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Prognostic Factors Associated with Biochemical Relapse After Radiotherapy in Localized Prostate Cancer: A Retrospective Cohort Study

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Abstract

Background: Biochemical recurrence (BCR) after definitive radiotherapy (RT) in localized prostate cancer (PC) is a clinically relevant event that impacts long-term management and prognosis. However, the prognostic value of certain biopsy-derived pathological parameters remains underexplored in RT-treated cohorts. Methods: We retrospectively analyzed 444 patients with localized PC treated with external beam radiotherapy (with or without androgen deprivation therapy) between 2013 and 2019. Clinical, radiological, and detailed histopathological data, including Gleason score, perineural invasion, and the number and proportion of positive biopsy cores—were collected. Logistic regression models were used to identify predictors of BCR. Results: After a median follow-up of 72 months, 11.7% of patients developed BCR. In multivariable analysis, higher PSA at diagnosis ($p = 0.05$), higher Gleason score (ISUP ≥4; $p = 0.036$), and greater tumor burden in biopsy cores—quantified as both number and proportion of positive cores per lobe and overall ($p < 0.05$)—were independently associated with BCR. Perineural invasion showed a univariable association ($p = 0.036$), though it did not remain significant after adjustment. Notably, nearly one-fourth of recurrences occurred beyond five years post-treatment, underscoring the need for prolonged follow-up. Conclusions: PSA level, Gleason grade, and extent of tumor involvement in diagnostic biopsies are strong, independent predictors of BCR following RT. These findings support the incorporation of detailed biopsy metrics into routine risk stratification to inform personalized surveillance strategies.

Keywords: prostate cancer; external-beam radiotherapy; biochemical recurrence; PSA; positive biopsy cores; perineural invasion; Gleason score/ISUP grade; risk stratification

1. Introduction

Prostate cancer (PC)is the second most frequently diagnosed malignancy among men worldwide. In Spain alone, 32 ,967 new cases were reported in 2022, according to GLOBOCAN data [1]. Since the introduction of the GS score (GS) , serum prostate-specific antigen (PSA) testing, and

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the ability to perform clinical staging through digital rectal examination or magnetic resonance imaging (MRI), these parameters have been widely used to predict disease progression and to guide therapeutic decision-making—whether surgery, radiotherapy (RT) , or active surveillance [2,3].

The combination of these three factors has enabled the identification of validated risk groups based on the likelihood of biochemical recurrence (BCR) [4]. These risk-stratification systems now constitute the backbone of major international clinical guidelines [5–7]. In addition to the classic predictors (PSA, clinical stage, and GS score), other markers have been proposed as potential predictors of BCR, such as the absolute number as well as the percentage of positive biopsy cores and the presence of perineural invasion (PNI), among others [8,9]. However, most of the available evidence for these factors comes from surgical series, and their prognostic value in patients treated with RT remains less well established and has been insufficiently investigated to date [10,11].

External-beam radiotherapy (EBRT), either alone or in combination with androgen-deprivation therapy (ADT), is a well-established and effective treatment modality for localized PC across all risk groups [12–14]. Nevertheless, despite modern image-guided and intensity-modulated techniques, a significant proportion of patients treated with curative intent will experience BCR in the years following therapy. It is estimated that 15–35 % of cases recur biochemically within the first five years after EBRT [15].

The detection of BCR has important clinical implications, as it frequently precedes overt disease progression. Identifying recurrence early, particularly at PSA levels near the Phoenix threshold, can allow for timely intervention during a less advanced stage of tumor evolution [16].

In this context, the high sensitivity and specificity of current imaging techniques—particularly prostate-specific membrane antigen positron-emission tomography (PSMA-PET)—have enabled targeted salvage treatments, such as focal or oligometastasis-directed therapies, with the goal of delaying or preventing progression to metastatic disease. These advances have significantly reshaped the personalized management of patients with recurrence after RT [16,17].

Even in patients who progress to metastatic stages, PC survival can be prolonged for several years, especially with the incorporation of novel hormonal agents such as androgen-receptor pathway inhibitors (ARPI) [18,19]. Nevertheless, early detection remains a cornerstone in optimizing long-term outcomes and guiding treatment decisions.

In this study, we retrospectively analyzed a cohort of patients with localized PC—without lymph-node involvement or distant metastasis—who underwent definitive treatment with EBRT ± ADT. Our objective was to identify clinical and pathological factors associated with BCR. We evaluated both traditional prognostic indicators and histopathological features obtained from diagnostic biopsies, as we believe these samples may hold more prognostic information than is currently incorporated into radiotherapy-based treatment decisions. Our aim was to explore whether integrating such data could improve risk-group stratification.

Furthermore, we assessed the patterns of recurrence, focusing on the anatomical sites and timing of recurrence events throughout follow-up, with the goal of providing evidence to optimize long-term surveillance strategies.

2. Materials and Methods

2.1. Patient Selection

We conducted a retrospective cohort study including 629 patients diagnosed with localized PC and treated exclusively with EBRT, with or without ADT: (Luteinizing hormone-releasing hormone [LHRH] agonists), between December 2013 and December 2019 at a single institution. A total of 444 patients met the eligibility criteria, which included a minimum follow-up of three years and at least four post-treatment PSA assessments. All cases were reviewed by a multidisciplinary tumor board, and written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Clinical

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Research Ethics Committee of Hospital Universitario de Terrassa (approval code: 02-21-100-020). The study is also registered under ClinicalTrials.gov identifier NCT06092918.

2.2. Risk Stratification

Patients were categorized into three risk groups based on established criteria:

Low-risk: International Society of Urological Pathology (ISUP)Grade 1, PSA <10 ng/mL, and clinical stage T1–T2a.

Intermediate-risk: ISUP Grade 2–3, PSA 10–20 ng/mL, or clinical stage T2b–T2c.

High-risk: ISUP Grade 4–5, PSA >20 ng/mL, or clinical stage ≥T3a.

Patients classified as high-risk—or intermediate-risk with a Gleason Score (GS) pattern of 4 + 3 (ISUP 3)—underwent staging with axial computed tomography (CT) combined with either whole-body bone scintigraphy or a PET/CT scan using [^18F]-choline, in order to exclude pelvic or distant metastases. [^18F]-choline PET/CT and [^68Ga]-PSMA PET/CT were employed at the time of BCR, depending on availability and institutional protocol.

2.3. Technical Parameters of Radiotherapy Planning and Treatment

RT planning was conducted using CT-based simulation with 3 mm slice thickness for accurate delineation of target volumes and organs at risk. Patients were treated with one of three techniques: three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), or volumetric-modulated arc therapy (VMAT), delivered in either normofractionated or hypofractionated schedules. Specifically, 3D-CRT was delivered using six-field plans with 15 MV or a combination of 6 MV and 15 MV photon beams; IMRT was implemented as step-and-shoot plans using five to seven 6 MV fields; and VMAT employed one or two full arcs with 6 MV photons. Image guidance consisted of weekly portal imaging for 3D-CRT and daily cone-beam CT for IMRT and VMAT.

For target volume delineation, when the clinical target volume (CTV) included only the prostate or the prostate and seminal vesicles (with the latter omitted in low-risk patients), an isotropic margin of 10 mm (for 3D-CRT) or 8 mm (for IMRT/VMAT) was used to define the planning target volume (PTV). In cases involving elective pelvic nodal irradiation, an isotropic margin of 7 mm was applied across all techniques. Pelvic lymph nodes were irradiated in all high-risk patients aged under 75 years and in intermediate-risk patients with a predicted nodal involvement risk greater than 15 %, as estimated by the Partin nomogram.

Regarding dose schedules, hypofractionated regimens consisted of either 2.5 Gray (Gy) per fraction to the prostate—with or without inclusion of the seminal vesicles—and an optional simultaneous dose of 1.8 Gy to the pelvic lymph nodes, or 3 Gy per fraction to the prostate and seminal vesicles alone, up to a total dose of 60 Gy. Normofractionated regimens were delivered as 2 Gy per fraction to a total dose of 78 Gy.

2.4. ADT (Androgen Deprivation Therapy)

LHRHa (luteinizing hormone-releasing hormone agonists) were administered according to international guidelines: 6 months for intermediate-risk patients and 18–36 months for high-risk patients, combined with oral antiandrogens during the first 30 days. Treatment began approximately two months prior to CT simulation.

2.5. PSA Monitoring and Definitions

Nadir PSA (nPSA) was the lowest level recorded after treatment.

BCR was defined according to the Phoenix criteria: a rise of ≥2 ng/mL above the nPSA.

PSA levels were monitored at 3, 6, and 12 months post-EBRT, and every 6 months thereafter.

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2.6. Statistical Analysis

Descriptive statistics were reported as means with standard deviations or medians with interquartile ranges (IQR, Q1–Q3) for continuous variables, and as absolute and relative frequencies for categorical variables. Group comparisons were performed using the Chi-square test or Fisher's exact test for categorical variables. For continuous variables, Student's t-test was applied when assumptions of normality and homogeneity of variances were met; otherwise, non-parametric tests were used.

Univariable analyses were first conducted to assess the association between each variable and BCR. Subsequently, a multivariable logistic regression model was constructed to identify independent predictors of BCR. Categorical variables with more than two levels were transformed into dummy variables. Model outputs included regression coefficients (estimates), standard errors, z-values, and p-values, indicating the strength and direction of association between each predictor and the outcome. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 27 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

3. Results

Of the 629 men recruited, 185 were excluded because of having less than 4 PSA determinations and/or less than 3 years of follow-up.

A total of 444 patients were included finally. The median age was 71 years (range 51–85), with a median follow-up of 72 months. Overall, 52 patients (11.7%) experienced BCR during follow-up. Baseline clinical and pathological characteristics are shown in Table 1.

Table 1. Baseline Characteristics of the Cohort (n = 444). Univariable Analysis.

Characteristic	**BCR (n = 52)**	**No BCR (n = 392)**	**p-value**
Age, median (range)	72 (54–83)	70 (51–85)	0.355
PSA at diagnosis, median / mean (ng/ml)	10.8 / 30.3	9.3 /12.9	0.045
ISUP Grade Group			0.011
- Grade 1	6 (7.8%)	70 (92%)	
- Grade 2–3	24 (9.4%)	231 (90.5%)	
- Grade ≥4	22 (19.4%)	91 (80.5%)	
Risk Group			0.035
- Low-risk	4 (9.3%)	39 (90.6%)	
- Intermediate-risk	16 (7.9%)	186 (92.1%)	
- High-risk	32 (16%)	167 (84%)	
RMI (resonance magnetic Image) cT2 cT3a cT3b	 10 (9.6 %) 5 (7%) 7 (18.4%)	 94 (91.4%) 66 (93%) 31 (81.6)	0.380
Exclusive Radiotherapy	11 (13.3%)	110 (86.7%)	0.189
Androgen Deprivation Therapy	41 (12.6%)	282 (77.4%)	0.36

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Radiotherapy Technique (3D-CRT / IMRT / VMAT)	16.7% / 14.3% / 9.5%	83.3% / 85.7% / 90.5%	0.242
Hypofractionated Normofractionaded	11 (16.9 %) 41 (10.9%)	54 (83.1%) 336 (89.1%)	0.119
Perineural Invasion	18 (17.4%)	85 (82.6%)	0.036
Positive cores (right lobe), count / proportion	2.98 / 57%	2.33 / 41%	0.014 / 0.046
Positive cores (left lobe), count / proportion	3.13 / 57%	2.36 / 41%	0.007 / 0.048
Total positive cores, count / proportion	6.11 / 57%	4.71 / 41%	0.01 / 0.005

3.1. Predictors Factors

No statistically significant differences were observed in age at diagnosis between patients with and without BCR (median: 72 [range: 54–83] vs. 70 years [51–85], respectively; $p = 0.355$).

PSA levels at diagnosis were significantly higher in patients who developed BCR (median: 10.8 ng/mL; mean: 30.3 ng/mL) compared to those without recurrence (median: 9.3 ng/mL; mean: 12.9 ng/mL; $p = 0.045$).

Regarding the ISUP Grade Group, the cohort included 76 patients with ISUP grade 1, 255 with ISUP grades 2–3, and 113 with ISUP grades 4–5. A significantly higher proportion of high-grade tumors was observed in the BCR group ($p = 0.011$). Similarly, patients with BCR were more frequently classified as high clinical risk (61.5% vs. 42.6%; $p = 0.035$).

The majority of cases (91.4%) were cT2. Although cT3b lesions showed numerically more failures (18.4 %), MRI stage did not reach significance ($p = 0.380$). Similarly, no significant differences were found regarding the administration of exclusive EBRT, with a BCR rate of 13.3% among patients who did not receive ADT ($p = 0.189$), nor among those treated with ADT, who presented a BCR rate of 12.6% ($p = 0.36$).

A total of 19 recurrences were recorded among 114 patients treated with the oldest radiotherapy technique (3D-CRT), representing a recurrence rate of 16.7%, the highest among all techniques. This was followed by IMRT with 5 recurrences in 35 patients (14.3%) and VMAT with 28 recurrences in 295 patients (9.5%). However, no statistically significant differences were observed according to the radiotherapy technique employed ($p = 0.242$). Likewise, no significant differences were found according to the fractionation schedule ($p = 0.119$).

PNI was more prevalent among patients with recurrence, with 18 cases of BCR among 103 patients with PNI and 8 cases among 116 patients without it ($p = 0.036$).

A higher tumor burden was observed in biopsy samples from patients with BCR, both in terms of the mean number of positive cores per lobe and the proportion of positive cores relative to the total number of sampled cores. The proportion of positive cores was consistently higher in the BCR group compared to the non-BCR group across both lobes (57% vs. 41%, respectively). Specifically, in the right lobe, the mean number of positive cores was 2.98 in the BCR group vs. 2.33 in the non-BCR group ($p = 0.014$); in the left lobe, 3.13 vs. 2.36 ($p = 0.007$); and for the total number of positive cores, 6.11 vs. 4.71 ($p = 0.01$). The differences in proportions between groups were also statistically significant (right lobe: $p = 0.046$; left lobe: $p = 0.048$; total: $p = 0.005$). (Figure 1)

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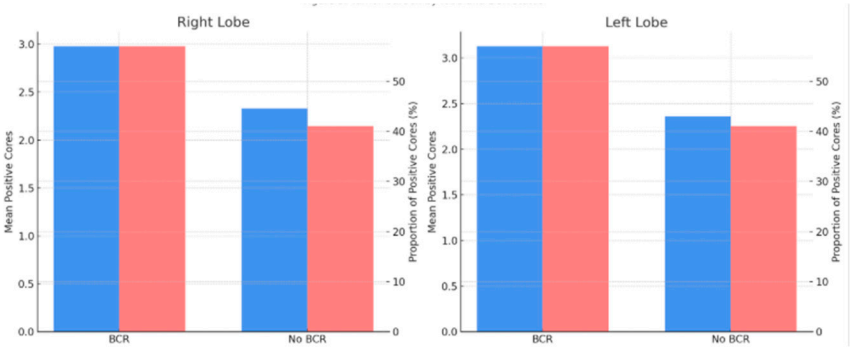

Figure 1. Tumor burden by lobe and BCR status. Bars in blue represent the mean number of positive cores, while bars in red represent the proportion (%) of positive cores in each lobe.

In the multivariable analysis, several independent factors remained statistically significantly associated with an increased risk of BCR.

PSA at diagnosis was confirmed as a significant predictor (OR: 1.01; 95% CI: 1.00–1.02; $p = 0.05$), indicating that higher PSA values are associated with an increased probability of recurrence, even after adjustment for other covariates.

Tumor burden in biopsy samples—expressed both as the absolute number and the proportion of positive cores—showed a strong and consistent association with BCR across all models. The number of positive cores in the right lobe (OR: 3.02; 95% CI: 1.25–7.32; $p = 0.014$), in the left lobe (OR: 2.70; 95% CI: 1.15–6.32; $p = 0.022$), and the total number of positive cores (OR: 8.26; 95% CI: 2.36–28.94; $p = 0.0009$) were all independently associated with a higher risk of recurrence.

Likewise, histological grade ISUP ≥ 4 was confirmed as a significant predictor in the adjusted model (OR: 2.25; 95% CI: 1.05–4.84; $p = 0.036$), reinforcing its prognostic value beyond the univariable analysis.

In contrast, the presence of PNI, although previously associated in the univariable analysis, did not reach statistical significance in the multivariable model (OR: 2.58; 95% CI: 1.02–6.81; $p = 0.234$), suggesting that its effect may be mediated or attenuated by other variables included in the model or possibly influenced by missing data. A summary of this analysis is presented in Table 2.

Table 2. Multivariable analysis.

Variable	Odds Ratio (OR)	95% CI	p Value
PSA	1.01	1.00-1.02	0.05
Positive right-side cores (count/proportion)	3.04	1.25-7.32	0.014
Positive left-side cores (count/proportion)	2.69	1.15-6.32	0.022
Total positive cores (count/proportion)	8.25	2.36-28.94	0.009
ISUP Grade distribution (ISUP ≥ 4)	2.25	1.05-4.84	0.036
Perineural invasion	2.58	1.02-6.81	0.234

3.2. Recurrence Patterns

Among the patients with biochemical recurrence, the extension study was negative in 12 cases. In 9 patients, recurrence was confined to the prostate only.

A total of 9 patients presented with M1a-exclusive disease (extra pelvis node metastases), while 6 patients had osseous-only metastases, and 5 showed exclusive pelvic nodal involvement.

The remaining 11 patients exhibited a mixed pattern of recurrence, involving two or more of the above sites.

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3.3. Time of Recurrence

Only two BCR (4.4%) occurred within the first year after treatment completion. In the second and third years, relapses were observed in 10 patients each (21.7% per year). Eight patients (17.4%) relapsed during the fourth year, and 12 (26.1%) during the fifth year. In total, approximately 20% of BCR occurred more than five years after RT. Figure 2

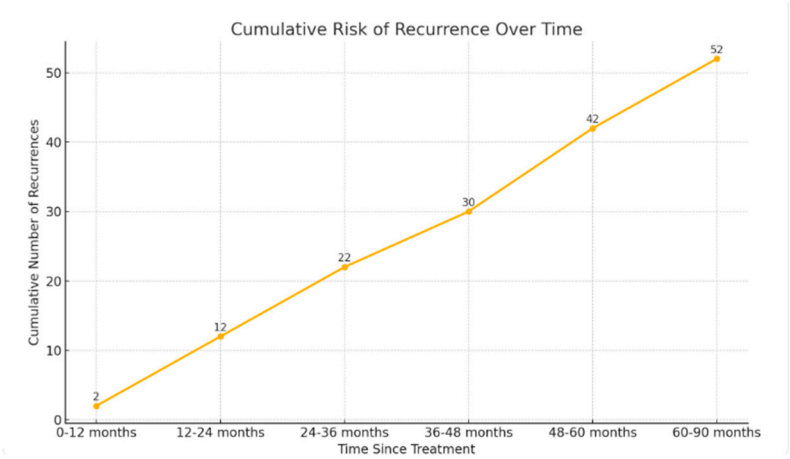

Figure 2. Time of recurrence.

4. Discussion

In this retrospective study, we analyzed a cohort of 444 patients with localized PC, without nodal involvement or distant metastases at the time of diagnosis, treated with modern RT techniques and standardized protocols regarding the indication and duration of ADT. The main objective was to confirm and/or identify clinical, pathological, and treatment-related factors that may influence the prediction of BCR, with the aim of enabling a more individualized risk stratification within the currently established risk groups. To this end, we explored the prognostic relevance of key variables such as baseline PSA, PNI, GS/ISUP, and the number- percentage of positive biopsy cores, as well as the timing and patterns of recurrence.

4.1. Prostate-Specific Antigen (PSA)

PSA remains one of the fundamental pillars in the diagnosis, risk stratification, and follow-up of PC. Baseline PSA at diagnosis has consistently been shown to be an independent predictor of BCR in multiple studies involving both surgical and RT-treated cohorts [20–22]. In our cohort, patients who developed BCR exhibited twice the mean PSA values compared to those without recurrence. Importantly, PSA remained statistically significant in the multivariable analysis, underscoring its prognostic value even after adjusting for other variables.

There is a proportional relationship between PSA levels and intraprostatic tumor burden, which may partially explain its predictive value for BCR observed in our cohort. However, exceptions do occur. Well-differentiated tumors, for instance, may not produce significantly elevated PSA levels, making the GS score essential for proper interpretation in such cases [23]. Conversely, elevated PSA levels may sometimes reflect false positives, most often due to lower urinary tract infections or other benign conditions [24].

PSA is a reliable, accessible, and quantifiable biomarker, but its use should always be complemented by prostate biopsy for diagnosis, and by appropriate imaging for staging or evaluation of recurrence.

Among the numerous studies assessing PSA as a prognostic factor, the retrospective study conducted at Memorial Sloan Kettering Cancer Center, published in 2010, stands out. Despite its retrospective design, the study employed modern radiation doses (>81 Gy) and found pretreatment

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PSA to be an independent predictor of BCR. Specifically, each 1 ng/mL increase in baseline PSA was associated with a 2% increase in the risk of biochemical failure (HR: 1.02; 95% CI: 1.01–1.03; $p = 0.0004$) [25].

4.2. Perineural Invasion (PNI)

In our cohort, the presence of PNI was more frequently observed in patients who developed BCR, reaching statistical significance in the univariable analysis (p = 0.036). However, this association did not remain significant in the multivariable logistic regression model (p = 0.234), suggesting that its effect may be attenuated by other covariates or limited by incomplete pathological reporting.

The biological relevance of PNI has been described in various solid tumors, including PC, where tumor cell infiltration of perineural spaces is thought to facilitate local tumor spread [26]. Several mechanistic hypotheses support its association with more aggressive behavior, including enhanced cellular proliferation and survival within the perineural niche [27,28].

Although PNI is widely recognized as a poor prognostic factor in surgical series [29], its role in patients treated with radiotherapy remains controversial. Some studies and pooled analyses suggest a potential association with BCR in this setting, yet evidence remains inconsistent [30,31]. This uncertainty may stem from heterogeneous definitions of PNI, variability in biopsy sampling, and limited quantification (e.g., percentage of nerves involved, number of foci).

In our study, PNI was not reported in nearly half of the biopsy reports, limiting the power of the multivariable analysis and reinforcing the need for standardized and systematic PNI documentation in pathology assessments. While our findings suggest that PNI may have prognostic value in radiotherapy-treated patients, further prospective studies with complete reporting are needed to clarify its independent contribution.

4.3. Positive Core Number-Percentage

The percentage of positive biopsy cores serves as an indirect marker of tumor burden or overall disease extent within the prostate, and therefore, it is expected that higher values correlate with an increased risk of BCR [32,33].

In our cohort, both the absolute number and the proportion of positive biopsy cores—whether analyzed by lobe or in total—were significantly associated with BCR. Patients who developed BCR had a higher mean number of positive cores in both lobes (right lobe: 2.98 vs. 2.33; left lobe: 3.13 vs. 2.36), as well as a greater proportion of positive cores (57% vs. 41%).

These associations remained significant in the multivariable logistic regression model. The total number of positive cores showed the strongest association with recurrence (OR: 8.25; 95% CI: 2.36–28.94; p = 0.009). Positive cores in the right and left lobes were also independently associated with BCR (OR: 3.04; 95% CI: 1.25–7.32; p = 0.014 and OR: 2.69; 95% CI: 1.15–6.32; p = 0.022, respectively). These findings confirm tumor burden, as measured by positive cores, as a robust and independent predictor of recurrence.

The proportion of positive cores was also remarkably consistent across lobes (57% in the BCR group vs. 41% in non-BCR), supporting its relevance as a global surrogate for intraprostatic tumor extent.

Although this variable is not routinely incorporated into standard risk models [34], its consistent and independent association with recurrence in our study suggests that the positive core percentage offers prognostic value beyond traditional indicators such as PSA, Gleason score, and clinical T stage.

Prior studies have also supported the prognostic utility of this marker. Kestin et al. (2002) were among the first to demonstrate the predictive role of positive core percentage in a cohort of 160 patients treated with EBRT and high-dose-rate brachytherapy. They reported a BCR rate below 7% in patients with <33% positive cores, compared to 25% in those with >66% [35]. Similarly, D'Amico et al. (2004) found that ≥50% positive cores significantly increased prostate cancer–specific mortality in patients with low- or intermediate-risk disease, leading to the recommendation of treatment intensification [36].

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Despite these findings, positive core percentage has not yet been systematically integrated into widely used prognostic models—particularly in radiotherapy-based cohorts. Our results support its inclusion in modern risk stratification frameworks, especially in the context of contemporary EBRT strategies.

4.4. Gleason Score (GS) - ISUP Grade

Histological grading based on the GS, introduced in the 1960s, remains the most widely established predictor of prostate cancer aggressiveness [37]. Although the system has undergone multiple refinements over time, its core principle persists: higher GS scores reflect less differentiated tumor architecture, which is associated with primary tumors that are more difficult to eradicate—either by surgery or RT—and a higher likelihood of distant metastasis [38–40].

In our cohort, the GS score was confirmed as a relevant predictor of BCR following definitive radiotherapy. In univariable analysis, stratification into three groups (G1: 3+3; G2: 3+4/4+3; G3: ≥4+4) showed a significant association with BCR risk ($p = 0.011$). This trend was sustained in multivariable analysis using separate categories, where group G3 exhibited a significantly higher risk compared to G1 and G2 ($p = 0.037$), while the joint model showed marginal significance ($p = 0.067$), due to interactions with other clinical variables.

These findings are consistent with large population-based studies, which used SEER data and identified the GS score as an independent predictor of both cancer-specific and overall survival in high-risk patients [38]. Notably, a progressive increase in risk was observed with higher scores (HR 2.66 for GS 10 vs. GS 8). Similarly, current international guidelines (EAU, ASCO, NCCN) define patients with GS 8–10 as a high-risk subgroup in the context of biochemical recurrence [5–7].

Taken together, these findings reinforce and confirm the robust prognostic value of the GS score as a cornerstone for initial risk stratification in PC.

4.5. Chronology of Recurrence

A particularly noteworthy finding was that 23% of biochemical recurrences occurred more than five years after the completion of radiotherapy. This observation reinforces two key points. First, the need for prolonged follow-up, even in patients who remain disease-free during the initial years after treatment [41,42]. Second, it highlights the advantage of PSA as a robust, cost-effective, and widely accessible biomarker for long-term monitoring.

However, we believe that PSA kinetics alone are insufficient and should be interpreted in conjunction with appropriate initial clinical risk stratification, as the likelihood of recurrence is influenced by pre-treatment clinicopathological features and treatment-related variables. This underscores the importance of early identification of patients at higher risk of biochemical recurrence, enabling targeted surveillance and helping to prevent unnecessary overburdening of clinical services.

4.6. Limitations and Future Directions

This study has several limitations, including its retrospective, single-center design, and incomplete reporting of certain pathological variables—most notably perineural invasion (PNI). Treatment heterogeneity and the lack of molecular profiling further limit the generalizability of the findings.

As a future step, we aim to construct a predictive model for biochemical recurrence (BCR) incorporating the clinical and pathological variables found to be independently associated in this cohort. Prospective validation and integration of emerging biomarkers will be essential to refine risk stratification and support personalized follow-up strategies.

5. Conclusions

Biochemical recurrence in localized prostate cancer after radiotherapy is significantly associated with higher PSA at diagnosis, higher Gleason score, presence of perineural invasion, and increased

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proportion of positive biopsy cores. These findings support the integration of detailed biopsy data into recurrence risk assessment.

The identification and understanding of these prognostic factors can guide decision-making prior to treatment and support individualized follow-up strategies in patients undergoing curative-intent radiotherapy for prostate cancer.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of the of Hospital Universitario de Terrassa (approval code: 02-21-100-020). The study is also registered under ClinicalTrials.gov identifier NCT06092918.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

PSA	Prostate-Specific Antigen
BCR	Biochemical Recurrence
PC	Prostate Cancer
GY	Gray
EBRT	External-Beam Radiotherapy
RT	Radiotherapy
ADT	Androgen-Deprivation Therapy
LHRH	Luteinizing Hormone-Releasing Hormone
MRI	Magnetic Resonance Imaging
PNI	Perineural Invasion
GS	Gleason Score
OR	Odds Ratio
CI	Confidence Interval
IQR	Interquartile Range
ISUP	International Society of Urological Pathology (ISUP)
PSMA-PET	Prostate-Specific Membrane Antigen Positron-Emission Tomograph

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