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Radiotherapy of Prostate Carcinoma: A Comparison of the Predictive Role of EAU *Versus* NCCN Risk Stratification Systems

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Abstract. *Background/Aim: To compare the predictive efficacy of National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) risk stratification systems in radiotherapy of prostate cancer. Patients and Methods: One-thousand-nine-hundred-nine patients treated with definitive (1,074), adjuvant (381), and salvage radiotherapy (454) were analysed. Results: Both systems significantly predicted biochemical-relapse-free-survival, metastasis-free-survival, and disease-free-survival, while only the NCCN system correlated with local-control in the definitive radiotherapy group. In the adjuvant setting, both systems failed to predict all outcomes. In the salvage setting, only the NCCN system significantly predicted biochemical-relapse-free-survival, metastasis-free-survival and disease-free-survival. Conclusion: This analysis confirms the efficacy of both systems in definitive radiotherapy and suggests the utility of the NCCN also in salvage radiotherapy.*

In 2018, prostate cancer (PCa) was the second most frequent cancer and the fifth cause of cancer death in males worldwide (1). In non-metastatic PCa, radiotherapy is a treatment option in different settings: definitive, adjuvant, and salvage therapy (2).

Predictive models are used in PCa for patients counselling, to tailor the treatment according to clinical and pathological variables, and to design clinical trials on homogeneous patients' categories in terms of prognosis (3). One of the simplest and most used ways to predict prognosis in PCa patients treated with radiotherapy is represented by risk stratifications systems (3). Typically, these systems stratify patients into three to five categories, from very low or low risk up to high or very high risk (3). The most used risk classification systems are the National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) ones (2, 4). However, a direct comparison between these two systems is not available in literature. Furthermore, the possible role of these stratification systems in the adjuvant and salvage settings is not known. Therefore, the aim of this analysis was to evaluate the predictive efficacy of these two risk stratification systems, on different clinical outcomes, in three different radiotherapy settings: definitive, adjuvant, and salvage treatment.

Patients and Methods

For the purposes of this analysis, we retrospectively evaluated the data of patients enrolled in a multicentre observational study. The predictive efficacy of NCCN and EAU stratification systems was evaluated on the following end points: biochemical relapse-free survival (bRFS), local control (LC), regional control (RC), metastasis-free survival (MFS), disease-free survival (DFS), and

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overall survival (OS). LC was defined in terms of freedom from tumor progression in the prostate or seminal vesicles (or in the tumor bed in resected patients). RC was defined as freedom from progressive or recurrent disease in the prostate (or prostatic bed) and regional (pelvic) lymph nodes.

Statistical analysis. The IBM SPSS Version 22.0 software package was used for statistical computation (IBM Corp, Armonk, NY, USA). Survival estimates were calculated by the Kaplan–Meier product-limit method (5) and compared with the log-rank test (6). In order to compare the homogeneity of the two systems (both based on three risk categories), we combined patients at very low and low risk and patients at high risk and very high in the NCCN classification. Similarly, in the EAU classification we combined the high-risk and locally advanced disease patients. The attribution to the different risk categories in both systems was performed considering the clinical tumor stage and clinical nodal stage in patients treated with definitive radiotherapy. Instead, in the operated patients (adjuvant and salvage settings) we used the pathological stage (for both tumor and lymph nodes). In all treatment settings, the prostate specific antigen (PSA) value before treatment (radiotherapy or surgery) was used. Finally, the Gleason score was obviously assessed by biopsy in patients treated with definitive radiotherapy, while in patients who underwent radical prostatectomy, the Gleason score defined on the surgical specimen was used. All tests were 2-sided, and the statistical significance was considered as $p<0.05$.

Ethical issues. This study was approved by the local institutional review board (311/2019/Oss/AOUBo, ICAROS-1 study). All patients included in the analysis had previously provided a written informed consent to the scientific use of their data.

Results

Patient characteristics. In this analysis, we included 1,909 patients (1,074, 381, 454) treated with definitive, adjuvant and salvage radiotherapy, respectively. In these three settings, median age was 74 years, 66 years, and 68 years, respectively. Median follow-up was 63 months, 48 months, and 45 months, respectively. Median PSA at diagnosis was 7.9 ng/ml, 7.9 ng/ml, and 10.4 ng/ml, respectively. Median total radiotherapy doses to the prostate or prostate bed was 70 Gy, 66 Gy, and 70 Gy, respectively. The percentage of patients receiving adjuvant androgen deprivation therapy was 74.5%, 63.3%, and 64.1%, respectively. Prophylactic irradiation of pelvic lymph nodes was delivered in 47.7%, 78.0%, and 59.9% of patients, respectively. Other patients' characteristics are shown in Table I.

Comparison between risk stratification systems. Both systems accurately predicted the bRFS ($p<0.001$) in patients treated with definitive radiotherapy (Table II, Figure 1a and b). In the same patients' group, only the NCCN system significantly correlated with LC ($p=0.023$). Both systems failed to predict RC and OS. Moreover, both systems significantly correlated with MFS and DFS, with lower *p*-values using the NCCN classification (Table II). In patients treated with adjuvant radiotherapy, both systems failed to significantly predict bRFS (Figure 2a and 2b) and all clinical outcomes (Table II). In the salvage radiotherapy setting, only the NCCN system was able to predict the bRFS ($p=0.002$), (Figures 3a and b), MFS ($p=0.002$), and DFS ($p=0.006$) (Table II).

Table I. *Patients characteristics in the three treatment settings*.

Variable	Definitive No of patients (%)	Adjuvant No of patients (%)	Salvage No of patients (%)
Prostate specific antigen level (ng/ml)			
<10	696 (64.8)	249 (65.4)	226 (49.8)
10-20	248 (23.1)	95 (24.9)	139 (30.6)
>20	130 (12.1)	37 (9.7)	89 (19.6)
Gleason score (ISUP grade)			
6	397 (37.0)	52 (13.6)	77 (17.0)
7 (3+4)	206 (19.2)	65 (17.1)	83 (18.3)
7 (4+3)	168 (15.6)	88 (23.1)	117 (25.8)
8	177 (16.5)	100 (26.2)	86 (18.9)
9-10	126 (11.7)	76 (19.9)	91 (20.0)
Tumor stage			
1	135 (12.6)	0 (0.0)	4 (0.9)
2	628 (58.5)	72 (18.9)	183 (40.3)
3	288 (26.8)	303 (79.5)	261 (57.5)
4	23 (2.1)	6 (1.6)	6 (1.3)
Nodal stage			
0	1043 (97.1)	325 (85.3)	392 (86.3)
1	31 (2.9)	56 (14.7)	62 (13.7)
NCCN risk category			
Very low-, low risk	123 (11.5)	1 (0.3)	11 (2.4)
Intermediate risk	422 (39.3)	42 (11.0)	128 (28.2)
High-, very high risk	529 (49.3)	338 (88.7)	315 (69.4)
EAU category			
Very low-, low risk	123 (11.5)	1 (0.3)	11 (2.4)
Intermediate risk	260 (24.2)	8 (2.1)	38 (8.4)
High-risk, locally advanced	691 (64.3)	372 (97.6)	405 (89.2)

EAU: European Association of Urology; ISUP: International Society of Urological Pathologists; NCCN: National Comprehensive Cancer Network.

Discussion

We used a large patient population to evaluate the predictive impact of the two most common risk stratification systems in PCa. The analysis in the group of patients treated with definitive radiotherapy showed a significant correlation with the biochemical outcome and with several clinical outcomes using both NCCN and EAU systems, with apparent higher predictive accuracy with the NCCN. In the adjuvant setting, both systems failed to significantly predict bRFS and all clinical outcomes, while in the salvage setting, only the NCCN system was able to significantly predict bRFS, MFS, and DFS.

Table II. *Predictive role of EAU and NCCN risk stratification systems.*

Variable	Value	Number of patients (%)	bRFS (%)	*p*-Value	LC (%)	*p*-Value	RC (%)	*p*-Value	MFS (%)	*p*-Value	DFS (%)	*p*-Value	OS (%)	*p*-Value
Definitive radiotherapy														
NCCN risk category	Very low-, low risk	123 (11.5)	95.4	0.000	97.7	0.023	100.0	0.240	98.7	0.000	96.4	0.000	97.4	0.466
	Intermediate risk	422 (39.3)	94.4		97.7		98.3		97.9		95.7		91.4	
	High-, very high risk	529 (49.3)	79.6		91.7		96.8		90.1		84.1		91.1	
EAU risk category	Very low-, low risk	123 (11.5)	95.4	0.000	97.7	0.145	100.0	0.136	98.7	0.003	96.4	0.006	97.4	0.326
	Intermediate risk	260 (24.2)	93.9		97.0		96.1		97.1		94.2		91.4	
	High-risk, locally advanced	691 (64.3)	82.9		93.3		97.5		92.1		87.2		91.3	
Adjuvant radiotherapy														
NCCN risk category	Very low- low risk	1 (0.3)	100.0	0.896	100.0	0.974	100.0	0.590	100.0	0.574	100.0	0.926	100.0	0.555
	Intermediate risk	42 (11.0)	92.7		96.9		95.7		100.0		92.7		100.0	
	High- very high risk	338 (88.7)	88.8		96.3		98.8		96.9		92.2		95.7	
EAU risk category	Very low-, low risk	1 (0.3)	100.0	0.848	100.0	0.906	100.0	0.958	100.0	0.898	100.0	0.762	100.0	0.893
	Intermediate risk	8 (2.1)	100.0		100.0		100.0		100.0		100.0		100.0	
	High-risk, locally advanced	372 (97.6)	89.0		96.4		98.5		97.1		92.1		96.1	
Salvage radiotherapy														
NCCN risk category	Very low-, low risk	11 (2.4)	100.0	0.002	100.0	0.644	100.0	0.279	100.0	0.002	100.0	0.006	100.0	0.761
	Intermediate risk	128 (28.2)	60.9		91.2		87.6		95.4		70.6		93.0	
	High-, very high risk	315 (69.4)	44.2		91.3		86.0		79.3		55.6		92.4	
EAU risk category	Very low-, low risk	11 (2.4)	100.0	0.150	100.0	0.742	100.0	0.533	100.0	0.326	100.0	0.243	100.0	0.435
	Intermediate risk	38 (8.4)	59.1		87.5		89.5		88.0		59.1		96.0	
	High-risk, locally advanced	405 (89.2)	47.4		91.7		86.1		83.1		59.6		92.3	

bRFS: Biochemical relapse free survival; EAU: European Association of Urology; DFS: disease-free survival; LC: local control; MFS: metastases-free survival; NCCN: National Comprehensive Cancer Network; OS: overall survival; RC: regional control.

Our study has several limitations and can be considered just as a hypothesis generating analysis. First, in both systems, the risk categories were simplified into three groups. Secondly, in the operated patients, these risk categories were adapted by replacing the clinical stage with the pathological one, while the Gleason score was based on the evaluation of the surgical specimen. Moreover, the three groups (definitive, adjuvant and salvage) included different numbers of patients. Therefore, the lack of statistically significant results, particularly in the smallest group (adjuvant), could simply be attributed to the sample size.

Even more important is the limited number of patients in some risk groups. For example, in the adjuvant setting, only 1 and 8 patients were included in the low and intermediate risk groups (EAU), respectively. Similarly, in the salvage setting, only 11 and 38 patients were included in the low and intermediate risk groups (EAU), respectively. This aspect further limits the possibility to identify statistically significant differences.

The inclusion of the adjuvant and salvage settings in the comparison between the two systems was simply an exploratory analysis. In fact, both risk classifications have been developed for the definitive treatment setting and do not consider well known prognostic factors in the other settings. In fact, the impact of other prognostic factors such as lymphovascular invasion has been demonstrated in patients undergoing adjuvant radiation therapy (7). Similarly, in patients undergoing salvage radiotherapy, the PSA level at the time of radiotherapy initiation and the PSA doubling time have a significant prognostic impact (8-10).

However, it was interesting to observe the significant prognostic impact of the NCCN classification in the salvage setting, despite the limitations of the sample size in some risk groups. This result could justify further analyses to develop predictive models including the factors defining the level of risk (according to the NCCN system) as adapted by us.

Finally, our study evaluated risk stratification systems that are based on grouping patients into different categories. This

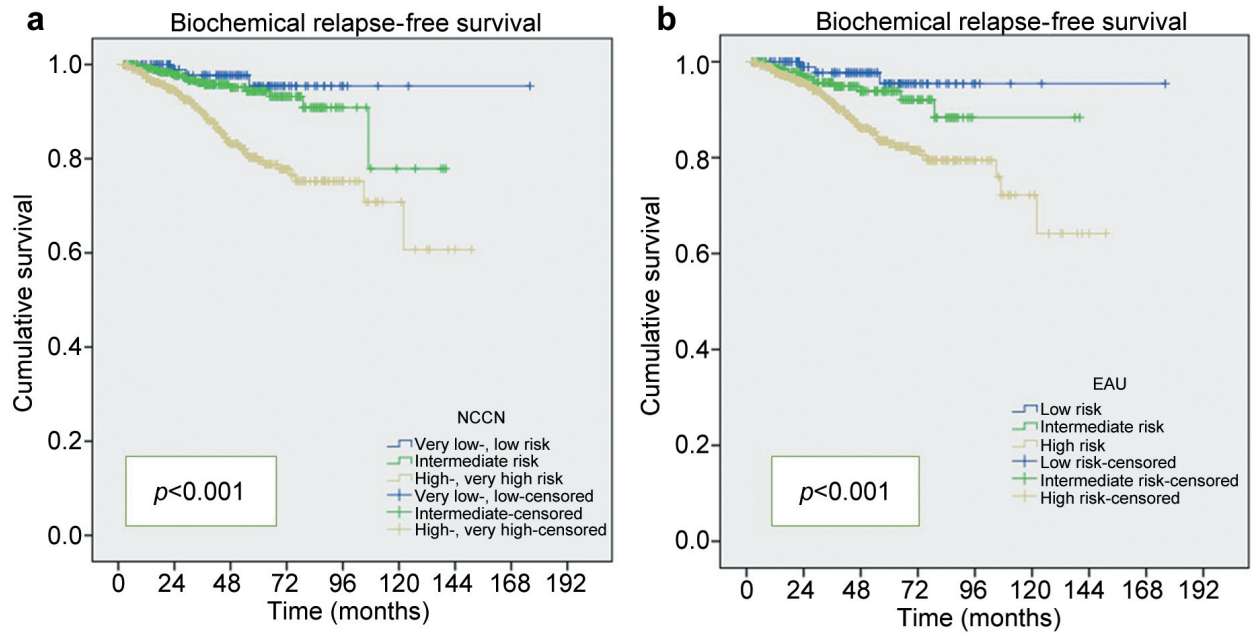

Figure 1. *Comparison of biochemical relapse-free survival between risk categories (a: NCCN; b: EAU) in patients treated with definitive radiotherapy.*

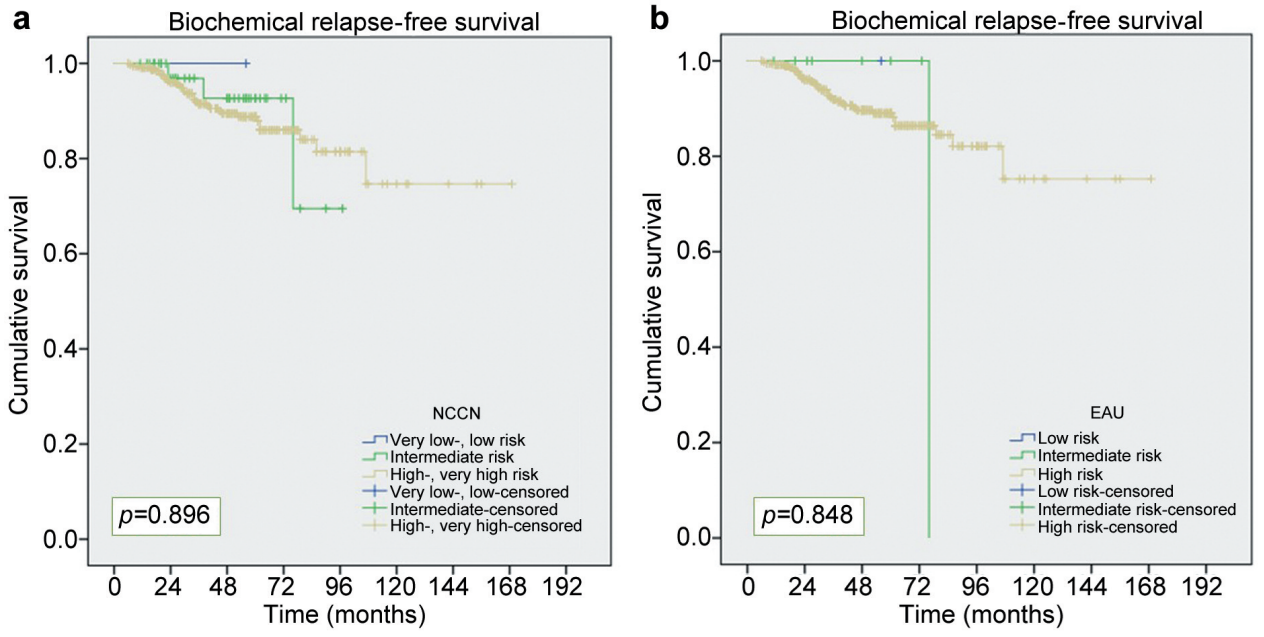

Figure 2. *Comparison of biochemical relapse-free survival between risk categories (a: NCCN; b: EAU) in patients treated with adjuvant radiotherapy.*

modality is theoretically associated to a reduced predictive accuracy due to the inclusion of patients in rather broad categories. On the contrary, individual risk estimation systems, based on predictive models, may allow to calculate the probability of a specific clinical outcome in the individual patient (3).

In the systematic review of Raymond and colleagues published in 2017, 66 predictive models for PCa patients treated with radiotherapy were analysed. However, this review demonstrated that most of these predictive models have clear limitations. In fact, 65% of them were not externally validated, 57% did not report accuracy, and 31%

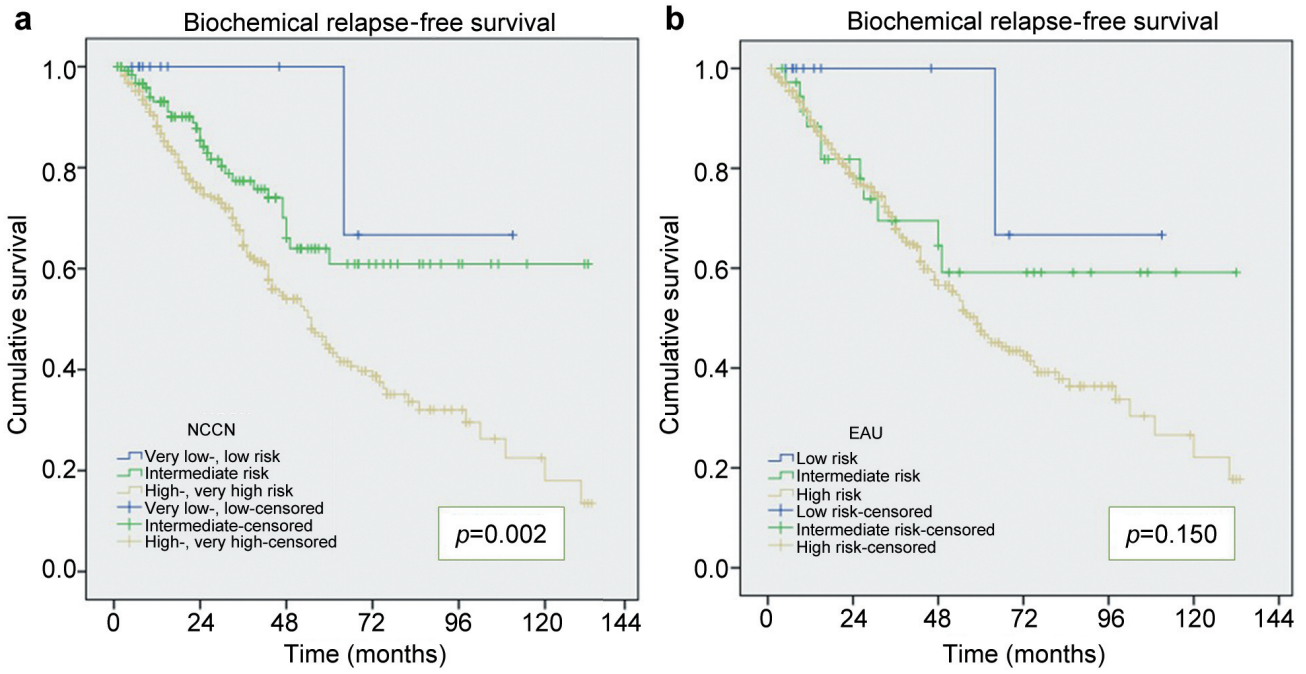

Figure 3. *Comparison of biochemical relapse-free survival between risk categories (a: NCCN; b: EAU) in patients treated with salvage radiotherapy.*

included variables which are not part of typical registry data sets and are therefore difficult to validate (11).

Considering that we simplified the two risk stratification systems, it is worth noting that the only difference between the NCCN and EAU is related to the T2c tumor classification. In fact, this stage has been classified as intermediate risk and high risk in NCCN and EAU, respectively. The better predictive performance of the NCCN system in the definitive setting suggests that, in patients treated with radiotherapy alone, the neoplastic invasion of both prostatic lobes has a limited impact.

In conclusion, from the clinical point of view, this analysis confirms the efficacy of both risk stratification systems in the definitive radiotherapy setting. Moreover, our analysis seems to suggest the prognostic role of the NCCN system also in the salvage setting but not in the adjuvant one. Further studies aimed to define risk categories in the adjuvant setting are therefore useful. Hopefully, in the future, more accurate and personalized individual risk evaluation and predictive tools will be developed. These systems could be based on the available knowledge of these neoplasms in terms of biomolecular, genetic, radiomic, and radiogenomic characteristics (12).

Conflicts of Interest

The Authors have stated that they have no conflicts of interest regarding this study.

Authors' Contributions

Conception and Design: MB, FD, MG and AGM; Data Collection: FD, GM, GS, ARA, SB, MN and VV; Analysis and Interpretation of Data: MB, ND, SC and AGM; Manuscript Writing: MB, FD, ND and AGM. All Authors read and approved the final manuscript and gave consent for publication.

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