Research and Reports in Urology

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Quantitative Morphometric Response to Neoadjuvant Androgen-Deprivation Therapy and Its Prognostic Role After Radical Prostatectomy

Yevhenii Afanasiev[1], Sergiy Vozianov[2], Rostyslav Danylets[1], Viacheslav Grygorenko[1], Oleksandr Shulyak[3], Mykola Sosnin[4]

[1]Department of Reconstructive Urology and New Technologies, O.F. Vozianov Institute of Urology, National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine; [2]Department of Endoscopic Urology and Lithotripsy, O.F. Vozianov Institute of Urology, National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine; [3]Department of Reconstructive and Geriatric Urology, O.F. Vozianov Institute of Urology, National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine; [4]Department of Oncourology, O.F. Vozianov Institute of Urology, National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine

Correspondence: Yevhenii Afanasiev, Department of Reconstructive Urology and New Technologies, O.F. Vozianov Institute of Urology, National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine, Tel +38 095 768 9400, Email evhenii.afanasev@gmail.com

Background: Neoadjuvant Androgen-Deprivation Therapy (Nadt) Prior to Radical Prostatectomy (Rp) Induces Heterogeneous Morphological Responses in Prostate Cancer (Pca). Complete Pathological Response Is Rare, Therefore, Quantitative Assessment of Residual Viable Tumor May Provide Additional Prognostic Information Beyond Conventional Clinicopathological Parameters.

Materials and Methods: In this retrospective single-center study conducted between 2015 and 2021, 84 patients with localized and locally advanced PCa treated with NADT followed by RP were analyzed. Residual tumor burden (RTB) and residual tumor area (RTA) were quantified using calibrated digital morphometry. Optimal cut-off values for biochemical recurrence (BCR) were determined using ROC analysis. Biochemical recurrence-free survival (BCRFS) and overall survival (OS) were evaluated using Kaplan-Meier analysis and Cox proportional hazards regression models.

Results: During a median follow-up of 56 months, 62 BCR events and 12 deaths were observed. ROC analysis identified cut-off values of 32.5% for RTB and 50.5 mm^2 for RTA. In univariable analysis, high RTB (HR 1.93, 95% CI 1.14–3.23, p=0.010) and high RTA (HR 2.11, 95% CI 1.24–3.62, p=0.006) were significantly associated with inferior BCRFS. However, in multivariable analysis, cribriform architecture (HR 1.85, 95% CI 1.05–3.27, p=0.035) and high NCCN risk category (HR 1.95, 95% CI 1.07–3.54, p=0.028) remained independent predictors of BCR, whereas RTB and RTA did not retain independent significance. No independent association between morphometric parameters and OS was observed.

Discussion and conclusion: Quantitative assessment of residual viable tumor following NADT is associated with BCR risk, however, their prognostic impact appears largely driven by intrinsic tumor biology, particularly cribriform architecture and baseline risk stratification. Morphometric assessment may complement postoperative risk evaluation but should not be used as a standalone prognostic marker.

Keywords: prostate cancer, neoadjuvant androgen-deprivation therapy, radical prostatectomy, treatment response, oncological outcomes

Introduction

Prostate cancer (PCa) remains one of the most commonly diagnosed malignancies among men worldwide and a leading cause of cancer-related mortality in men.[1] The global burden of PCa is expected to increase substantially in the coming decades, with projections suggesting a substantial increase in both incidence and mortality by 2040.[2] While radical prostatectomy (RP) represents an established treatment option for patients with low- and intermediate-risk,[3] oncological outcomes remain suboptimal in men with high- and very high-risk features, frequently necessitating multimodal treatment strategies.[4,5]

https://doi.org/10.2147/RRU.S601959
Received: 20 February 2026
Accepted: 2 April 2026
Published: 8 April 2026

Neoadjuvant androgen deprivation therapy (NADT) has been explored as a strategy to improve surgical and pathological outcomes prior to RP. Although NADT has been shown to reduce tumor volume and improve certain pathological parameters, its impact on long-term oncological outcomes remains inconsistent.[6–8] One of the key challenges in evaluating the effectiveness of NADT in PCa is the low incidence of pathological complete response, even with intensified treatment regimens.[9–12]

Consequently, increasing attention has been directed toward quantitative pathological measures of treatment response, such as minimal residual disease (MRD) and residual tumor burden (RTB), which may provide a more objective and reproducible assessment of tumor sensitivity to neoadjuvant therapy.[13,14] However, the prognostic significance and clinical applicability of quantitative morphometric parameters following NADT, particularly in routine clinical practice remain insufficiently defined.

The present study aimed to evaluate the association between quantitative morphometric indicators of residual viable tumor following NADT and oncological outcomes after RP. In addition, selected morphological features of treatment response were analyzed to assess their potential prognostic relevance in patients with PCa. We hypothesized that higher quantitative RTB after NADT would be associated with worse oncological outcomes after RP.

Materials and Methods

Study Design and Patient Population

This retrospective single-center study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Institute of Urology named after Academician O.F. Vozianov, National Academy of Medical Sciences of Ukraine (Protocol No. 6, December 14, 2023). Due to the retrospective design of the study and the use of previously collected medical records, the requirement for informed consent was waived by the Ethics Committee. All patient data were anonymized prior to analysis, and confidentiality of personal information was strictly maintained throughout the study. Medical records of patients with PCa who received NADT followed by RP between January 2015 and December 2021 were reviewed. The requirement for informed consent was waived due to the retrospective design.

Patients were eligible for inclusion if they had histologically confirmed PCa with a clinical stage ≤cT4 and no evidence of pelvic wall or urethral sphincter invasion on pretreatment magnetic resonance imaging performed prior to initiation of any systemic or local therapy. Availability of baseline clinical data, including biopsy ISUP grade and pretreatment prostate-specific antigen (PSA) concentration, as well as long-term oncological outcomes (date of biochemical recurrence (BCR) and survival status), was required.

Patients with oligometastatic or metastatic disease at diagnosis, prior intermittent androgen deprivation therapy, previous radiation therapy and/or systemic chemotherapy before RP, treatment with antiandrogens (AA) monotherapy, or insufficient clinical data precluding reliable oncological assessment were excluded. A total of 84 patients met the inclusion criteria and were included in the final study cohort. The decision to administer NADT was based on institutional clinical practice and was predominantly administered in patients with higher-risk disease features, including elevated PSA concentration (>20 ng/mL) and/or locally advanced stage (≥cT_3). Multiparametric MRI was performed in all patients prior to prostate biopsy and initiation of NADT. Repeat MRI after completion of NADT was performed selectively based on clinical indication and was not mandatory for all patients. This study represents a retrospective analysis of consecutively treated patients who met predefined inclusion criteria during the study period. Patients who did not meet these criteria were excluded from the analysis.

Neoadjuvant Androgen-Deprivation Therapy

NADT consisted of luteinizing hormone-releasing hormone (LHRH) agonists administered as monotherapy or in combination with nonsteroidal AA. Combined androgen blockade was preferentially used in patients with high-risk disease characteristics. The duration of NADT ranged from 1 to 12 months and was determined by clinical considerations, tumor burden, and treatment planning factors. For analytical purposes, patients were stratified by duration (1–2, 3, and >3 months) and regimen (LHRH alone vs LHRH + AA).

Pathological Evaluation and Morphometric Analysis

RP specimens were processed according to standard pathological protocols.[15] Tissue samples were fixed in formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. All specimens were reviewed by an experienced genitourinary pathologist.

Quantitative morphometric assessment of residual tumor burden (RTB) and residual tumor area (RTA) was conducted using digital microphotographs of histological sections obtained from RP specimens following NADT. Hematoxylin and eosin-stained slides were reviewed, and representative areas containing viable tumor were selected under the supervision of an experienced genitourinary pathologist. For each case, approximately 5–6 microphotographs were acquired using the light microscope (Olympus BX41) equipped with a digital camera (Olympus E-410) at magnifications of x4, x10, and x20. Images were captured at a native resolution of 2048×1536 pixels, ensuring sufficient detail for quantitative morphometric analysis. Image analysis was performed using dedicated digital pathology software (QuPath, version 0.6.0). Calibration was conducted for each image based on known field-of-view dimensions corresponding to the objective magnification, enabling accurate conversion of pixel-based measurements into real-world area units. On each image, total tissue area and areas of viable residual tumor were manually annotated, excluding background, artifacts, and non-tissue regions. Only areas with preserved tumor architecture, based on established morphological criteria for prostate adenocarcinoma and clearly identifiable viable tumor cells were included in the analysis, while fibrotic tissue, necrosis, inflammatory infiltrates, and benign glands were excluded. Tumor area measurements were obtained for each image and integrated across multiple sections, taking into account standard histological section thickness, to estimate RTB. RTB was expressed both as an absolute value and as a percentage of total tissue area.

Morphometric evaluation was performed by an experienced genitourinary pathologist blinded to clinical outcomes. Interobserver variability was not assessed and is acknowledged as a limitation of the study.

Assessment of Morphological Features

In addition to quantitative morphometric parameters, selected qualitative morphological features associated with treatment response were evaluated within areas of residual viable tumor. These included the presence of cribriform growth pattern, tumor-infiltrating lymphocytes, apoptotic changes, nuclear size reduction, and foamy macrophages. Morphological features were assessed using a semi-quantitative approach.

Outcomes and Follow-Up

Median follow-up was calculated using the reverse Kaplan-Meier method. The primary endpoint was BCR following RP, defined as a PSA level $\geq$0.2 ng/mL confirmed by a second consecutive measurement. Overall survival (OS) was evaluated as a secondary endpoint. Follow-up data were obtained from institutional medical records.

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics. Continuous variables were reported as medians and interquartile ranges (IQR) and compared using the nonparametric Kruskal–Wallis test. Categorical variables were compared using chi-square tests.

Receiver operating characteristics (ROC) curve analysis was performed to identify optimal cut-off values for quantitative morphometric parameters in relation to BCR occurrence (yes/no) as a binary endpoint at last follow-up. Survival outcomes were analyzed using the Kaplan-Meier method and compared using the Log rank test. Cox proportional hazards regression models were used to evaluate the association between clinical and pathological variables and oncological outcomes. Due to collinearity between RTB and RTA, these variables were not included simultaneously in the same multivariable model. Therefore, two separate multivariable Cox regression models were constructed to evaluate their independent prognostic value. The proportional hazards assumption was assessed using Schoenfeld residuals. Statistical analyses were performed using IBM SPSS Statistics v22 (IBM Corp., Armonk, NY, USA) and GraphPad Prism v10.4.1. (GraphPad Software, Boston, MA, USA), and a two-sided p value <0.05 was considered statistically significant.

Results

Baseline Clinical and Pathological Characteristics

A total of 84 patients who received NADT prior to RP were included in the analysis. The median age at RP was 64.5 years (IQR 60.0–68.8), and the median baseline PSA concentration was 20.9 ng/mL (IQR 11.6–38.4). Biopsy ISUP grade group ≥4 was identified in 20/84 patients (23.8%). Clinically locally advanced disease (≥cT3a) was present in 30/84 patients (35.7%). According to NCCN risk stratification, 57/84 patients (67.9%) were classified as having high-risk disease (Table 1).

Neoadjuvant Therapy Characteristics

The duration of NADT was 1–2 months in 28/84 patients (33.3%), 3 months in 29/84 patients (34.5%), and more than 3 months in 27/84 patients (32.1%). LHRH agonist monotherapy was administered in 54/84 patients (64.3%), whereas combined androgen blockade was used in 30/84 patients (35.7%) (Table 2).

Table 1 Baseline Cohort Parameters

Parameter	Overall (n=84)
Clinical Parameters	
Age, years, median (IQR)	64.5 (60.0–68.8)
PSA, ng/mL, median (IQR)	20.9 (11.6–38.4)
Biopsy ISUP Grade, n (%)	
ISUP <4	64 (76.2%)
ISUP ≥4	20 (23.8%)
Clinical Stage, n (%)	
≤T2c	54 (64.3%)
≥T3a	30 (35.7%)
NCCN Stratification Risk Group, n (%)	
≤Intermediate unfavorable-risk	27 (32.1%)
≥High-risk	57 (67.9%)

Abbreviations: IQR, interquartile range; PSA, prostate-specific antigen; ISUP, International Society of Urological Pathology; NCCN, National Comprehensive Cancer Network.

Table 2 Neoadjuvant Androgen-Deprivation Therapy Characteristics

Parameter	n (%)
Neoadjuvant Androgen-Deprivation Therapy Duration	
Duration 1–2 months	28 (33.3%)
Duration 3 months	29 (34.5%)
Duration >3 months	27 (32.1%)
Neoadjuvant Androgen-Deprivation Therapy Type	
LHRH agonist	54 (64.3%)
LHRH agonist + AA	30 (35.7%)

Abbreviations: LHRH, luteinizing hormone-releasing hormone; AA, antiandrogens.

Morphological and Morphometric Findings

Quantitative morphometric analysis revealed substantial interindividual heterogeneity in residual viable tumor following neoadjuvant therapy. RTB (%) and RTA (mm^2) varied widely across the cohort. Stratification by neoadjuvant treatment duration and intensity demonstrated significant differences in RTB (p=0.037) and RTA (p=0.003). In contrast, the frequencies of cribriform architecture, foamy macrophages, apoptotic changes, and nuclear reduction did not differ significantly between subgroups (p>0.05), while lymphocytic infiltration showed a trend toward significance (p=0.086) (Table 3).

Table 3 Morphological Response to Neoadjuvant Androgen-Deprivation Therapy According to Treatment Duration and Type

Parameter	LHRH Agonist Duration 1–2 Months	LHRH Agonist Duration 3 Months	LHRH Agonist Duration >3 Months	LHRH Agonist + AA Duration 1–2 Months	LHRH Agonist + AA Duration 3 Months	LHRH Agonist + AA Duration >3 Months	p-value
Residual Tumor Burden, %, median (IQR)	25.0 (6.3–55.0)	32.5 (18.8–60.0)	15.0 (6.0–20.0)	12.0 (15.0–30.0)	22.0 (15.0–30.0)	25.0 (18.0–70.0)	0.037*
Residual Tumor Area, mm^2, median (IQR)	78.0 (29.8–260.0)	132.5 (64.3–198.8)	40.0 (9.0–63.0)	25.0 (11.0–66.0)	51.0 (28.0–70.0)	100.0 (50.0–160.0)	0.003*
Cribriform Growth Pattern, n (%)							
Absent	14 (16.7%)	8 (9.5%)	13 (15.5%)	3 (3.6%)	8 (9.5%)	5 (6.0%)	
Present	6 (7.1%)	10 (11.9%)	4 (4.8%)	4 (4.8%)	3 (3.6%)	6 (7.1%)	0.209χ^2
Foamy Macrophages, n (%)							
Absent	14 (16.7%)	12 (14.3%)	9 (10.7%)	3 (3.6%)	6 (7.1%)	5 (6.0%)	
Present	6 (7.1%)	6 (7.1%)	8 (9.5%)	4 (4.8%)	5 (6.0%)	6 (7.1%)	0.647χ^2
Apoptosis, n (%)							
Absent	13 (15.5%)	10 (11.9%)	7 (8.3%)	3 (3.6%)	4 (4.8%)	6 (7.1%)	
Present	7 (8.3%)	8 (9.5%)	10 (11.9%)	4 (4.8%)	7 (8.3%)	5 (6.0%)	0.615χ^2
Nuclear Reduction, n (%)							
Absent	13 (15.5%)	14 (16.7%)	10 (11.9%)	3 (3.6%)	7 (8.3%)	8 (9.5%)	
Present	7 (8.3%)	4 (4.8%)	7 (8.3%)	4 (4.8%)	4 (4.8%)	3 (3.6%)	0.639χ^2
Tumor Lymphocytic Infiltration, n, (%)							
Absent	10 (11.9%)	7 (8.3%)	7 (8.3%)	1 (1.2%)	2 (2.4%)	8 (9.5%)	
Present	10 (11.9%)	11 (13.1%)	10 (11.9%)	6 (7.1%)	9 (10.7%)	3 (3.6%)	0.086χ^2

Notes: *indicates comparison of groups by Kruskall-Wallis test; χ^2 indicates comparison of categorical variables by chi-square test;
Abbreviations: IQR, interquartile range; LHRH, luteinizing hormone-releasing hormone; AA, antiandrogen.

ROC-Derived Cut-off Values

Optimal cut-off values for RTB and RTA were determined using receiver operating characteristic (ROC) curve analysis with BCR as the endpoint. The Youden index was used to identify the optimal threshold. Cut-off values were internally derived from the study cohort and identified as 32.5% for RTB and 50.5 mm^2 for RTA. The AUC for RTB was 0.711 (95% CI 0.60–0.82, p=0.001) and for RTA 0.676 (95% CI 0.56–0.792, p=0.005). Both parameters demonstrated moderate discriminatory ability for predicting BCR.

Association Between RTB and Clinicopathological Features

Patients with high RTB (≥32.5%) demonstrated a significantly higher prevalence of cribriform architecture compared with those with low RTB (77.8% vs 21.1%, p<0.001). In contrast, foamy macrophages (14.8% vs 54.4%, p<0.001), apoptotic changes (25.9% vs 59.6%, p=0.004), nuclear reduction (11.1% vs 45.6%, p=0.001), and lymphocytic infiltration (33.3% vs 70.2%, p=0.002) were significantly less frequent in the high RTB group. No significant differences were observed in baseline PSA concentration, biopsy ISUP grade group, NCCN risk category, or the use of adjuvant radiotherapy (Table 4).

Table 4 Cohort Characteristic Among RTB Groups (Low Vs High)

Residual Tumor Burden, %	**Low (<32.5%)**	**High (≥32.5%)**	**p-value**
PSA, ng/mL, median (IQR)	21.8 (11.7–38.1)	19.1 (11.0–45.2)	0.695*
Biopsy ISUP Grade, n (%)			
ISUP <4 ISUP ≥4	44 (77.2%) 13 (22.8%)	20 (74.1%) 7 (29.5%)	0.477 χ^2
Clinical Stage, n (%)			
≤T2c ≥T3a	40 (70.2%) 17 (29.8%)	14 (51.9%) 13 (48.1%)	0.083 χ^2
NCCN Stratification Risk Group, n (%)			
≤Intermediate unfavorable-risk ≥High-risk	19 (33.3%) 38 (66.7%)	8 (29.6%) 19 (70.4%)	0.469 χ^2
External Beam Radiation Therapy, n (%)			
No Adjuvant/Salvage EBRT Adjuvant/Salvage EBRT	27 (47.4%) 30 (52.6%)	13 (48.1%) 14 (51.9%)	0.566 χ^2
Morphological Parameters, n (%)			
Cribriform pattern			<0.001 χ^2
Absent	45 (78.5%)	6 (22.2%)	
Present	12 (21.1%)	21 (77.8%)	
Foamy Macrophages			<0.001 χ^2
Absent	26 (45.6%)	23 (85.2%)	
Present	31 (54.4%)	4 (14.8%)	
Apoptosis			0.004 χ^2
Absent	23 (40.4%)	20 (74.1%)	
Present	34 (59,6%)	7 (25.9%)	
Nuclear reduction			0.001 χ^2
Absent	31 (54.4%)	24 (88.9%)	
Present	26 (45.6%)	3 (11.1%)	

(*Continued*)

Table 4 (Continued).

Residual Tumor Burden, %	Low (<32.5%)	High (≥32.5%)	p-value
Tumor lymphocyte infiltration			0.002 χ^2
Absent	17 (29.8%)	18 (66.7%)	
Present	40 (70.2%)	9 (33.3%)	

Notes: * indicates comparison of groups by Mann–Whitney test; χ^2 indicates comparison of categorical variables by chi-square test.
Abbreviations: RTB, residual tumor burden; PSA, prostate-specific antigen; IQR, interquartile range; ISUP, International Society of Urological Pathology; NCCN, National Comprehensive Cancer Network; EBRT, external beam-radiation therapy.

Association Between RTA and Clinicopathological Features

Patients with high RTA (≥50.5 mm^2) more frequently presented with clinically locally advanced disease (≥T3a) compared with those with low RTA (44.0% vs 21.2%, p=0.028). Cribriform architecture was also more prevalent in the high RTA group (50.0% vs 21.2%, p=0.007). Conversely, nuclear reduction (26.0% vs 48.5%, p=0.031) and lymphocytic infiltration (50.0% vs 72.7%, p=0.033) were significantly less frequent among patients with high RTA. Differences in foamy macrophages and apoptotic changes did not reach statistical significance (p=0.052 and p=0.075, respectively) (Table 5).

Table 5 Cohort Characteristic Among RTA Groups (Low vs High)

Residual Tumor Area, mm^2	Low (<50.5 mm^2)	High (≥50.5 mm^2)	p-value
PSA, ng/mL, median (IQR)	20.0 (12.3–31.3)	24.1 (11.0–50.7)	0.416*
Biopsy ISUP Grade, n (%)			
ISUP <4	24 (72.7%)	40 (80.0%)	0.305 χ^2
ISUP ≥4	9 (27.3%)	10 (20.0%)	
Clinical Stage, n (%)			
≤T2c	26 (78.8%)	28 (56.0%)	0.028 χ^2
≥T3a	7 (21.2%)	22 (44.0%)	
NCCN Stratification Risk Group, n (%)			
≤Intermediate unfavorable-risk	13 (39.4%)	14 (28.0%)	0.199 χ^2
≥High-risk	20 (60.6%)	36 (72.0%)	
External Beam Radiation Therapy, n (%)			
No Adjuvant/Salvage EBRT	15 (45.5%)	24 (48.0%)	0.499 χ^2
Adjuvant/Salvage EBRT	18 (54.5%)	26 (52.0%)	
Morphological Parameters, n (%)			
Cribriform patter			0.007 χ^2
Absent	26 (78.8%)	25 (50.0%)	
Present	7 (21.2%)	25 (50.0%)	
Foamy Macrophages			0.052 χ^2
Absent	15 (45.5%)	33 (66.0%)	
Present	18 (54.5%)	17 (34.0%)	
Apoptosis			0.075 χ^2
Absent	13 (39.4%)	29 (58.0%)	
Present	20 (60.6%)	21 (42.0%)	

(*Continued*)

Table 5 (Continued).

Residual Tumor Area, mm^2	Low (<50.5 mm^2)	High (≥50.5 mm^2)	p-value
Nuclear reduction			0.031 χ^2
Absent	17 (51.5%)	37 (74.0%)	
Present	16 (48.5%)	13 (26.0%)	
Tumor lymphocyte infiltration			0.033 χ^2
Absent	9 (27.3%)	25 (50.0%)	
Present	24 (72.7%)	25 (50.0%)	

Notes: * indicates comparison of groups by Mann–Whitney test; χ^2 indicates comparison of categorical variables by chi-square test;

Abbreviations: RTA, residual tumor area; PSA, prostate-specific antigen; IQR, interquartile range; ISUP, International Society of Urological Pathology; NCCN, National Comprehensive Cancer Network; EBRT, external beam-radiation therapy.

Biochemical Recurrence-Free Survival

Median follow-up was 56 months (IQR 38–82). A total of 62 BCRs were observed. Kaplan-Meier analysis demonstrated significantly reduced biochemical recurrence-free survival (BCRFS) in patients with high RTB compared with those with low RTB (median 26.0 vs 57.0 months, log-rank p=0.016) (Figure 1a). Similarly, high RTA was associated with inferior BCRFS (median 29.0 vs 65.0 months, log-rank p=0.017) (Figure 1b).

In univariate Cox regression analysis, high RTB (HR 1.93, 95% CI 1.14–3.23, p=0.01), high RTA (HR 2.11, 95% CI 1.23–3.61, p=0.006), and the presence of cribriform architecture (HR 2.02, 95% CI 1.21–3.33, p=0.006) were associated with an increased risk of BCR (Table 6). In multivariable analysis, cribriform architecture (HR 1.85, 95% CI 1.04–3.27, p=0.035) and high NCCN risk category (HR 1.95, 95% CI 1.07–3.54, p=0.028) remained independently associated with BCR, whereas RTB (Table 7) and RTA (Table 8) did not retain independent prognostic significance.

Overall Survival

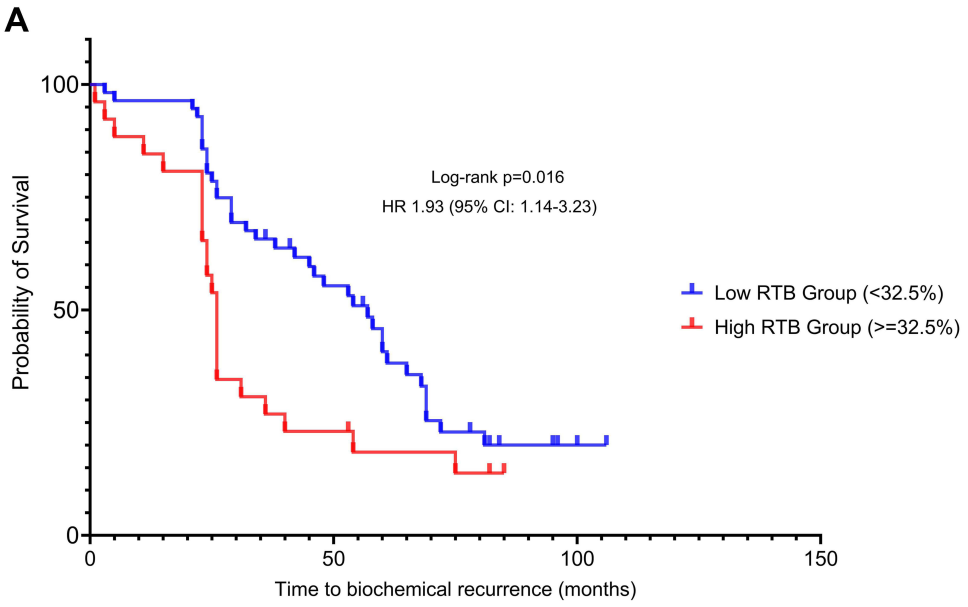
During a median follow-up of 56 months (IQR 38–82), 12 deaths occurred. Kaplan-Meier analysis demonstrated no statistically significant differences in OS between patients stratified by RTB or RTA categories (Figure 1c and d). In Cox regression analysis, none of the evaluated morphometric parameters were independently associated with OS (Table 9). These findings should be interpreted cautiously given the limited number of death events.

Discussion

In this retrospective single-center study, we evaluated the prognostic relevance of morphological response to NADT prior to RP, with a particular focus on quantitative morphometric parameters reflecting residual viable tumor. The main findings of our study indicate that higher RTB and RTA were associated with an increased risk of BCR in univariate analyses, however, after adjustment for established clinicopathological factors only cribriform architecture and high NCCN risk category retained independent prognostic significance.

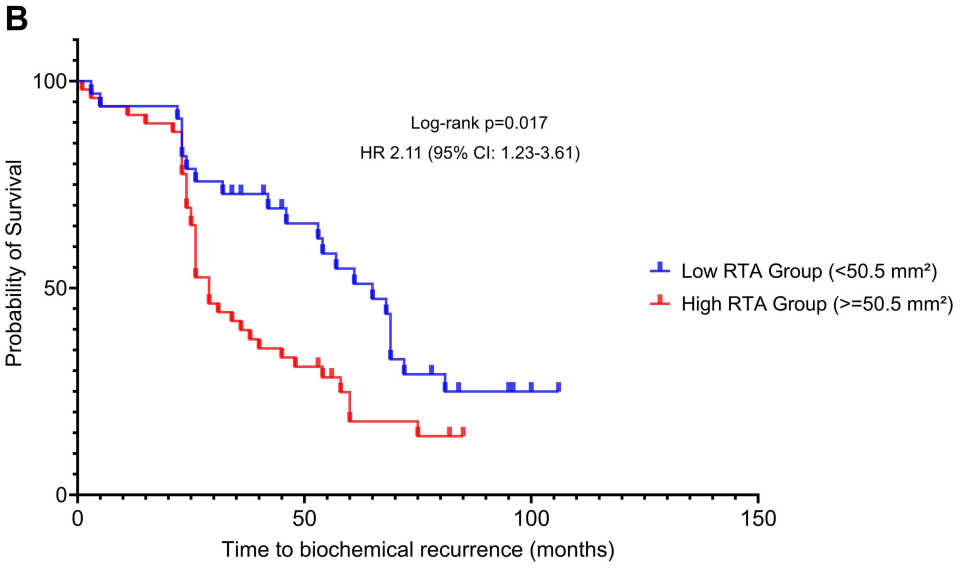
The limited clinical utility of pathological complete response in neoadjuvant PCa studies is well recognized, as complete eradication of tumor tissue is rarely achieved even in intensified systemic approaches.[11,16] Consequently, recent neoadjuvant trials have increasingly relied on quantitative pathological endpoints, such as MRD and RTB, as more sensitive measures of treatment response.[9,12]

Our findings are consistent with this evolving paradigm demonstrating that higher RTB and RTA reflect inferior BCRFS. However, the loss of independent prognostic significance of these morphometric parameters in multivariable analysis suggests that they may primarily capture intrinsic tumor aggressiveness rather than function as autonomous prognostic markers. Similar observations have been reported in neoadjuvant studies incorporating morphometric assessment, where quantitative measures correlated with outcomes but were strongly influenced by baseline biological features.[17]



Number at risk

RTB Groups	Months	0	5	15	36	56	65	75	106
<32.5%		56	55	55	37	24	15	10	2
≥32.5%		26	24	24	9	5	5	4	1

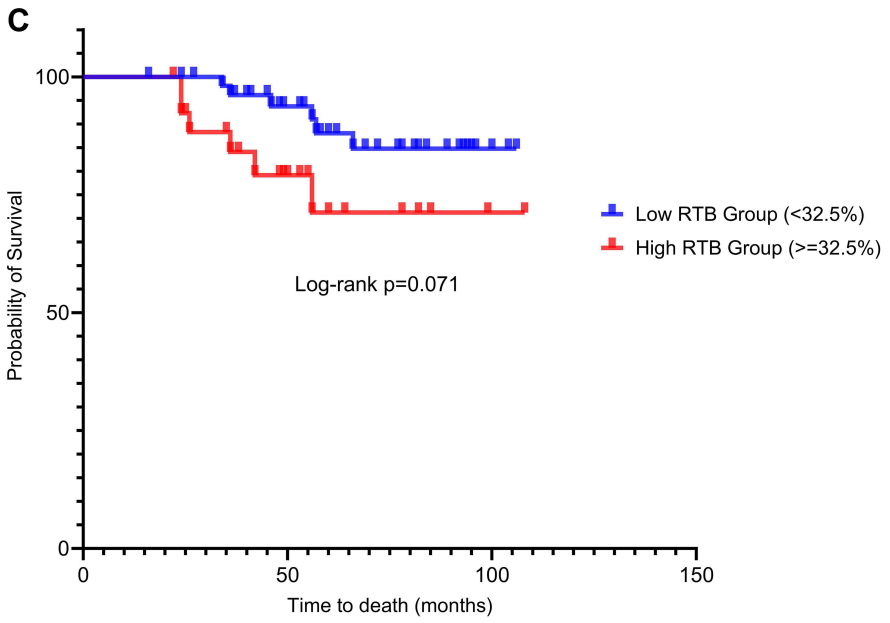


Number at risk

RTA Groups	Months	0	5	15	36	56	65	75	106
<50.5 mm^2		33	32	32	23	17	14	9	2
≥50.5 mm^2		49	47	45	19	12	7	5	1

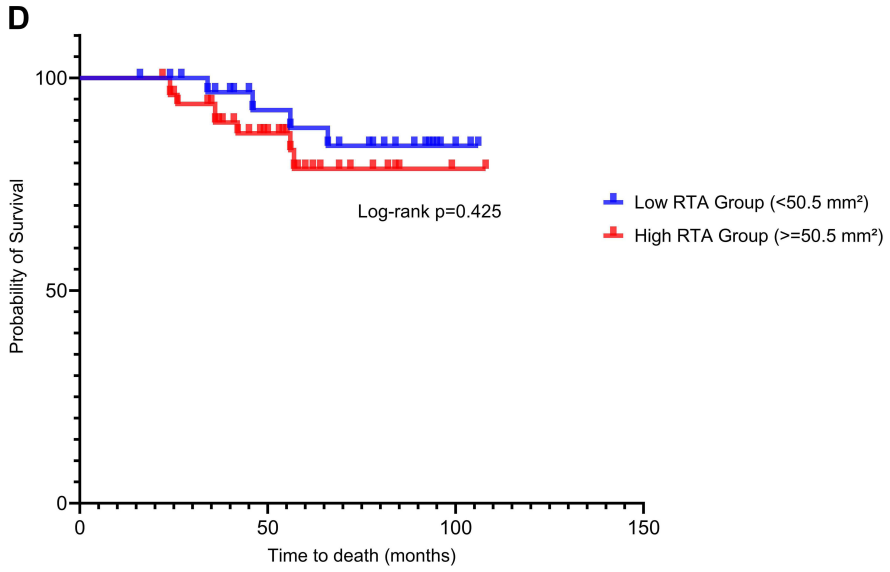
Figure 1 Continued.

https://doi.org/10.2147/RRU.S601959



Number at risk

RTB Groups	Months	0	5	15	36	56	65	75	106
<32.5%		57	57	57	50	34	28	24	2
≥32.5%		27	27	27	21	10	7	7	2



Number at risk

RTA Groups	Months	0	5	15	36	56	65	75	106
<50.5 mm²		33	33	32	28	23	22	20	2
≥50.5 mm²		51	51	51	43	23	14	11	1

Figure 1 (**A**) Biochemical recurrence-free survival stratified by residual tumor burden (**B**). Biochemical recurrence-free survival stratified by residual tumor area (**C**). Overall survival stratified by residual tumor burden (**D**). Overall survival stratified by residual tumor area.

https://doi.org/10.2147/RRU.S601959

Table 6 Univariable Proportional Hazard Cox-Regression Analysis for BCRFS

Parameter	HR	95% CI	p-value
Univariable Analysis			
RTB			
≥32.5%	1.926	1.146–3.238	0.010
RTA			
≥50.5 mm^2	2.113	1.236–3.615	0.006
Cribriform pattern			
Present	2.016	1.217–3.337	0.006
NCCN Risk Group			
≥High-risk	1.977	1.102–3.548	0.022

Abbreviations: BCRFS, biochemical recurrence-free survival; HR, hazard ratio; CI, confidence interval; RTB, residual tumor burden; RTA, residual tumor area; NCCN, National Comprehensive Cancer Network.

Table 7 Multivariable Proportional Hazard Cox-Regression Analysis for BCRFS Stratified by RTB

Parameter	HR	95% CI	p-value
Multivariable analysis			
RTB			
≥32.5%	1.325	0.732–2.398	0.353
NCCN Risk Group			
≥High-risk	1.950	1.074–3.542	0.028
Cribriform pattern			
Present	1.850	1.046–3.273	0.035

Abbreviations: BCRFS, biochemical recurrence-free survival; HR, hazard ratio; CI, confidence interval; RTB, residual tumor burden; NCCN, National Comprehensive Cancer Network.

Table 8 Multivariable Proportional Hazard Cox-Regression Analysis for BCRFS Stratified by RTA

Parameter	HR	95% CI	p-value
Multivariable Analysis			
RTA			
≥50.5mm^2	1.504	0.856–2.644	0.156
NCCN Risk Group			
≥High-risk	1.880	1.033–3.420	0.039
Cribriform pattern			
Present	1.873	1.109–3.164	0.019

Abbreviations: BCRFS, biochemical recurrence-free survival; HR, hazard ratio; CI, confidence interval; RTA, residual tumor area; NCCN, National Comprehensive Cancer Network.

Cribriform architecture emerged as the strongest and most consistent predictor of BCR in our cohort. This finding aligns with robust evidence identifying cribriform growth as a marker of aggressive PCa biology, independently associated with early biochemical failure, metastatic progression, and cancer-specific mortality.[18,19] Importantly, the

Table 9 Proportional Hazard Cox-Regression Analysis for OS Stratified by External-Beam Radiation Therapy

Parameter	HR	95% CI	p-value
Univariable Analysis			
RTB			
≥32.5%	2.654	0.846–8.329	0.094
RTA			
≥50.5 mm^2	1.408	0.404–4.902	0.591
Cribriform pattern			
Present	2.571	0.815–8.106	0.107
NCCN Risk Group			
≥High-risk	2.559	0.684–9.575	0.163

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; RTB, residual tumor burden; RTA, residual tumor area; NCCN, National Comprehensive Cancer Network.

strong association between cribriform architecture and elevated RTB/RTA observed in our study underscores the close interplay between qualitative architectural patterns and quantitative morphometric measures, suggesting that architectural phenotype may dominate prognostic stratification following neoadjuvant therapy.

The relatively high BCR rate observed in this cohort likely reflects the predominance of high-risk disease (67.9% NCCN high-risk). Although RTB and RTA were associated with BCRFS in Kaplan-Meier analyses, neither parameter independently predicted outcome after multivariable adjustment. This finding highlights the heterogeneity of morphological response to NADT and suggests that volumetric tumor regression alone may be insufficient to overcome adverse biological characteristics inherent to high-risk disease. Notably, patients with lower RTB more frequently exhibited regressive morphological features, including nuclear reduction, apoptotic changes and lymphocytic infiltration, supporting prior observations that these features reflect treatment sensitivity rather than long-term oncological control.[20]

No independent association between morphometric parameters and OS was observed. Interpretation of OS in this cohort requires particular caution, as a substantial proportion of patients received radiotherapy following RP. In our cohort, postoperative radiotherapy was administered exclusively in the salvage setting, triggered by BCR, even in patients with adverse pathological features such as nodal involvement. Therefore, radiotherapy was not treated as a baseline prognostic variable in BCRFS models, as its inclusion would introduce reverse-causation bias. This reflects real-world clinical practice but should be carefully considered when interpreting the results. Additionally, salvage radiotherapy may have influenced long-term outcomes, particularly OS, and should be considered as a potential treatment-related confounder when interpreting survival analyses. Stratification by receipt of postoperative radiotherapy suggests that subsequent local treatment likely modified survival trajectories, potentially attenuating differences attributable to neoadjuvant morphological response. Similar confounding effects of multimodal postoperative therapy on OS have been reported in high-risk PCa cohorts.[21]

Several limitations of this study merit consideration. Its retrospective design and single-center nature introduce potential selection bias, and neoadjuvant treatment regimens and durations were not standardized. The categorization of NADT duration, particularly the grouping of patients receiving more than 3 months of therapy, may have introduced heterogeneity within this subgroup, which should be considered when interpreting the results The lack of standardized post-NADT imaging in all patients represents a limitation of this retrospective study and reflects real-world clinical practice. Another limitation of this study is that all patients received conventional NADT, including LHRH agonists with or without AA, without incorporating contemporary intensified treatment strategies such as androgen receptor pathway inhibitors or chemotherapy. Therefore, the applicability of the present findings to modern treatment paradigms may be limited and requires further validation in cohorts receiving current standard-of-care regimens. The cut-off values were

internally derived and require external validation prior to clinical implementation. In addition, the limited number of death events (n=12) restricts the statistical power of OS analysis and may have precluded detection of independent associations. Nevertheless, the strengths of this study include centralized pathological review, application of reproducible digital morphometric techniques and comprehensive integration of quantitative and qualitative morphological parameters.

In summary, our results indicate that quantitative morphometric parameters reflect morphological response to NADT but do not independently predict oncological outcomes beyond established clinical risk stratification and adverse architectural features. Integration of morphometric assessment with qualitative pathological patterns, particularly cribriform architecture, may improve postoperative risk assessment. Future prospective and multicenter studies incorporating morphometric, molecular, and genomic data are warranted to refine patient selection and optimize neoadjuvant treatment strategies in PCa. Recent studies have highlighted the role of tumor immune microenvironment and molecular mechanisms of treatment resistance in PCa progression and therapeutic response. Intergrative multi-omics analyses have demonstrated that immune contexture and resistance-associated pathways may influence treatment outcomes, particularly in advanced and castration-resistant disease. These findings further support the need for comprehensive approaches combining morphological, molecular, and clinical parameters for improved risk stratification and personalized treatment strategies.[22–24]

Conclusion

In patients with PCa treated with NADT prior to RP, quantitative morphometric measures of residual viable tumor were associated with disease recurrence but did not provide independent prognostic information beyond established risk factors. Cribriform architecture and NCCN risk category remained the most informative indicators of adverse oncological outcomes. These findings suggest that morphometric assessment reflects treatment response but should be interpreted in the context of tumor architecture and clinical risk stratification and should not be used as a standalone prognostic marker.

Abbreviations

PCa, prostate cancer; RP, radical prostatectomy; NADT, neoadjuvant androgen-deprivation therapy; RTB, residual tumor burden; PSA, prostate-specific antigen; BCR, biochemical recurrence; AA, antiandrogens; LHRH, luteinizing hormone-releasing hormone; RTA, residual tumor area; OS, overall survival; IQR, interquartile range; ROC, receiver operating characteristics; HR, hazard ratio; CI, confidence interval; AUC, area under curve; ISUP, International Society of Urological Pathology, NCCN, National Comprehensive Cancer Network; BCRFS, biochemical recurrence-free survival.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Institute of Urology named after Academician O.F. Vozianov, National Academy of Medical Sciences of Ukraine (Protocol #6, 14 December 2023 year).

Given the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

Acknowledgments

The authors thank the clinical and pathology teams of the Institute of Urology for their contribution to patient management and histopathological assessment.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Ferlay J, Ervik M, Lam F, et al. Global cancer observatory: cancer tomorrow [internet]. Lyon, France: International Agency for Research on Cancer; 2020 [Available from: https://gco.iarc.fr/tomorrow. Accessed April 2, 2026.
3. Luo X, Yi M, Hu Q, Yin W. Prostatectomy versus observation for localized prostate cancer: a meta-analysis. *Scand J Surg*. 2021;110(1):78–85. doi:10.1177/1457496919883962
4. Donohue JF, Bianco FJ Jr, Kuroiwa K, et al. Poorly differentiated prostate cancer treated with radical prostatectomy: long-term outcome and incidence of pathological downgrading. *J Urol*. 2006;176(3):991–995. doi:10.1016/j.juro.2006.04.048
5. Eastham JA, Heller G, Halabi S, et al. Cancer and Leukemia Group B 90203 (Alliance): radical prostatectomy with or without neoadjuvant chemohormonal therapy in localized, high-risk prostate cancer. *J Clin Oncol*. 2020;38(26):3042–3050. doi:10.1200/JCO.20.00315
6. Soloway MS, Pareek K, Sharifi R, et al. Neoadjuvant androgen ablation before radical prostatectomy in cT2bNxMo prostate cancer: 5-year results. *J Urol*. 2002;167(1):112–116. doi:10.1016/S0022-5347(05)65393-1
7. Yee DS, Lowrance WT, Eastham JA, Maschino AC, Cronin AM, Rabbani F. Long-term follow-up of 3-month neoadjuvant hormone therapy before radical prostatectomy in a randomized trial. *BJU Int*. 2010;105(2):185–190. doi:10.1111/j.1464-410X.2009.08698.x
8. Akitake N, Shiota M, Obata H, et al. Neoadjuvant androgen-deprivation therapy with radical prostatectomy for prostate cancer in association with age and serum testosterone. *Prostate Int*. 2018;6(3):104–109. doi:10.1016/j.prnil.2017.10.002
9. Efstathiou E, Davis JW, Pisters L, et al. Clinical and biological characterisation of localised high-risk prostate cancer: results of a randomised preoperative study of a luteinising hormone-releasing hormone agonist with or without abiraterone acetate plus prednisone. *Eur Urol*. 2019;76(4):418–424. doi:10.1016/j.eururo.2019.05.010
10. McKay RR, Ye H, Xie W, et al. Evaluation of intense androgen deprivation before prostatectomy: a randomized phase ii trial of enzalutamide and leuprolide with or without abiraterone. *J Clin Oncol*. 2019;37(11):923–931. doi:10.1200/JCO.18.01777
11. Montgomery B, Tretiakova MS, Joshua AM, et al. Neoadjuvant enzalutamide prior to prostatectomy. *Clin Cancer Res*. 2017;23(9):2169–2176. doi:10.1158/1078-0432.CCR-16-1357
12. Taplin ME, Montgomery B, Logothetis CJ, et al. Intense androgen-deprivation therapy with Abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. *J Clin Oncol*. 2014;32(33):3705–3715. doi:10.1200/JCO.2013.53.4578
13. McKay RR, Xie WL, Ye HH, et al. Results of a randomized phase ii trial of intense androgen deprivation therapy prior to radical prostatectomy in men with high-risk localized prostate cancer. *J Urol*. 2021;206(1):80–87. doi:10.1097/JU.0000000000001702
14. Devos G, Tosco L, Baldewijns M, et al. ARNEO: a randomized phase ii trial of neoadjuvant degarelix with or without apalutamide prior to radical prostatectomy for high-risk prostate cancer. *Europ urol*. 2023;83(6):508–518. doi:10.1016/j.eururo.2022.09.009
15. Spratt DE, Srinivas S, Adra N, et al. Prostate cancer, version 3.2026, nccn clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2025;23(11):469–493. doi:10.6004/jnccn.2025.0052
16. McKay RR, Berchuck J, Kwak L, et al. Outcomes of post-neoadjuvant intense hormone therapy and surgery for high risk localized prostate cancer: results of a pooled analysis of contemporary clinical trials. *J Urol*. 2021;205(6):1689–1697. doi:10.1097/JU.0000000000001632
17. McKay RR, Montgomery B, Xie WL, et al. Post prostatectomy outcomes of patients with high-risk prostate cancer treated with neoadjuvant androgen blockade. *Prostate Cancer Prostatic Dis*. 2018;21(3):364–372. doi:10.1038/s41391-017-0009-6
18. der Kwast TV, Al Daoud N, Collette L, et al. Biopsy diagnosis of intraductal carcinoma is prognostic in intermediate and high risk prostate cancer patients treated by radiotherapy. *Eur J Cancer*. 2012;48(9):1318–1325. doi:10.1016/j.ejca.2012.02.003
19. Hollemans E, Verhoef EI, Bangma CH, et al. Large cribriform growth pattern identifies ISUP grade 2 prostate cancer at high risk for recurrence and metastasis. *Mod Pathol*. 2019;32(1):139–146. doi:10.1038/s41379-018-0157-9
20. Efstathiou E, Abrahams NA, Tibbs RF, et al. Morphologic characterization of preoperatively treated prostate cancer: toward a post-therapy histologic classification. *Eur Urol*. 2010;57(6):1030–1038. doi:10.1016/j.eururo.2009.10.020
21. Tilki D, Chen MH, Wu J, Huland H, Graefen M, D'Amico AV. Adjuvant versus early salvage radiation therapy after radical prostatectomy for pn1 prostate cancer and the risk of death. *J Clin Oncol*. 2022;40(20):2186–2192. doi:10.1200/JCO.21.02800
22. Li C, Wu L, Zhong B, et al. Integrated multi-omics profiling of immune microenvironment and drug resistance signatures for precision prognosis in prostate cancer. *Cancer Drug Resist*. 2025;8:31. doi:10.20517/cdr.2025.47
23. Guo T, Yuan Z, Wang T, et al. Integrative analysis of ferroptosis regulators for clinical prognosis based on deep learning and potential chemotherapy sensitivity of prostate cancer. *Precis Clin Med*. 2023;6(1):pbad001. doi:10.1093/pcmedi/pbad001
24. Khorasanchi A, Hong F, Yang Y, et al. Overcoming drug resistance in castrate-resistant prostate cancer: current mechanisms and emerging therapeutic approaches. *Cancer Drug Resist*. 2025;8:9. doi:10.20517/cdr.2024.173