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DEVELOPMENT OF A LARGE DATABASE ON PROSTATE CARCINOMA

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SUMMARY

ABSTRACT

The main aim of this study was to analyze the prognostic impact on outcome and toxicity of patients with prostate cancer [PCa] treated with radiotherapy [RT] in three different settings [curative, adjuvant, and salvage RT] based on a comprehensive analysis of parameters related to tumor, patients, and treatment characteristics. Furthermore, we aimed to develop simple risk stratification systems, based on real life data from a large patient population including the three different RT settings.

A retrospective analysis of 1909 patients [curative: 1074, adjuvant: 381, salvage: 454] enrolled in an observational study [311/2019/Oss/AOUBo, ICAROS-1 study] was performed. Endpoints of the study in terms of outcome were biochemical relapse-free survival [bRFS], local control [LC], regional control [RC], metastasis-free survival [MFS], disease-free survival [DFS], and overall survival [OS]. In terms of toxicity both acute and late toxicity were assessed.

Survival estimates were calculated by the Kaplan-Meier product-limit method and compared with the log-rank test. Variables with P value less than *0.05* or with a trend *[$p < 0.1$]* at univariate analysis were entered into a multivariate Cox's regression model. *$P < 0.05$* values were considered statistically significant. Acute toxicity was assessed by RTOG scale while late toxicity was evaluated with the RTOG/EORTC scale.

In the "**curative RT**" group [Chapter 1], at multivariate analysis, a worse bRFS was observed in patients with higher PSA levels, in patients with higher Gleason Score [GS] values, and in patients with wider margins between CTV and PTV. A lower LC rate was observed in patients with higher GS and

with a larger CTV to PTV margin while higher values were recorded in patients treated with adjuvant ADT or with a Charlson's comorbidity index > 1. A worse MFS was recorded in patients with higher GS values. Similarly, DFS was worse in patients with higher GS values. DFS was lower also in patients with larger margins between CTV and PTV while a higher DFS was recorded in patients undergoing TURP or adjuvant ADT. OS was correlated only with the presence of a GTV to CTV margin. In fact, patients planned using this margin showed an improved OS. Multivariate analysis of late toxicity showed a higher rate of Grade > 1 genitourinary toxicity in patients irradiated with cone-beam CT and previously treated with TURP. Late Grade > 1 gastrointestinal toxicity was lower in patients treated with cone-beam CT and with larger CTV to PTV margins. Late Grade > 2 gastrointestinal toxicity was significantly higher in patients receiving prophylactic nodal irradiation [PNI].

We designed a prognostic model of the 5-year biochemical outcome using three PSA categories and 5 GS categories to define 15 different groups of patients. We arranged these 15 groups in only 4 categories based on 5-year bRFS values: group 1: very low-risk [bRFS > 90%], group 2: low risk [bRFS: 80-90%], group 3: intermediate risk [bRFS: 60-79.9%], group 4: high risk [bRFS < 60%].

In the "**adjuvant RT**" group [Chapter 2], multivariate analysis showed a lower risk of biochemical recurrence in patients older than 61 years, with pN0 pathological stage, and with lower levels of postoperative PSA. In terms of GS, only patients with a value of 7 [4 + 3] showed a lower risk. In terms of LC, multivariate analysis confirmed a higher risk in patients with lymph node metastases, similar to what was observed for RC. In addition, a higher risk of

regional relapses was observed in patients with preoperative PSA levels higher than 10 ng/ml. In terms of toxicity, multivariate analysis showed only a lower risk of gastrointestinal complications in patients undergoing hypofractionation.

We designed a predictive model of biochemical outcome using two age categories, two nodal stage categories, and four PSA categories to define 16 different groups of patients. These 16 groups were arranged in only 3 categories based on 5-year bRFS values: group 1: very low-risk [bRFS > 95%], group 2: low-intermediate risk [bRFS: 76-95%], group 3: high risk [bRFS: < 76%].

In the "**salvage RT**" group [Chapter 3], multivariate analysis showed a higher bRFS rates in patients with pN0 stage, lower GS and treated with PNI. Moreover, it showed improved LC in patients treated with hypofractionated regimens. In terms of RC, multivariate analysis showed better results in patients with lower GS and worse results in patients with negative surgical margins, treated with IMRT/VMAT technique and not receiving PNI. The analysis on MFS showed a better outcome in pN0 and low GS patients and a higher failure risk in patients receiving adjuvant ADT. Higher DFS rates were confirmed in patients with pN0 or low GS or low PSA levels at salvage treatment as well as in patients treated with cone-beam CT. Furthermore, multivariate analysis showed better DFS rates in patients receiving PNI. The multivariate analysis on OS confirmed the positive impact of IMRT/VMAT techniques. No parameter significantly predicted toxicity at multivariate analysis.

We designed a prognostic model using 4 GS categories, 2 nodal stage categories, and 2 nodal irradiation categories to define 16 different groups of patients. These 16 groups were arranged in only 4 categories based on 5-year bRFS values: group 1: low-risk [bRFS > 80%], group 2: intermediate risk

[bRFS: 60-80%], group 3: high risk [bRFS: 40-< 59.9%], and group 4: very high risk [bRFS: < 40%].

Furthermore [Chapter 4], a retrospective study on 2526 previously irradiated PCa patients was performed to study the possible correlation between treatment technique and PNI and second tumors incidence in patients with PCa treated with RT. Patients were treated with 3D-CRT [21.3%], IMRT [68.1%], or VMAT [10.6%]. A total of 1294 patients [51.2%] underwent PNI and 1689 patients [66.9%] received adjuvant ADT.

At univariate analysis, a significantly higher 10-year cumulative incidence of second tumors in the pelvis was registered in patients treated with IMRT/VMAT compared to 3D-CRT [10.7% vs 6.0%; p: .033]. Moreover, PNI showed a trend for increased 10-year incidence of second tumors in both pelvis [9.4% vs 5.6%, p: .092] and pelvis-abdomen [10.9% vs 7.4%, p: .064]. Furthermore, the lower incidence of second pelvic cancers in patients treated with 3D-CRT was confirmed at multivariable analysis [HR: 0.42, 95%CI: 0.19-0.95, *p: .037*].

Finally, [Chapter 5], we analyzed the 1909 patients [1074, 381, 454] treated with exclusive, adjuvant and salvage radiotherapy, respectively, to test and compared the predictive power of two risk stratification systems [NCCN and EAU]. Both systems accurately predicted bRFS in patients treated with exclusive RT [p < 0.001]. In the same patients' group, only the NCCN system was significantly correlated with LC [p: 0.023]. Both systems failed to predict RC and OS, while both were significantly correlated with MFS and DFS, with lower p values using the NCCN classification. In patients treated in the adjuvant setting, both systems failed to significantly predict bRFS and all clinical

outcomes. Finally, only the NCCN system was able to significantly predict bRFS, MFS, and DFS in the salvage RT setting.

CHAPTER 1

CURATIVE RADIOTHERAPY OF PROSTATE CANCER: ANALYSIS OF PROGNOSTIC FACTORS AND DEVELOPMENT OF A RISK STRATIFICATION SYSTEM.

ABSTRACT

Background

The aim of this study was to analyze the prognostic impact on outcome and toxicity of patients with prostate cancer [PCa] treated with curative radiotherapy [RT] based on a comprehensive analysis of parameters related to tumor, patients, and treatment characteristics. Furthermore, we aimed to develop a simple risk stratification system based on real life data from a large patient population

Material and methods

A retrospective analysis of 1074 patients enrolled in an observational study was performed. Endpoints of the study in terms of outcome were biochemical relapse-free survival [bRFS], local control [LC], regional control [RC], metastasis-free survival [MFS], disease-free survival [DFS], and overall survival [OS]. In terms of toxicity both acute and late toxicity were assessed.

Survival estimates were calculated by the Kaplan-Meier product-limit method and compared with the log-rank test. Variables with P value less than 0.05 or with a trend [$p < 0.1$] at univariate analysis were entered into a multivariate Cox's regression model. $P < 0.05$ value was considered statistically significant. Acute toxicity was assessed by RTOG scale while late toxicity was evaluated with the RTOG/EORTC scale.

Results

At multivariate analysis a worse bRFS was observed in patients with higher PSA levels, in patients with higher Gleason Score values, and in patients with wider margins between CTV and PTV. A lower LC rate was observed in patients with higher Gleason score and with a larger CTV to PTV margin while

higher values were recorded in patients treated with adjuvant ADT or with a Charlson's comorbidity index > 1. A worse MFS was recorded in patients with higher Gleason score values. Similarly, DFS was worse in patients with higher Gleason score values. DFS was lower also in patients with larger margins between CTV and PTV while a higher DFS was recorded in patients undergoing TURP or adjuvant ADT. OS correlated only with the presence of a GTV to CTV margin. In fact, patients planned using this margin showed an improved OS.

Multivariate analysis of late toxicity showed a higher rate of Grade > 1 genitourinary toxicity in patients irradiated with cone-beam CT and previously treated with TURP. Late Grade > 1 gastrointestinal toxicity was lower in patients treated with cone-beam CT and with larger CTV to PTV margins. Late Grade > 2 gastrointestinal toxicity was significantly higher in patients receiving prophylactic nodal irradiation.

We designed a prognostic model of the 5-year biochemical outcome using three PSA categories and 5 Gleason score categories to define 15 different groups of patients. We arranged these 15 groups in only 4 categories based on the 5-year bRFS values: group 1: very low-risk [bRFS > 90%], group 2: low risk [bRFS: 80-90%], group 3: intermediate risk [bRFS: 60-79.9%], group 4: high risk [bRFS < 60%].

Conclusions

This systematic analysis of a large database allowed to identify unforeseen correlations that can generate new hypotheses. These results justifies further analysis of large series of patients with PCa treated with RT, possibly performed with more advanced statistical analysis methods.

INTRODUCTION

Prostate cancer [PCa] represents the second and fifth cancer in terms of incidence and mortality in the male population, respectively [1]. Curative radiotherapy [RT] is one of the main therapeutic options of PCa.

Several studies evaluated the impact of different prognostic factors related to tumor [prostate specific antigen [PSA] level, Gleason score [GS], tumor stage] or patient [age, comorbidities] characteristics [2]. Other studies analyzed the impact of RT related techniques on clinical outcomes and toxicity [3]. Particularly, several studies explored the advantages achievable from the introduction of new technologies such as intensity modulated radiotherapy [IMRT], volumetric modulated arc therapy [VMAT] and image guided radiation therapy [IGRT] [4, 5]. However, the different impact of tumor, patients and treatment characteristics were generally analyzed separately.

Furthermore, many predictive models have been developed [3]. The most frequently used are risk stratification systems [6]. These systems are based on the definition of different risk categories [7, 8]. Their main advantage is represented by the simplicity of use in clinical practice. However, these systems have the disadvantage of grouping patients in large categories which can include patients with rather different characteristics [6]. To avoid this problem, several risk estimation systems have been developed through which, on the basis of a series of parameters, it is possible to estimate the percentage of risk for an individual patient. However, these models also present frequent limits among which lack of accuracy estimation, lack of validation, and the inclusion of parameters rarely recorded in clinical practice with consequent validation problems [6]. Moreover, in most cases these models only consider tumor-related factors and not RT-related parameters [9, 10]. Furthermore, also in the models including treatment characteristics, only the delivered RT dose [11] and/or use of androgen deprivation therapy [ADT] were considered [12].

Therefore, in this study we performed an analysis of the prognostic impact on clinical outcomes and toxicity based on a comprehensive analysis of parameters related to tumor, patients, and treatment characteristics. Furthermore, we developed a simple risk stratification system based on real life data from a large patient population.

MATERIAL AND METHODS

Study design and endpoints

This is a retrospective analysis of patients enrolled in an observational study. Endpoints of the study in terms of clinical outcomes were biochemical relapse-free survival [bRFS], local control [LC] defined as control of tumor in the prostate and seminal vesicles, regional control [RC] defined as control of the disease in the prostate, seminal vesicles and pelvic nodes, metastasis-free survival [MFS], disease-free survival [DFS], and overall survival [OS]. In terms of toxicity both acute and late toxicity were assessed.

Inclusion criteria

The following inclusion criteria were used: 1] prostatic biopsy-proven adenocarcinoma, 2] absence of distant metastases, 3] RT delivered with external beams techniques using photons beams. Exclusion criteria were as follows: 1] patients treated with brachytherapy, 2] local recurrences or progression after radical prostatectomy or ADT.

Evaluated parameters

The recorded and evaluated patients-related characteristics were age and Charson's comorbidity index. Tumor-related parameters were PSA level, GS, clinical tumor stage, clinical nodal stage, and risk category according to National Comprehensive Cancer Network [NCCN] and European Association of Urologists [EAU] classifications. Analyzed treatment characteristics were delivery of prophylactic lymph nodes irradiation, seminal vesicles irradiation, previous Transurethral resection of the prostate [TURP], use of adjuvant ADT

and its type [LH-RH analogues or high-dose Bicalutamide] and duration, RT fractionation and technique, type of used image-guidance systems, addition of a margin to the gross tumor volume [GTV] to define the clinical tumor volume [CTV], and equivalent dose [EQD2] to prostate, seminal vesicles, and pelvic nodes. Used dose volume constraints were according to QUANTEC [13]

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 [14] and compared with the log-rank test [15]. Variables with *P* value less than 0.05 or with a trend [$p < 0.1$] at univariate analysis were entered into a multivariate Cox regression model [16]. $P < 0.05$ value was considered statistically significant. Acute toxicity was assessed by RTOG scale while late toxicity was evaluated with the RTOG/EORTC scale [17].

Ethical issues

The local institutional review board approved this analysis [311/2019/Oss/AOUBo, ICAROS-1 study]. Only patients who had provided a written informed consent to the scientific use of their data were included.

RESULTS

Patients characteristics

A total of 1074 patients were included in this analysis. **Table 1** shows the patients and tumor characteristics and **Table 2** presents the general characteristics of the treatment. **Table 3** shows the specific characteristics of RT technique.

Univariate analysis

Biochemical and clinical outcomes

Patients with higher PSA levels and GS showed worse bRFS as well as subjects with higher tumor and nodal clinical stage and with the highest risk category according to both NCCN and EAU systems [**Table 1**]. A lower bRFS was also recorded in patients undergoing ADT for a duration of more than 36 months [**Table 2**] and in those with larger CTV to planning tumor volume [PTV] margins [**Table 3**].

LC was significantly lower in patients with higher GS and belonging to higher risk categories according to the NCCN system [**Table 1**]. LC was higher in patients undergoing adjuvant ADT [**Table 2**], while the use of larger CTV to PTV margins was significantly correlated with a worse LC [**Table 3**].

RC was lower in patients with higher GS [**Table 1**] and in those not irradiated on the lymph nodes [**Table 2**]. A worse RC was also observed in patients subjected to treatment verification by cone-beam CT. Finally, RC was higher in patients receiving a higher RT dose to the seminal vesicles [**Table 3**].

MFS was lower in patients with higher PSA levels and GS values, in patients with cT3-4 clinical tumor stage, in those with metastatic pelvic lymph nodes and in patients belonging to the highest risk categories according to both NCCN and EAU systems [**Table 1**]. Furthermore, a significantly higher MFS was observed in patients undergoing adjuvant ADT for more than 2 years [**Table 2**]. Finally, MFS was lower in patients undergoing pelvic lymph node irradiation at higher RT doses [**Table 3**].

DFS was significantly lower in patients with higher PSA levels and GS values as well as in patients with cT3-4 clinical tumor stage, in patients with metastatic pelvic lymph nodes, and in patients belonging to the highest risk categories according to both NCCN and EAU risk stratification systems [**Table 1**]. Moreover, a higher DFS was observed in patients who

received ADT longer than 36 months [**Table 2**]. Finally, a significantly lower DFS was recorded in patients undergoing a cone beam CT and in those with larger margins between CTV and PTV [**Table 3**].

A higher OS was observed in patients undergoing ADT [**Table 2**] and treated with the VMAT technique as well as in patients in whom a margin was added between GTV and CTV while OS was significantly lower in patients who received a higher RT dose to pelvic lymph nodes and in those who received an EQD2 ≥ 81 Gy [**Table 3**].

Toxicity

Table 4 shows the results in terms of acute toxicity. None of the patients showed acute grade > 3 toxicity and patients who experienced gastrointestinal and genitourinary grade 3 toxicity were 1.6% and 1.7%, respectively. Acute G3 toxicity rates were significantly higher in patients treated with adjuvant ADT and in those with a GTV to PTV margin. Acute G3 genitourinary toxicity rates were higher in patients receiving adjuvant ADT, irradiated without intra-prostatic fiducials, with a GTV to CTV margin, and in those with larger CTV to PTV margin [**Table 5**].

Late grade > 2 gastrointestinal toxicity was significantly higher in patients receiving prophylactic nodal irradiation while no parameter was significantly correlated with grade > 2 genitourinary late toxicity [**Table 6**]

Multivariate analysis

Biochemical and clinical outcomes

At multivariate analysis a worse bRFS was observed in patients with higher PSA levels, in patients with higher GS values, and in patients with wider margins between CTV and PTV. A lower LC was observed in patients with higher Gleason score and with a larger CTV to PTV margin while higher values were recorded in patients treated with adjuvant

ADT or with a Charlson's comorbidity index > 1. A worse MFS was recorded in patients with higher GS values. Similarly, DFS was worse in patients with higher GS values. DFS was lower also in patients with larger margins between CTV and PTV while a higher DFS was recorded in patients undergoing TURP or adjuvant ADT. OS correlated only with the presence of a GTV to CTV margin. In fact, patients planned with this margin showed an improved OS [**Table 7**].

Toxicity

Multivariate analysis of late treatment related toxicity showed a higher rate of grade > 1 genitourinary toxicity in patients irradiated with cone-beam CT and previously treated with TURP. Late grade > 1 gastrointestinal toxicity was lower in patients treated with cone-beam CT and with larger CTV to PTV margins. Late grade > 2 gastrointestinal toxicity was significantly higher in patients receiving prophylactic nodal irradiation [**Table 8**].

Predictive model

We designed a prognostic model for the biochemical outcome according to the following modalities. The parameters significantly correlated to bRFS at multivariate analysis were considered. From these parameters was excluded, despite the apparent statistical significance, the CTV-PTV margin considering as reasonable that the best results achieved with smaller margins were likely to be attributed to confounding factors. Therefore, we used the three PSA categories and the 5 GS categories to define 15 different groups of patients [**Table 9**]. At this point we arranged these 15 groups in only 4 categories based on 5-year bRFS values: group 1: very low-risk [bRFS > 90%], group 2: low risk [bRFS: 80-90%], group 3: intermediate risk [bRFS: 60-79.9%], group 4: high risk [bRFS < 60%] [**Figure 1**].

DISCUSSION

Using a large database of PCa patients treated with external beam RT, an analysis of the potential predictors of biochemical-clinical outcome and acute-late toxicity was performed. At multivariate analysis resulted a close correlation of biochemical outcome with PSA levels and GS values. In terms of late toxicity, a significant correlation was observed between prophylactic lymph nodes irradiation and gastrointestinal toxicity and between previous TURP and genitourinary toxicity. The use of verification systems by cone-beam CT correlated to a higher risk of genitourinary toxicity and to a lower risk of gastrointestinal toxicity. On the basis of this multivariate analysis, a simple risk stratification system was designed to stratify patients with different probability of biochemical recurrence.

Our study has obvious limitations and in particular the use of a relatively simple statistical analysis methods. Therefore, we are planning to repeat this analysis with more advanced statistical methods such as the use of neural networks. Furthermore, some parameters with known prognostic impact, such as PSA kinetics and number of positive biopsies, have not been considered. However, this aspect will probably facilitate the use of this system given its simplicity, and a future validation of the model. Furthermore, compared to the NCCN and EAU risk stratification systems, our model not only allows to define the risk class, but also to quantify the risk percentage. This aspect could favor patient counseling when choosing the treatment type and modality.

Univariate analysis showed several significant correlations both on clinical outcomes and toxicity. In part these correlations can be simply explained as an effect of chance. Some of these, in particular, present rather paradoxical aspects for example, the worse OS in patients undergoing treatment verification by cone-beam CT and the worse bRFS and LC in case of wider margins between CTV and PTV. If the first correlation can probably be attributed to the case, the second could be due to confounding factors. In fact, it is likely that

larger margins have been used in patients treated with less advanced techniques and therefore with lower doses.

Even the multivariate analysis presented rather surprising results. In fact, if the negative impact of the GS on bRFS, LC, MFS, and DFS was predictable as well as the negative impact of the PSA levels on bRFS and the positive impact of ADT on LC and DFS [surprisingly, an impact of ADT on bRFS was not recorded], moreover other correlations are difficult to explain explicitly. For example, multivariate analysis confirmed the negative impact of large margins between CTV and PTV on bRFS, LC and DFS. It is obviously a correlation that is difficult to explain unless we assume that high RT dose irradiation on a greater volume of normal tissues may inhibit the immune response. However, this hypothesis is unlikely also because it is contradicted by the higher OS in patients treated adding a margin to the GTV to define the CTV. It is equally difficult to explain the higher DFS in patients undergoing TURP unless it is hypothesized that tumors were detected by TURP in a very early stage and therefore with better prognosis. However, even in this case it is not clear why a similar impact of TURP on bRFS, LC and MFS was not recorded.

It is equally difficult to interpret the results of multivariate toxicity analysis. Whilst the negative effect of TURP on genitourinary toxicity, the negative impact of prophylactic lymph node irradiation on gastrointestinal toxicity and the positive impact of cone-beam CT use on gastrointestinal toxicity, it is difficult to explain why the use of cone-beam CT had a negative impact on genitourinary toxicity, unless we assume that the cone-beam CT was mainly used in combination with more advanced irradiation techniques and therefore with higher doses, able to produce a more serious urethral damage.

The general feeling about these unexpected results is that the method used for multivariate analysis was not completely able to eliminate the impact of confounding factors or that in our analysis some relevant parameters are missing from the database. Similar

considerations can be made regarding the protective effect on gastrointestinal toxicity of large margins between CTV and PTV. On the other hand, it is considered an advantage of systematic analysis of large databases the possibility to identify unforeseen correlations that can generate new hypotheses.

This aspect justifies further analysis of large series of patients with PCa treated with RT, possibly performed with advanced methods of statistical analysis.

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Table 1: Univariate analysis. Reported are 5-year results

Variable	**Value**	**No of patients [%]**	**bRFS [%]**	**P**	**LC [%]**	**P**	**RC [%]**	**P**	**MFS [%]**	**P**	**DFS [%]**	**p**	**OS [%]**	**p**
Age	Median [range]	74 [50-90]												
CCI	0	692 [64.4]	86.9	.769	93.9	.445	97.2	.809	93.3	.307	89.3	.747	91.7	.125
	1	256 [23.8]	85.0		94.3		98.4		96.7		90.3		94.5	
	2	95 [8.8]	92.0		100.0		98.9		93.7		93.7		89.6	
	3	27 [2.5]	90.9		100.0		90.0		90.0		90.0		84.8	
	4	4 [0.4]	NE		NE		NE		NE		NE		100	
CCI cat	0: 0-1	948 [88.3]	86.3	.332	94.0	.055	97.5	.896	94.2	.281	89.6	.591	92.5	.097
	1: > 1	126 [11.7]	92.1		100.0		97.1		93.2		93.2		88.8	
PSA [ng/mL]	Median [range]	7.90 [0.36-159.64]												
PSA category	1: < 10	696 [64.8]	91.9	**.000**	95.6	.132	97.5	.253	96.0	**.001**	91.9	**.005**	92.3	.866
	2: 10-20	248 [23.1]	81.9		92.6		99.1		94.0		89.2		90.3	
	3: > 20	130 [12.1]	70.4		94.1		94.8		84.9		81.7		93.8	
Gleason score new [ISUP grade]	1: ≤ 6	397 [37.0]	96.4	**.000**	98.9	**.000**	100.0	**.001**	99.3	**.000**	98.3	**.000**	95.6	.155
	2: 7 [3+4]	206 [19.2]	88.5		94.5		97.4		97.7		91.9		91.4	
	3: 7 [4+3]	168 [15.6]	83.6		93.4		98.8		89.4		88.0		92.9	
	4: 8	177 [16.5]	81.0		90.5		95.0		95.1		87.6		85.6	
	5: 9-10	126 [11.7]	63.9		85.7		90.0		74.6		62.6		86.4	
Clinical tumor stage	1	135 [12.6]	89.1	**.000**	97.2	.152	94.2	.249	96.8	**.000**	89.7	**.000**	91.3	.530
	2	628 [58.5]	89.3		94.9		97.2		96.4		92.3		91.6	
	3-4	311 [29.0]	84.2		95.1		99.3		90.1		88.0		94.3	
Clinical nodal stage	0	1043 [97.1]	87.6	**.011**	95.0	.109	97.4	.499	94.4	**.034**	90.4	**.032**	91.7	.317

	1	31 [2.9]	66.3		88.8		100.0		85.4		81.7		100.0	
NCCN category simplified*	Very low-, low risk	123 [11.5]	95.4	**.000**	97.7	**.023**	100.0	.240	98.7	**.000**	96.4	**.000**	97.4	.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 category	Very low-, low risk	123 [11.5]	95.4	**.000**	97.7	.145	100.0	.136	98.7	**.003**	96.4	**0.006**	97.4	.326
	Intermediate risk	260 [24.2]	93.9		97.0		96.1		97.1		94.2		91.4	
	High-, very high risk	691 [64.3]	82.9		93.3		97.5		92.1		87.2		91.3	

Legend: bRFS: biochemical relapse-free survival; CCI: Charlson's Comorbidity Index; DFS: Disease-free survival [DFS]; EAU : European Association of Urologists; ISUP: International Society of Urological Pathologists; LC: Local control; MFS: Metastasis-free survival; NCCN: National Comprehensive Cancer Network; OS: Overall survival; PSA: Prostate Specific Antigen; RC: Regional control; *: very low and low risk together; high and very high risk together

Table 2. Univariate analysis. Reported are 5-year results

Variable	Value	Number of patients [%]	bRFS [%]	P	LC [%]	P	RC [%]	P	MFS [%]	P	DFS [%]	p	OS [%]	p
Nodal irradiation	No	562 [52.3]	88.0	.439	91.3	.130	96.1	**.008**	94.9	.395	87.6	.320	91.3	.130
	Yes	513 [47.7]	85.7		92.8		99.1		93.3		86.4		92.8	
SV Irradiation	No	274 [25.5]	89.4	.478	95.7	.368	95.9	.164	95.2	.602	89.2	.258	92.6	.436
	Yes	800 [74.5]	86.3		94.5		98.1		93.8		86.5		91.9	
TURP	No	992 [92.4]	86.7	.371	94.6	.544	97.4	.719	94.2	.738	86.8	.213	92.2	.818
	Yes	82 [7.6]	90.9		96.7		98.0		92.8		90.6		89.3	
Adjuvant HT	No	274 [25.5]	87.9	.646	92.3	**.010**	96.7	.179	94.7	.575	87.4	.637	88.7	**.002**
	Yes	800 [74.5]	86.8		95.6		97.8		94.0		87.1		93.2	
Type of HT	Not prescribed	274 [25.5]	87.9	.666	92.3	**.034**	96.7	.317	94.7	.600	87.4	.581	88.7	**.010**
	LH-RH	519 [48.3]	85.6		96.4		97.6		92.6		85.9		92.7	
	Bicalutamide	281 [26.2]	88.4		94.6		97.8		95.7		88.8		93.9	
Actual duration of HT [months]	not prescribed	255 [23.7]	89.2	**.001**	93.8	.261	96.9	.504	95.7	**.007**	89.6	**.002**	90.2	.153
	≤ 6	236 [22.0]	94.3		96.9		97.8		98.1		95.8		95.4	
	6.1- 2	146 [13.6]	88.3		93.9		100		95.4		91.5		97.9	
	13-24	360 [33.5]	81.0		94.7		96.7		88.6		85.4		89.1	
	25-36	61 [5.7]	89.5		93.4		97.9		100.0		93.4		93.6	
	> 36	16 [1.5]	70.7		100.0		100.0		100.0		100.0		83.6	

Legend: bRFS: biochemical relapse-free survival; DFS: Disease-free survival [DFS]; HT: hormone therapy; LC: Local control; MFS: Metastasis-free survival; OS: Overall survival; RC: Regional control; SV: Seminal vesicles; TURP: Transurethral resection of the prostate.

Table 3. Radiotherapy technique characteristics [%] univariate analysis. Reported 5-year results

Variable	**Value**	**Number of patients [%]**	**bRFS [%]**	**P**	**LC [%]**	**P**	**RC [%]**	**P**	**MFS [%]**	**P**	**DFS [%]**	**p**	**OS [%]**	**p**
Hypofractionation	No	227 [21.1]	86.6	.859	94.9	.235	98.9	.287	95.7	.314	87.5	.670	94.9	.235
	Yes	847 [78.8]	87.4		90.3		96.9		93.3		87.2		90.3	
Radiotherapy technique	3D-CRT	151 [14.1]	85.4	.398	92.3	.387	98.4	.834	95.4	.146	90.0	.068	93.7	**.024**
	IMRT	758 [70.5]	88.9		95.6		97.7		94.1		90.9		90.6	
	VMAT	165 [15.4]	77.6		96.9		97.7		92.3		88.2		100.0	
Image guidance	EPID	110 [10.2]	86.1	.058	92.1	.272	100.0	**.002**	95.0	.513	89.7	**.009**	95.6	**.004**
	EPID + Fiducial	672 [62.6]	89.1		96.4		97.9		94.4		92.3		91.0	
	Cone Beam + Fiducial	235 [21.9]	81.9		93.4		92.3		92.6		83.2		88.9	
GTV to CTV	No	627 [58.4]	87.7	.372	94.6	.397	95.7	**.001**	93.4	.169	88.9	.074	89.8	**.000**
	Yes	447 [41.6]	86.3		95.0		99.8		95.0		91.5		95.0	
Minimum margin CTV to PTV [mm]	≤ 60	831 [77.4]	88.7	**.041**	96.1	**.044**	98.0	.233	94.2	.585	91.8	**.026**	92.1	.122
	> 60	243 [22.6]	82.8		91.4		96.1		93.8		85.5		92.2	
Maximum margin CTV to PTV [mm]	≤ 50	786 [73.2]	89.3	**.011**	96.1	**.030**	98.0	.340	94.1	.862	91.8	**.034**	92.0	.096
	> 50	288 [26.8]	81.7		91.4		96.3		94.1		85.8		92.2	
EQD2 to the prostate 1.5 [GY]	≤ 81.0	659 [61.4]	87.7	.216	93.9	.281	97.7	.786	94.1	.511	88.4	.092	91.6	.105
	> 81.0	415 [38.6]	85.5		96.9		97.1		94.6		85.0		91.1	
EQD2 to the lymph nodes 1.5 [Gy]	Not prescribed	533 [49.6]	88.7	.149	94.6	.604	96.1	**.033**	95.7	**.028**	88.3	.361	91.4	**.000**
	≤ 42.4	425 [40.2]	86.3		95.3		99.5		94.4		86.2		94.5	
	> 42.4	116 [10.1]	80.4		92.3		96.0		87.4		83.8		85.0	
EQD2 to the lymph nodes 1.5 [Gy]	≤ 42.4	425 [78.6]	86.3	.080	95.3	.227	99.5	.122	94.4	**.016**	86.2	.195	94.5	**.000**
	> 42.4	116 [21.4]	80.4		92.3		96.0		87.4		83.8		85.0	

EQD2 to the Seminal vesicles 1.5 [Gy]	Not prescribed	274 [25.5]	89.4	.774	95.7	.111	95.9	.068	95.2	.864	89.2	.506	92.6	.323
	≤ 60.3	380 [35.4]	86.7		92.6		96.9		94.2		87.2		90.1	
	> 60.3	420 [39.1]	85.8		96.6		99.4		93.4		85.7		93.8	
EQD2 to the Seminal vesicles 1.5 [Gy]	≤ 60.3	380 [47.5]	86.7	.850	92.6	.056	96.9	**.042**	94.2	.795	87.2	.687	90.1	.147
	> 60.3	420 [52.5]	85.8		96.6		99.4		93.4		85.7		93.8	
EQD2 to the prostate 1.5 [Gy]	< 81	327 [30.4]	88.7	.361	94.5	.391	98.4	.722	96.3	.132	91.9	.262	94.4	**.037**
	81.0	323 [30.1]	86.4		92.9		96.6		90.9		86.9		87.3	
	> 81.0	424 [39.5]	85.8		97.0		97.1		94.7		91.2		91.4	

Legend: bRFS: biochemical relapse-free survival; CTV: Clinical tumor volume; DFS: Disease-free survival [DFS]; EPID: Electronic portal imaging device; GTV: Gross tumor volume; HT: hormone therapy; EQD2: equivalent dose; IMRT: Intensity modulated radiotherapy; LC: Local control; MFS: Metastasis-free survival; OS: Overall survival; PTV: Planning target volume; RC: Regional control; SV: Seminal vesicles; TURP: Transurethral resection of the prostate; VMAT: Volumetric modulated arc therapy; 3D-CRT: three dimensional conformal radiotherapy.

Table 4: Acute toxicity

	Grade					
	0	1	2	3	4	5
Gastrointestinal	531 [49.4]	314 [29.2]	218 [20.2]	11 [1.6]	0 [0.0]	0 [0.0]
Genitourinary	336 [31.3]	424 [39.5]	296 [27.6]	18 [1.7]	0 [0.0]	0 [0.0]
Skin	890 [82.9]	144 [13.4]	40 [3.7]	0 [0.0]	0 [0.0]	0 [0.0]

Table 5: Acute gastrointestinal and genitourinary toxicity Grade ≥ 2 and Grade ≥ 3

		Gastrointestinal				**Genitourinary**			
		Grade ≥ 2 [%]	p	Grade ≥ 3 [%]	p	Grade ≥ 2 [%]	P	Grade ≥ 3 [%]	P
Minimum CTV/PTV margin [mm]	≤ 6	19.0	.132	0.4	.100	34.2	**.002**	0.4	**.006**
	> 6	22.6		1.4		25.8		2.5	
Maximum CTV/PTV margin [mm]	≤ 5	20.5	.153	1.0	.600	31.0	**.026**	1.4	.182
	> 5	23.6		1.1		24.7		2.4	
Nodal irradiation	No	17.3	**.000**	0.5	.085	32.9	**.003**	1.2	.181
	Yes	25.8		2.1		25.2		2.1	
Hypofractionation	No	31.7	**.000**	1.3	.420	27.3	.264	2.2	.327
	Yes	18.5		0.9		29.6		1.5	
SV Irradiation	No	16.4	**.012**	0.7	.439	28.8	.465	1.1	.286
	Yes	23.0		1.1		29.4		1.9	
EQD2 to the prostate 10	< 72.6	26.6	**.014**	0.9	.549	31.2	.062	2.1	.071
	72.6	25.7		0.6		32.5		0.3	
	> 72.6	17.9		1.4		22.2		2.4	
Radiotherapy technique	3D-CRT	31.8	**.001**	1.3	.923	27.2	.631	2.6	.158
	IMRT	20.7		0.9		30.2		1.3	
	VMAT	15.6		1.3		26.0		1.9	
Image guidance	EPID	32.3	**.001**	2.4	.063	29.9	.974	4.8	**.003**
	EPID + Fiducial	19.0		1.0		29.2		1.0	
	Cone beam + Fiducial	20.0		0.0		28.9		1.3	
Previous abd-pelvic surgery	No	22.2	.110	1.3	.073	30.4	.056	1.9	.235
	Yes	18.1		0.0		24.8		0.9	
TURP	No	21.1	.202	1.1	.414	30.4	**.006**	1.6	.407
	Yes	25.6		0.0		17.1		2.4	
Adjuvant hormone therapy	No	22.3	.359	0.0	**.038**	39.1	**.000**	0.0	**.005**
	Yes	21.0		1.4		25.9		2.3	
Type of hormone therapy	LHRH	21.6	.326	1.3	.579	27.0	.189	2.1	.455
	Bicalutamide	22.3		1.4		23.8		2.5	
EQD2 to the seminal vesicles 10	≤ 57.4	23.7	.362	0.8	.304	32.4	**.046**	1.6	.375
	> 57.4	22.4		1.4		26.7		2.1	
EQD2 to the lymph nodes 10	≤ 44.3	24.7	.369	1.9	.143	25.2	.409	2.4	.279
	> 44.3	26.7		0.0		26.7		0.8	
GTV to CTV margin	No	19.9	**.000**	1.3	**.000**	32.4	.107	6.4	**.000**
	yes	31.5		8.9		28.6		8.9	

Legend: bRFS: biochemical relapse-free survival; GS: Gleason score; ISUP: International Society of Urological Pathologists; PSA: Prostate Specific Antigen; TURP: Transurethral resection of the prostate.

Table 6: Five-year late gastrointestinal and genitourinary toxicity Grade ≥ 2 and Grade ≥ 3

		Gastrointestinal				**Genitourinary**			
		G ≥ 2 [%]	p	G ≥ 3 [%]	p	G ≥ 2 [%]	p	G ≥ 3 [%]	P
Minimum CTV/PTV margin [mm]	≤ 6	87.0	**.001**	97.7	.180	92.4	**.012**	98.2	.982
	> 6	95.0		99.6		87.1		98.6	
Maximum CTV/PTV margin [mm]	≤ 5	86.9	**.001**	97.7	.141	92.3	**.022**	98.2	.898
	> 5	94.7		99.6		87.7		98.7	
Nodal irradiation	No	87.8	.728	99.0	**.020**	88.2	**.004**	98.6	.952
	Yes	90.9		97.5		94.2		97.9	
Hypofractionation	No	86.1	.286	98.8	.509	91.8	.978	99.0	.373
	Yes	90.8		98.1		90.5		97.7	
Seminal vesicles Irradiation	No	89.3	.324	98.8	.216	88.2	.075	99.6	.585
	Yes	89.1		98.1		92.0		98.3	
EQD2 to the pro 3.0 [Gy]	≤ 77.0	88.8	.925	98.7	.135	90.4	.384	98.9	.289
	> 77.0	89.9		97.9		91.6		97.2	
Radiotherapy technique	3D-CRT	87.2	.104	98.3	.501	93.1	.055	99.2	.941
	IMRT	88.8		98.0		91.6		97.7	
	VMAT/SBRT	96.1		100.0		85.7		100.0	
Image guidance	EPID	86.7	**.005**	99.4	.732	91.2	**.006**	97.9	.526
	EPID + Fiducial	87.4		97.4		93.4		98.1	
	Cone beam + Fiducial	98.0		100.0		82.7		100.0	
Previous abd-pelvic surgery	No	88.5	.301	98.2	.821	91.7	.320	98.6	.606
	Yes	91.5		98.5		88.6		97.3	
TURP	No	89.4	.273	98.5	.182	92.0	**.000**	98.4	.176
	Yes	86.1		94.3		78.3		97.3	
Adjuvant hormone therapy	No	88.8	.937	98.9	.205	87.4	.136	98.8	.205
	Yes	89.3		98.0		92.3		98.2	
Type of hormone therapy	LHRH	90.2	.703	97.9	.552	92.8	.271	98.8	.479
	Bicalutamide	88.0		98.3		91.5		97.3	
EQD2 to the seminal vesicles 3.0 [Gy]	≤ 59.1	90.4	.741	98.2	.359	89.0	.061	97.7	.982
	> 59.1	88.4		98.0		93.5		97.9	
EQD2 to the lymph node 3.0 [Gy]	≤ 43.2	90.9	.437	97.6	.648	94.0	.668	97.7	.348
	> 43.2	91.8		97.6		95.0		100.0	
GTV to CTV margin	No	88.6	.647	98.7	.057	88.6	**.007**	98.6	.963
	yes	89.7		97.7		94.1		97.9	

Legend: CTV: Clinical tumor volume; EPID: Electronic portal imaging device; EQD2: equivalent dose; GTV: Gross tumor volume; IMRT: Intensity modulated radiotherapy; PTV: Planning target volume; TURP: Transurethral resection of the prostate; VMAT: Volumetric modulated arc therapy; 3D-CRT: three-dimensional conformal radiotherapy.

Table 7: Multivariate analysis on biochemical and clinical outcomes

Variable	***value***	***bRFS***			***LC***			***MFS***			***DFS***			***OS***		
		HR	***95%CI***	***p***	***HR***	***95%CI***	***p***	***HR***	***95%CI***	***P***				***HR***	***95%CI***	***p***
PSA category	< 10	Ref		**.009**												
	10-20	1.60	0.98-2.60	.059												
	> 20	2.21	1.31-3.74	**.003**												
Gleason score new [ISUP grade]	≤ 6	Ref		**.000**	Ref		**.000**	Ref		**.000**	Ref		**.000**			
	7 [3+4]	4.88	2.22-10.70	**.000**	5.99	1.78-20.08	**.004**	2.41	0.49-11.95	.283	5.26	2.09-13.25	**.000**			
	7 [4+3]	5.09	2.33-11.14	**.000**	8.15	2.50-26.65	**.001**	11.01	3.07-39.58	**.000**	7.20	2.89-17.96	**.000**			
	8	5.41	2.48-11.83	**.000**	8.26	2.37-28.86	**.001**	6.76	1.72-26.53	**.006**	7.39	2.86-19.10	**.000**			
	9-10	12.88	6.19-26.78	**.000**	17.53	5.27-58.33	**.000**	24.17	6.96-83-93	**.000**	24.90	10.56-58.75	**.000**			
Maximum margin CTV to PTV [mm]	≤ 50	1.00 [Ref]			1.00 [Ref]											
	> 50	1.82	1.19-2.77	**.005**	2.87	1.45-5.67	**.002**									
Minimum margin CTV to PTV [mm]	≤ 60										1.00 [Ref]					
	> 60										2.14	1.31-3.50	**.002**			
margin GTV to CTV [mm]	No													1.00 [Ref]		
	Yes													0.33	0.17-0.62	**.001**
TURP	No										1.00 [Ref]					
	Yes										0.32	0.10-1.03	.057			
Hormone therapy type	No				Ref		**.005**						**.017**			
	LHRH				0.31	0.14-0.69	**.004**				0.45	0.25-0.80	**.006**			
	Bicalutamide				0.29	0.12-0.73	**.008**				0.49	0.26-0.95	**.034**			
CCI	≤ 1				1.00 [Ref]											
	> 1				0.17	0.02-1.26	.083									

Legend: bRFS: biochemical relapse-free survival; CCI: Charlson's Comorbidity Index; CTV: Clinical tumor volumeDFS: Disease-free survival [DFS]; GTV: Gross tumor volume; HT: hormone therapy; ISUP: International Society of Urological Pathologists; LC: Local control; MFS: Metastasis-free survival; OS: Overall survival; PSA: Prostate Specific Antigen; PTV: planning target volume; RC: Regional control; SV: Seminal vesicles; TURP: Transurethral resection of the prostate.

Table 8: Multivariate results of late toxicity

Variable	*value*	*LTGU ≥ 2*			*LTGI ≥ 2*			*LTGI ≥ 3*		
		HR	***95%CI***	***p***	***HR***	***95%CI***	***p***	***HR***	***95%CI***	***p***
Image guidance radiotherapy	EPID	**Ref**		**.000**	**Ref**		**.019**			
	EPID + fiducial	0.70	0.38-1.31	.267	0.65	0.35-1.22	.179			
	Cone beam	2.11	1.10-4.05	**.025**	0.18	0.05-0.63	**.000**			
TURP	No	**1.00 [Ref]**								
	Yes	3.33	1.91-5.80	**.000**						
Minimum margin CTV to PTV [mm]	≤ 60				**1.00 [Ref]**					
	> 60				0.42	0.18-0.99	**.047**			
Prophylactic nodal irradiation	No							**1.00 [Ref]**		
	Yes							5.14	1.11-23.81	**.036**

Legend: PTV: planning tumor volume; TURP: Transurethral resection of the prostate.

Table 9: Prediction of 5-year biochemical Relapse-Free Survival [%] according to the variables included in the model

Variables		**Prostate Specific Antigen category [ng/mL]**		
		< 10	**10-20**	**> 20**
Gleason score [ISUP grade]	6	97.6 ± 1.2 [280]	94.8 ± 3.0 [90]	89.1 ± 7.3 [27]
	7 [3+4]	94.1 ± 2.6 [152]	69.3 ± 1.4 [44]	77.8 ± 13.9 [10]
	7 [4+3]	92.9 ± 3.2 [98]	76.4 ± 11.4 [39]	67.4 ± 10.4 [31]
	8	89.9 ± 4.2 [97]	73.4 ± 9.9 [46]	55.4 ± 19.6 [34]
	9-10	64.2 ± 7.9 [69]	70.2 ± 10.9 [29]	49.6 ± 17.5 [28]

Figure 1

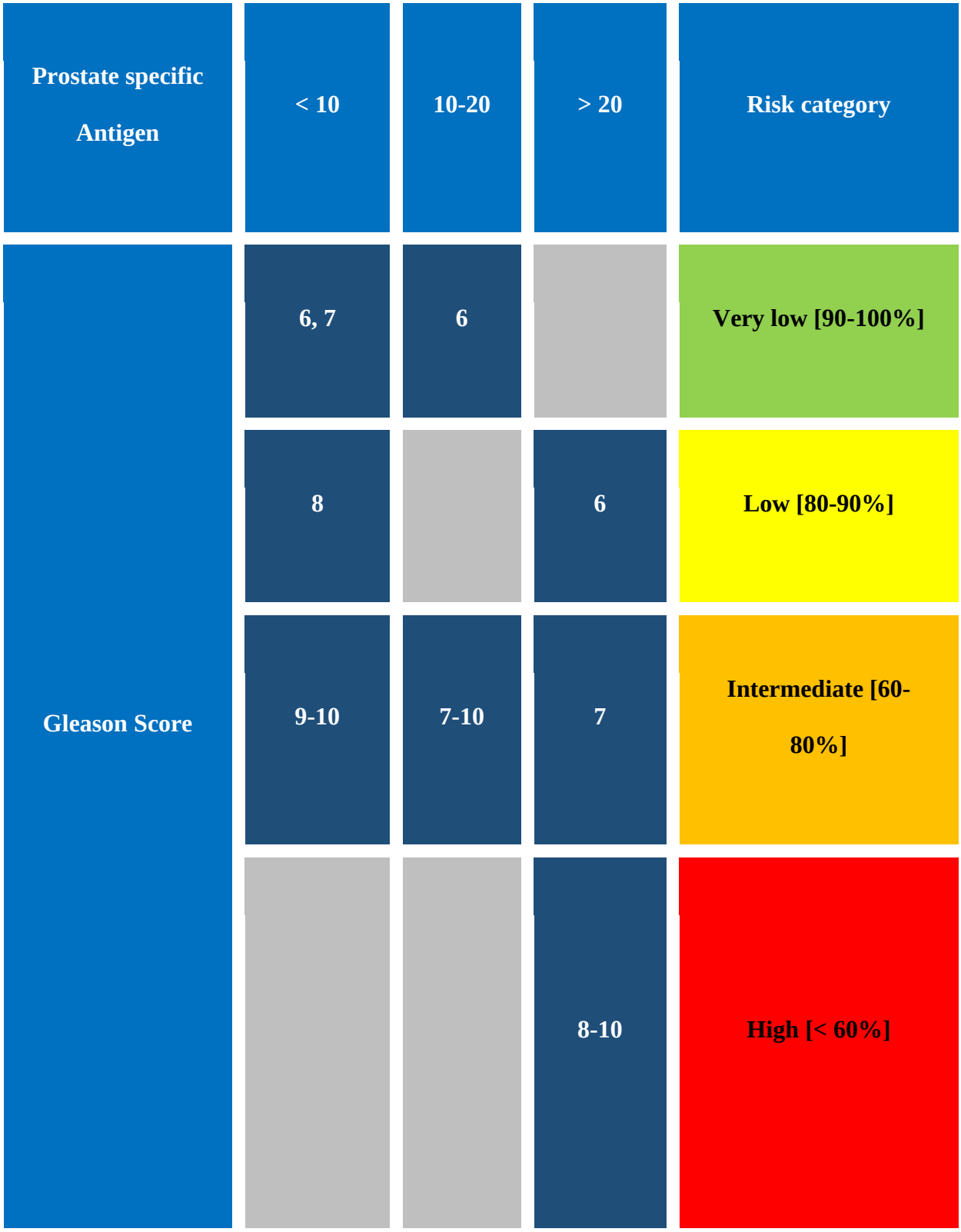

Figure 1: categorization of 5-year biochemical Relapse-Free survival risk

CHAPTER 2

POSTOPERATIVE RADIOTHERAPY OF PROSTATE CANCER: ANALYSIS OF PROGNOSTIC FACTORS AND DEVELOPMENT OF A RISK STRATIFICATION SYSTEM

ABSTRACT

Background

The aim of this study was to analyze the prognostic impact on clinical outcomes and toxicity of patients with prostate cancer treated with postoperative radiotherapy based on a comprehensive analysis of parameters related to tumor, patients, and treatment characteristics. Furthermore, we aimed to develop a simple risk stratification system based on real life data from a large patient population

Material and methods

A retrospective analysis of 381 patients enrolled in an observational study was performed. Endpoints of the study in terms of clinical outcomes were biochemical relapse-free survival [bRFS], local control [LC], regional control [RC], metastasis-free survival [MFS], disease-free survival [DFS], and overall survival [OS]. In terms of toxicity both acute and late toxicity were assessed.

Survival estimates were calculated by the Kaplan-Meier product-limit method and compared with the log-rank test. Variables with P value less than 0.05 or with a trend [$p < 0.1$] at univariate analysis were entered into a multivariate Cox's regression model. $P < 0.05$ value was considered statistically significant. Acute toxicity was assessed by RTOG scale while late toxicity was evaluated with the RTOG/EORTC scale.

Results

Multivariate analysis showed a lower risk of biochemical recurrence in patients older than 61 years, with pN_0 pathological stage, and with lower levels of postoperative PSA. In terms of Gleason score, only patients with a value of 7 [4 + 3] showed a lower risk. In terms of LC, multivariate analysis confirmed a

higher risk in patients with lymph node metastases, similar to what was observed for RC. In addition, a higher risk of regional relapses was observed in patients with preoperative PSA levels higher than 10 ng/ml. In terms of toxicity, multivariate analysis showed only a lower risk of gastrointestinal complications in patients undergoing hypofractionation.

We designed a predictive model of biochemical outcome using two age categories, two nodal stage categories, and four PSA categories to define 16 different groups of patients. These 16 groups were arranged in only 3 categories based on 5-year bRFS values: group 1: very low-risk [bRFS > 95%], group 2: low-intermediate risk [bRFS: 76-95%], group 3: high risk [bRFS: < 76%].

Conclusions

This systematic analysis of a large patients series allowed to identify unforeseen correlations that can generate new hypotheses. These results justifies further analysis of large series of patients with prostate cancer treated with postoperative radiotherapy, possibly performed with more advanced methods of statistical analysis.

INTRODUCTION

Prostate cancer [PCa] represents the second and fifth cancer in terms of incidence and mortality in the male population, respectively [1]. Radical prostatectomy [RP] is one of the main therapeutic options of PCa. However, in patients treated with RP, the 5-year biochemical Relapse Free Survival [bRFS] is around 50% [2-4].

The results of postoperative radiotherapy [RT] as reported in three randomized studies [2-4], showed an increase of about 25% in bRFS compared to RP alone. This means that bRFS in patients undergoing postoperative RT is about 75% with room for further improvement. A modulation of therapy in terms of prostatic bed dose, prophylactic pelvic lymph node irradiation, and prescription of androgen deprivation therapy [ADT] has been shown to be able to further improve these results [5]. However, treatment modulation requires knowledge of the predictors of clinical outcomes such as bRFS, local control [LC], and metastasis-free survival [MFS].

Some studies evaluated the impact of different prognostic factors related to tumor [prostate specific antigen [PSA] level, Gleason score [GS], tumor stage] or patient [age, comorbidities] characteristics [6,7]. Other studies analyzed the impact of RT characteristics on clinical outcomes and toxicity]. Particularly, several studies evaluated the advantages achievable from the introduction of new technologies such as intensity modulated radiotherapy [IMRT], volumetric modulated arc therapy [VMAT] and image guided radiation therapy [IGRT] [8,9]. However, the different impact of tumor, patients and treatment characteristics was generally analyzed separately.

Many predictive models have been developed in the setting of curative RT [10]. However, the same is not true for adjuvant postoperative RT. The most frequently used predictive models in curative RT are risk stratification systems [11]. These systems are based on the definition of different risk categories [12,13]. Their main advantage is represented by

the simplicity of use in clinical practice. However, these systems have the disadvantage of grouping patients in large categories which can include patients with rather different characteristics [11] and they are not providing a quantitative estimation of the risk in terms of percentage of failure risk. More importantly, they have not been developed for patients previously treated with RP and they are not significantly correlated with prognosis in the adjuvant setting [see Chapter 5].

Therefore, in this study we performed an analysis of the prognostic impact on clinical outcomes and toxicity based on a comprehensive analysis of parameters related to the tumor, patients, and treatment characteristics. Furthermore, we developed a simple risk stratification system based on real life data from a large patient population.

MATERIAL AND METHODS

Study design and endpoints

This is a retrospective analysis of patients enrolled in an observational study. Endpoints of the study in terms of clinical outcomes were biochemical relapse-free survival [bRFS], local control [LC] defined as control of tumor in the prostate and seminal vesicles, regional control [RC] defined as control of the disease in the prostate, seminal vesicles and pelvic nodes, metastasis-free survival [MFS], disease-free survival [DFS], and overall survival [OS]. In terms of toxicity both acute and late toxicity were assessed.

Inclusion criteria

The following inclusion criteria were used: 1] patients with prostatic adenocarcinoma who underwent RP with negative or microscopically positive margins [R0-1] absence of distant metastases, 3] RT delivered with external beams techniques using photons beams. Exclusion criteria were as follows: 1] macroscopic [R2] residual disease after RP, 2] postoperative PSA level < 0.2 ng/ml, 3] postoperative RT delivered after < 1 year from RP.

Evaluated parameters

The recorded and evaluated patients-related characteristics were age and Charson's comorbidity index. Tumor-related parameters were preoperative and postoperative PSA levels, GS, pathological tumor stage, pathological nodal stage, margin status, and risk category according to NCCN [12] and EAU [13] classifications. Analyzed treatment characteristics were delivery of prophylactic lymph nodes irradiation, previous TURP, use of adjuvant ADT and its type [LH-RH analogues or high-dose Bicalutamide] and duration, fractionation, RT technique, type of used image-guidance systems, and equivalent dose [EQD2] to prostate bed and pelvic 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 [14] and compared with the log-rank test [15]. Variables with *P* value less than 0.05 or with a trend [$p < 0.1$] at univariate analysis were entered into a multivariate Cox regression model [16]. $P < 0.05$ value was considered statistically significant. Acute toxicity was assessed by RTOG scale while late toxicity was evaluated with the RTOG/EORTC scale [17].

Ethical issues

The local institutional review board approved this analysis [311/2019/Oss/AOUBo, ICAROS-1 study]. Only patients who had provided a written informed consent to the scientific use of their data were included.

RESULTS

Patients characteristics

A total of 381 patients were included in this analysis. **Table 1** shows the patients and tumor characteristics and **Table 2** presents the general characteristics of the treatment. **Table 3** shows the specific characteristics of RT technique.

Univariate analysis

Biochemical and clinical outcomes

A higher bRFS was observed in patients older than 61 years, with higher Charlson's comorbidity index adjusted for age, in subjects with lower levels of post-operative PS, in patients with lower GS values, and in patients without lymph node metastases [**Table 1**]. Instead, a worse biochemical recurrence-free survival was observed in patients undergoing cone-beam CT verification [**Table 3**].

LC was better in patients with higher values of Charlson's age-adjusted comorbidity index, in patients without lymph node metastases [**Table 1**], in patients who did not receive adjuvant ADT [Table 2] and in patients who received a higher EQD2 to regional lymph nodes [**Table 3**].

RC was higher in patients receiving prophylactic nodal irradiation [**Table 2**] while no significant correlations were observed between the analyzed parameters and MFS.

DFS was higher in patients aged more than 61 years, in patients with higher Charlson’s comorbidity index corrected by age, and in node-negative patients [**Table 1**]. Also OS was significantly better in patients without lymph node metastases [**Table 1**].

Toxicity

Table 4 shows the results in terms of acute toxicity. None of the patients showed acute grade > 3 toxicity and patients who experienced gastrointestinal and genitourinary

grade 3 toxicity were 0.5% and 1.3%, respectively. Acute grade > 2 gastrointestinal and genitourinary toxicity rates were not correlated with any of analyzed parameters [**Table 5**].

Late grade > 2 gastrointestinal toxicity was significantly lower in patients treated with hypofractionation and with IMRT or VMAT techniques. Late grade > 2 genitourinary toxicity was not correlated with any of the analyzed parameters. [**Table 6**].

Multivariate analysis

Biochemical and clinical outcomes

Multivariate analysis confirmed a lower risk of biochemical recurrence in patients older than 61 years, with pN_0 pathological stage, and with lower levels of postoperative PSA. In terms of GS, only patients with a value of 7 [4 + 3] showed a lower risk. In terms of LC, multivariate analysis confirmed a higher risk in patients with lymph node metastases, similar to what was observed for RC. in addition, a higher risk of regional relapses was observed in patients with preoperative PSA levels higher than 10ng/ml. [**Table 7**].

Toxicity

Multivariate analysis confirmed only a lower risk of gastrointestinal toxicity in patients undergoing hypofractionation [**Table 8**].

Predictive model

We designed a prognostic model of the biochemical outcome according to the following modalities. The parameters significantly correlated to bRFS at multivariate analysis were considered [age, pathological nodal stage, and postoperative PSA level]. Then, we used the two age categories, the two nodal stage categories, and the four PSA categories to define 16 different groups of patients [**Table 9**. At this point we arranged these 16 groups in only 3 categories based on 5-year bRFS values: group 1: very low-risk [bRFS > 95%], group 2: low-intermediate risk [bRFS: 76-95%], group 3: high risk [bRFS: < 76%] [**Figure 1**].

DISCUSSION

Retrospectively analyzing a large series of PCa patients treated with postoperative-adjuvant external beam RT, an analysis of the potential predictors of biochemical-clinical outcomes and acute-late toxicity was performed. Multivariate analysis showed a lower risk of biochemical recurrence in patients older than 61 years, with pN_0 pathological stage, and with lower levels of postoperative PSA. In terms of GS, only patients with a value of 7 [4 + 3] showed a lower risk. In terms of LC, multivariate analysis confirmed a higher risk in patients with lymph node metastases, similar to what was observed for RC. in addition, a higher risk of regional relapses was observed in patients with preoperative PSA levels higher than 10ng/ml. On the basis of this multivariate analysis, a simple risk stratification system was designed to stratify patients with different probability of biochemical recurrence.

Our study has obvious limitations and in particular the use of a relatively simple statistical analysis methods. Therefore, we are planning to repeat this analysis with more advanced statistical methods such as the use of neural networks. Furthermore, some parameters with known prognostic impact such as postoperative PSA kinetics and number of positive margins, have not been considered. However, this aspect will probably facilitate the use of this system, given its simplicity, and a future validation of the model. Furthermore, compared to other risk stratification systems [12, 13], our model allows to define the risk class and also to quantify the risk percentage. This aspect could favor patient counseling when choosing treatment type and modality.

Univariate analysis showed several significant correlations both on clinical outcomes and toxicity. In part these correlations can be simply explained as an effect of chance. Some of these, in particular, present rather paradoxical aspects for example, the worse bRFS, LC and DFS in patients with higher Charlson's comorbidity index corrected by age and the worse bRFS in patients undergoing cone-beam CT verification. If the correlation between cone-

beam CT and bRFS can probably be attributed to the case, the correlation of Charlson's comorbidity index corrected by age could be explained as the favorable impact of older age.

Even the multivariate analysis presented rather surprising results. In fact, GS presented only a marginal impact on prognosis with higher bRFS only in the category of patients with score 7 [4+3]. These results as others could be explained by the modulation of the treatment based on prognostic factors. In fact, as shown in **Tables 2**, 78% of patients received prophylactic nodal irradiation, 66.3% were treated with adjuvant ADT, and the dose to the prostatic bed ranged between 62.5 up to 78.0 Gy. Obviously, patients with worse prognostic profile were treated more aggressively, eliminating or at least reducing the impact of some negative prognostic factors. Also the reduced gastrointestinal toxicity in patients treated with hypofractionated regimen is a paradoxical result. We could only hypothesize that patients treated with hypofractionated regimen were also treated with more advanced RT techniques.

The general feeling about these unexpected results is that the method used for multivariate analysis was not completely able to eliminate the impact of confounding factors or that in our analysis some relevant parameters are missing from the database. On the other hand, it is considered an advantage of systematic analysis of large databases the possibility to identify unforeseen correlations that can generate new hypotheses.

This aspect justifies further analysis of large series of patients with PCa treated with postoperative RT, possibly performed with advanced methods of statistical analysis.

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Table 1: Univariate analysis. Reported are 5-year results

Variable	Value	No of patients [%]	bRFS [%]	P	LC [%]	P	RC [%]	P	MFS [%]	P	DFS [%]	p	OS [%]	p
Age [years]	Median [range]	66 [43 – 79]												
Age category [years]	< 62	91 [23.9]	82.0	**.021**	92.5	**.078**	97.3	.218	95.7	.150	86.8	**.018**	92.4	.209
	≥ 62	290 [76.1]	91.5		97.7		98.9		97.6		94.0		97.4	
CCI	0	309 [81.1]	87.9	.552	96.8	.771	100.0	1.00	96.5	.535	91.0	.576	95.6	.858
	1	57 [15.0]	94.2		93.3		100.0		100.0		96.7		98.1	
	2	13 [3.4]	100.0		100.0		100.0		100.0		100		100.0	
	3	2 [0.5]	100.0		100.0		100.0		100.0		100		100.0	
CCI cat	0	309 [81.1]	87.8	.149	96.8	.711	98.2	.334	96.5	.256	91.7	.254	95.6	.451
	> 1	72 [18.9]	95.8		95.2		100.0		100.0		95.2		98.5	
CCI total category	1-2	227 [59.6]	87.7	.648	97.0	.628	98.2	.526	95.9	.558	90.6	.273	95.7	.931
	> 2	154 [40.4]	91.6		95.7		98.9		99.1		94.9		96.8	
CCI + age	0	7 [1.8]	57.1	**.006**	66.7	**.000**	100.0	.915	83.3	.306	66.7	**.016**	80.0	.324
	1	51 [13.4]	80.9		93.9		97.7		97.7		85.6		94.1	
	2	226 [59.3]	92.7		99.2		98.7		96.3		94.6		97.1	
	3	97 [25.5]	89.4		95.0		98.3		100.0		93.3		97.6	
PSA preop [ng/mL]	Median [range]	7.94 [3.30 – 99.00]												
PSA preop category	< 10	249 [65.4]	90.5	.249	96.8	.360	99.4	.067	97.1	.888	93.9	.599	96.4	.926
	10-20	95 [24.9]	86.2		98.0		95.7		96.2		89.7		95.8	
	> 20	37 [9.7]	88.8		90.9		100.0		100.0		88.4		95.7	
PSA postop ng/mL]	Median [range]	0.04 [0.00 - 0.20]												
PSA postop category	≤ 0.013	98 [25.7]	96.8	**.047**	98.0	.782	100.0	.261	98.4	.416	98.4	.107	95.6	.302

	0.114- 0.039	90 [23.6]	84.1		96.8		100.0		94.2		89.9		93.4	
	0.040 – 0.09	95 [24.9]	87.7		94.8		96.9		96.9		90.6		95.6	
	> 0.09	98 [25.7]	88.9		96.0		97.1		98.9		90.3		100.0	
Gleason score new [ISUP grade]	≤ 6	52 [13.6]	93.2	**.004**	97.6	.277	100.0	.488	100.0	.209	95.3	.353	100.0	.082
	7 [3+4]	65 [17.1]	93.9		100.0		97.8		97.8		95.7		97.4	
	7 [4+3]	88 [23.1]	77.6		93.6		96.4		97.4		87.7		95.0	
	8	100 [26.2]	94.7		98.1		100.0		97.1		93.2		98.2	
	9-10	76 [19.9]	87.8		93.1		98.2		94.5		90.4		90.8	
pathological tumor stage	2	72 [18.9]	93.3	.736	95.7	.849	97.5	.901	100.0	.747	93.2	.824	100.0	.727
	3	303 [79.5]	88.2		96.6		98.7		96.5		92.0		95.2	
	4	6 [1.6]	100.0		100.0		100.0		100.0		100.0		100.0	
pathological nodal stage	No	325 [85.3]	91.4	**.000**	97.5	**.016**	98.7	.445	97.9	.152	93.7	**.012**	98.1	**.000**
	Yes	56 [14.7]	75.3		88.4		97.4		92.4		82.8		82.9	
NCCN category simplified*	Very low-, low risk	1 [0.3]	100.0	.896	100.0	.974	100.0	.590	100.0	.574	100.0	.926	100.0	.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 category	Very low-, low risk	1 [0.3]	100.0	.848	100.0	.906	100.0	.958	100.0	.898	100.0	.762	100.0	.893
	Intermediate risk	8 [2.1]	100.0		100.0		100.0		100.0		100.0		100.0	
	High-, very high risk	372 [97.6]	89.0		96.4		98.5		97.1		92.1		96.1	

Legend: bRFS: biochemical relapse-free survival; CCI: Charlson's Comorbidity Index; DFS: Disease-free survival [DFS]; EAU : European Association of Urologists; ISUP: International Society of Urological Pathologists; LC: Local control; MFS: Metastasis-free survival; NCCN: National Comprehensive Cancer Network; OS: Overall survival; PSA: Prostate Specific Antigen; RC: Regional control; *: very low and low risk together; high and very high risk together

Table 2. Univariate analysis. Reported are 5-year results

Variable	Value	No of patients [%]	bRFS [%]	P	LC [%]	P	RC [%]	P	MFS [%]	P	DFS [%]	p	OS [%]	p
Surgical technique	Open	195 [51.2]	87.9	.590	94.2	.184	99.2	.428	98.2	.889	90.9	.444	98.1	**.077**
	Laparoscopic	169 [44.4]	90.8		99.3		97.6		95.7		93.8		93.4	
	Robotic	17 [4.5]	100.0		100.0		100.0		100.0		100.0		100.0	
Nodal irradiation	No	84 [22.0]	91.2	.789	100.0	.160	94.6	**.004**	94.5	.550	91.9	.970	93.5	.404
	Yes	297 [78.0]	88.9		95.6		99.5		97.8		92.4		96.7	
Lymphadenectomy	No	94 [24.7]	84.9	.376	96.9	.967	100.0	.116	94.7	.283	91.2	.678	98.3	.745
	< 15 nodes	166 [43.6]	91.7		96.2		99.0		98.5		92.4		96.2	
	≥ 15 nodes	121 [31.8]	89.2		96.5		96.5		97.5		93.1		94.3	
Margin status	R0	104 [27.3]	87.2	.380	96.2	.938	98.0	.927	99.0	.647	91.6	.169	100.0	.058
	R1	277 [72.7]	90.0		96.5		98.6		96.5		92.6		94.8	
Previous abdominal-pelvic surgery	No	367 [96.3]	89.3	.757	96.3	.573	98.5	.702	97.5	.275	92.4	.885	96.5	.339
	Yes	14 [3.7]	88.9		100.0		100.0		88.9		88.9		88.9	
Previous Oncological histology	No	364 [95.5]	89.1	.697	96.3	.577	98.4	.669	97.4	.316	92.3	.944	96.5	**.017**
	Yes	17 [4.5]	94.1		100.0		100.5		94.1		94.1		87.5	
Adjuvant hormone therapy	No	127 [33.3]	89.8	.884	100.0	**.043**	97.9	.469	97.9	.540	94.2	.910	96.2	.688
	Yes	254 [66.3]	89.0		94.7		98.8		96.8		91.3		96.1	
Type of hormone therapy	Not prescribed	127 [33.3]	88.9	.909	100.0	.116	97.9	.664	97.9	.807	94.2	.987	96.2	.728
	LHRH	183 [48.0]	89.5		95.1		99.3		96.9		91.5		96.0	
	Bicalutamide	71 [18.7]	87.6		93.7		97.9		96.5		90.8		96.7	
Actual duration of hormone therapy [months]	Not prescribed	127 [33.3]	88.9	.342	100.0	.330	97.9	.592	97.9	.362	94.2	.417	96.2	.851
	≤ 6	78 [20.5]	86.1		94.0		96.5		98.4		90.5		96.5	
	< 12	23 [6.0]	84.6		90.9		100.0		92.3		84.6		88.9	
	12-24	105 [27.6]	87.4		95.0		100.0		94.5		90.4		95.5	
	25-36	30 [7.9]	100.0		100.0		100.0		100.0		100.0		100.0	
	> 36	18 [4.7]	94.4		93.8		100.0		100.0		93.8		100.0	

Legend: bRFS: biochemical relapse-free survival; DFS: Disease-free survival [DFS]; HT: hormone therapy; LC: Local control; MFS: Metastasis-free survival; OS: Overall survival; RC: Regional control; SV: Seminal vesicles; TURP: Transurethral resection of the prostate.

Table 3. Radiotherapy technique characteristics [%] univariate analysis. Reported 5-year results

Variable	Value	Number of patients [%]	bRFS [%]	P	LC [%]	P	RC [%]	P	MFS [%]	P	DFS [%]	p	OS [%]	p
Hypofractionation	No	127 [33.3]	87.6	.355	97.6	.585	98.8	.756	96.6	.730	93.9	.812	92.7	**.030**
	Yes	254 [66.7]	90.1		95.8		98.4		97.4		91.4		98.2	
Radiotherapy technique	3D-CRT	94 [24.7]	89.6	.992	100.0	.161	98.5	.933	97.2	.871	96.2	.235	95.4	.732
	IMRT	273 [71.7]	89.3		94.9		98.5		97.0		90.4		96.3	
	VMAT	14 [3.7]	85.7		100.0		100.0		100.0		100.0		100.0	
Image guidance	EPID	351 [92.1]	89.9	**.040**	96.6	.344	98.4	.624	97.3	.442	92.5	.424	96.8	**.030**
	Cone Beam	30 [7.9]	79.8		94.4		100.0		94.4		88.9		85.9	
EQD2 to the prostate $\alpha/\beta_{1.5}$ [Gy]	< 71.4	147 [38.6]	88.0	.609	97.9	.365	97.2	.216	96.2	.808	93.1	.997	93.7	.150
	71.4	145 [38.1]	89.3		94.1		100.0		98.5		92.2		99.2	
	> 71.4	89 [23.4]	91.2		97.8		97.8		96.1		90.3		96.0	
EQD2 to the lymph node $\alpha/\beta_{1.5}$ [Gy]	not prescribed	85 [22.3]	91.3	.394	100.0	**.031**	94.7	**.018**	94.6	.807	92.1	.101	93.7	.341
	≤ 42.4	196 [51.4]	87.1		93.5		99.2		98.2		90.1		97.4	
	> 42.4	100 [26.2]	92.8		100.0		100.0		96.8		97.1		95.0	
EQD2 to the lymph node $\alpha/\beta_{1.5}$ [Gy]	≤ 42.4	196 [66.2]	87.1	.166	93.5	**.048**	99.2	.508	98.2	.749	90.1	**.034**	97.4	.202
	> 42.4	100 [33.8]	92.8		100.0		100.0		96.8		97.1		95.0	
EQD2 to the prostate α $\alpha/\beta_{1.5}$ [Gy]	≤ 71.4	292 [76.6]	88.6	.512	96.1	.527	98.7	.867	97.4	.860	92.8	.943	96.2	.931
	> 71.4	89 [23.4]	91.2		97.8		97.8		96.1		90.3		96.0	

Legend: bRFS: biochemical relapse-free survival; CTV: Clinical tumor volume; DFS: Disease-free survival [DFS]; EPID: Electronic portal imaging device; GTV: Gross tumor volume; HT: hormone therapy; EQD2: equivalent dose; IMRT: Intensity modulated radiotherapy; LC: Local control; MFS: Metastasis-free survival; OS: Overall survival; PTV: Planning tumor volume; RC: Regional control; SV: Seminal vesicles; TURP: Transurethral resection of the prostate; VMAT: Volumetric modulated arc therapy; 3D-CRT: three dimensional conformal radiotherapy.

Table 4: Acute toxicity

	Grade					
	0	1	2	3	4	5
Gastrointestinal	162 [42.5]	148 [38.8]	69 [18.1]	2 [0.5]	0 [0.0]	0 [0.0]
Genitourinary	150 [39.4]	162 [42.5]	64 [16.8]	5 [1.3]	0 [0.0]	0 [0.0]
Skin	304 [79.8]	61 [16.0]	15 [3.9]	1 [0.3]	0 [0.0]	0 [0.0]

Table 5: Acute gastrointestinal and genitourinary toxicity Grade ≥ 2 and Grade ≥ 3

		Gastrointestinal				**Genitourinary**			
		G ≥ 2 [%]	**p**	**G≥ 3 [%]**	**P**	**G ≥ 2 [%]**	**p**	**G ≥ 3 [%]**	**P**
Nodal irradiation	No	11 [13.1]	.091	0 [0.0]	.607	9 [10.7]	**.029**	0 [0.0]	.286
	Yes	60 [20.2]		2 [0.7]		60 [20.2]		5 [1.7]	
Hypofractionation	No	20 [15.7]	.189	2 [1.6]	.111	20 [15.7]	.242	3 [2.4]	.209
	Yes	51 [20.1]		0 [0.0]		49 [19.3]		2 [0.8]	
Lymphadenectomy	No	20 [21.3]	.289	0 [0.0]	.696	18 [19.1]	.707	2 [2.1]	.539
	< 15 nodes	34 [20.5]		1 [0.6]		32 [19.3]		1 [0.6]	
	≥ 15 nodes	17 [14.0]		1 [0.8]		19 [15.7]		2 [1.7]	
EQD2 to the prostate α/β_{10} [Gy]	≤ 68.3	34 [17.6]	.350	0 [0.0]	.243	31 [16.1]	.179	2 [1.0]	.488
	> 68.3	37 [19.7]		2 [1.1]		38 [20.2]		3 [1.6]	
Radiotherapy technique	3D-CRT	13 [13.8]	.169	0 [0.0]	.672	13 [13.8]	.217	3 [3.2]	.177
	IMRT	57 [20.9]		2 [0.7]		55 [20.1]		2 [0.7]	
	VMAT	1 [7.1]		0 [0.0]		1 [7.1]		0 [0.0]	
Image guidance	EPID	42 [21.6]	.301	2 [1.0]	.379	36 [18.6]	.481	3 [1.5]	.786
	Cone Beam	5 [16.7]		0 [0.0]		3 [10.0]		0 [0.0]	
Previous abd-pelvic surgery	No	71 [19.3]	.053	2 [0.5]	.928	65 [17.7]	.236	4 [1.1]	.172
	Yes	0 [0.0]		0 [0.0]		4 [28.6]		1 [7.1]	
Adjuvant hormone therapy	No	24 [18.9]	.515	1 [0.8]	.556	17 [13.4]	.058	1 [0.8]	.460
	Yes	47 [18.5]		1 [0.4]		52 [20.5]		4 [1.6]	
Type of hormone therapy	LHRH	30 [16.4]	.114	0 [0.0]	.280	34 [18.6]	.152	3 [1.6]	.688
	Bicalutamide	17 [23.9]		1 [1.4]		18 [25.4]		1 [1.4]	
EQD2 to the lymph node α/β_{10} [Gy]	≤ 44.3	40 [20.4]	.516	2 [1.0]	.435	37 [18.9]	.260	3 [1.5]	.554
	> 44.3	20 [19.8]		0 [0.0]		23 [22.8]		2 [2.0]	

Legend: EPID: Electronic portal imaging device; EQD2: equivalent dose; IMRT: Intensity modulated radiotherapy; VMAT: Volumetric modulated arc therapy; 3D-CRT: three-dimensional conformal radiotherapy.

Table 6: Five-year late gastrointestinal and genitourinary toxicity Grade ≥ 2 and Grade ≥ 3

		Number of patients [%]	Gastrointestinal				Genitourinary			
			G ≥ 2 [%]	p	G ≥ 3 [%]	p	G ≥ 2 [%]	p	G ≥ 3 [%]	P
Nodal irradiation	No	84 [22.0]	80.2	**.009**	96.8	.288	87.7	.139	98.0	.204
	Yes	297 [78.0]	92.9		98.4		82.4		93.5	
Hypofractionation	No	127 [33.3]	84.0	**.006**	96.1	**.033**	83.2	.764	93.2	.533
	Yes	254 [66.7]	93.6		99.2		83.6		95.2	
Lymphadenectomy	No	94 [24.7]	92.6	.098	98.6	.259	79.2	.464	95.9	.758
	< 15 nodes	166 [43.6]	92.9		99.2		86.9		94.1	
	≥ 15 nodes	121 [31.8]	84.4		96.0		83.0		93.9	
EQD2 to the prostate $\alpha/\beta_{3.0}$ [Gy]	≤ 68.3	226 [59.3]	91.1	.808	98.1	.973	84.2	.603	92.7	.120
	> 68.3	155 [40.7]	89.3		98.2		83.2		97.0	
Radiotherapy technique	3D-CRT	94 [24.7]	82.6	**.027**	93.5	**.002**	83.4	.524	96.4	.692
	IMRT	273 [71.7]	93.2		100.0		83.1		93.2	
	VMAT	14 [3.7]	100.0		100.0		100.0		100.0	
Image guidance	EPID	351 [92.1]	90.0	.455	98.0	.556	82.4	.059	94.1	.319
	Cone Beam	30 [7.9]	96.6		100.0		100.0		100.0	
Previous abdominal-pelvic surgery	No	367 [96.3]	90.3	.914	98.1	.662	83.6	.718	94.3	.467
	Yes	14 [3.7]	90.0		100.0		84.4		100.0	
Adjuvant hormone therapy	No	127 [33.3]	89.2	.836	98.0	.829	85.9	.341	95.6	.267
	Yes	254 [66.3]	91.0		98.2		82.3		93.9	
EQD2 to the lymph node $\alpha/\beta_{3.0}$ [Gy]	No	84 [22.0]	80.2	**.033**	96.8	.329	87.7	.236	98.0	.121
	≤ 43.2	196 [51.4]	93.0		99.5		82.2		91.7	
	> 43.2	101 [26.5]	92.7		96.6		83.5		96.9	

Legend: EPID: Electronic portal imaging device; EQD2: equivalent dose; IMRT: Intensity modulated radiotherapy; VMAT: Volumetric modulated arc therapy; 3D-CRT: three-dimensional conformal radiotherapy.

Table 7: Multivariate analysis on biochemical and clinical outcomes

Variable	***value***	***bRFS***			***DFS***			***LC***			***RC***			***OS***		
		HR	***95%CI***	***p***	***HR***	***95%CI***	***p***	***HR***	***95%CI***	***p***				***HR***	***95%CI***	***p***
Age category [years]	< 62	1.00 [Ref]			1.00 [Ref]											
	≥ 62	0.35	0.17-0.70	**.003**	0.42	0.19-0.91	**.029**									
Pathological nodal stage	No	1.00 [Ref]			1.00 [Ref]			1.00 [Ref]						1.00 [Ref]		
	Yes	2.94	1.39-6.17	**.004**	2.78	1.16-6.69	**.022**	4.93	1.18-20.71	**.029**				11.81	2.82-49.51	**.001**
PSA postop category	≤ 0.013	Ref		**.017**												
	0.114- 0.039	11.14	2.44-50.82	**.002**												
	0.040 – 0.09	5.89	1.27-27.26	**.023**												
	> 0.09	6.27	1.36-28.93	**.019**												
Gleason score new [ISUP grade]	6	Ref		**.018**												
	7 [3+4]	1.07	0.23-4.89	.928												
	7 [4+3]	3.83	1.07-13.80	**.040**												
	8	0.90	0.21-3.91	.891												
	9-10	2.50	0.66-9.48	.176												
Previous Oncological histology	No													1.00 [Ref]		
	Yes													12.63	2.11-75.66	**.005**
Nodal irradiation	No										1.00 [Ref]					
	Yes										0.05	0.004-0.45	**.008**			
PSA preop category	< 10										Ref		.068			
	10-20										15.23	1.53-151.77	**.020**			
	> 20										0.00	0.00-	.994			

Legend: bRFS: biochemical relapse-free survival; DFS: Disease-free survival [DFS]; ISUP: International Society of Urological Pathologists; LC: Local control; MFS: Metastasis-free survival; OS: Overall survival; PSA: Prostate Specific Antigen

Table 8: Multivariate results of late toxicity

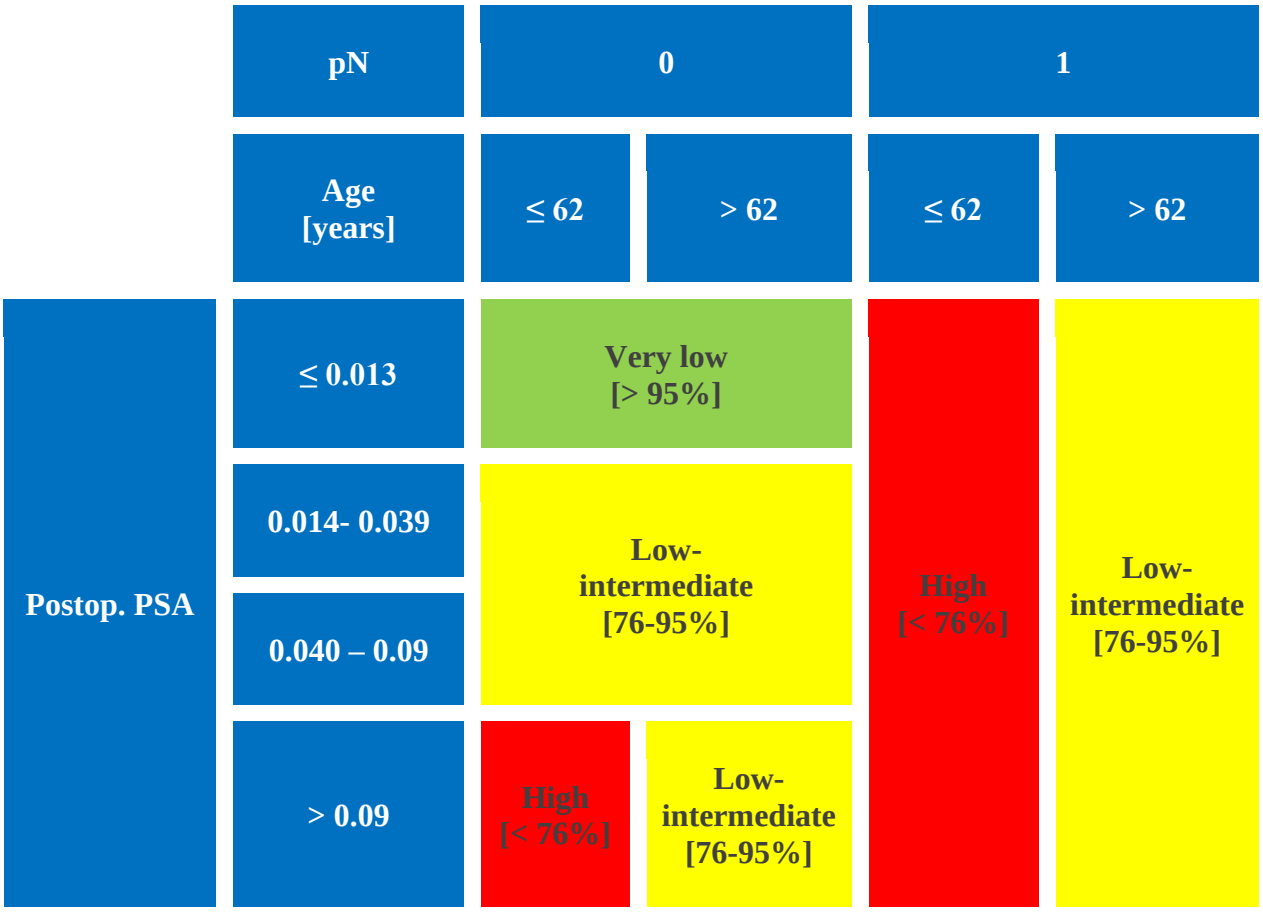
variable	***value***	***Late gastrointestinal ≥ 2***		
		HR	***95%CI***	***p***
Hypofractionation [Gy]	≤ 2			
	> 2	0.38	0.18-0.78	**.008**

Table 9: Prediction of 5-year biochemical Relapse-Free Survival [%] according to the variables included in the model

Variables		5-year biochemical Relapse-Free Survival			
		pN_0		pN_1	
		Age < 62 yrs	Age ≥ 62 yrs	Age < 62 yrs	Age ≥ 62 yrs
Postoperative PSA level [ng/ml]	≤ 0.013	100.0 [26]	100.0 [59]	75.0 ± 21.7 [5]	75.0 ± 21.7 [8]
	0.014-0.039	87.5 ± 11.7 [9]	86.9 ± 4.7 [69]	NR [3]	83.3 ± 15.2 [9]
	0.040 – 0.09	92.9 ± 6.9 [19]	90.4 ± 4.6 [62]	NR [7]	85.7 ± 13.2 [7]
	> 0.09	69.7 ± 13.1 [18]	93.9 ± 3.5 [63]	75.0 ± 21.7 [4]	100.0 [13]

Legend: NR: not reached; PSA= prostate specific antigen; yrs = years

Figure 1: Categorization risk [5-year biochemical Relapse-Free survival]



CHAPTER 3

PROSTATE CANCER TREATED WITH SALVAGE RADIOTHERAPY: ANALYSIS OF PROGNOSTIC FACTORS AND DEVELOPMENT OF A VISUAL RISK STRATIFICATION SYSTEM.

ABSTRACT

Background

The aim of this study was to analyze the prognostic impact on outcome and toxicity of patients with prostate cancer [PCa] treated with salvage radiotherapy [RT] based on a comprehensive analysis of parameters related to tumor, patients, and treatment characteristics. Furthermore, we aimed to develop a simple risk stratification system based on real life data from a large patient population

Material and methods

A retrospective analysis of 454 patients enrolled in an observational study was performed. Endpoints of the study in terms of clinical outcomes were biochemical relapse-free survival [bRFS], local control [LC], regional control [RC], metastasis-free survival [MFS], disease-free survival [DFS], and overall survival [OS]. In terms of toxicity both acute and late toxicity were assessed.

Survival estimates were calculated by the Kaplan-Meier product-limit method and compared with the log-rank test. Variables with P value less than 0.05 or with a trend [$p < 0.1$] at univariate analysis were entered into a multivariate Cox's regression model. $P < 0.05$ value was considered statistically significant. Acute toxicity was assessed by RTOG scale while late toxicity was evaluated with the RTOG/EORTC scale.

Results

Multivariate analysis showed a higher bRFS rates in patients with pN_0 stage, lower Gleason score [GS] and treated with prophylactic nodal irradiation [PNI]. Moreover, it showed improved LC in patients treated with hypofractionated regimens. In terms of RC, multivariate analysis showed better results in patients

with lower GS and worse results in patients with negative surgical margins, treated with IMRT/VMAT technique and not receiving PNI. The analysis on MFS showed a better outcome in pN_0 and low GS patients and a higher failure risk in patients receiving adjuvant ADT. Higher DFS rates were confirmed in patients with pN_0 or low GS or low PSA levels at salvage treatment as well as in patients treated with cone-beam CT. Furthermore, multivariate analysis showed better DFS rates in patients receiving PNI. The multivariate analysis on OS confirmed the positive impact of IMRT/VMAT techniques. No parameter significantly predicted toxicity at multivariate analysis.

We designed a prognostic model using 4 Gleason score categories, 2 nodal stage categories, and 2 nodal irradiation categories to define 16 different groups of patients. These 16 groups were arranged in only 4 categories based on 5-year bRFS values: group 1: low-risk [bRFS > 80%], group 2: intermediate risk [bRFS: 60-80%], group 3: high risk [bRFS: 40-< 59.9%], and group 4: very high risk [bRFS: < 40%].

Conclusions

This systematic analysis of a large patients series allowed the identification of unpredictable correlations potentially useful to generate new hypotheses. These results justify further analysis of large series of patients with PCa cancer treated with salvage RT, possibly performed with more advanced statistical analysis methods.

INTRODUCTION

Prostate cancer [PCa] represents the second and fifth cancer in terms of incidence and mortality in the male population, respectively [1]. Radical prostatectomy [RP] is one of the main therapeutic options of PCa. However, in patients treated with RP the 5-year biochemical Relapse Free Survival [bRFS] is around 50% [2-4].

However, if post-operative RT is able to improve the clinical outcomes, it is also true that the same produces increased rates of side effects [2-4]. Therefore, it has been proposed, at least in some clinical situations, only to monitor patients after RP with delayed salvage RT in case of biochemical recurrence [5]. As for the other RT settings of PCa [curative and adjuvant], salvage RT can be modulated in terms of prostatic bed RT dose, eventual prophylactic nodal irradiation, and possible integration with adjuvant hormone therapy. In fact, the efficacy of the latter has been demonstrated by two randomized studies although its usefulness in all patients undergoing salvage RT is not completely clear [6,7].

For an effective treatment modulation able to adapt the intensity and characteristics of the therapy to those of the recurrent disease, the availability of predictive models for risks would be obviously useful. Some of these have been proposed in the past [8,9]. However, a subsequent analysis showed their limits in terms of predictive power [10]. Therefore, further studies are needed to develop effective models that can predict the prognosis of these patients by adapting the treatment to the specific clinical situation.

Based on this background, in this study we performed an analysis of the prognostic impact on clinical outcomes and toxicity based on a comprehensive analysis of parameters related to tumor, patients, and treatment characteristics. Furthermore, we developed a simple risk stratification system based on real life data from a large patient population.

MATERIAL AND METHODS

Study design and endpoints

This is a retrospective analysis of patients enrolled in an observational study. Endpoints of the study in terms of clinical outcomes were biochemical relapse-free survival [bRFS], local control [LC] defined as control of tumor in the prostate and seminal vesicles, regional control [RC] defined as control of the disease in the prostate, seminal vesicles and pelvic nodes, metastasis-free survival [MFS], disease-free survival [DFS], and overall survival [OS]. In terms of toxicity both acute and late toxicity were assessed.

Inclusion criteria

This is a retrospective analysis of patients enrolled in an observational study. Endpoints of the study in terms of outcomes were biochemical relapse-free survival [bRFS], local control [LC], defined as control of tumor control in prostate bed, regional control [RC], defined as control of the disease in the prostate bed and pelvic nodes, metastasis-free survival [MFS], disease-free survival [DFS], and overall survival [OS]. In terms of toxicity both acute and late toxicity were assessed.

Evaluated parameters

The following inclusion criteria were used: 1] patients with prostatic adenocarcinoma who underwent previous RP, 2] absence of distant metastases, 3] postoperative PSA > 0.2 ng/ml or rise of PSA with almost two increments and a value > 0.2 ng/ml, 4] RT delivered with external beams techniques using photons beams. Exclusion criteria were as follows: 1] macroscopic recurrent residual disease at biochemical relapse, 2] previous RT on the pelvic region, 3] contraindication to RT [active inflammatory bowel diseases, pelvic abscesses or fistulas, 4] previous salvage therapy of biochemical recurrence with Androgen Deprivation Therapy [ADT].

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 [14] and compared with the log-rank test [15]. Variables with *P* value less than 0.05 or with a trend [$p < 0.1$] at univariate analysis were entered into a multivariate Cox regression model [16]. $P < 0.05$ value was considered statistically significant. Acute toxicity was assessed by RTOG scale while late toxicity was evaluated with the RTOG/EORTC scale [17].

Ethical issues

The local institutional review board approved this analysis [311/2019/Oss/AOUBo, ICAROS-1 study]. Only patients who had provided a written informed consent to the scientific use of their data were included.

RESULTS

Patients characteristics

A total of 454 patients were included in this analysis. **Table 1** shows the patients and tumor characteristics and **Table 2** presents the general characteristics of the treatment. **Table 3** shows the specific characteristics of RT technique.

Univariate analysis

Biochemical and clinical outcomes

Higher rates of bRFS were recorded in patients with lower GS values and pathological tumor and nodal stage, and in patients in lower risk categories according to the NCCN stratification system [**Table 1**]. Worse bRFS results were observed in patients undergoing RP with robotic technique, not receiving prophylactic nodal irradiation [**Table 2**],

and irradiated with cone-beam CT verification technique or with higher EQD2 on lymph nodes or with hypofractionated RT [**Table 3**].

LC was significantly higher in patients with lower GS values [**Table 1**] and receiving prophylactic nodal irradiation while LC was worse in patients who underwent RP with robotic technique [**Table 2**].

RC was better in patients with lower GS values [**Table 1**] and receiving adjuvant ADT [**Table 2**] while it was worse in patients irradiated with cone-beam CT verification technique or with lower EQD2 to regional nodes [**Table 3**].

MFS rates were higher in patients with lower Gleason score values, lower pathological tumor stage, negative pathological nodal stage and lower risk category according to NCCN [**Table 1**]. MFS was reduced in patients receiving adjuvant ADT [**Table 2**].

DFS was better in patients with lower GS values, lower pathological tumor stage, negative pathological nodal stage, lower risk category according to NCCN, lower PSA levels at salvage treatment [**Table 1**] and treated with cone-beam CT technique and lower EQD2 on lymph nodes [**Table 3**].

OS rates were higher in patients with lower PSA levels at salvage treatment [**Table 1**], receiving prophylactic nodal irradiation [**Table 2**] or treated with hypofractionated regimen or with IMRT/VMAT techniques [**Table 3**]. OS was worse in patients undergoing RP with robotic technique [**Table 2**] or receiving higher EQD2 on the nodes [**Table 3**].

Toxicity

None of the patients showed acute grade > 3 toxicity and patients who experienced gastrointestinal and genitourinary grade 3 toxicity were 0.9% and 0.7%, respectively [**Table 4**]. No significant correlations were recorded between grade > 2 acute toxicity and the analyzed parameters [**Table 5**]. Considering late grade > 2 late toxicity, the only significant

correlation was a reduction of gastrointestinal complications in patients treated with hypofractionated regimen or IMRT/VMAT techniques [**Table 6**].

Multivariate analysis

Biochemical and clinical outcomes

Multivariate analysis confirmed the higher bRFS rates in patients with pN_0 stage, lower GS and treated with prophylactic nodal irradiation. Moreover, it showed improved LC in patients treated with hypofractionated regimens. In terms of RC, multivariate analysis confirmed the better results in patients with lower GS and showed worse results in patients with negative surgical margins, treated with IMRT/VMAT technique and not receiving prophylactic nodal irradiation. The analysis on MFS confirmed the better outcomes in pN_0 and low GS patients and the higher risk in patients receiving adjuvant ADT. Higher DFS rates were confirmed in pN_0 or low GS or low PSA levels at salvage treatment patients as well as in patients treated with cone-beam CT. Furthermore, multivariate analysis showed better DFS rates in patients receiving prophylactic nodal irradiation. The multivariate analysis on OS confirmed the positive impact of IMRT/VMAT techniques [**Table 7**].

Toxicity

The significant correlations at univariate analysis between gastrointestinal toxicity and hypofractionated RT and IMRT/VMAT techniques were not confirmed.

Predictive model

We designed a prognostic model of the biochemical outcome according to the following modalities. The parameters significantly correlated to bRFS at multivariate analysis were considered [GS, pathological nodal stage and prophylactic nodal irradiation]. Then, we used the four Gleason score categories, the 2 nodal stage categories, and the two nodal irradiation categories to define 16 different groups of patients [**Table 8**]. At this point we arranged these 16 groups in only 4 categories based on 5-year bRFS values: group 1: low-risk

[bRFS > 80%], group 2: intermediate risk [bRFS: 60-80%], group 3: high risk [bRFS: 40-< 59.9%], and group 4: very high risk [bRFS: < 40%] [**Figure 1**].

DISCUSSION

Retrospectively reviewing a large series of PCa patients treated with salvage external beam RT, an analysis of the potential predictors of biochemical-clinical outcome and acute-late toxicity was performed. Multivariate analysis showed a higher bRFS rates in patients with pN_0 stage, lower GS and treated with prophylactic nodal irradiation. No parameter was significantly correlated with acute or late toxicity. On the basis of this multivariate analysis, a simple risk stratification system was designed to stratify patients with different probability of biochemical recurrence.

Our study has obvious limitations and in particular the use of a relatively simple statistical analysis methods. Therefore, we are planning to repeat this analysis with more advanced statistical methods such as the use of neural networks. Furthermore, some parameters with known prognostic impact, such as PSA doubling time at recurrence and interval between RP and biochemical relapse, have not been considered. However, this aspect will probably facilitate the use of this system, given its simplicity, and a future validation of the model. Furthermore, compared to other risk stratification systems [15,16], our model not only allows to define the risk class but also to quantify the risk percentage. This aspect could favor patient counseling when choosing treatment type and modality.

Univariate analysis showed several significant correlations both on outcomes and toxicity. In part these correlations can be simply explained as an effect of chance. Some of these, in particular, present rather paradoxical aspects for example, the worse bRFS in patients operated with robotic technique, irradiated with cone-beam CT, with higher EQD2 on lymph nodes and hypofractionated regimen. It is likely that many of these unexpected results are due to the impact of confounding factors.

However, it is more difficult to explain some rather surprising results of multivariate analysis. In fact, RC was worse in patients with negative surgical margin, treated with IMRT/VMAT. We can only imagine that patients with negative margins have had a lower risk of relapse in the prostate bed and that therefore, in most cases, relapses have occurred at the lymph node level. As for the negative impact of the modulated techniques, we can hypothesize that the higher conformality of these techniques compared to 3D-conformal RT has caused cases of geographical miss at the level of the pelvic lymph nodes. Moreover, this result contradicts the improved OS in patients undergoing IMRT/VMAT. The worse MFS in patients receiving adjuvant ADT can only be explained by the worse prognostic profile of patients receiving hormonal therapy.

The general feeling about these unexpected results is that the method used for multivariate analysis was not completely able to eliminate the impact of confounding factors or that in our analysis some relevant parameters are missing from the database. On the other hand, it is considered an advantage of systematic analysis of large databases the possibility to identify unforeseen correlations that can generate new hypotheses.

This aspect justifies further analysis of large series of patients with PCa treated with postoperative RT, possibly performed with advanced methods of statistical analysis.

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Table 1: Univariate analysis. Reported are 5-year results

Variable	Value	Number of patients [%]	bRFS [%]	P	LC [%]	P	RC [%]	P	MFS [%]	P	DFS [%]	p	OS [%]	p
Age [years]	Median [range]	68 [45-82]												
Age category [years]	< 63	92 [20.3]	50.2	.898	88.9	.522	95.2	.247	80.1	.684	67.3	.265	91.5	.892
	≥ 63	362 [79.7]	48.9		91.9		84.5		84.8		58.4		93.1	
CCI	0	321 [70.7]	46.6	.120	90.7	.900	85.4	.335	82.8	.731	60.7	.084	92.8	.748
	1	68 [15.0]	43.6		91.0		86.6		83.7		46.0		88.8	
	2	56 [12.3]	65.1		94.5		92.3		89.1		70.8		96.2	
	3	7 [1.5]	100.0		100.0		100.0		100.0		100.0		100.0	
	4	2 [0.4]	50.0		100.0		50.0		50.0		50.0		100.0	
CCI category	0	321 [70.7]	46.6	.408	90.7	.807	85.4	.294	82.8	.869	60.7	.589	92.8	.576
	≥ 1	133 [29.3]	55.3		93.1		89.6		86.1		59.0		92.6	
PSA preop [ng/mL]	Median [range]	10.42 [3.0-129.0]												
PSA preop category	< 10	226 [49.8]	52.4	.537	91.3	.370	84.5	.182	85.4	.448	64.8	.420	94.3	.472
	10-20	139 [30.6]	51.8		92.4		86.0		85.3		59.8		93.7	
	> 20	89 [19.6]	39.6		89.3		92.7		79.1		50.3		88.9	
PSA postop ng/mL]	Median [range]	0.77 [0.08-56.0]												
PSA at treatment category	≤ 0.39	115 [25.3]	56.5	.117	91.7	.165	93.2	.126	90.1	.217	66.1	**.008**	97.9	**.035**
	0.391-0.769	112 [24.7]	50.6		95.1		91.6		85.5		71.1		97.0	
	0.77 – 2.0	115 [25.3]	45.5		92.1		81.0		83.5		55.8		84.8	
	> 2.0	112 [24.7]	43.3		86.1		81.4		75.9		46.5		91.9	
Gleason score new [ISUP grade]	≤ 6	77 [17.0]	66.3	**.000**	95.2	**.040**	93.8	**.041**	96.6	**.000**	75.2	**.000**	93.0	.453
	7 [3+4]	83 [18.3]	65.2		100.0		97.2		94.2		77.2		95.2	
	7 [4+3]	117 [25.8]	49.5		86.2		83.2		90.9		60.7		97.3	
	8	86 [18.9]	51.5		88.0		86.9		84.2		65.6		90.9	
	9-10	91 [20.0]	22.8		91.0		76.8		58.6		31.7		87.2	
Pathological tumor stage	1-2	187 [41.2]	57.1	**.004**	88.5	.826	86.3	.420	91.2	**.008**	66.5	**.009**	93.9	.974
	3-4	267 [57.8]	44.5		93.2		87.0		79.3		56.1		92.0	
Pathological nodal stage	No	392 [86.3]	52.1	**.000**	91.0	.528	86.8	.664	89.0	**.000**	62.5	**.000**	93.8	.837
	Yes	62 [13.7]	32.4		93.7		85.7		54.0		45.1		87.1	
NCCN category	Very low-, low risk	11 [2.4]	100.0	**.002**	100.0	.644	100.0	.279	100.0	**.002**	100.0	**.006**	100.0	.761
	Intermediate risk	128 [28.2]	60.9		91.2		87.6		95.4		70.6		93.0	

simplified*	High-, very high risk	315 [69.4]	44.2		91.3		86.0		79.3		55.6		92.4	
EAU category	Very low-, low risk	11 [2.4]	100.0	.150	100.0	.742	100.0	.533	100.0	.326	100.0	.243	100.0	.435
	Intermediate risk	38 [8.4]	59.1		87.5		89.5		88.0		59.1		96.0	
	High-, very high risk	405 [89.2]	47.4		91.7		86.1		83.1		59.6		92.3	

Legend: bRFS: biochemical relapse-free survival; CCI: Charlson's Comorbidity Index; DFS: Disease-free survival [DFS]; EAU : European Association of Urologists; ISUP: International Society of Urological Pathologists; LC: Local control; MFS: Metastasis-free survival; NCCN: National Comprehensive Cancer Network; OS: Overall survival; PSA: Prostate Specific Antigen; RC: Regional control; *: very low and low risk together; high and very high risk together

Table 2. Univariate analysis. Reported are 5-year results

Variable	Value	No of patients [%]	bRFS [%]	P	LC [%]	P	RC [%]	P	MFS [%]	P	DFS [%]	p	OS [%]	p
Surgical technique	Open	184 [40.5]	62.7	**.000**	86.6	.119	93.2	**.000**	84.2	.857	65.8	.107	95.9	**.008**
	Laparoscopic	216 [47.6]	40.1		95.1		84.8		84.1		58.2		89.9	
	Robotic	54 [11.9]	27.0		97.7		61.7		78.9		38.6		88.9	
Nodal irradiation	No	184 [40.5]	35.1	**.000**	93.5	.273	76.3	**.000**	86.7	.902	55.2	.213	89.8	**.025**
	Yes	270 [59.5]	58.3		90.2		93.5		82.2		63.5		94.5	
Lymphadenectomy	No	178 [39.2]	52.6	.504	91.5	.999	85.0	.224	85.0	.797	59.7	.476	91.8	.443
	< 15 nodes	137 [30.2]	51.4		89.3		92.6		84.9		64.5		94.0	
	≥ 15 nodes	139 [30.5]	43.8		93.0		83.7		81.8		57.0		93.1	
Margin status	R0	212 [46.7]	55.2	.098	93.1	.175	85.7	.355	85.5	.298	61.5	.762	94.0	.122
	R1	242 [53.3]	44.7		90.1		87.7		82.5		59.3		91.9	
Previous abd-pelvic surgery	No	417 [91.9]	49.7	.177	91.1	.756	86.4	.684	83.5	.325	60.1	.302	91.9	.399
	Yes	37 [8.1]	42.8		93.5		88.4		87.5		60.5		100.0	
Previous Onco histology	No	430 [94.7]	49.3	.812	91.3	.387	86.5	.693	84.2	.501	60.0	.682	92.5	.763
	Yes	24 [5.3]	55.9		95.2		92.3		76.0		70.2		100.0	
Adjuvant hormone therapy	No	163 [35.9]	48.1	.333	96.1	.064	78.4	**.010**	93.7	**.001**	61.8	.660	96.1	.122
	Yes	291 [64.1]	50.1		88.8		91.9		78.4		59.4		91.0	
Type of hormone therapy	Not prescribed	163 [35.9]	48.1	.348	96.1	.132	78.4	**.020**	93.7	**.002**	61.8	.903	96.1	.286
	LHRH	215 [47.4]	44.4		89.6		89.9		77.7		57.7		89.5	
	Bicalutamide	76 [16.7]	61.0		86.5		96.3		78.7		61.5		93.6	
Actual duration of Hormone therapy [months]	not prescribed	163 [35.9]	48.1	.114	96.1	.169	78.4	.145	93.7	**.010**	61.8	.255	96.1	.051
	≤ 6	60 [13.2]	29.8		90.9		91.1		64.0		43.9		89.7	
	< 12	33 [7.3]	51.5		90.5		100.0		90.2		62.7		95.0	
	12-24	138 [30.4]	54.3		89.1		89.8		78.0		65.2		88.6	
	25-36	34 [7.5]	59.0		80.1		85.8		90.2		62.9		96.2	
	> 36	26 [5.7]	52.0		90.1		100.0		76.5		54.6		94.1	

Legend: bRFS: biochemical relapse-free survival; DFS: Disease-free survival [DFS]; HT: hormone therapy; LC: Local control; MFS: Metastasis-free survival; OS: Overall survival; RC: Regional control.

Table 3. Radiotherapy technique characteristics [%] univariate analysis. Reported 5-year results

Variable	Value	Number of patients [%]	bRFS [%]	P	LC [%]	P	RC [%]	P	MFS [%]	P	DFS [%]	p	OS [%]	p
Hypofractionation	No	154 [33.9]	46.6	.211	97.6	**.029**	88.2	.802	81.3	.222	56.8	.212	89.1	**.001**
	Yes	300 [66.1]	51.2		86.9		87.0		86.1		63.6		96.7	
Radiotherapy technique	3D-CRT	119 [26.2]	46.7	.257	98.0	.071	89.4	.373	81.5	.267	56.1	.232	89.2	**.001**
	IMRT/VMAT	335 [73.8]	50.1		88.0		86.2		85.4		62.6		95.8	
Image guidance	EPID	367 [80.8]	52.3	**.000**	90.8	.401	87.9	**.010**	83.7	.438	56.6	**.004**	94.0	.263
	Cone Beam	87 [19.2]	31.0		96.1		78.7		87.5		87.4		83.0	
.EQD2 to the prostate $\alpha/\beta_{1.5}$ [Gy]	< 71.4	182 [40.1]	43.6	.157	94.9	.059	81.8	.064	85.5	.778	55.2	.084	90.8	.235
	≥ 71.4	272 [59.9]	54.4		88.9		91.0		82.6		64.7		94.3	
EQD2 to the lymph nodes $\alpha/\beta_{1.5}$ [Gy]	not prescribed	184 [40.5]	35.1	**.000**	93.5	.218	76.3	**.000**	86.7	.908	55.2	**.038**	89.8	**.012**
	≤ 42.4	179 [39.4]	63.6		87.0		95.1		83.9		66.2		95.9	
	> 42.4	91 [20.0]	45.7		98.2		89.6		78.3		58.4		91.0	
EQD2 to the lymph nodes $\alpha/\beta_{1.5}$ [Gy]	≤ 42.4	179 [39.4]	63.6	**.000**	87.0	.222	95.1	**.028**	83.9	.686	66.2	**.016**	95.9	**.034**
	> 42.4	91 [20.0]	45.7		98.2		89.6		78.3		58.4		91.0	

Legend: bRFS: biochemical relapse-free survival; DFS: Disease-free survival [DFS]; EPID: Electronic portal imaging device; EQD2: equivalent dose; IMRT: Intensity modulated radiotherapy; LC: Local control; MFS: Metastasis-free survival; OS: Overall survival; RC: Regional control; VMAT: Volumetric modulated arc therapy; 3D-CRT: three dimensional conformal radiotherapy.

Table 4: Acute toxicity

	0	1	2	3
Gastrointestinal	215 [47.4]	140 [30.8]	95 [20.9]	4 [0.9]
Genitourinary	213 [46.9]	164 [36.1]	74 [16.3]	3 [0.7]
Skin	367 [82.6]	60 [13.2]	19 [4.2]	0 [0.0]

Table 5: Acute gastrointestinal and genitourinary toxicity Grade ≥ 2 and Grade ≥ 3

		Gastrointestinal				**Genitourinary**			
		G ≥ 2 [%]	p	G ≥ 3 [%]	p	G ≥ 2 [%]	p	G ≥ 3 [%]	P
Nodal irradiation	No	34 [18.9]	.096	0 [0.0]	.124	23 [12.5]	**.024**	2 [1.1]	.534
	Yes	49 [24.1]		4 [1.5]		54 [20.0]		2 [0.7]	
Hypofractionation	No	34 [22.1]	.505	1 [0.6]	.582	28 [18.2]	.355	1 [0.6]	.582
	Yes	65 [21.7]		3 [1.0]		49 [16.3]		3 [1.0]	
Lymphadenectomy	No	40 [21.1]	.869	0 [0.0]	.282	27 [15.6]	.636	3 [1.7]	.261
	< 15 nodes	29 [21.2]		2 [1.5]		22 [16.1]		1 [0.7]	
	≥ 15 nodes	29 [20.9]		2 [1.4]		27 [19.4]		0 [0.0]	
EQD2 to the prostate α/β_{10} [Gy]	< 68.3	36 [19.8]	.231	1 [0.5]	.473	32 [17.6]	.434	2 [1.1]	.527
	≥ 68.3	63 [23.2]		3 [1.1]		45 [16.5]		2 [0.7]	
EQD2 to the lymph node α/β_{10} [Gy]	≤ 44.3	45 [25.1]	.339	4 [2.2]	.191	42 [23.5]	.031	2 [1.1]	.439
	> 44.3	20 [22.0]		0 [0.0]		12 [13.2]		0 [0.0]	
Radiotherapy technique	3D-CRT	25 [21.0]	.458	1 [0.8]	.718	15 [12.6]	.089	1 [0.8]	.718
	IMRT/VMAT	74 [22.1]		3 [0.9]		62 [18.5]		3 [0.9]	
Image guidance	EPID	78 [21.3]	.325	4 [1.1]	.426	66 [18.0]	.150	4 [1.1]	.426
	Cone Beam	21 [24.2]		0 [0.0]		11 [12.6]		0 [0.0]	
Previous abd-pelvic surgery	No	94 [22.5]	.142	4 [1.0]	.711	74 [17.4]	.096	4 [1.0]	.711
	Yes	5 [13.5]		0 [0.0]		3 [0.7]		0 [0.0]	
Adjuvant hormone therapy	No	28 [17.2]	.046	0 [0.0]	.168	23 [14.7]	.207	1 [0.6]	.547
	Yes	71 [24.4]		4 [1.4]		53 [18.2]		3 [1.0]	
Type of hormone therapy	LHRH	49 [22.8]	.179	4 [1.9]	.296	41 [19.1]	.327	2 [0.0]	.598
	Bicalutamide	22 [40.7]		0 [0.0]		12 [15.8]		1 [1.3]	

Legend: EPID: Electronic portal imaging device; EQD2: equivalent dose; IMRT: Intensity modulated radiotherapy; VMAT: Volumetric modulated arc therapy; 3D-CRT: three-dimensional conformal radiotherapy.

Table 6: Five-year late gastrointestinal and genitourinary toxicity Grade ≥ 2 and Grade ≥ 3

		Number of patients [%]	**Gastrointestinal**				**Genitourinary**			
			G ≥ 2 [%]	p	G ≥ 3 [%]	p	G ≥ 2 [%]	p	G ≥ 3 [%]	P
Nodal irradiation	No	154 [33.9]	93.8	.144	98.1	.428	79.7	.482	96.4	.565
	Yes	300 [66.1]	90.2		97.0		82.9		94.7	
Hypofractionation	No	154 [33.9]	86.9	**.035**	94.1	**.002**	82.5	.845	94.6	.196
	Yes	300 [66.1]	94.2		99.3		80.2		95.0	
Lymphadenectomy	No	178 [39.2]	90.1	.767	95.3	.124	85.2	.290	93.8	.511
	< 15 nodes	137 [30.2]	92.7		98.6		75.1		96.1	
	≥ 15 nodes	139 [30.5]	92.5		99.1		83.6		96.7	
EQD2 to the prostate $\alpha/\beta_{3.0}$ [Gy]	< 68.3	203 [44.7]	92.9	.956	98.0	.678	77.7	.256	91.3	.114
	≥ 68.3	251 [55.3]	90.8		97.0		84.3		98.0	
RT technique	3D-CRT	119 [26.2]	85.7	**.032**	93.6	**.004**	85.1	.645	94.4	.466
	IMRT/VMAT	335 [73.8]	94.2		99.0		79.4		95.2	
Image guidance	EPID	367 [80.8]	91.3	**.083**	97.0	.235	80.8	.220	94.7	.578
	Cone Beam	87 [19.2]	95.0		100.0		84.5		100.0	
Previous abd-pelvic surgery	No	212 [46.7]	92.1	.757	97.6	.764	80.8	.485	95.1	.823
	Yes	242 [53.3]	88.0		95.8		88.9		96.8	
Adjuvant hormone therapy	No	163 [35.9]	93.7	.226	98.9	.154	82.5	.842	96.2	.903
	Yes	291 [64.1]	90.3		96.6		81.0		94.8	
EQD2 to the lymph node$\alpha/\beta_{3.0}$ [Gy]	No	184 [40.5]	93.8	.258	98.1	.501	79.7	.610	96.4	.369
	≤ 43.2	179 [39.4]	90.4		96.6		83.3		92.5	
	> 43.2	91 [20.0]	89.4		97.6		81.8		100.0	

Legend: EPID: Electronic portal imaging device; EQD2: equivalent dose; IMRT: Intensity modulated radiotherapy; VMAT: Volumetric modulated arc therapy; 3D-CRT: three-dimensional conformal radiotherapy.

Table 7: Multivariate analysis on biochemical and clinical outcomes

Variable	*value*	*bRFS*			*DFS*			*LC*			*RC*			*MFS*			*OS*		
		HR	***95%CI***	***p***	***HR***	***95%CI***	***p***	***HR***	***95%CI***	***p***	***HR***	***95%CI***	***p***	***HR***	***95%CI***	***p***	***HR***	***95%CI***	***p***
Margin status	R0										1.00 [Ref]								
	R1										0.52	0.27-0.99	**.049**						
Pathological nodal stage	No	1.00 [Ref]			1.00 [Ref]									1.00 [Ref]					
	Yes	1.91	1.29-2.83	**.001**	2.27	1.44-3.58	**.000**							2.46	1.39-4.36	**.002**			
Image guidance radiotherapy	EPID				1.00 [Ref]														
	Cone beam				0.21	0.09-0.48	**.000**												
Gleason score new [ISUP grade]	6	1.00 [Ref]		**.000**	Ref		**.000**				Ref		**.003**	Ref		**.000**			
	7 [3+4]	1.05	0.54-2.04	.884	1.13	0.53-2.43	.746				1.01	0.25-4.09	.990	1.34	0.32-5.65	.687			
	7 [4+3]	2.37	1.34-4.19	**.003**	2.16	1.08-4.31	**.030**				2.88	0.90-9.17	.074	2.85	0.77-10.54	.116			
	8	2.09	1.16-3.79	**.014**	2.08	1.01-4.25	**.044**				2.77	0.83-9.30	.099	2.87	0.76-10.83	.120			
	9-10	3.99	2.28-7.01	**.000**	4.46	2.31-8.57	**.000**				7.17	2.20-23.37	**.001**	9.22	2.67-31.77	**.000**			
Radiotherapy technique	3D-CRT										1.00 [Ref]						1.00 [Ref]		
	IMRT/VMAT										3.03	1.39-6.56	**.005**				0.25	0.09-0.62	**.003**
Nodal irradiation	No	1.00 [Ref]			1.00 [Ref]						1.00 [Ref]								
	Yes	0.44	0.32-0.61	**.000**	0.49	0.33-0.72	**.000**				0.14	0.06-0.29	**.000**						
PSA at treatment category					1.00 [Ref]		**.024**												
					1.17	0.68-2.06	.582												
					1.69	0.99-2.89	.056												
					2.01	1.21-3.34	**.007**												
Hypofractionation	≤ 2							1.00 [Ref]											
	> 2							2.61	1.02-6.70	**.046**									
Hormone type type	Not prescribed													Ref		**.013**			
	LHRH													2.81	1.22-6.51	**.016**			
	Bicalutamide													3.91	1.58-9.68	**.003**			

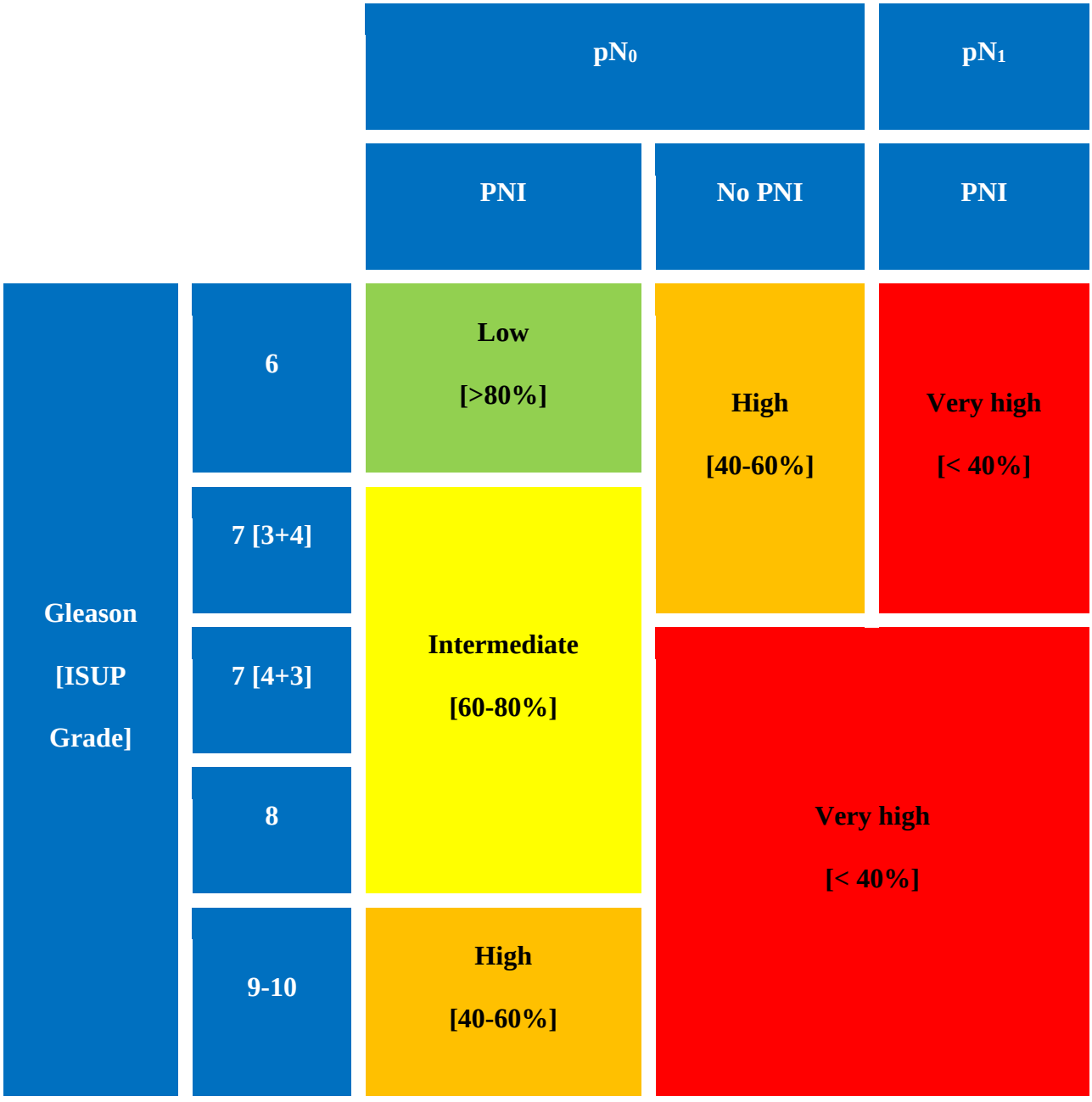
Legend: bRFS: biochemical relapse-free survival; DFS: Disease-free survival [DFS]; EPID: Electronic portal imaging device; IMRT: Intensity modulated radiotherapy; ISUP: International Society of Urological Pathologists; LC: Local control; MFS: Metastasis-free survival; OS: Overall survival; PSA: Prostate Specific Antigen; VMAT: Volumetric modulated arc therapy; 3D-CRT: three-dimensional conformal radiotherapy.

Table 8: Prediction of 5-year biochemical Relapse-Free Survival [%] according to the variables included in the model

Variables		5-year biochemical Relapse-Free Survival			
		pN0		pN1	
		PNI	No PNI	PNI	No PNI
Gleason Score [ISUP Grade]	6	81.3 ± 8.7 [35]	55.4 ± 11.2 [38]	50.0 ± 35.4 [4]	- [0]
	7 [3+4]	66.5 ± 9.8 [44]	50.2 ± 18.1 [34]	100.0 [5]	- [0]
	7 [4+3]	60.9 ± 8.5 [55]	33.3 ± 9.9 [53]	100.0 [5]	NR [4]
	8	71.5 ± 9.5 [42]	35.4 ± 11.3 [29]	30.8 ± 16.8 [12]	33.3 ± 27.2 [3]
	9-10	43.0 ± 10.9 [43]	9.5 ± 8.3 [19]	17.2 ± 9.9 [25]	NR [4]

Legend: NR: not reached; PNI= prophylactic nodal irradiation

Figure 1: categorization risk [5-year biochemical Relapse-Free survival]



CHAPTER 4

RADIOTHERAPY OF PROSTATE CANCER: IMPACT OF TREATMENT CHARACTERISTICS ON THE INCIDENCE OF SECOND TUMORS.

ABSTRACT

Background

It has been hypothesized that radiotherapy [RT] techniques delivering radiations to larger volumes [IMRT, VMAT] are potentially associated with a higher risk of second primary tumors. The aim of this study was to analyse the impact of RT technique [3D-CRT vs IMRT/VMAT] on the incidence of second tumors in prostate cancer [PCa] patients.

Materials and methods

A retrospective study on 2526 previously irradiated PCa patients was performed. Patients were treated with 3D-CRT [21.3%], IMRT [68.1%], or VMAT [10.6%]. Second tumors incidence was analysed in 3 categories: pelvic, pelvic and abdominal, and "any site". The correlation with RT technique was analysed using log-rank test and Cox's proportional hazard method.

Results

With a median follow-up of 72 months [range: 9-185], 92 [3.6%] cases of second tumors were recorded with 48 months [range: 9-152] median interval from RT. Actuarial 10-year second tumor free survival [STFS] was 87.3%. Ten-year STFS in patients treated with 3D-CRT and IMRT/VMAT was 85.8% and 84.5%, respectively [*p: .627*]. A significantly higher 10-year cumulative incidence of second tumors in the pelvis was registered in patients treated with IMRT/VMAT compared to 3D-CRT [10.7% vs 6.0%; *p: .033*]. The lower incidence of second pelvic cancers in patients treated with 3D-CRT was confirmed at multivariable analysis [HR: 2.42, 95%CI: 1.07-5.47, *p: .034*].

Conclusions

The incidence of second pelvic tumors after RT of PCa showed a significant correlation with treatment technique. Further analyses in larger series with prolonged follow-up are needed to confirm these results.

INTRODUCTION

Prostate cancer [PCa] is the second most common cancer in men worldwide [1]. In the USA, data from the Surveillance, Epidemiology and End Results database led to a forecast of approximately 174,650 new diagnoses and 31,620 deaths from PCa in 2019 [2].

Radiotherapy [RT] has been used in the treatment of PCa for over 70 years. RT results have gradually improved over time thanks to the technological evolution and to the combination with adjuvant androgen deprivation therapy [ADT]. However, some studies suggested that patients undergoing RT show a slightly higher incidence of second primary tumors particularly in the pelvis [3, 4, 5], although other authors attributed this increased risk to other factors such as age and lifestyle [6].

In the late 1990s, 3-dimensional conformal RT [3D-CRT] emerged as the optimal RT technique for this tumor due to improved dose distribution compared to conventional 2-dimensional RT. In fact, a significant reduction of acute and late toxicity was demonstrated [7, 8]. In the following decade, 3D-CRT was progressively replaced in this setting by modulated RT techniques such as intensity-modulated RT [IMRT] first, and volumetric modulated arc therapy [VMAT] subsequently. In fact, these techniques allow a higher dose conformity due to the steeper dose gradients around the target volume, reduced irradiation of organs at risk [OAR], and therefore the delivery of higher RT doses to the tumor [9, 10, 11, 12, 13]. A meta-analysis showed that IMRT, compared to 3D-CRT, can achieve lower G2-4 rectal toxicity rates and improve biochemical relapse-free survival [14].

However, it is well known that modulated RT techniques lead to low-level doses in larger body volumes compared to 3D-CRT. Theoretically, this characteristic could increase the risk of RT-induced carcinogenesis and then of second tumors. The theoretically increased risk of IMRT/VMAT induced second tumors in PCa patients has been largely discussed in literature. Several studies addressed this topic mainly in planning and dosimetric analyses

[15, 16, 17, 18]. However, comparisons between 3D-CRT and modulated RT techniques in terms of second tumors incidence based on real clinical data are still lacking.

Therefore, the aim of this retrospective analysis was to evaluate the impact of RT technique [3D-CRT vs IMRT/VMAT] on the incidence of second primary tumors in PCa patients. Moreover, also the impact of ADT and irradiated volumes in terms of delivery or not of prophylactic nodal irradiation [PNI], was investigated.

MATERIALS AND METHODS

End points and study design

The primary end point of this study was the correlation of RT technique with second primary cancers incidence in PCa. The secondary objectives of the analysis were the correlation of ADT and PNI on the same outcome. The study design was a monocentric retrospective analysis on all PCa patients previously treated with external beam RT [EBRT] included in our institutional PCa database.

Inclusion criteria

Inclusion criteria were as follows: 1] histologically confirmed prostatic adenocarcinoma; 2] curative aim of RT; 3] age > 18 years. Exclusion criteria were: 1] patients with distant metastases; 2] palliative aim of RT; 3] previous chemotherapy or RT on any site of the body; 4] some diseases potentially affecting tolerance to radiation therapy and potentially associated to a higher risk of cancer: ulcerative colitis, Crohn's disease, familial adenomatous polyposis, and bladder papilloma; 5] patients with malignancies diagnosed prior to PCa diagnosis; 6] patients with malignancies diagnosed during PCa staging and planning.

Radiotherapy

All patients underwent computed tomography [CT] simulation in supine position using a personalized immobilization system. In some patients, Positron Emission

Tomography [18F-choline or 11C-choline or 68-Ga-PSMA] - CT simulation and/or CT-simulation image fusion with MRI scans were performed. The Clinical Target Volumes [CTV] were defined based on risk categories to include only the prostate [or prostatic bed] +/- seminal vesicles or also pelvic lymph nodes. An isotropic margin ranging between 5 and 10 mm was added to the CTV to define the Planning Target Volumes. The photon beam energy was 10-15 MV and 6 MV in patients treated with 3D-CRT and IMRT/VMAT, respectively. As previously described, daily set-up verification was performed using an Electronic Portal Imaging Device in most patients [19]. Only in a small minority of patients treated after 2016, set-up and organ motion evaluation was performed using a cone-beam CT. Dose specification and prescription were performed based on the International Commission of Radiation Unit reports 62 and 83 for 3D-CRT and IMRT/VMAT techniques, respectively [20, 21]. ADT was prescribed according to risk categories.

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 and compared with the log-rank test. Multivariate analysis was performed using a Cox regression model [22]. A $p < 0.05$ value was considered statistically significant. The impact of RT technique [3D-CRT vs IMRT/VMAT], ADT [yes or not], and PNI [yes or not] on the incidence of second primary tumors was estimated. Second tumors incidence was evaluated not only as “any second tumor” detected during the follow-up but also considering other 2 groups: i] second tumors in the pelvis and ii] second tumors in the abdomen or pelvis. In cases of doubtful interpretation of the information contained in the database for the purposes of this stratification, the diagnostic images of the second tumor were analysed.

Ethical issues

The local institutional review board approved this analysis [311/2019/Oss/AOUBo, ICAROS-1 study]. Only patients who had provided a written informed consent to the scientific use of their data were included.

RESULTS

Patients characteristics

We included in the analysis 2526 PCa patients who met the inclusion criteria and received EBRT between 2002 and 2018. Median follow-up was 72 months [range: 9-185 months] and median age was 71 years [range: 43-93 years]. The RT settings were definitive [54.2%], adjuvant [32.8%], or salvage treatment [13.0%]. Patients were treated with 3D-CRT technique [21.3%], IMRT [68.1%], or VMAT [10.6%]. Total 3D-CRT median delivered dose was 70 Gy [median dose/fraction: 2.5 Gy] and the total IMRT/VMAT median dose was 67.5 Gy [median dose/fraction: 2.6 Gy]. PNI and ADT were prescribed to 1294 [51.2%] and 1689 [66.9%] patients, respectively. Patients treated with 3D-CRT and IMRT/VMAT received PNI in 39.4% and 54.4% of cases, respectively.

Incidence of second tumors

Ninety-two [3.6%] cases of second tumors were recorded. Median interval between RT and second tumor was 48 months [range: 9-152 months] and median age was 70 years [range: 45-83 years] at diagnosis of the second cancer. Moreover, there were 31 [1.2%], 26 [1.0%], and 35 [1.4%] cases of second primary cancers detected in the pelvis, abdomen, and other sites, respectively. Considering the group of younger patients [≤ 66 years: first quartile], we recorded 25 second tumors out of 688 cases. This information on second tumors was collected from patient chart-records. **Table 1** shows the number and percentages of detected second tumors. The 10-year actuarial cumulative incidence of second tumors was 14.4%.

Impact of treatment characteristics on second tumors incidence

For the entire cohort, the calculated 10-year second tumor-free survival [STFS] in patients treated with 3D-CRT and IMRT/VMAT was 85.8% and 84.5%, respectively [*p: .627*].

At univariate analysis, 10-year STFS in patients treated with or without PNI was 84.9% and 88.1%, respectively [*p: .770*]. Ten-year STFS in patients receiving or not ADT was 83.8% and 92.8%, respectively [*p: .999*]. A significantly higher 10-year cumulative incidence of second tumors in the pelvis was registered in patients treated with IMRT/VMAT compared to 3D-CRT [10.7% vs 6.0%; *p: .033*]. Moreover, PNI showed a trend [*p: 0.1*] for increased 10-year incidence of second tumors in both pelvis [9.4% vs 5.6%, *p: .092*] and pelvis-abdomen [10.9% vs 7.4%, *p: .064*] [**Table 2, Figure 1**].

Stratifying patients in 4 groups according to used RT technique and irradiated volumes, a statistically significant difference was recorded in terms of STFS in the pelvis [*p: .044*]. The 10-year STFS were as follows: 3D-CRT without PNI: 96.6%; 3D-CRT with PNI: 93.7%; IMRT/VMAT without PNI: 89.9%; and IMRT/VMAT with PNI: 87.6% **[Table 2, Figure 2**].

On multivariate analysis **[Table 3]**, the lower incidence of second pelvic cancers in patients treated with 3D-CRT was confirmed [hazard ratio [HR]: 2.42, 95%CI: 1.07-5.47, *p: .034*]. Furthermore, the incidence of second pelvis-abdomen cancers were found to have a trend in case of PNI delivery [HR: 1.63, 95%CI: 0.95-2.79, *p: .067*]. Moreover, in a separate multivariate analysis where RT techniques and irradiated volumes were combined, patients treated with IMRT/VMAT plus PNI were found to have a significantly increased risk of second pelvic cancers [HR: 3.24, 95%CI: 1.09-9.65, *p: .035*] and second pelvis-abdomen cancers [HR: 2.61, 95%CI: 1.06-6.41, *p: .037]*. **Figure 3** shows a simple risk stratification system based on these parameters.

DISCUSSION

We performed an analysis on the incidence of second cancers in PCa patients treated with EBRT to evaluate the impact of RT technique, irradiated volumes, and ADT. The analysis showed a significant correlation between second tumors located in the pelvis and RT technique [3D-CRT vs IMRT [6.0% vs 10.7%, *p: .033*]], while PNI showed a trend for increased 10-year incidence of second tumors in both pelvis [9.4% vs 5.6%, p: .092] and pelvis-abdomen [10.9% vs 7.4%, p: .064].

Our study has several limitations. First, the median follow-up is relatively short [72 months]. In fact, in a cohort of Hodgkin's Lymphoma patients treated with RT, the median latency time to second tumor was 7.5 years [23]. Moreover, the sample size [2526 patients] can be considered relatively small. In fact, other studies in this field [3, 6, 24], two of which were registry studies [3, 24], included 9,538 – 619,479 patients. Furthermore, although image guided RT could add a non-negligible risk for second tumors when daily set-up verification with high-resolution modality is performed [13], we did not consider this issue in our analysis. However, it should be noted that no extra dose was delivered for set-up verification in most patients. Furthermore, only a small minority of patients treated in the last 2 years had their treatment position and organ motion checked using a daily cone-beam CT. In addition, the evaluation of other potential factors correlated with second tumors are lacking in our analysis. For example, the first 2 primary tumors recorded in this study were bladder and lung cancers and both are smoking-related malignancies. Therefore, it would have been interesting to evaluate the impact of RT techniques also considering the smoking habits of individual patients. Unfortunately, even in this case, this data is only available in a minority of patients and therefore could not be analysed.

Finally, patients with short observation time were not excluded in order to consider a reasonable latency time between RT and onset of the second tumor. For example, in a

previous study, the analysis of second solid cancers was based only on 5-year survivors and analysis of leukemia were based only on 2-year survivors [25]. However, given the uncertainty about the latency times of second tumors occurrence, we decided to use a conservative criterion and therefore to include all primitive tumors diagnosed after RT.

In the past, even if the results are somehow contradictory [26] and the incidence of second tumors could also be attributed to age and lifestyles [6], several analyses showed an increased risk for second tumors after EBRT of PCa [3, 4, 5, 24]. Probably these data should be considered with caution. In fact, in previously cited studies [3, 4, 5, 24], the incidence of second tumors was evaluated by comparing PCa patients who underwent RT with subjects receiving other treatments, mainly represented by radical prostatectomy [RP]. In this regard, it should be noted that in different risk categories, RT and RP are considered as alternative therapeutic options. However, in daily clinical practice, the choice between the two treatments is often based on patient's comorbidities. In particular, RT is preferred to RP in case of contraindications to surgery. These contraindications [COPD, cardiovascular diseases, metabolic syndrome] are more frequent in smoking patients and these subjects are obviously more prone to smoke-related malignancies such as bladder or lung tumors.

Some studies evaluated also the impact of RT technique on the incidence of second tumors. In particular, three meta-analyses uniformly recorded a higher incidence of second rectal tumors after EBRT but not after brachytherapy [4, 5, 26]. In another study no differences were observed in terms of overall incidence of second tumors between 2D-conventional and 3D-CRT but only an advantage in patients undergoing 3D-CRT in terms of second rectal tumors. In the same analysis, no significant differences were observed based on beams photons energy [> 10 MV versus ≤ 10 MV] but a reduction in colon and leukaemia tumors in patients undergoing brachytherapy compared to those treated with external beams [25].

However, to the best of our knowledge, our study is the first analysis comparing 3D-CRT vs IMRT/VMAT techniques and evaluating also the impact of PNI and ADT. Furthermore, we considered the incidence of second tumors in different body regions [pelvis, pelvis or abdomen, and all together]. The results of our analysis based on clinical data are in agreement with several dosimetric and planning studies predicting a higher incidence of bladder and/or rectal second cancers in patients treated with modulated techniques [15, 16, 17, 18].

More generally, our study showed a 14.4% 10-year incidence of second tumors. Considering the favourable prognosis related to PCa [10-year OS: 87.3% in our series], this result should stimulate attention during the follow-up of patients not only to eventual PCa relapse but also to the risk of second tumors. In particular, haematuria or rectal bleeding should not be automatically considered as late RT induced toxicity but should also lead to further investigations on the possibility of bladder or rectal cancer, respectively.

Given the increased risk of radiation induced second tumors in PCa patients receiving RT, this possibility should be discussed with patients before treatment [3]. Based on our analysis, not showing a significant increase in the overall incidence of second cancers, further explanations about the potential additional risk from modulated RT techniques seem not required.

However, further analysis with prolonged follow-up, possibly on larger patients' population and considering other risk factors such as smoking habits, should be performed to confirm our findings.

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Table 1: Number and crude percentages of detected second tumors

Incidence of second tumors	**Technique**			
	3D-CRT	**IMRT**	**VMAT**	**Total**
	538 [%]	**1719 [%]**	**269 [%]**	**2526 [%]**
No	515 [95.7]	1660 [96.6]	259 [96.3]	2434 [96.4]
Pelvis				
Bladder	8 [1.5]	19 [1.1]	4 [1.5]	31 [1.2]
Rectum	0 [0.0]	4 [0.2]	1 [0.4]	5 [0.2]
Sigma	0 [0.0]	2 [0.1]	0 [0.0]	2 [0.1]
Abdomen				
Colon	0 [0.0]	4 [0.2]	1 [0.4]	5 [0.2]
Stomach	0 [0.0]	4 [0.2]	1 [0.4]	5 [0.2]
Kidney	2 [0.4]	1 [0.1]	0 [0.0]	3 [0.1]
Pancreas	2 [0.4]	0 [0.0]	0 [0.0]	2 [0.1]
Small bowel [duodenal]	1 [0.2]	0 [0.0]	0 [0.0]	1 [0.0]
Small bowel [ileum]	0 [0.0]	1 [0.1]	0 [0.0]	1 [0.0]
Other sites				
Lung	4 [0.7]	6 [0.3]	2 [0.7]	12 [0.5]
Melanoma	1 [0.2]	7 [0.4]	0 [0.0]	8 [0.3]
Skin	0 [0.0]	6 [0.3]	0 [0.0]	6 [0.2]
Head and neck	2 [0.4]	2 [0.1]	0 [0.0]	4 [0.2]
Brain	0 [0.0]	3 [0.2]	0 [0.0]	3 [0.1]
Lymphoma	0 [0.0]	0 [0.0]	1 [0.4]	1 [0.0]
Leukaemia	1 [0.0]	0 [0.0]	0 [0.0]	1 [0.0]
Oesophagus	1 [0.2]	0 [0.0]	0 [0.0]	1 [0.0]
Lip	1 [0.2]	0 [0.0]	0 [0.0]	1 [0.0]

Legend: 3D-CRT: three-dimensional conformal radiotherapy; IMRT: Intensity modulated radiotherapy; VMAT: volumetric modulated radiotherapy

Table 2: Univariate analysis [10-year Second Tumor-Free Survival]

Variables		Number. of patients [%]	all sites STFS	p	pelvis STFS	p	pelvis/abdomen STFS	p
Radiotherapy technique	3D-CRT	538 [21.3]	85.8	.627	94.0	**.033**	92.2	.125
	IMRT/VMAT	1988 [78.7]	84.5		89.3		87.5	
Prophylactic nodal irradiation	No	1232 [48.8]	88.1	.770	94.4	.092	92.6	.064
	Yes	1294 [51.2]	84.9		90.6		89.1	
Androgen deprivation therapy	No	837 [33.1]	92.8	.999	93.1	.546	92.0	.345
	Yes	1689 [66.9]	83.8		91.9		89.9	
Age, years	≤ 66	688 [27.2]	85.3	.352	90.5	.981	89.6	.374
	> 66	1838 [72.8]	86.0		93.5		91.4	
Combination of radiotherapy technique and irradiated volumes	3D-CRT without PNI	326 [12.9]	91.0	.887	96.6	**.044**	95.3	.140
	IMRT/VMAT without PNI	906 [35.9]	78.9		89.9		87.8	
	3D-CRT with PNI	212 [8.4]	85.6		93.7		91.1	
	IMRT/VMAT with PNI	1082 [42.8]	86.6		87.6		86.3	

Legend: 3D-CRT: three-dimensional conformal radiotherapy; IMRT: Intensity modulated radiotherapy; PNI: prophylactic nodal irradiation; STFS: second tumor free survival; VMAT: volumetric modulated radiotherapy.

Table 3: Multivariate analysis on second tumor free survival

Variable	***value***	***pelvic***			***Pelvic-abdominal***		
		HR	***95%CI***	***p***	***HR***	***95%CI***	***p***
Radiotherapy technique	3D-CRT	Ref					
	IMRT/VMAT	2.42	1.07-5.47	**.034**			
Prophylactic nodal irradiation	No				Ref		
	Yes				1.63	0.95-2.79	.067
Combination of radiotherapy technique and irradiated volumes	3D-CRT without PNI	Ref			Ref		
	IMRT/VMAT without PNI	1.70	0.53-5.51	.375	1.66	0.64-4.29	.294
	3D-CRT with PNI	1.10	0.27-4.46	.892	1.73	0.61-4.92	.303
	IMRT/VMAT with PNI	3.24	1.09-9.65	**.035**	2.61	1.06-6.41	**.037**

Legend: 3D-CRT: three-dimensional conformal radiotherapy; IMRT: Intensity modulated radiotherapy; PNI: prophylactic nodal irradiation; VMAT: volumetric modulated radiotherapy

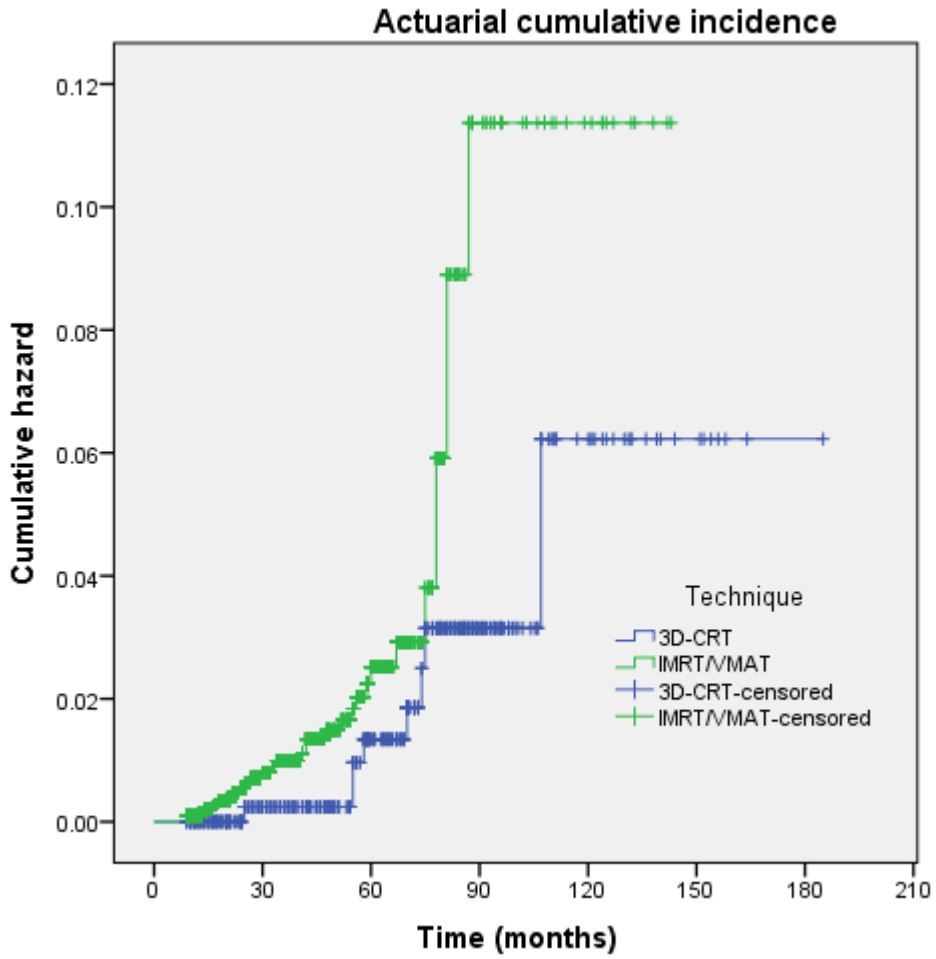

Figure 1: actuarial cumulative risk of pelvic second primary tumors after radiotherapy [3D-conformal therapy vs modulated techniques; *p: .033*]

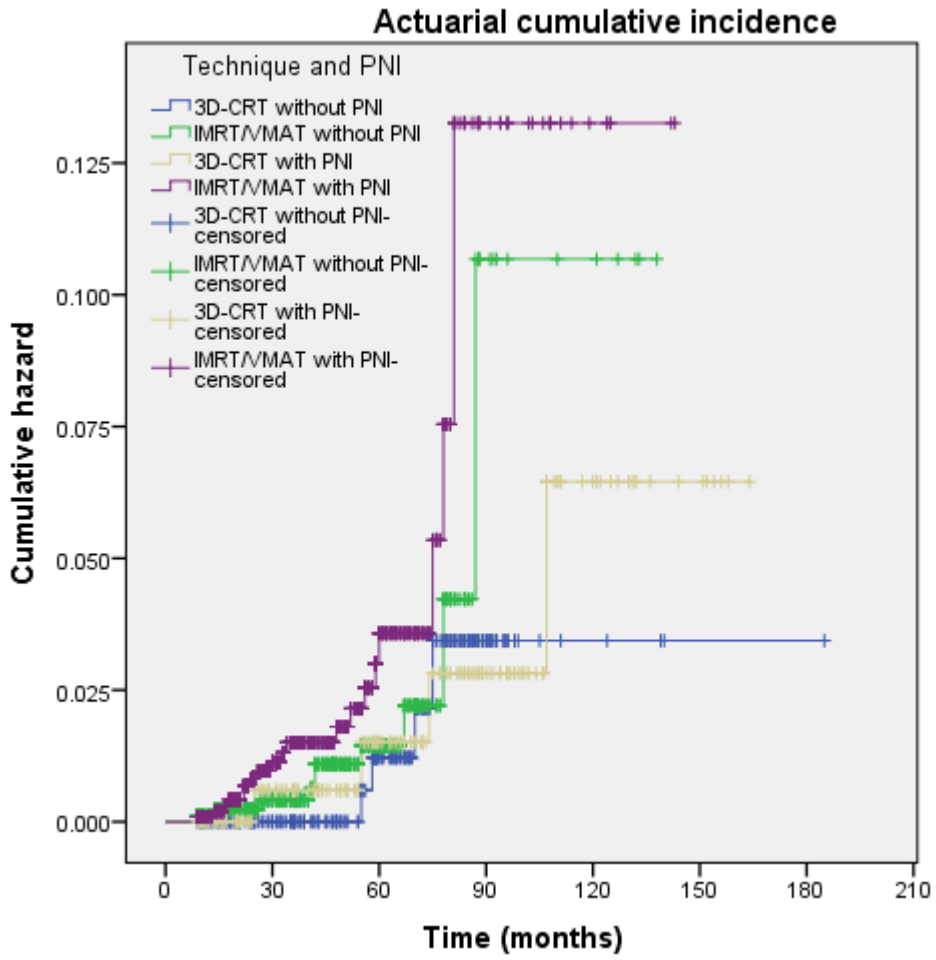

Figure 2: actuarial cumulative risk of pelvic second primary tumors after radiotherapy [3D-conformal radiotherapy without prophylactic nodal irradiation versus 3D-conformal radiotherapy with prophylactic nodal irradiation versus modulated radiotherapy techniques without prophylactic nodal irradiation versus modulated radiotherapy techniques with prophylactic nodal irradiation; *p: .044*]

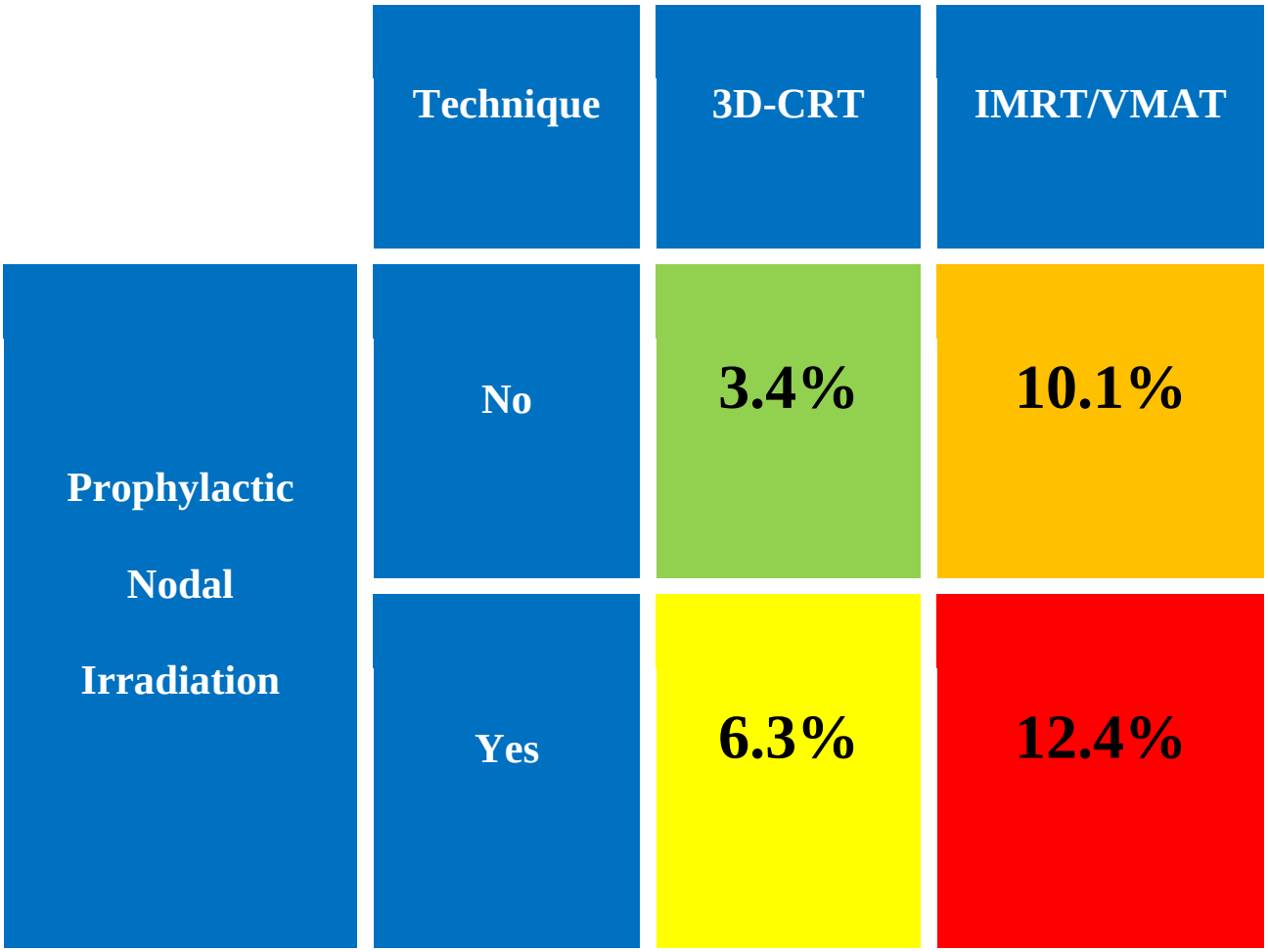

Figure 3: Risk stratification [5-year incidence of second pelvic tumors]

CHAPTER 5

RADIOTHERAPY OF PROSTATE CARCINOMA: A COMPARISON OF THE PREDICTIVE ROLE OF EAU VERSUS NCCN RISK STRATIFICATION SYSTEMS

ABSTRACT

Introduction

One of the simplest way to predict prognosis in radiotherapy [RT] treated prostate cancer [PCa] is represented by risk stratifications systems. The two best known and frequently used risk classification systems are the NCCN and EAU. 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 on different clinical outcomes, of NCCN and EAU risk stratification systems in three different RT settings: exclusive, adjuvant and salvage RT.

Material and methods

Data from a multicentre observational study [311/2019/Oss/AOUBo, ICAROS-1 study] were used. 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 overall survival [OS]. Survival estimates were calculated by the Kaplan-Meier product-limit method and compared with the log-rank test. In order to compare two homogeneous systems, both based on three risk categories, we grouped 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 grouped patients with high risk and with locally advanced disease.

Results

In this analysis, we included 1909 patients [1174, 381, 454] treated with exclusive, adjuvant and salvage RT, respectively. Both systems accurately predicted bRFS in patients treated with exclusive RT [$p < 0.001$]. In the same patients' group, only the NCCN system was significantly correlated with local control [p: 0.023]. Both systems

failed to predict RC and OS, while both were significantly correlated with MFS and DFS, with lower p values using the NCCN classification. In patients treated in the adjuvant setting, both systems failed to significantly predict bRFS and all clinical outcomes. In the salvage setting, only the NCCN system was able to significantly predict bRFS [p: 0.002], MFS [p: 0.002], and DFS [p: 0.006].

Conclusions

This analysis confirms the efficacy of both risk stratification systems in exclusive RT setting. Moreover, our analysis seems to suggest the utility also in the salvage setting but not in the adjuvant one. Therefore, further studies aimed at defining new risk categorization systems in post-operative adjuvant setting are needed.

INTRODUCTION

In 2018 prostate cancer [PCa] was the second most frequent cancer and the fifth cause of cancer death always in males worldwide [1]. In non-metastatic PCa, radiotherapy is a treatment option in the different settings of exclusive, adjuvant or salvage therapy [2].

Predictive models are used in this neoplasm 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 more used way to predict prognosis in radiotherapy treated PCa is represented by risk stratifications systems [3]. Typically, these systems stratify patients in three to five categories, from very low or low risk up to high or very high risk [3]. The two commonly and frequently used risk classification systems are the National Comprehensive Cancer Network [NCCN] and European Association of Urology [EAU] [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 on different clinical outcomes, of these two risk stratification systems in three different radiotherapy settings: exclusive, adjuvant and salvage.

MATERIAL AND METHODS

Study design

For the purposes of this analysis, we retrospectively evaluated the data of patients enrolled in a multicentre observational study.

End points

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 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 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 have combined the high-risk patients with locally advanced disease.

The attribution to the different risk categories in both systems was performed considering the clinical tumor stage and clinical nodal stage in patients subjected to exclusive radiotherapy. Instead, in the operated patients [adjuvant and salvage settings] the pathological stage was used [both for the tumor and for the lymph nodes].

In all treatment settings, the PSA value was considered before treatment [radiotherapy or surgery]. Finally, the Gleason score assessed by biopsy was obviously considered in patients treated with exclusive radiotherapy, while in patients undergoing radical prostatectomy, the Gleason score obtained by the surgical specimen was used.

Ethical issues

This study was approved by the local institutional review board [311/2019/Oss/AOUBo, ICAROS-1 study]. In the analysis were included only patients who had provided a written informed consent to the scientific use of their data.

RESULTS

Patients' characteristics

In this analysis we included 1909 patients [1174, 381, 454] treated with exclusive, adjuvant and salvage radiotherapy, respectively. In these three settings median age was 74 years, 66 years, 68 years, respectively. Median PSA at diagnosis was 7.9 ng/mL, 7.9 ng/mL, and 10.4 ng/mL, respectively. Median total RT doses to the prostate were 70 Gy, 66 Gy, and 70 Gy, respectively. The percentage of patients receiving adjuvant ADT was 74.5%, 63.3%, and 64.1%, respectively. Prophylactic nodal 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 1**.

Comparison between risk stratification systems

Both systems accurately predicted the bRFS [p< 0.001] in patients treated with exclusive radiotherapy [**Table 2, Figures 1a** and **1b**]. In the same patients' group, only the NCCN system was significantly correlated with LC [p: 0.023]. Both systems failed to predict RC and OS, while both were significantly correlated with MFS and DFS, with lower p values using the NCCN classification [**Table 2**].

In patients treated with RT in the adjuvant setting, both systems failed to significantly predict bRFS [**Figures 2a** and **2b**] and all clinical outcomes [**Table 2**].

In the salvage radiotherapy setting, only the NCCN system was able to predict the bRFS [p: 0.002], [**Figures 3a, 3b**], MFS [p: 0.002], and DFS [p: 0.006] [**Table 2**].

DISCUSSION

We used a large patient population to evaluate the predictive impact of the two most common systems of risk stratification in PCa. The analysis in the group of patients treated with exclusive 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. Similar reasons, but with no apparent advantage nor significant correlation for the EAU system has been recorded in both the adjuvant and salvage settings.

Our study has several limitations. First in both systems the categories were simplified in only three groups. Secondly, these categories were adopted in operated patients replacing the clinical stage with pathological stage, while the Gleason score was based on surgical specimen biopsies. Moreover, the three groups [exclusive, adjuvant and salvage] included different numbers of patients. Therefore, the lack of statistically significant results, particularly in the smaller group [adjuvant], could be a consequence of the small samples size. Finally, our study evaluated risk stratification systems that actually group patients in categories. This modality is theoretically associated to reduced predictive accuracy due to the inclusion of patients in broad categories. On the contrary, individual risk estimation systems based on predictive models may allow to calculate the continues probability of a specific clinical outcome [3].

In the systematic review of Raymond and colleagues published in 2017, 66 predictive models for PCa patients treated with RT 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% included variables which are not part of typical registry data sets and are therefore difficult to validate [7].

Considering that we simplified the two risk stratification systems, we can observe [supplementary **Tables 1** and **2**] that the only difference between the two systems, in our analysis, is related to the classification of T2c tumors. In fact, this has been classified as high risk and intermediate risk in EAU and NCCN systems, respectively. The better predictive performance of the NCCN system in exclusive patients suggests that, in patients treated with RT alone the neoplastic invasion of both prostatic lobes has a limited impact. On the contrary, this tumor extension seems to be more important in the salvage setting.

In conclusion, from the clinical point of view this analysis confirms the efficacy of both risk stratification systems in exclusive radiotherapy setting. Moreover, our analysis seems to suggest the

efficiency of the NCCN system also in the salvage setting but not in the adjuvant one. Further studies aimed to define risk categories in post-operative setting are therefore useful.

Hopefully in the future, a more accurate and personalized individual risk evaluation and estimation new tools based on the available knowledge of these neoplasms in terms of bio molecular, genetic, radiomic, and radiogenomic characteristics will be developed [8].

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Table 1: patients characteristics

Variable	Value	Exclusive	Adjuvant	Salvage
		No of patients [%]	**No of patients [%]**	**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-, very high risk	691 [64.3]	372 [97.6]	405[89.2]

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

Table 4: predictive role of EAU and NCCN risk stratification systems

Variable	Value	Number of patients [%]	bRFS [%]	P	LC [%]	P	RC [%]	P	MFS [%]	P	DFS [%]	p	OS [%]	P
Exclusive radiotherapy														
NCCN risk category simplified*	Very low-, low risk	123 [11.5]	95.4	**.000**	97.7	**0.023**	100.0	.240	98.7	**.000**	96.4	**.000**	97.4	.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 simplified §	Very low-, low risk	123 [11.5]	95.4	**.000**	97.7	0.145	100.0	.136	98.7	**.003**	96.4	**.006**	97.4	.326
	Intermediate risk	260 [24.2]	93.9		97.0		96.1		97.1		94.2		91.4	
	High-, very high risk	691 [64.3]	82.9		93.3		97.5		92.1		87.2		91.3	
Adjuvant radiotherapy														
NCCN risk category simplified*	Very low- low	1 [0.3]	100.0	.896	100.0	.974	100.0	.590	100.0	.574	100.0	.926	100.0	0.555
	Intermediate	42 [11.0]	92.7		96.9		95.7		100.0		92.7		100.0	
	High- very high	338 [88.7]	88.8		96.3		98.8		96.9		92.2		95.7	
EAU risk category simplified §	Very low-, low risk	1 [0.3]	100.0	.848	100.0	.906	100.0	.958	100.0	.898	100.0	.762	100.0	0.893
	Intermediate risk	8 [2.1]	100.0		100.0		100.0		100.0		100.0		100.0	
	High-, very high risk	372 [97.6]	89.0		96.4		98.5		97.1		92.1		96.1	
Salvage radiotherapy														
NCCN risk category simplified*	Very low-, low risk	11 [2.4]	100.0	**.002**	100.0	.644	100.0	.279	100.0	**.002**	100.0	**.006**	100.0	.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 simplified §	Very low-, low risk	11 [2.4]	100.0	.150	100.0	.742	100.0	.533	100.0	.326	100.0	.243	100.0	.435
	Intermediate risk	38 [8.4]	59.1		87.5		89.5		88.0		59.1		96.0	
	High-, very high risk	405 [89.2]	47.4		91.7		86.1		83.1		59.6		92.3	

Legend: bRFS: biochemical relapse free survival; EAU : European Association of Urologists; DFS: Disease free survival; LC : local control; MFS: Metastases free survival; NCCN: National Comprehensive Cancer Network; OS: Overall survival; RC: regional control.

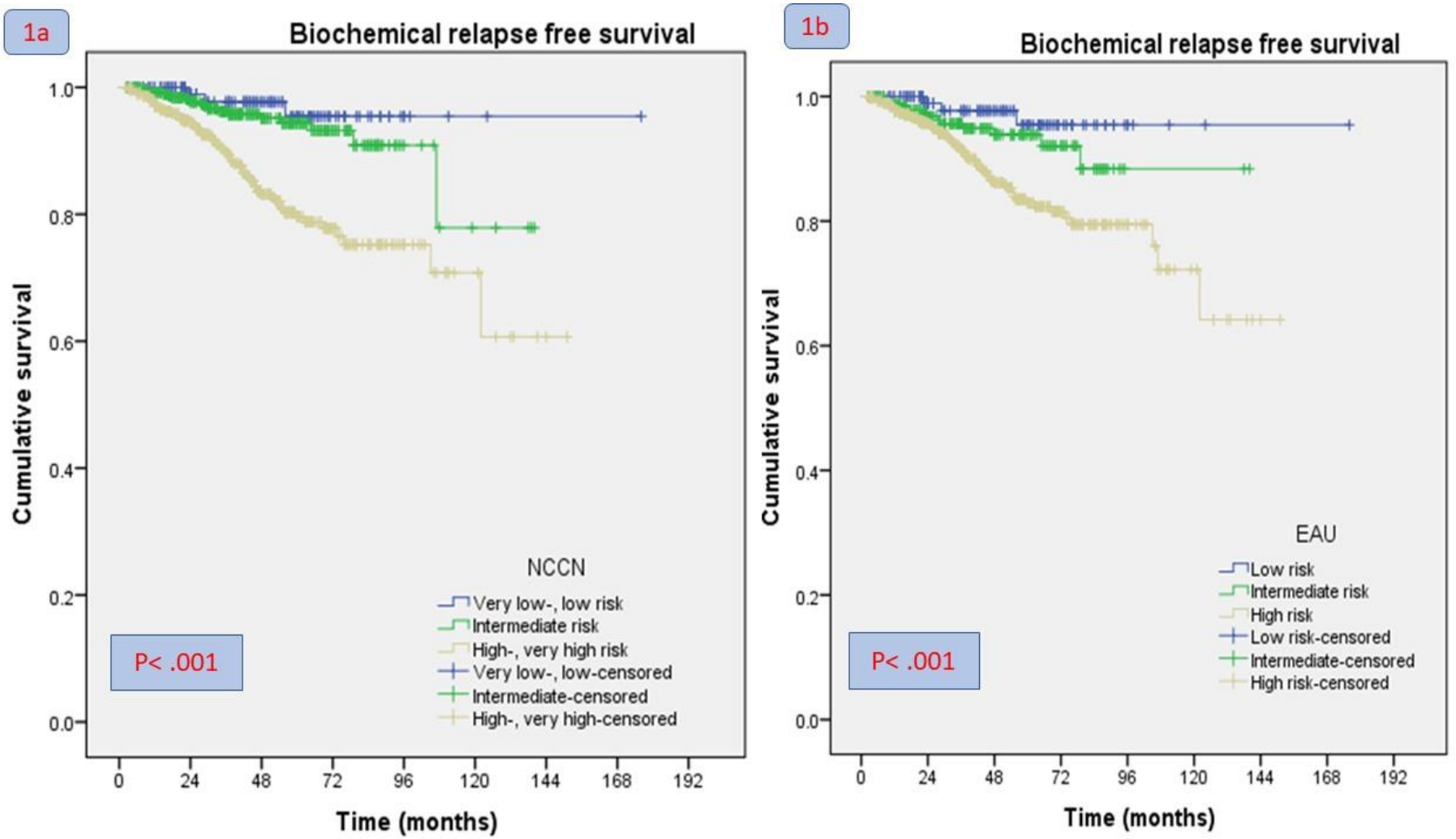

Figure 1: comparison of biochemical Relapse-Free Survival between risk categories [Figure 1a: NCCN; Figure 1b: EAU] in patients treated with exclusive radiotherapy.

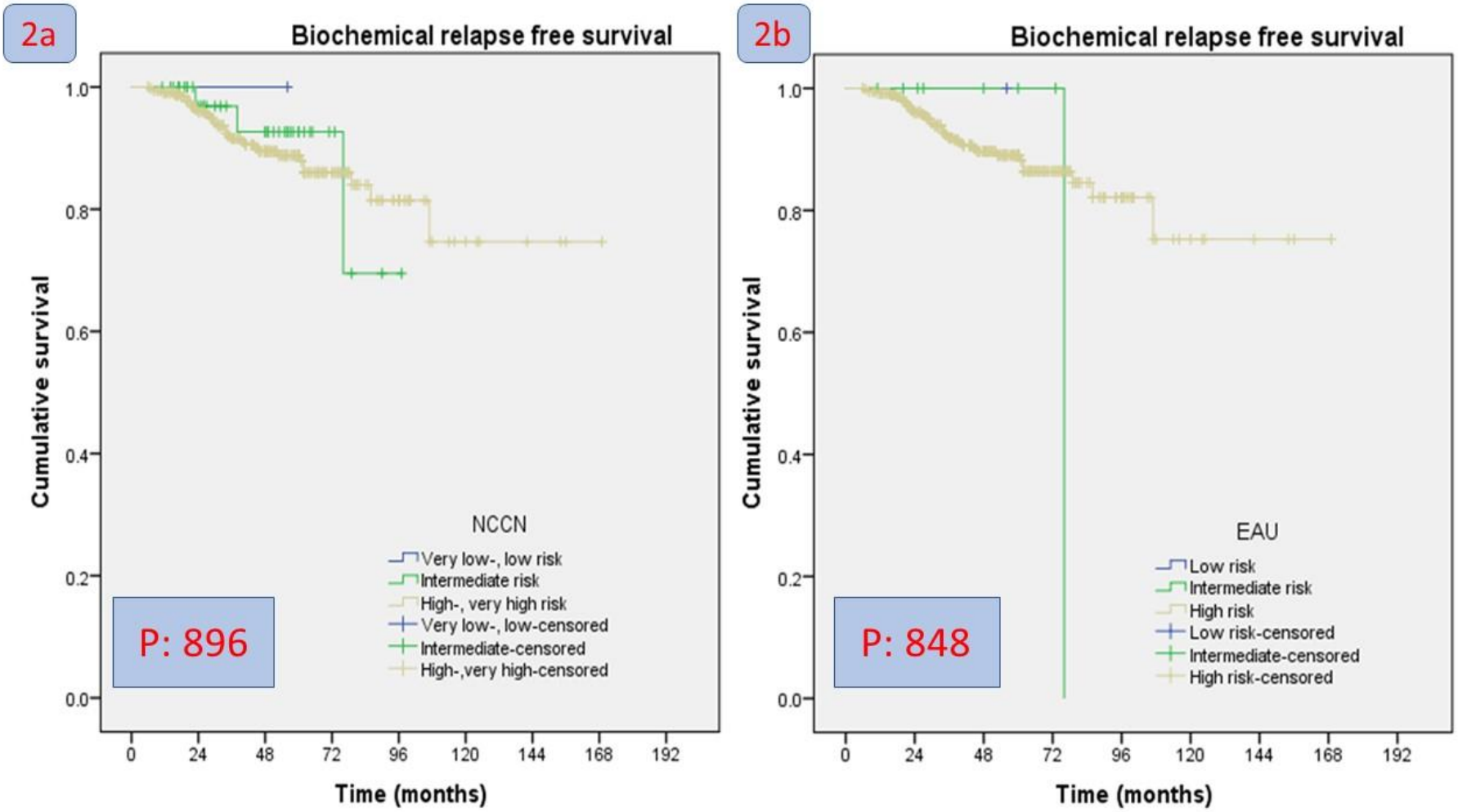

Figure 2: comparison of biochemical Relapse-Free Survival between risk categories [Figure 1a: NCCN; Figure 1b: EAU] in patients treated with adjuvant radiotherapy.

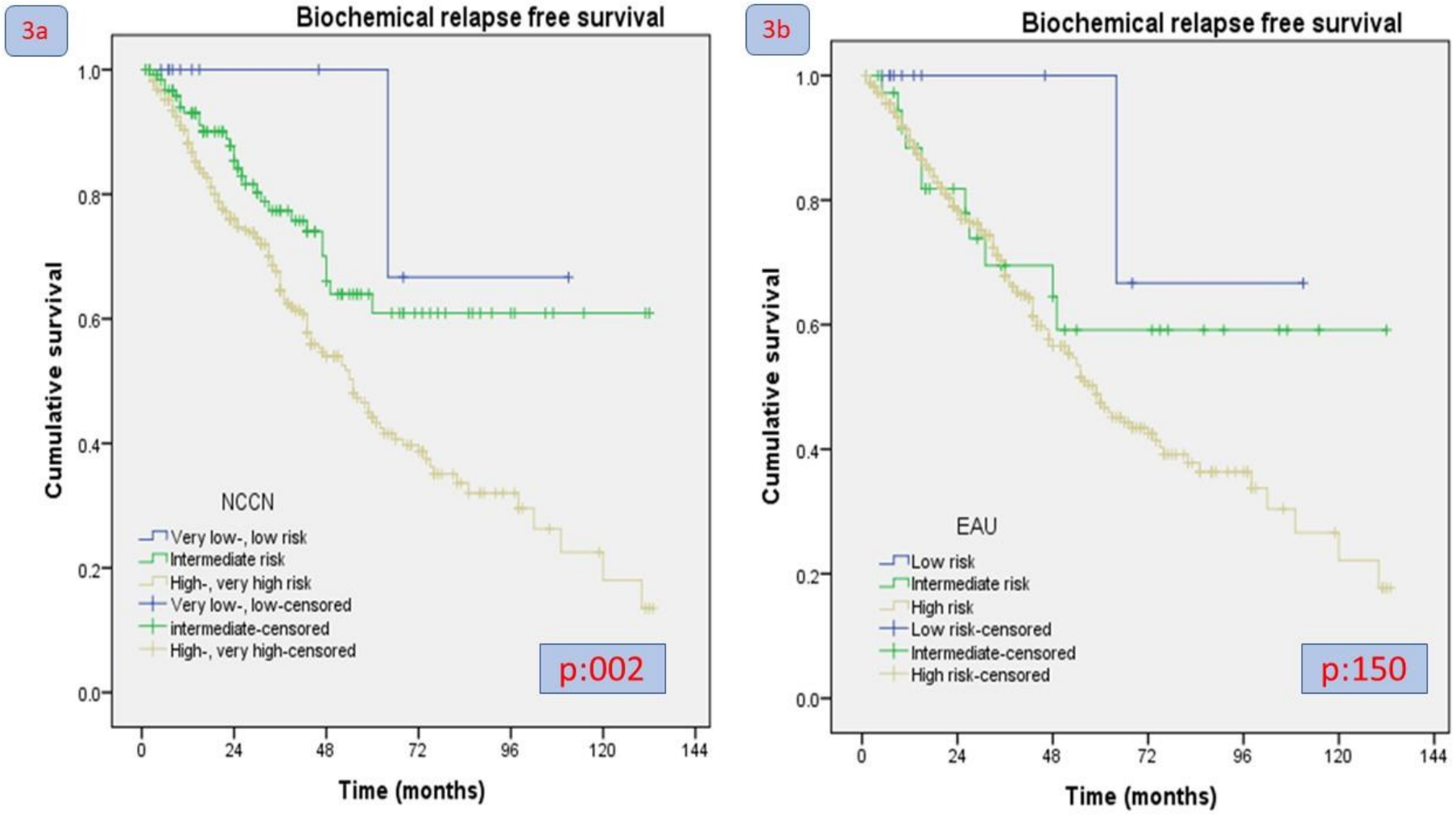

Figure 3: comparison of biochemical Relapse-Free Survival between risk categories [Figure 1a: NCCN; Figure 1b: EAU] in patients treated with salvage radiotherapy.

Supplementary Table 1: NCCN risk groups definitions

Risk Group	Clinical/Pathologic Features
Very low	All of the following: • T1c • Gleason score ≤6/grade group 1 • PSA <10ng/mL • <3 prostate biopsy fragments/ cores positive, ≤50% cancer in each fragment/core • PSA density <0.15 ng/mL/g
Low	All of the following: • T1-T2a • Gleason score ≤6/grade group 1 • PSA <10ng/mL
Intermediate-favorable	Any of the following: • T2b-T2c • Gleason score 3+4=7/grade group 2 • PSA 10-20 ng/mL PLUS percentage of positive biopsy cores <50%
Intermediate-unfavorable	Any of the following: • T2b-T2c • Gleason score 3+4=7/grade group 2 or Gleason score 4+3=7/grade group 3 • PSA 10-20 ng/mL
High	Any of the following: • T3a • Gleason score 8/grade group 4 or Gleason score 4+5=9/grade group 5 • PSA >20 ng/mL
Very high	Any of the following: • T3b-T4 • Primary Gleason pattern 5 • >4 cores with Gleason core 8-10/ grade group 4 or 5
Regional	Any T, N1, M0
Metastatic	Any T, any N, M1

Supplementary Table 2: EAU risk groups definitions

Risk group	Clinical / Pathologic Feature
Low risk	PAS <10 ng/mL and GS<7 [ISUP grade 1] and cT1-2a
Intermediate risk	PSA 10-20 ng/mL or GS 7 [ISUP grade 2/3] or cT2b
High risk Localized	PSA>20 ng/mL or GS>7 [ISUP grade 4/5] or cT2c
High risk Locally advanced	Any PSA Any GS [any ISUP grade] cT3-4 or cN+

CONCLUSIONS

The systematic analyses of large patients series treated in three different settings [curative, adjuvant, and salvage RT] allowed the identification of several unpredicted correlations, potentially useful to generate new hypotheses. This results justifies further analysis of large patients series with PCa cancer treated with RT, possibly performed with more advanced methods of statistical analysis [**Chapters 1-3**].

The incidence of second malignancies was relatively high in our large analyzed series. This risk should be considered during the follow-up. Moreover, the incidence of second pelvic-abdominal tumors after RT of PCa showed a significant correlation with treatment technique being higher in patients treated with modulated RT [IMRT, VMAT] and with prophylactic nodal irradiation. Further analyses in larger series with prolonged follow-up are needed to confirm these results [**Chapter 4**].

Finally, we compared two risk stratification systems [NCCN and EAU] in terms of prediction of biochemical and clinical outcomes [**Chapter 5**]. This analysis confirmed the efficacy of both risk stratification systems in the curative RT setting. Moreover, our analysis seems to suggest the utility also in the salvage setting but not in the adjuvant one. Therefore, further studies aimed at defining new risk categorization systems for patients treated with postoperative-adjuvant RT are needed.