Med Glas (Zenica) 2025;22(1)
https://doi.org/10.17392/1796-22-01

Med Glas (Zenica)

ORIGINAL ARTICLE

Predictive factors for biochemical relapse in non-metastatic prostate cancer following primary radiotherapy

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ABSTRACT

Aim To investigate the predictors of biochemical relapse (BCR) among patients with non-metastatic prostate cancer treated with radiotherapy as the first-line therapy.

Methods The study included 91 patients diagnosed with prostate cancer at the University Clinical Centre in Tuzla, Bosnia and Herzegovina. After the radiation treatment as the first line of treatment, the patients were monitored for the next 36 months. If patients were classified in medium and high-risk groups, hormone therapy was administered. The occurrence of BCR was determined based on prostate-specific antigen (PSA) values. Potential prognostic parameters, including Gleason score (GS), PSA, tumour size (TNM), and standardised risk classification (RC), were monitored.

Results A total of 46 (50.5%) patients were aged 66-75, with a median PSA of 14.50 ng/mL. A Gleason score <6 was found in 72 (79.1%) of patients, and 31 (34.1%) had T2c tumours. The BCR occurred in 32 (35.2%) patients, with a median relapse time of 18 months. Significant predictors of BCR were Gleason score ≥6 (OR:4.46; p=0.006) and tumour stage >T2b (OR:3.59; p=0.021). The RC showed an Area Under Curve (AUC) of 0.634 (p=0.050), indicating its potential diagnostic accuracy.

Conclusion Gleason score ≥6 and TNM>T2b are significant predictors of biochemical relapse in prostate cancer patients treated with radiotherapy. These results emphasize the need for additional monitoring and timely treatment of clinical disease progression in patients with Gleason score ≥6 and tumour stage >T2b.

Keywords: androgen antagonists, prostate-specific antigen, radiotherapy

INTRODUCTION

Prostate cancer is the most frequently diagnosed malignant disease in the world in the male population and is the fifth leading cause of death from cancer in the male population (1). The disease is extremely heterogeneous and varies from a disease limited to the prostate to a metastatic disease, and in 15% of all cases it is diagnosed as a high-risk localized disease (2). The treatment of prostate cancer is based on a multidisciplinary approach and depends on the pathohistological diagnosis, stage of the disease, assessed risk factors, clinical condition, and expected length of life of the patient (3). The first line of treatment for patients with localized prostate cancer includes the use of radiotherapy with possible addition of hormone therapy, depending on the risk group of patients, and surgical treatment (4). If the disease is detected at an older age, depending on the clinical condition and the potential risks of the treatment, the clinician may decide on active monitoring, until the moment of the appearance of the symptomatic disease when the treatment is carried out (5).

Prostate-specific antigen (PSA) is of significant use in monitoring patients after the initial treatment (6). Biochemical relapse (BCR) is defined as an increase in PSA of 2 ng/mL above the lowest PSA value achieved after the radiation therapy. This definition applies regardless of whether hormonal treatment was used in addition to radiotherapy or not (7).

Risk classification (RC) for prostate cancer consists of elements that include the initial value of prostate-specific antigen, Gleason score, and tumour size (TNM) (8). Although this classification is simple, the range of categories is large, especially in the high-risk category. Several recent studies have reported that subclassification of high-risk prostate cancer is useful for predicting cancer-related mortality and the occurrence of BCR after initial treatment, including radical prostatectomy and radiotherapy (8).

High-risk prostate cancer is a heterogeneous group, and patients do not have a uniform prognosis after the initial treatment (9). According to the current guidelines, hormone therapy is recommended for high-risk patients as adjuvant and neoadjuvant, and intermediate-risk patients as neoadjuvant, while it is not recommended for low-risk patients (10).

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 Submitted: 03. Jun. 2024. Revised: 29 Sep. 2024. Accepted: 01 Oct. 2024.

Although numerous treatment protocols for prostate cancer are currently available, there is a notable lack of studies that systematically assess BCR and its associated prognostic factors across different risk categories. This study represents the first of its kind in Bosnia and Herzegovina (B&H), offering a scientific rationale for further exploration of these factors to enhance the understanding and optimization of therapeutic strategies in prostate cancer management.

The aim of this study is to investigate the predictors of biochemical relapse (BCR) among patients with non-metastatic prostate cancer treated with radiotherapy as the first-line therapy.

PATIENTS AND METHODS

Patients and study design

This prospective study encompassed 91 patients who received treatment for prostate cancer at the University Clinical Centre in Tuzla, B&H), between January 2019 and May 2020. The follow-up period for these patients was 36 months.

The inclusion criteria mandated a histologically confirmed diagnosis of non-metastatic prostate cancer, with transcutaneous irradiation as the primary treatment modality. Exclusion criteria encompassed patients with metastatic disease, those with a history of multiple malignancies, patients who underwent radical prostatectomy as the initial treatment, patients who had died from non-prostate cancer-related causes, and those who continued therapy at external institutions.

The Ethical Committee of the University Clinical Centre Tuzla approved the study.

Methods

For each patient, data extracted from medical records included age, gender, pre-biopsy PSA level, Gleason score, TNM, post-radiation hormonal therapy status, and BCR. Patients were stratified into three risk groups based on RC: low risk (tumour confined to one lobe, PSA <10 ng/mL, GS<6), medium risk (tumour involving more than half of one lobe or bilateral without extracapsular extension, PSA 10-20 ng/mL, GS of 7), and high risk (extracapsular extension, PSA >20 ng/mL, or GS of 8-10)(8,11). TNM for prostate cancer was graded as follows: T2a (tumour in ≤50% of one lobe), T2b (tumour in >50% of one lobe), T2c (tumour in both lobes), T3 (tumour has spread through the capsule), T3a (tumour has spread through the capsule), and T3b (tumour has invaded one or both seminal vesicles) (12).

All patients received transcutaneous irradiation as the first-line treatment with a total dose of 74 Gy (1.8-2 Gy per fraction) in three phases: 46 Gy in 23 fractions, 20 Gy in 10 fractions, and 6-8 Gy in 3-4 fractions.

Hormonal therapy comprises luteinizing hormone-releasing hormone (LHRH) agonists, specifically leuprolide acetate (LA). The LA was administered to patients either every three months at 22.5 mg subcutaneously or every six months at 45 mg subcutaneously, for a maximum duration of two years. Hormonal therapy was prescribed for patients classified as medium to high-risk.

A follow-up had been conducted for 36 months from the initial patient examination monitoring biochemical relapse.

Statistical analysis

Data were presented as frequencies (N) and percentages (%) for categorical variables and as medians and interquartile ranges (IQR) for continuous variables. The normality of distribution was tested using the Kolmogorov-Smirnov test. Associations between observed variables were analysed using binary logistic regression. Kaplan-Meier plots illustrated survival periods relative to the examined potential factors with a log-rank test. Receiver operating curve (ROC) analysis was utilized to assess the diagnostic accuracy of the observed predictive variables. Statistical significance was set at $p \leq 0.05$.

RESULTS

The research sample primarily consisted of older adults, with the majority (N=46; 50.5%) aged 66-75 years followed by those older than 75 (N=30; 33.0%) years. The median PSA level was 14.50 ng/mL (IQR:7-33). Most participants had a Gleason score <6 (N=72; 79.1%), indicating less aggressive prostate cancer, while 19 (20.9%) had a score of ≥6. TNM varied, with 31 (34.1%) having T2c tumours and smaller percentages in other categories including T3a (N=10; 11.0%) and T3b (N=6; 6.6%). Regarding the disease risk, 42 (46.2%) were classified as high risk, 27 (29.7%) as medium risk and 22 (24.2%) as low risk. Over a half (N=52; 75%) of patients received hormone therapy. The BCR occurred in 32 (35.2%) patients, with a median time to relapse of 18 months (IQR: 12-30) (Table 1).

Table 1. Demographic and clinical characteristics of patients with non-metastatic prostate cancer

Variable	Value
	No (%)
Age (years)	
≤65	15 (16.5)
66-75	46 (50.5)
>75	30 (33.0)
Gleason score	
<6	72 (79.1)
≥6	19 (20.9)
Tumor size	
T2a	19 (20.9)
T2b	19 (20.9)
T2c	31 (34.1)
T3	6 (34.1)
T3a	10 (11.0)
T3b	6 (6.6)
Disease risk	
Low	22 (24.2)
Medium	49 (29.7)
High	42 (46.2)
Hormone therapy	
YES	47 (52.75)
NO	43 (47.25)
Biochemical relapse	
YES	32 (35.2)
NO	59 (64.8)
	Median (IQR)
PSA (ng/mL)	14.50 (7-33)
Months until disease relapse	24 (12-30)

N, frequency; PSA, prostate-specific antigen; IQR, interquartile range

The patient's age ≥75 and PSA ≥20 was not significantly associated with the disease relapse (p>0.05). The Gleason score ≥6 (OR:4.46; 95% CI:1.54-12.93; p=0.006) and tumour stage >T2b (OR: 3.59; 95% CI:1.08-13.46; p=0.021) were significantly associated with the disease relapse (Table 2).

Table 2. Logistic regression analysis for predicting biochemical relapse (BCR) among patients with non-metastatic prostate cancer

Variable	Odds ratio	95% CI	p
Age≥75	1.36	0.55 - 3.38	0.498
PSA≥20	1.56	0.63 - 3.82	0.332
GS≥6	4.46	1.54 - 12.93	0.006
TNM>T2b	3.59	1.08 - 13.46	0.021

CI, confidence interval; PSA, prostate-specific antigen; GS, Gleason score; TNM, tumour size;

The analysis of predictors of relapse time indicated varying median months to relapse across different factors: for age <75 experienced a median of 15 months (95% CI: 12 -24), while those ≥75 had the median of 24 months (95% CI:6-36) (Figure 1A); regarding Gleason score, patients with a score <6 showed the median of 22 months (95% CI: 12-30), while those with a score ≥6 had the median of 12 months (95% CI: 6-30) (Figure 1B); for PSA <20 had the median of 15 months (95% CI:10-24), whereas those with PSA ≥20 had the median of 24 months (95% CI:12-30) (Figure 1C); and for TNM<T2b experienced the median of 15 months (95% CI:12-36), whereas those ≥T2b had the median of 18 months (95% CI:12-30) (Figure 1D). Statistical significance (p>0.05) was not confirmed for the tested predictors of biochemical relapse.

BCR's prognostic accuracy showed the following results: PSA had an AUC of 0.568 (95% CI:0.437-0.699; p=0.308), risk stratification had an AUC of 0.634 (95% CI:0.501-0.743; p=0.050), and the Gleason score had an AUC of 0.587 (95% CI:0.464-0.710; p = 0.165) (Figure 2).

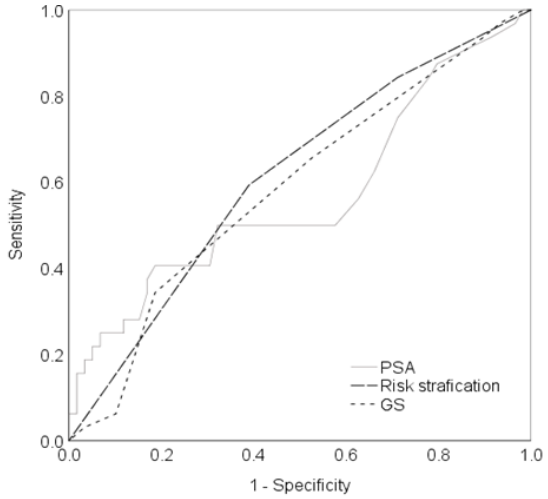

Figure 2. Receiver operating characteristic (ROC) analysis of prostate-specific antigen (PSA), risk stratification, and Gleason score as prognostic factors for biochemical relapse (BCR)

DISCUSSION

The study, which primarily involved older adults with prostate cancer, found that a Gleason score ≥6 and tumour stage >T2b were significantly associated with an increased risk of BCR among patients with hormone and radiotherapy. The results indicate that higher risk level correspond to shorter periods until BCR. The risk classification for BCR had the highest prognostic accuracy.

The combination of hormone therapy and radiation treatment in several studies showed a positive effect on the survival of patients with prostate cancer, which was observed in patients with locally advanced disease and in those at high risk. Bolla et al. (13) compared the use of mono-radiotherapy with radiotherapy in addition to hormone therapy for 3 years, with the

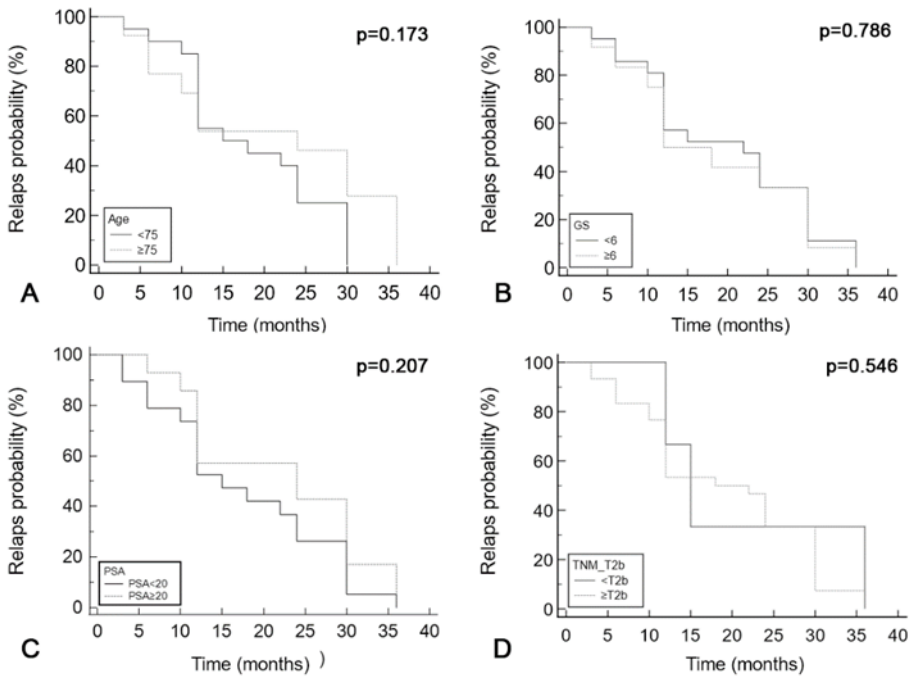

Figure 1. Relapse probability based on A) age, B) Gleason score, C) prostate-specific antigen (PSA), and D) tumour size (TNM)

advantage of combined therapy being noted in terms of overall and prostate cancer-specific survival (13). Previous studies showed that the use of hormone therapy slows down the clinical and biochemical progression of the disease, while the data on overall survival are different (14–16). Hormonal therapy reduces the likelihood of the disease progression and consequently the occurrence of BCR. Our study identified that prostate cancer patients with a grade higher than T2b have a greater likelihood of experiencing BCR. It was found that tumour volume and prostate-tumour ratio are independent predictors of BCR (17). Reportedly, pT3 increases the likelihood of BCR by 1.7 times in patients undergoing radical prostatectomy (18). To our knowledge, this is the first study focusing on BCR predictors in patients treated with radiotherapy and hormonal therapy.

Our results showed the Gleason score ≥6 was a significant predictor of BCR. Other studies have emphasized the predictive value of Gleason grading, noting that a score ≥3 increases the risk of BCR by 1.9 times (19), while a Gleason score ≥7 elevates the risk by 2.7 times following radical prostatectomy (20). Additionally, it was found that a Gleason score of 6 results in BCR in 3.4% of cases, further supporting its role as a predictor (21).

In terms of classifying patients into risk groups for BCR, ROC analysis in our study confirmed the statistical significance of the classification system employed (AUC: 0.634; p=0.050). Some studies reported the diagnostic accuracy of 74% for this classification system (22). In a study with a 96-month follow-up period (23), a higher AUC value of 0.818 was reported for RC in BCR. Our findings suggest that this patient stratification serves as a potential prognostic tool for predicting BCR in prostate cancer patients treated with radiotherapy. However, advancements in artificial intelligence (AI) and machine-learning algorithms have demonstrated even greater precision in predicting BCR (24) and survival period (25).

Limitations of this study include its monocentric nature and the small sample size, as it included only patients treated with radiotherapy.

In conclusion, TNM and Gleason score have predictive roles in BCR among patients treated with radiotherapy and hormonal therapy. Further research is needed to refine this classification and tailor it to patients treated with radiotherapy to achieve greater diagnostic accuracy.

AUTHOR CONTRIBUTIONS

Conceptualization, A.K., Š.U., H.O., A.B. and E.B.; Data curation, A.K. and A.M.; Methodology, A.K. and H.O.; Writing – original draft preparation, A.K., Š.U., A.M., E.T., E.H., E.B., S.H., M.B. and E.B.; Formal Analysis, Š.U. and E.B.; Supervision, Š.U., E.B. and E.B.; Writing – review & editing, Š.U. and E.B.; Investigation, E.T., E.B., A.B., M.B. and E.B.; Resources, E.T., E.H., S.H. and M.B.; Project administration, A.B.; Software, E.B. All authors have read and agreed to the published version of the manuscript.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATION

Conflict of interests: None to declare.

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