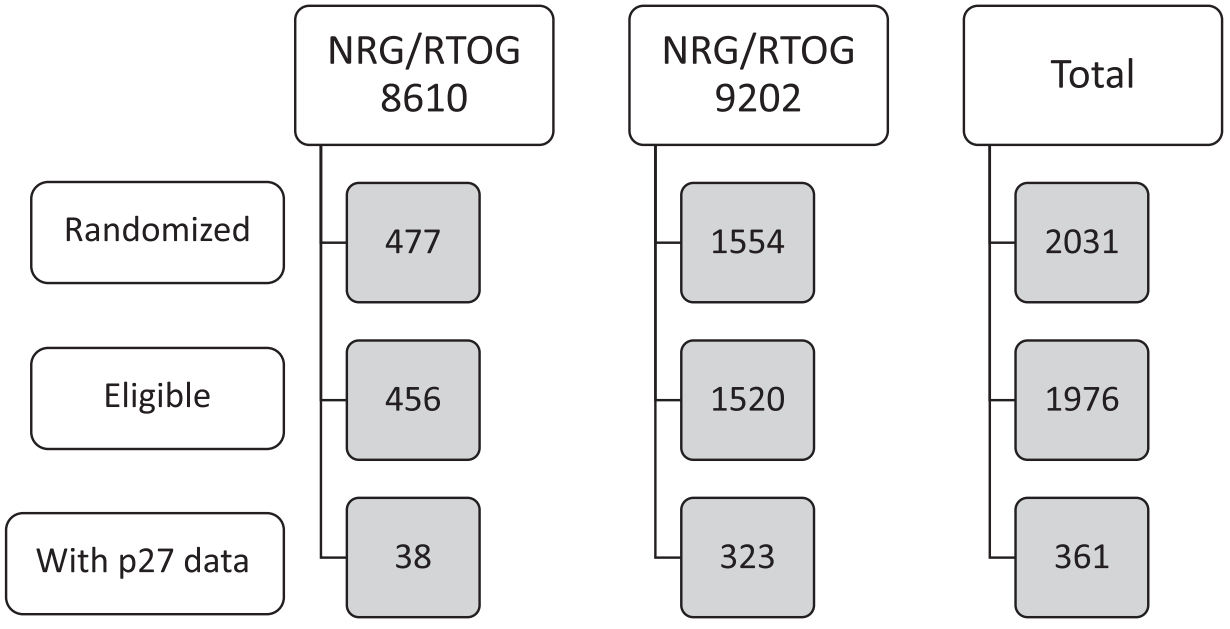

Figure 2 Flow diagram representing analytical cohort composition by trial.

Table 1 Baseline characteristics of the study cohort

	NRG/RTOG 8610 *n* = 38	NRG/RTOG 9202 *n* = 323	Analytical cohort *n* = 361
Age, y	71 (66-75)	70 (65-74)	70 (66-74)
Randomization arm			
RT alone	21 (55.3%)	-	21 (5.8%)
RT + 4 mo ADT	17 (44.7%)	140 (43.3%)	157 (43.5%)
RT + 28 moADT	-	183 (56.7%)	183 (50.7%)
KPS			
70	-	3 (0.9%)	3 (0.8%)
80	3 (7.9%)	27 (8.4%)	30 (8.3%)
90	22 (57.9%)	164 (50.8%)	186 (51.5%)
100	13 (34.2%)	129 (39.9%)	142 (39.3%)
Race			
White	34 (89.5%)	259 (80.2%)	293 (81.2%)
Black	4 (10.5%)	57 (17.6%)	61 (16.9%)
Other	-	7 (2.2%)	7 (1.9%)
Gleason score (GS)			
GS ≤6	12 (34.3%)	96 (31.7%)	108 (32.1%)
GS 7	9 (25.7%)	113 (37.4%)	122 (36.2%)
GS ≥8	14 (40.0%)	93 (30.8%)	107 (31.8%)
Missing	3 (7.9%)	21 (6.5%)	24 (6.6%)
PSA	23.9 (6.3-23.2)	21.4 (11.6-40.8)	21.3 (11.2-40.7)
Total	38/456 (8.3%)	323/1520 (21.3%)	361/1976 (18.3%)

ADT, androgen deprivation therapy; GS, Gleason score; NRG/RTOG, NRG Oncology/ Radiation Therapy Oncology Group; KPS, Karnofsky Performance Status; PSA, prostate-specific antigen; RT, radiation therapy.
Note: Values in cells represent the number of specimens with corresponding percentage or a median with quartile 1 and 3 values.

0.87-5.78], P = .09), DFS ($HR_{adjusted}$, 1.26 [95% CI, 0.80−1.99], P = .32), DM ($HR_{adjusted}$, 1.21 [95% CI, 0.76-1.93], P = .42), or BF ($HR_{adjusted}$, 1.25 [95% CI, 0.79-1.98], P = .38).

A similar nonsignificant association was observed when p27 score was analyzed as a categorical variable (≥ median vs < median) for OS ($HR_{adjusted}$, 1.17 [95% CI, 0.92-1.49], P = .21), DSS $HR_{adjusted}$, 1.51 [95% CI, 0.95-2.41], P = .08), DFS ($HR_{adjusted}$, 1.13 [95% CI, 0.90-1.42], P = .29), DM ($HR_{adjusted}$, 1.23 [95% CI, 0.80-1.88], P = .34), or BF ($HR_{adjusted}$, 1.16 [95% CI, 0.85-1.56], P = .35). A summary of the adjusted estimates for prognostic effect is shown in Table 3 and Figure E2.

Discussion

In this translational study of two, multi-institutional, phase 3 trials, NRG/RTOG 8610[22] and 9202,[23] we did not observe nuclear p27 levels to be a prognostic biomarker associated with worse outcomes for patients undergoing definitive RT with or without ADT for treatment of localized, high-risk prostate cancer. Although on UVA higher p27 levels were associated with worse OS, this was not observed when p27 levels were examined as a continuous variable, suggesting these findings may be spurious, especially in the context of the multiplicity of hypotheses tested in this exploratory analysis. This was in contrast to most[19,26,27] but not all[28] prior studies in prostate cancer, suggesting the prognostic value of this CDKi in the postoperative setting. These findings may be reflective of the following: (1) the different mechanisms of cancer control intrinsic to radiation therapy when compared with surgery, (2) the effect of ADT used in conjunction with RT in the vast majority (94%) of this patient cohort, or (3) the lack of a true prognostic influence of nuclear p27 level.[28]

The cyclin-dependent kinase inhibitor, p27, functions as a normal checkpoint on cell cycle progression at multiple stages.[29] It has been identified that a biomarker either alone or in combination with other factors associated with oncologic outcomes in several solid malignancies, including head and neck cancer,[30] breast cancer,[31] lung

Table 2 Prognostic estimates of p27 on univariable analysis

	Continuous p27			Categorical p27 (≥ median vs < median [ref.])		
	HR	95% CI	*P* value	HR	95% CI	*P* value
NRG/RTOG 8610						
OS	5.22	0.53-51.71	0.16	2.20	1.04-4.69	0.040
DSS	11.3	0.68-186.0	0.090	2.39	0.86-6.61	0.095
DFS	0.34	0.03-4.00	0.39	0.92	0.48-1.78	0.80
DM	2.41	0.18-31.6	0.50	1.79	0.79-4.07	0.16
BF	1.34	0.10-18.7	0.83	1.27	0.59-2.72	0.53
NRG/RTOG 9202						
OS	1.35	0.85-2.14	0.20	1.09	0.86-1.39	0.47
DSS	1.80	0.72-4.50	0.21	1.33	0.82-2.17	0.24
DFS	1.33	0.85-2.08	0.21	1.13	0.90-1.42	0.29
DM	1.35	0.57-3.19	0.49	1.22	0.78-1.91	0.39
BF	1.18	0.65-2.14	0.58	1.11	0.82-1.51	0.49
Analytical cohort (adjusted for study)						
OS	1.43	0.91-2.24	0.12	1.19	0.94-1.49	0.14
DSS	2.18	0.90-5.28	0.085	1.57	1.01-2.43	0.044
DFS	1.26	0.81-1.95	0.30	1.12	0.90-1.39	0.31
DM	1.44	0.65-3.27	0.38	1.36	0.92-2.02	0.13
BF	1.17	0.65-2.08	0.60	1.14	0.86-1.51	0.35

BF, biochemical failure; DFS, disease-free survival; DM, distant metastasis; DSS, disease-specific survival; HR, hazard ratio; NRG/RTOG, NRG Oncology/ Radiation Therapy Oncology Group; OS, overall survival.

cancer,[32] hepatocellular carcinoma,[33] colon cancer,[34] bladder cancer,[35] endometrial cancer,[36] ovarian cancer,[32] and prostate cancer.[19,26,27] Low levels of p27 have been associated with poor outcomes in several cancers,[37] including prostate cancer.[18,21] Specifically, several studies have demonstrated low nuclear levels of p27 to be an adverse prognostic factor for both BF[18,19] and DSS[18] after surgery for prostate cancer. Our study failed to replicate these observations, finding a trend in the opposite direction in the context of limited power resulting from low precision effect estimates.

Based on current knowledge regarding the biology of p27 (Fig. 1), we speculate that this may be a result of the difference in the mechanism of cancer control after surgery and RT with ADT. Surgery physically removes tumor cells with recurrent disease presumably because of unmodified residual tumor tissue, which was not extirpated, and thus, the native p27 levels in untreated tissue are a valuable window into the eventual outcome after surgery. In contrast, RT with ADT acts via modification and targeted damage of tumor tissue, impacting their viability for continued division and metastasis. In this case, the influence of pretreatment p27 level may be modified by the receipt of treatment, thus obviating the prognostic impact of this information.

Mechanistically, it is understood that ionizing radiation, unlike surgery, can serve to stabilize p27 via Ataxia-Telangiectasia Mutated (ATM)-mediated phosphorylation.[32] Additionally, ADT may act to increase p27 levels.[13,14] These 2 factors may either alone or in conjunction attenuate or negate the poor prognostic effect of low p27 levels observed in patients who have undergone surgery. Based on comparisons to the available prior surgical literature in which low p27 appeared deleterious,[18,21,26] these findings suggest the hypothesis that p27 may be a candidate biomarker to help select which patients with low p27 tumors are best suited for management with definitive RT ± ADT. It should be cautioned that this is a hypothesis based on a global evaluation of the sparse literature and thus would require rigorous confirmatory testing prior to acceptance.

Furthermore, p27 biology suggests a complex relationship between p27 levels and prognosis. Although nuclear p27 is a well-profiled inhibitor of cyclin D-CDK 4/6 complexes with an inhibitory effect on cell cycle progression,[32] it also serves a dual role in stabilizing cyclin D-CDK complexes and therefore also is required for normal cell cycle progression.[16,17] Thus, both extremes, high and low nuclear p27 levels, may be inhibitory.[27] Under such a model, there may be a nonmonotonic relationship of

Table 3 Prognostic estimates of continuous p27 on multivariable analysis

	Multivariable analysis		
	HR	95% CI	*P* value
NRG/RTOG 8610			
OS	3.32	0.15-72.51	0.45
DSS	5.75	0.11-287.7	0.38
DFS	1.19	0.04-37.50	0.92
DM	1.44	0.06-33.31	0.82
BF	1.55	0.04-58.73	0.81
NRG/RTOG 9202			
OS	1.30	0.81-2.09	0.27
DSS	1.91	0.73-5.01	0.19
DFS	1.29	0.81-2.04	0.28
DM	1.21	0.76-1.93	0.43
BF	1.27	0.80-2.02	0.31
Analytical cohort			
OS	1.39	0.87-2.22	0.16
DSS	2.10	0.82-5.37	0.12
DFS	1.27	0.80-2.00	0.31
DM	1.27	0.80-2.01	0.32
BF	1.26	0.80-1.99	0.33

BF, biochemical failure; DFS, disease-free survival; DM, distant metastasis; DSS, disease-specific survival; HR, hazard ratio; KPS, Karnofsky Performance Status; NRG/RTOG, NRG Oncology/ Radiation Therapy Oncology Group; OS, overall survival.
Multivariable models are adjusted for treatment arm, age (continuous), Gleason score, race, and KPS.

nuclear p27 levels with risk, as observed previously.[27] Furthermore, p27 also exists in the cytoplasm, where high levels appear to portend worse prognoses.[27] As automated p27 quantification may have in some cases identified cytoplasmic p27, any detection of the cytoplasmic fraction may also explain the incongruence of our results with the current body of literature.

Limitations

This study has several limitations. First, the analytical cohort comprised only approximately one-fifth of the combined trial population of NRG/RTOG 8610 and 9202 (n = 361/1976). This was because of both the incomplete specimen collection and the age of these samples, making p27 levels unevaluable for many specimens. This served to limit the sample size, which, in turn, limited the statistical power to detect statistically significant effects. Additionally, the analytical cohort was not entirely representative of the full combined cohort with higher proportions of patients with Gleason score 8 to 10 prostate cancer and PSAs >30. Furthermore, because of stage migration related to the adoption of PSA screening, modern-day high-risk prostate cancer may represent a different clinical entity, impacting the generalizability of these findings to modern practice. Additionally, it is important to note that given the structure of this study, no causal claims can be made. Instead, the objective was to profile the association of p27 with oncologic outcome. Finally, it is important to note that this report reflects a negative study, and findings herein should be regarded as strictly hypothesis-generating.

Conclusions

In the first study to evaluate nuclear p27 level as a prognostic biomarker in the postradiotherapy population, we did not find evidence of the prognostic utility of this biomarker, despite prior evidence of its utility postsurgically. Several plausible explanations exist, and this difference may help to highlight important differences in the underlying mechanism of treatment effect between surgery and RT + ADT. A hypothesis generated from this work is that for patients with low p27 levels, the adverse prognostic impact of p27 may be obviated by electing for RT + ADT as opposed to surgery.

Disclosures

Adam Currey declares that in the last 36 months, participation on the Data Safety Monitoring Board for the Advisory Board for Serve on the Data Safety Monitoring Board for Medical College of Wisconsin with specifications/comments, a volunteer position and no salary support is received for work on this committee; leadership or fiduciary role in other board, society, committee, or advocacy group, paid or unpaid, for Association of Directors of Radiation Oncology Programs (ADROP) with specifications/comments of served on the executive committee of ADROP, a group designed to support radiation oncology residency program directors. This is an unpaid position.

Adam Dicker declares that in the last 36 months, grants or contracts from any entity including Prostate Cancer Foundation, DOD; consulting fees received from Janssen, NCI; participation on a Data Safety Monitoring Board or Advisory Board for Janssen; and leadership or fiduciary roles in other boards, societies, committees, or advocacy groups, paid or unpaid, for NRG Oncology.

Jason A. Efstathiou declares in the last 36 months, consulting fees received from Blue Earth Diagnostics, Boston Scientific, AstraZeneca, Lantheus, Astellas/Pfizer, Clarity Pharmaceuticals, Genentech, Janssen/Johnson&Johnson, MDxHealth, Bioprotect with Specifications/Comments of to me; payment or honoraria for lectures, presentations,

speakers, bureaus, manuscript writing or educational events from Elekta, IBA with Specifications/Comments of to me; participation on a Data Safety Monitoring Board or Advisory Board for Merck, Roivant Pharma, Myovant Sciences, Bayer Healthcare, Progenics Pharmaceuticals, Gilead, Angiodynamics with Specifications/Comments of to me; leadership or fiduciary role in other board, society, committee, or advocacy group, paid or unpaid from board member (unpaid): Massachusetts Prostate Cancer Coalition (MPCC); American College of Radiation Oncology (ACRO); and Radiation Oncology Institute (ROI) with Specifications/Comments of unpaid.

Paul L. Nguyen declares in the last 36 months, grants or contracts from Astellas, Bayer, Janssen; consulting fees received from Novartis, Blue Earth, Boston Scientific, Amgen, Nanocan, Janssen; leadership or fiduciary role in other boards, societies, committees, or advocacy groups, paid or unpaid, from NRG Oncology chair; and stock or stock options received from Nanocan, reversal therapeutics, and Stratagen bio.

Stephanie L. Pugh declares that in the last 36 months, since the initial planning of the work, all support for the present manuscript (eg, funding, provision of study materials, medical writing, article processing charges) from the National Cancer Institute, with specifications/comments of the grant paid to my institution.

Jeffry P. Simko declares that in the last 36 months, since the initial planning of the work, all support for the present manuscript (eg, funding, provision of study materials, medical writing, article processing charges) from NCI, with specifications/comments to my institution.

Bradley J. Stish declares that in the last 36 months, grants or contracts from Varian Medical Systems with specifications/comments of research funding; payment or honoraria for lectures, presentations, speakers, bureaus, and manuscript writing or educational events from Kansas Society of Clinical Oncology with specifications/comments of invited speaker at annual meeting; and support for attending meetings and/or travel from Kansas Society of Clinical Oncology with specifications/comments of invited speaker at annual meeting.

Phuoc T. Tran declares that in the last 36 months, grants or contracts from consulting/advisory roles for Astellas Pharma, Regeneron, Reflexion Medical, and Den; royalties or licenses received from patents with Natsar Pharmaceuticals (compounds and methods of use in ablative radiation therapy). Patent filed 3/9/2012, PCT/US2012/028475, licensed with royalties; consulting fees received from consulting/advisory role for Astellas Pharma, Regeneron, Reflexion Medical, Dendreon, Noxopharm, Janssen, Myovant Sciences, AstraZeneca, Lantheus, Pfizer, and Bayer Health; and patents planned, issued, or pending from patent with Natsar Pharmaceuticals (compounds and methods of use in ablative radiation therapy). Patent filed 3/9/2012, PCT/US2012/028475, licensed with royalties.

Michael Dominello, David Paul D'Souza, Michelangelo Fiorentino, George Daniel Grass, Eric M. Horwitz, Massimo Loda, Samir Narayan, Krishnan R. Patel, Christopher Peters, Zaker H. Rana, Tyler P. Robin, Seth Rosenthal, Anthony Zietman, and Kwang Choi have nothing to disclose.

Funding

This research was supported in part by the Intramural Research Program of the National Institutes of Health (NIH) (Z99 CA999999).

Acknowledgments

Krishnan R. Patel, MD, MHS, and NRG Oncology would like to thank the following accrual institutions, which have been part of our mission to improve the lives of patients with cancer by conducting practice-changing multi-institutional clinical and translational research. Stephanie Pugh performed the statistical analysis.

21st Century Oncology, Inc, Akron City Hospital, Akron General Medical Center, Albany Medical Center Hospital, Albert Einstein Medical Center, Arizona Oncology Services Foundation, Baptist Cancer Institute, Baptist Hospital of Miami, Boca Raton Community Hospital-Lynn Regional Cancer Center, Brooklyn MB-CCOP/SUNY Downstate, California Cancer Center CGOP, Cancer Care Manitoba Foundation, Cancer Resource Network, Clarkson Hospital, Cooper Health System, Cox Medical Center, Dakota Cancer Institute, Dartmouth Hitchcock Medical Center, David Grant USAF Medical Center, Delaware County Memorial Hospital, Don & Sybil Harrington Cancer Center, Elizabeth General Medical Center, Elliot Hospital, Florida Community Cancer Center, Florida Oncology Center, Fox Chase Cancer Center, Froedtert and the Medical College of Wisconsin, Greater Baltimore Medical Center, Greenville Health System Cancer Institute-International, Gunderson Clinic, H. Lee Moffitt Cancer Center & Research Institute, Highland Hospital, Jackson-Madison County General Hospital, Johns Hopkins Hospital, Kalamazoo CCOP-West Michigan Cancer Center, LDS Hospital, Loma Linda University Cancer Institute, London Regional Cancer Program, Loyola University Medical Center, Marquette General Hospital, Mary Bird Perkins Cancer Center, Mayo Clinic, McGill University, Methodist Medical Center of Illinois, Michigan Cancer Research Consortium CCOP, Montefiore Medical Center - Moses Campus, Munson Medical Center, New York Methodist Hospital, Ochsner Clinic CCOP, Piedmont Hospital, Radiological Associates of Sacramento, Regional Hospital of Scranton, Riverside Radiation Therapy, Roswell Park Cancer Institute, Saint Agnes Medical Center, Saint Elizabeth Medical Center

South, Saint John Regional Hospital, Sanford Roger Maris Cancer Center, Santa Rosa Memorial Hospital CCOP, Saskatoon Cancer Center, Sequoia Regional Cancer Center, Southern Wisconsin Radiotherapy Center, St Mary Medical Center, St. Agnes Hospital/Agnesian Cancer Center, St. Francis Medical Center, St. Luke's Medical Center, Stanford University Medical Center, Stony Brook University Medical Center, The Christ Hospital, The James Graham Brown Cancer Center at University of Louisville, The Ottawa Hospital Regional Cancer Centre, Tom Baker Cancer Centre, Trinity Cancer Care Center, UF Health Cancer Center at Orlando Health, University of Pennsylvania Medical Center, University of Rochester, University of Utah Health Science Center, Valley Regional Cancer Center, Veterans Affairs Medical Center, Virginia Mason CCOP, Virtua Memorial, Washington University, Wayne State University/Karmanos Cancer Institute, and West Penn Hospital.

This research was supported by the Intramural Research Program of the NIH. The contributions of the NIH author(s) are considered Works of the United States Government. The findings and conclusions presented in this paper are those of the author(s) and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2026.102022.

References

1. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol*. 2015;33:272-277.
2. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2011;364:1708-1717.
3. D'Amico AV, Chen M-H, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA*. 2008;299:289-295.
4. Jones CU, Hunt D, Mcgowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med*. 2011;365:107-118.
5. Attard G, Murphy L, Clarke NW, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. *Lancet*. 2022;399:447-460.
6. Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual*. 8th ed. Springer; 2017.
7. D'Amico AV, Cote K, Loffredo M, Renshaw AA, Schultz D. Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. *J Clin Oncol*. 2002;20:4567-4573.
8. Spratt DE, Zhang J, Santiago-Jiménez M, et al. Development and validation of a novel integrated clinical-genomic risk group classification for localized prostate cancer. *J Clin Oncol*. 2018;36:581-590.
9. Esteva A, Feng J, van der Wal D, et al. Prostate cancer therapy personalization via multi-modal deep learning on randomized phase III clinical trials. *NPJ Digit Med*. 2022;5:71.
10. Weiner AB, Liu Y, Hakansson A, et al. A novel prostate cancer subtyping classifier based on luminal and basal phenotypes. *Cancer*. 2023;129:2169-2178.
11. Cuzick J, Swanson GP, Fisher G, et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. *Lancet Oncol*. 2011;12:245-255.
12. Zabihi M, Lotfi R, Yousefi A-M, Bashash D. Cyclins and cyclin-dependent kinases: from biology to tumorigenesis and therapeutic opportunities. *J Cancer Res Clin Oncol*. 2023;149:1585-1606.
13. Waltregny D, Leav I, Signoretti S, et al. Androgen-driven prostate epithelial cell proliferation and differentiation in vivo involve the regulation of p27. *Mol Endocrinol*. 2001;15:765-782.
14. Schiewer MJ, Augello MA, Knudsen KE. The AR-dependent cell cycle: mechanisms and cancer relevance. *Mol Cell Endocrinol*. 2012;352:34-45.
15. Cassimere EK, Mauvais C, Denicourt C. p27Kip1 is required to mediate a G1 cell cycle arrest downstream of ATM following genotoxic stress. *PLoS One*. 2016;11:e0162806.
16. Cheng M, Olivier P, Diehl JA, et al. The p21(Cip1) and p27(Kip1) CDK 'inhibitors' are essential activators of cyclin D-dependent kinases in murine fibroblasts. *Embo J*. 1999;18:1571-1583.
17. Muraoka RS, Lenferink AEG, Simpson J, et al. Cyclin-dependent kinase inhibitor P27Kip1 is required for mouse mammary gland morphogenesis and function. *J Cell Biol*. 2001;153:917-932.
18. Yang RM, Naitoh J, Murphy M, et al. Low p27 expression predicts poor disease-free survival in patients with prostate cancer. *J Urol*. 1998;159:941-945.
19. Freedland SJ, Degregorio F, Sacoolidge JC, et al. Preoperative p27 status is an independent predictor of prostate-specific antigen failure following radical prostatectomy. *J Urol*. 2003;169:1325-1330.
20. Cote RJ, Shi Y, Groshen S, et al. Association of p27Kipl levels with recurrence and survival in patients with stage C prostate carcinoma. *J Natl Cancer Inst*. 1998;90:916-920.
21. Tsihlias J, Kapusta LR, DeBoer G, et al. Loss of cyclin-dependent kinase inhibitor p27Kip1 is a novel prognostic factor in localized human prostate adenocarcinoma. *Cancer Res*. 1998;58:542-548.
22. Roach 3rd M, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *J Clin Oncol*. 2008;26:585-591.
23. Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol*. 2003;21:3972-3978.
24. Roach 3rd M, Hanks G, Thames Jr. H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys*. 2006;65:965-974.
25. Cox DR. Regression models and life-tables. *J R Stat Soc Series B Stat Methodol*. 1972;34:187-202.
26. Zhan B, Huang L, Chen Y, et al. miR-196a-mediated downregulation of p27kip1 protein promotes prostate cancer proliferation and relates to biochemical recurrence after radical prostatectomy. *Prostate*. 2020;80:1024-1037.
27. Li R, Wheeler TM, Dai H, et al. Biological correlates of p27 compartmental expression in prostate cancer. *J Urol*. 2006;175:528-532.

28. Vlachostergios PJ, Karasavvidou F, Kakkas G, et al. Lack of prognostic significance of p16 and p27 after radical prostatectomy in hormone-naïve prostate cancer. *J Negative Results Biomed*. 2012;11:1-7.
29. Razavipour SF, Harikumar KB, Slingerland JM. p27 as a transcriptional regulator: new roles in development and cancer. *Cancer Res*. 2020;80:3451-3458.
30. De Almeida MR, Perez-Sayans M, Suarez-Penaranda JM, Somoza-Martín JM, Garcia-Garcia A. p27Kip1 expression as a prognostic marker for squamous cell carcinoma of the head and neck. *Oncology Lett*. 2015;10:2675-2682.
31. Park IA, Noh YK, Min KW, et al. p27 cell cycle inhibitor and survival in luminal-type breast cancer: gene ontology, machine learning, and drug screening analysis. *J Breast Cancer*. 2024;27:305-322.
32. Chu IM, Hengst L, Slingerland JM. The CDK inhibitor p27 in human cancer: prognostic potential and relevance to anticancer therapy. *Nat Rev Cancer*. 2008;8:253-267.
33. Luo Y, Fu Z, Wu P, Zheng D, Zhang X. The clinicopathological and prognostic significance of P27kip in hepatocellular carcinoma patients: a systemic review and meta-analysis. *Gene*. 2020;734:144351.
34. Loda M, Cukor B, Tam SW, et al. Increased proteasome-dependent degradation of the cyclin-dependent kinase inhibitor p27 in aggressive colorectal carcinomas. *Nat Med*. 1997;3:231-234.
35. Wu J, Wen J-M, Wang Y-C, et al. Prognostic value of an immunohistochemical signature in patients with bladder cancer undergoing radical cystectomy. *Front Oncol*. 2021;11:641385.
36. Santala S, Talvensaari-Mattila A, Soini Y, Kuvaja P, Santala M. Cyclins A, B, E and p27 in endometrial endometrioid adenocarcinoma. *Anticancer Res*. 2016;36:6467-6473.
37. Slingerland J, Pagano M. Regulation of the CDK inhibitor p27 and its deregulation in cancer. *J Cell Physiol*. 2000;183:10-17.