ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

DOTTORATO DI RICERCA IN

ONCOLOGIA, EMATOLOGIA E PATOLOGIA

Ciclo 36

Settore Concorsuale: 06/I1 - DIAGNOSTICA PER IMMAGINI, RADIOTERAPIA E NEURORADIOLOGIA

Settore Scientifico Disciplinare: MED/36 - DIAGNOSTICA PER IMMAGINI E RADIOTERAPIA

PROSTATE CANCER: EVALUATION OF OUTCOMES AND PROGNOSTIC FACTORS IN ADJUVANT AND SALVAGE RADIATION TREATMENT

Presentata da: Annalisa Cortesi

Coordinatore Dottorato

Manuela Ferracin

Supervisore

Giovanni Luca Paolo Frassineti

Co-supervisore

Alessio Giuseppe Morganti

Esame finale anno 2024

Introduction

Prostate cancer is currently the most frequent neoplasm in male population and represents approximately 21% of all tumors in men.
Radiotherapy (RT) represents an important treatment option for prostate cancer in different settings: exclusive RT (with radical intent), adjuvant RT after surgery, salvage RT in case of biochemical disease recurrence and palliative RT.
There are still a series of unclear aspects about RT: the current scientific literature presents a lack of randomized studies with large series comparing different radiation treatment techniques, such as 3D radiotherapy, IMRT (Intensity Modulated Radiotherapy), VMAT (Volumetric Modulated Arc Therapy) and stereotaxis. Furthermore, there are few studies analyzing the different available therapeutic options, such as surgery, radiotherapy and combination of radiotherapy and hormone therapy. The lack of specific data makes it difficult to establish which treatment is most effective and appropriate for individual patients. Even the assessments necessary for the indication of personalized radiation treatment, such as margins, lymph node irradiation and fractionation, are also unclear and there are doubts about which is the optimal approach to adopt in different clinical contexts.

The aim of the doctoral project was to analyze the impact of different parameters relating to the treatment methods on outcome and toxicity in different settings, thanks to the creation of a large multicenter database, which takes into consideration genetic, clinical and radiological aspects.

The first analysis performed was about patients who underwent postoperative adjuvant RT, to assess the impact of age and other patient and treatment characteristics on both acute and late gastrointestinal (GI) and genitourinary (GU) toxicity. The recorded and evaluated patients-related characteristics were age and Charlson's comorbidity index. 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, RT fractionation and technique (including type of image-guidance systems), and Equivalent Dose in 2 Gy/fraction (EQD2) to the prostate bed and pelvic lymph nodes. Late toxicity-free survival curves 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. Acute toxicity was assessed by RTOG scale while late toxicity was evaluated with the RTOG/EORTC scale. Three-hundred-eighty-one patients were enrolled in this analysis, with a media age of 65 years. Acute GI and GU G3 toxicity rates were 0.5% and 1.3%, respectively. Median EQD2 to the prostate bed ($\alpha/\beta=1.5$) was 71.4 Gy. Most patients (75.4%) were treated with IMRT/VMAT techniques. No patient

showed G>3 acute toxicity. At multivariable logistic regression only younger age (< 65 years) was significantly correlated with increased acute toxicity (both GI and GU). Five-year GI and GU grade ≥ 3 late toxicity-free survival was 98.1% and 94.5%, respectively. The only significant correlation at Cox's regression model was in terms of reduced risk of GI toxicity in patients undergoing hypofractionation (HR: 0.38; 95%CI: 0.18- 0.78; p: 0.008). In conclusion, "modern" postoperative radiotherapy is safe, both in terms of acute and late effects, also in subjects undergoing hypofractionated regimens and especially in elderly patients.

Subsequently a second analysis was carried out, concerning effectiveness and outcomes of salvage radiation treatment in patients who have shown biochemical evidence of recurrent disease after radical prostatectomy. Several factors need to be considered when determining the appropriateness of salvage radiation treatment, including the PSA level at recurrence, the time to recurrence, the presence of local or distant metastases, and the patient's overall health status. It is crucial to evaluate these factors to determine the potential benefits and risks associated with salvage radiation treatment. 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. Another objective of the study was to evaluate the impact of prophylactic pelvic lymph node irradiation on outcomes and toxicity. A total of 454 patients were included in this analysis. The multivariate analysis found several factors that influenced the outcomes of patient. These factors included the nodal stage, Gleason score, prophylactic nodal irradiation, hypofractionated regimens, use of IMRT/VMAT techniques, receipt of adjuvant ADT and use of cone-beam CT. Different factors were associated with different outcomes, such as better biochemical recurrence-free survival (bRFS), local control (LC), distant metastasis-free survival (MFS), disease-free survival (DFS), and overall survival (OS). Based on these findings, a prognostic model was developed that categorized patients into four risk groups based on their Gleason score, nodal stage, and nodal irradiation status. This model can help predict the 5-year bRFS for patients in each risk group. The risk categories were defined as low-risk, intermediate risk, high risk, and very high risk.

Adjuvant radiotherapy in prostate cancer: impact of older age and hypofractionated regimens on acute and late toxicity.

A multicenter comprehensive analysis

Abstract

Background: The objective of this study was to assess the impact of age and other patient and treatment characteristics on toxicity in prostate cancer patients receiving adjuvant radiotherapy (RT).

Materials and methods: This observational study (ICAROS-1) evaluated both acute (RTOG) and late (RTOG/EORTC) toxicity. Patient- (age; Charlson's comorbidity index) and treatment-related characteristics (nodal irradiation; previous TURP; use, type, and duration of ADT, RT fractionation and technique, image-guidance systems, EQD2 delivered to the prostate bed and pelvic nodes) were recorded and analyzed.

Results: A total of 381 patients were enrolled. The median EQD2 to the prostate bed (a/b=1.5) was 71.4 Gy. The majority of patients (75.4%) were treated with intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT). Acute G3 gastrointestinal (GI) and genitourinary (GU) toxicity rates were 0.5% and 1.3%, respectively. No patients experienced >G3 acute toxicity. The multivariable analysis of acute toxicity (binomial logistic regression) showed a statistically significant association between older age (> 65) and decreased odds of G≥2 GI acute toxicity (OR: 0.569; 95%CI: 0.329-0.973; p: 0.040) and decreased odds of G≥2 GU acute toxicity (OR: 0.956; 95%CI: 0.918- 0.996; p: 0.031). The 5-year late toxicity-free survival rates for G≥3 GI and GU toxicity were 98.1% and 94.5%, respectively. The only significant correlation found (Cox's regression model) was a reduced risk of late GI toxicity in patients undergoing hypofractionation (HR: 0.38; 95% CI: 0.18-0.78; p: 0.008).

Conclusions: The unexpected results of this analysis could be explained by a "response shift bias" concerning the protective effect of older age and by treatment in later periods (using IMRT/VMAT) concerning the favorable effect of hypofractionation. However, overall, the study suggests that age should not be a reason to avoid adjuvant RT and that the latter is well-tolerated even with moderately hypofractionated regimens.

Introduction

Prostate cancer (PCa) is a significant health concern, ranking second in terms of incidence and fifth in terms of mortality among male populations (1). Radical prostatectomy (RP) is a commonly employed treatment option for PCa. However, the five-year biochemical relapse-free survival (bRFS) rate after RP is approximately 50% of patients with high-risk features at pathological evaluation (2–4). Postoperative radiotherapy (RT) has been investigated as an adjunctive treatment following RP, and the results of four randomized studies (2–5) have demonstrated improved bRFS rates (around 25% at five years) compared to RP alone. Moreover, one of these studies has shown a significantly reduced risk of metastasis and improved overall survival (OS) with postoperative RT (6). Consequently, international guidelines, such as those from the European Association of Urology1 (EAU 2022) and the National Comprehensive Cancer Network2 (NCCN 2022), recommend postoperative RT as an adjuvant therapy for selected PCa patients. Specifically, EAU guidelines recommend adjuvant RT for high-risk patients (pN0) with at least two of the following high-risk features: International Society of Urological Pathology (ISUP) grade group 4–5, pT3 stage, and positive surgical margins. Nevertheless, recent randomized trials (7–9) and a meta analysis (10) have demonstrated that early salvage RT can achieve biochemical and clinical outcomes comparable to those of adjuvant RT, while significantly reducing the number of patients requiring pelvic RT and improving overall treatment tolerability. These findings highlight the importance of careful patient selection for adjuvant RT, considering the cost/benefit ratio. In this regard, it is crucial to consider both factors that predict greater benefit from adjuvant RT, such as seminal vesicle involvement (11) and positive surgical margins (12) as well as factors that indicate a higher risk of side effects. However, the available evidence on the latter topic is limited and often derived from small studies that have analyzed only specific patient and/or treatment characteristics (13–17). Therefore, the aim of this study is to analyze multiple patient and treatment-related factors in a large multicenter series of PCa patients who underwent adjuvant RT, with the goal of identifying predictors of increased toxicity, and in particular to evaluate whether older age is associated with a greater risk of radiation-induced side effects.

Material and methods

Study design and endpoints

This sub-analysis is part of a multicenter observational study (311/2019/Oss/AOUBo, ICAROS-1 study) focusing specifically on patients with PCa who underwent postoperative adjuvant RT. The study endpoints encompass both acute and late gastrointestinal (GI) and genitourinary (GU) toxicities.

Inclusion criteria

The inclusion criteria were as follows: 1) patients diagnosed with PCa who underwent RP with negative or microscopically positive margins (R0-1) and no distant metastases, and 2) RT delivered using external beam techniques with photon beams. Exclusion criteria were: 1) presence of macroscopic (R2) residual disease after RP, 2) postoperative PSA level exceeding 0.2 ng/ml, and 3) postoperative RT delivered more than one year after RP.

Evaluated parameters

The recorded and evaluated patient-related characteristics included age and Charlson's comorbidity index. Age was analyzed both as a continuous variable and as a dichotomous variable using a cut-off at the median value. The analyzed treatment characteristics encompassed the delivery of prophylactic lymph node irradiation (PNI), previous transurethral resection of the prostate (TURP), use and type of adjuvant androgen deprivation therapy (ADT) (LH-RH analogues or high-dose bicalutamide) and its duration, RT fractionation and technique (including the type of image-guidance systems employed), as well as the Equivalent Dose in 2 Gy per fraction (EQD2) delivered to the prostate bed and pelvic lymph nodes. Acute toxicity was monitored with weekly visits during treatment and with a follow-up visit 2 months after the end of treatment. Late toxicity was evaluated with a first follow-up visit 6 months after the end of treatment and then with further visits every 6 months up to 24 months after treatment, followed by annual assessments up to 10 years. Gastrointestinal toxicity was evaluated by patient interviews and proctoscopy, if necessary. Genitourinary toxicity was assessed through patient interviews and urine analysis during follow-up.

Statistical analysis

Statistical computations were performed using IBM SPSS Version 22.0 software package (IBM Corp, Armonk, NY, USA). A p-value less than 0.05 was considered statistically significant. Acute toxicity was evaluated using the RTOG scale, while late toxicity was assessed using the RTOG/EORTC scale (18). The chi-squared test with Yates' continuity correction and Fisher's exact test were employed in univariate logistic regression to examine the correlation between the analyzed variables and acute toxicity. Additionally, a binomial logistic stepwise regression was used to estimate the likelihood of acute toxicity based on the aforementioned variables. Late toxicity-free survival estimates were calculated using the Kaplan-Meier product-limit method (19) and compared using the log-rank test (20). Variables with a p-value less than 0.05 or showing a trend ($p < 0.1$) in the univariate analysis were included in a multivariate Cox regression model (21).

Results

Patients, tumors, and treatment characteristics

A total of 381 patients were included in this analysis, with a median age of 65 years (range: 43-79 years). Table 1 presents the patients, tumor, and treatment characteristics. The median delivered EQD2 to the prostate bed, calculated using a/b ratios of 1.5 Gy, 3 Gy, and 10 Gy, was 71.4 (range: 66.2-78.0), 68.7 (range: 67.0-78.0), and 68.2 (range: 65.1-78.0), respectively. Among the patients, 127 (33.3%) were treated with standard fractionation, while 254 (66.7%) received a hypofractionated regimen. EQD2a/ b=3 was significantly higher in patients treated with hypofractionated regimens compared to standard fractionation protocols (mean: 71.3 Gy versus 69.7 Gy; p<0.001). RT was delivered using either 3D-conformal RT (94 patients, 24.7%) or modulated techniques such as intensity modulated arc therapy (IMRT) or volumetric modulated arc therapy (VMAT) (287 patients, 75.3%). The dose to the prostatic bed ranged between 65 and 78 Gy (median: 66 Gy). Moreover, of 254 patients treated with hypofractionation, the dose per fraction was 2.2 Gy in 100 patients, 2.5 Gy in 142 patients, and 2.6 Gy in 12 patients. Furthermore, of 127 patients treated with standard fractionation, the dose per fraction was 1.8 Gy in 42 patients and 2 Gy in 85 patients. Additionally, out of 254 patients treated with hypofractionation, 239 (94.1%) were treated with IMRT/VMAT and 15 (5.9%) with 3D-CRT. Finally, out of 297 patients receiving nodal irradiation, 250 (84.2%) were treated with IMRT/VMAT, while 47 (15.8%) were treated with 3D-CRT. Daily on-line set-up corrections were performed using an electronic portal imaging device (351 patients, 92.1%) or an on-board cone-beam CT (30 patients, 7.9%), as previously described (22).

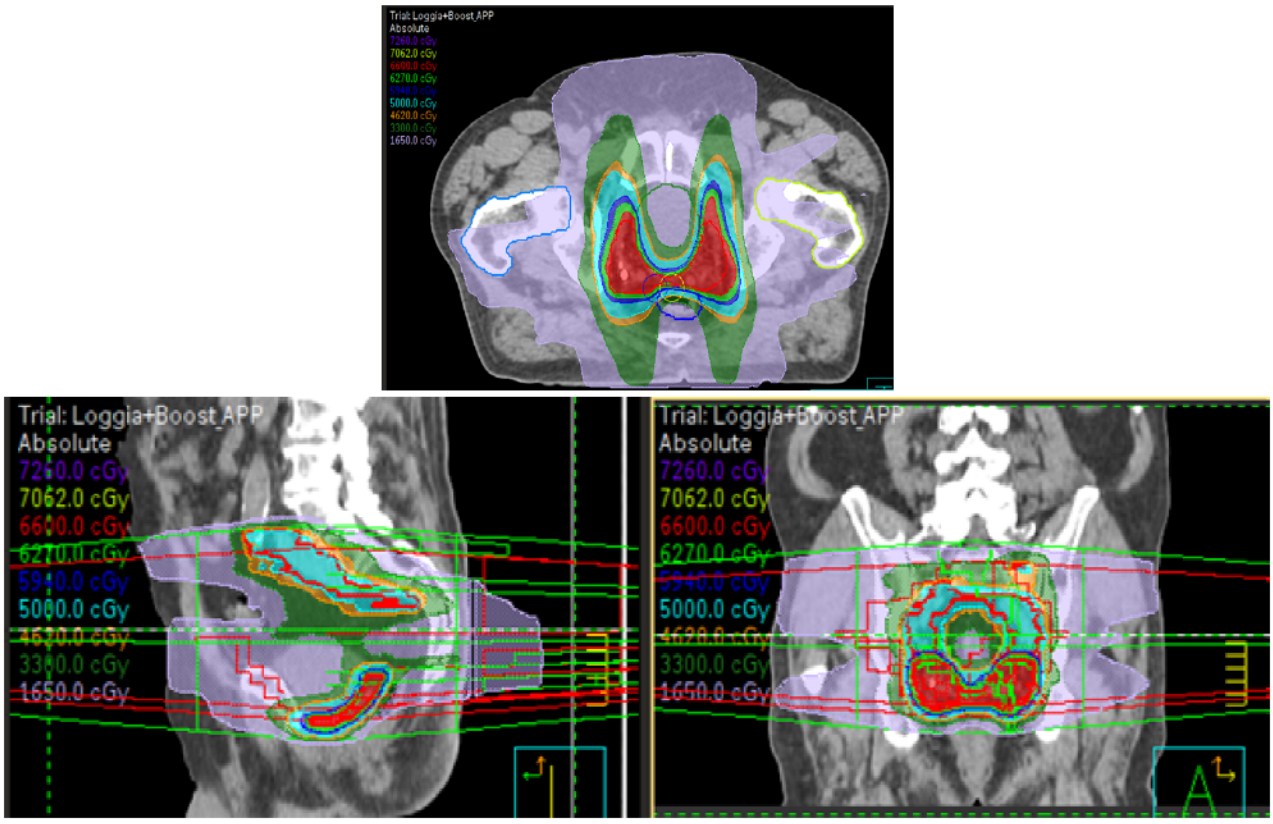


Fig. 1. Radiotherapy treatment plan. Volumetric Modulated Arc Therapy

Fig. 2. Dose distribution and DVH (dose-volume histogram).

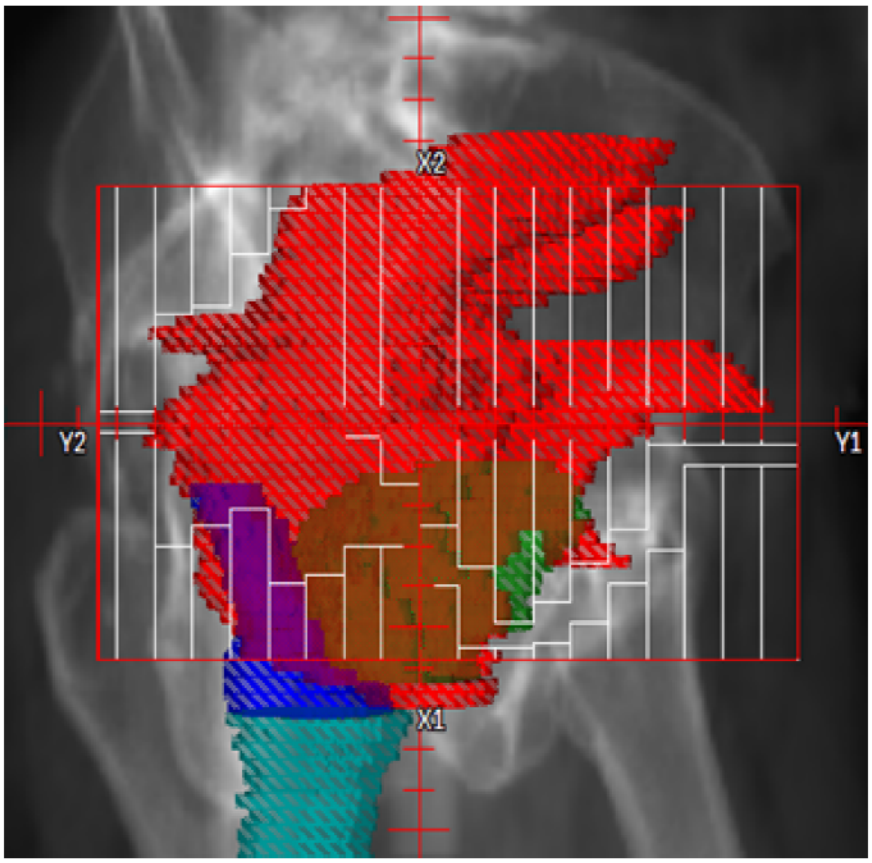


Fig. 3. 3D reconstruction of treatment plan: target (prostate bed and lymph nodes) and main organ at risk (bladder, rectum, anal canal).

Acute and late toxicity

Table 1 provides the results in terms of acute toxicity. None of the patients experienced acute toxicity greater than Grade 3, and the rates of Grade 3 gastrointestinal (GI) and genitourinary (GU) toxicity were 0.5% and 1.3%, respectively. The actuarial 5-year rates of Grade ≥ 2 GI and GU late toxicity-free survival were 90.4% and 83.5%, respectively. The actuarial 5-year rates of Grade ≥ 3 GI and GU late toxicity-free survival were 98.1% and 94.5%, respectively.

Table 1: Patients and treatment characteristics and results of univariate analysis on acute toxicity

		n° of pts (%)	Gastrointestinal				Genitourinary			
			Grade ≥ 2 (%)	χ (Fisher's exact test)	Univariate logistic regression		Grade ≥ 2 (%)	χ (Fisher's exact test)	Univariate logistic regression	
				p-value	OR	p-value		p-value	OR	p-value
Age	≤ 65	174 (45.7)	23.5	**0.032**	ref.		20.1	0.424	ref.	
	> 65	207 (54.3)	14.5		0.55	**0.024**	16.4		0.78	0.352
	CV	381 (100)			0.97	0.078			0.96	**0.044**
Charlson's comorbidity index	0	309 (81.1)	19.4	0.161	ref.		18.1	0.971	ref.	
	1	57 (15.0)	17.5		0.88	0.741	19.3		1.08	0.833
	2	13 (3.4)	0		0.00	0.982	15.4		0.82	0.802
	3	2 (0.5)	50.0		4.15	0.317	0		0.00	0.983
Age adjusted Charlson's comorbidity index	0	6 (1.6)	16.7	0.173	ref.		33.3	0.237	ref.	
	1	49 (12.9)	16.3		0.98	0.983	15.7		0.88	0.892
	2	178 (46.7)	24.7		1.64	0.655	16.8		0.37	0.268
	3	119 (31.2)	12.6		0.72	0.772	16.0		0.40	0.314
	4	25 (6.6)	12.0		0.68	0.761	0		0.38	0.346
	5	3 (0.8)	0		0.00	0.987	0		0.0	0.986
	6	1 (0.3)	0		0.00	0.992	0		0.0	0.992

PNI	No	84 (22)	13.1	0.187	ref.		10.7	0.053	ref.	
	Yes	297 (78)	20.2		1.68	0.143	20.2		2.11	0.050
Hypofractionation	No	127 (33.3)	15.7	0.376	ref.		15.7	0.480	ref.	
	Yes	254 (66.7)	20.1		1.34	0.307	19.3		1.28	0.398
Lymphadenectomy	No	94 (24.7)	21.3	0.288	ref.		19.1	0.706	ref.	
	< 15*	121 (31.8)	14.0		0.60	0.166	15.7		0.79	0.507
	≥ 15*	166 (43.8)	20.5		0.95	0.879	1.2		1.01	0.980
EQD_2 prostate bed α/β_{10} (Gy)	≤ 68.3	193 (50.7)	17.3	0.699	ref.		16.2	0.358	ref.	
	> 68.3	188 (49.3)	19.7		1.15	0.605	20.2		1.32	0.294
	CV	381 (100)			1.00	0.164			1.00	0.103
Radiotherapy Technique	3D-CRT	94 (24.7)	13.8	0.214	ref.		13.8	0.271	ref.	
	IMRT	273 (71.7)	20.9		1.64	0.136	20.1		1.57	0.177
	VMAT	14 (3.7)	7.1		0.48	0.496	7.1		0.48	0.496
Image guidance	EPID	351 (92.1)	18.8	1	ref.		18.8	0.480	ref.	
	CB-CT	30 (7.9)	16.7		0.86	0.773	10.0		0.48	0.239
ADT	No	127 (33.)	18.9	1	ref.		13.4	0.120	ref.	
	Yes	254 (66.7)	18.5		0.97	0.926	20.5		1.67	0.092
Type of ADT	None	127 (33.3)	18.9	0.381	ref.		13.4	0.108	ref.	
	LHRH	183 (48.0)	16.4		0.84	0.568	18.6		1.48	0.227
	HD-Bic	71 (18.6)	23.9		1.35	0.402	25.4		2.20	**0.036**

EQD_2 lymph nodes α/β_{10} (Gy)	≤ 44.3	280 (73.5)	18.2	0.839	ref.		16.4	0.204	ref.	
	> 44.3	101 (26.5)	19.8		1.11	0.725	22.8		1.5	0.158
	CV	381 (100)			1.00	0.126			1.0001	**0.035**

Legend: ADT: adjuvant deprivation therapy; CV: Continuous variable; PNI: prophylactic nodal irradiation

Univariate analysis

Univariate analysis revealed that acute Grade ≥ 3 GI and GU toxicity rates were not significantly correlated with any of the analyzed parameters. However, the delivery of PNI showed a trend for correlation with higher rates of Grade ≥ 2 acute GU toxicity (Table 1). The actuarial 5-year late Grade ≥ 2 GI toxicity was significantly lower in patients treated with hypofractionation (dose per fraction > 2 Gy compared to ≤ 2 Gy; 93.6% vs 84.0%; p: 0.006), IMRT or VMAT techniques (compared to 3D-conformal therapy; 93.2- 100.0% vs 82.6%; p: 0.027), and PNI (compared to irradiation of the prostate bed only; 92.9% vs 80.2%; p: 0.009). Moreover, actuarial 5-year late Grade ≥ 2 GU toxicity did not show any significant correlation with the analyzed parameters. Furthermore, actuarial 5- year late Grade ≥ 3 GI toxicity was significantly lower in patients treated with hypofractionation (dose per fraction > 2 Gy compared to ≤ 2 Gy; 99.2% vs 96.1%; p-value: 0.033) and IMRT or VMAT techniques (compared to 3D-conformal therapy; 100.0% vs 93.5%; p-value: 0.022). Late Grade ≥ 3 GU toxicity did not exhibit any significant correlation with the analyzed parameters (Table 2).

Table 2: Actuarial 5-year gastrointestinal and genitourinary late toxicity-free survival rates (Grade ≥ 2 and Grade ≥ 3; Kaplan-Meier) and results of univariate analysis (log-rank).

		No of pts (%)	Gastrointestinal				Genitourinary			
			G ≥ 2 (%)	P	G ≥ 3 (%)	p	G ≥ 2 (%)	P	G ≥ 3 (%)	P
Age	≤ 65 years	174 (45.7)	94.1	.065	100.0	**.037**	83.4	.909	94.3	.683
	> 65 years	207 (54.3)	87.2		96.5		83.7		94.6	
Charlson's comorbidity Index	0	309 (81.1)	91.5	.331	98.1	.900	82.6	.890	93.9	.688
	1	57 (15.0)	85.6		98.1		84.4		98.2	
	2	13 (3.4)	83.9		100.0		92.3		92.3	
	3	2 (0.5)	100.0		100.0		100.0		100	
Age adjusted Charlson's comorbidity index	0	6 (1.6)	100.0	.396	100.0	.811	75.0	.865	100.0	.651
	1	49 (12.9)	95.8		100.0		90.9		96.8	
	2	178 (46.7)	92.5		98.3		79.8		93.2	
	3	119 (31.2)	85.4		97.4		85.4		95.8	
	4	25 (6.6)	83.0		95.7		86.6		92.0	
	5	3 (0.8)	100.0		100.0		64.9		100.0	
	6	1 (0.3)	100.0		100.0		100.0		100.0	
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		98.6		79.2		95.9	
	< 15*	166 (43.6)	92.9	.098	99.2	.259	86.9	.464	94.1	.758
	≥ 15*	121 (31.8)	84.4		96.0		83.0		93.9	
EQD_2 to the prostate bed α/β_3 (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	3DCRT	94 (24.7)	82.6		93.5		83.4		96.4	
	IMRT	273 (71.7)	93.2	**.027**	100.0	**.002**	83.1	.524	93.2	.692
	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
	CB	30 (7.9)	96.6		100.0		100.0		100.0	
Previous abdominal or 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	
EQD_2 to the lymph node α/β_3 (Gy)	No	84 (22.0)	80.2		96.8		87.7		98.0	
	≤ 43.2	196 (51.4)	93.0	**.033**	99.5	.329	82.2	.236	91.7	.121
	> 43.2	101 (26.5)	92.7		96.6		83.5		96.9	
Acute GI toxicity	G 0	162 (42.5)	91.3		99.0		NA	NA	NA	NA
	G 1	148 (38.8)	88.2	.601	97.1	.442	NA	NA	NA	NA
	G 2-3	71 (18.6)	92.5		98.3		NA	NA	NA	NA
Acute GU toxicity	G 0	150 (39.4)	NA	NA	NA	NA	90.7		95.3	
	G 1	162 (42.5)	NA	NA	NA	NA	85.5	**.000**	92.1	.390
	G 2-3	69 (18.1)	NA	NA	NA	NA	65.2		98.0	

Legend: 3D-CRT: 3-dimensional conformal radiotherapy, CB: cone beam; EQD_2: Equivalent Dose in 2 Gy/fraction; EPID: Electronic portal imaging device; G: Grade; GI: gastrointestinal; GU: genitourinary; NA: not assessed; No: Number; Pts: patients; *: number of resected lymph nodes.

Multivariate analysis

The multivariable analysis of acute toxicity, conducted using binomial logistic regression, revealed a statistically significant association between older age and a reduced risk of Grade ≥ 2 GI acute toxicity (age analyzed as a dichotomous variable: OR: 0.569; 95% confidence interval [95%CI]: 0.329-0.973; p: 0.040). Apart from age, no other variable fitted in the multivariable logistic model for GI Grade ≥ 2 toxicity. Moreover, older age was significantly associated to a lower risk of Grade ≥ 2 GU acute toxicity (age analyzed as a continuous variable: OR: 0.956; 95%CI: 0.918-0.996; p: 0.031). Regarding dichotomous variable GU Grade ≥ 2 acute toxicity, three variables were included in the multivariable model, including age as a continuous variable, ADT, and EQD2 a/b=10 to the prostate bed. While ADT and EQD2 enhanced the predictive model, they were not statistically significant (ADT: OR: 1.730, 95% CI: 0.966-3.234, p: 0.073; EQD2: OR: 1.0005, 95%CI: 0.9999-1.0010, p = 0.075). In contrast, the age variable remained statistically significant, with age showing an inverse association with toxicity (OR: 0.956, 95% CI: 0.918-0.996, p: 0.031). The multivariable analysis of late toxicity confirmed only a lower risk of Grade ≥ 2 GI toxicity in patients undergoing hypofractionation (OR: 0.38; 95% CI: 0.18-0.78; p: 0.008). (Table 3).

Table 3: Multivariable analysis of late gastrointestinal and genitourinary toxicity

Gastrointestinal toxicity (Grade ≥ 2)				
Variable	*Value*	*Hazard Ratio*	*95%CI*	*p=*
Age	CV	1.036	0.976-1.107	0.232
Charlson's comorbidity index	0	Ref		
	> 0	1.678	0.953-2.955	0.073
Nodal irradiation	No	Ref		0.802
	Yes	0.974	0.593-1.498	
Hypofractionation	No	Ref		0.008
	Yes	0.381	0.184-0.783	
Lymphadenectomy	No/sampling	Ref		0.802
	Yes (>15)	0.942	0.589-1.505	
EQD_2 to the prostate bed α/β_3 (Gy)	CV	1.000	0.998-1.002	0.936
Radiotherapy technique	3D-CRT	Ref		0.929
	IMRT/VMAT	0.945	0.275-3.251	
Image guidance	EPID	Ref		0.267
	Cone-beam CT	0.561	0.202-1.557	
EQD2 to the lymph node α/β_3 (Gy)	CV	1.001	0.998-1.003	0.580

Genitourinary toxicity (Grade ≥ 2)				
Variable	*Value*	*Hazard Ratio*	*95%CI*	*p=*
Age	CV	0.991	0.945-1.040	0.710
Charlson's comorbidity index	0	Ref		0.468
	> 0	0.807	0.452-1.440	
Nodal irradiation	No	Ref		0.890
	Yes	0.744	0.110-4.894	
Hypofractionation	No	Ref		0.250
	Yes	0.544	0.193-1.534	
Lymphadenectomy	No/sampling	Ref		0.074
	Yes (>15*)	0.724	0.508-1.031	
EQD_2 to the prostate bed α/β_3 (Gy)	CV	1.001	0.998-1.003	0.120
Radiotherapy technique	3D-CRT	Ref		0.621
	IMRT/VMAT	0.767	0.269-2.191	
Image guidance	EPID	Ref		0.400
	Cone-beam CT	0.803	0.606-1.365	
EQD2 to the lymph node α/β_3 (Gy)	CV	1.000	0.999-1.001	0.972
Acute GU toxicity	Grade 0-1	Ref		0.059
	Grade 2-3	3.060	0.882-13.658	

3D-CRT: 3-dimensional conformal radiotherapy; EQD2: Equivalent Dose in 2 Gy/fraction; EPID: Electronic portal imaging device; *: number of resected lymph nodes.

Discussion

Adjuvant RT has been associated with an increased risk of side effects compared to surgery alone (4) and early salvage RT (7–9). However, it is important to note that, in selected high-risk PCa patients, adjuvant RT offers a higher chance of cure compared to surgery alone. Our multicenter observational study confirms that severe acute toxicity is rare in this setting. The rates of acute Grade ≥ 3 GI and GU toxicity were only 0.5% and 1.3%, respectively, and the 5-year actuarial cumulative incidence of late Grade ≥ 3 GI and GU toxicity rates were 1.9% and 5.5%, respectively.

Furthermore, our analysis demonstrated lower rates of GI acute toxicity in older patients. This unexpected result may arise from the fact that elderly patients may be more likely to have pre-existing symptoms or discomfort due to age-related health issues or comorbidities. As a result, they might be less inclined to report or attribute certain side effects to RT, especially if these side effects are mild or non-serious. The phenomenon of underreporting or downplaying side effects in elderly patients is known as “response shift” or “response shift bias” (23).

Other studies have reported an increased risk of GI early adverse effects in patients with higher mean rectal dose (16) or larger irradiated bowel volumes (24), those receiving PNI (25, 26), individuals with previous abdominal surgery (24), and those under anticoagulant or antiplatelet therapy (16). Additionally, Fiorino et al. observed reduced toxicity rates in patients receiving IMRT (24), although this effect was not observed in our cohort or in the study by Flores-Balcazar et al. (27).

Furthermore, our study demonstrated a reduced risk of GU acute toxicity in older patients, while Martinez-Arribas et al. reported higher GU acute toxicity rates in patients with urinary symptoms before RT. Additionally, similar to our findings, FloresBalcazar et al. (27) and Deville et al. (26) did not observe a significant impact of IMRT/VMAT and PNI, respectively.

Moreover, our analysis revealed a reduced risk of GI late toxicity in patients treated with hypofractionated RT. Another study observed a higher risk of late GI adverse effects in subjects with higher body mass index values and those treated with higher RT doses (17). Furthermore, Flores-Balcazar et al. did not find a significant impact of IMRT/VMAT, in line with our findings, while Goenka et al. reported significantly reduced toxicity in patients treated with IMRT (28). Similarly, Deville et al. did not find different toxicity rates in subjects treated with PNI (26). **.

In our analysis, no parameter was significantly correlated with late GU toxicity. However, other studies have reported a significant correlation between higher toxicity rates and older age and receiving > 70 Gy to larger bladder volumes (17), hypofractionated RT (15), and Grade > 2 acute GU toxicity (13, 15). Interestingly, IMRT did not show an impact on late GU toxicity in two studies (27, 28), consistent with our analysis. Waldstein et al. reported increased toxicity rates in patients treated with PNI (25), while Deville et al. did not observe this correlation (26), similar to our series.

In conclusion, the results of available evidence conflict regarding: i) the impact of modulated RT techniques on acute GU toxicity and late GI side effects, and ii) the impact of PNI on late GU toxicity. Moreover, there is limited evidence available regarding parameters predicting acute GU side effects.

The use of hypofractionation in the adjuvant RT setting of PCa remains a controversial topic. Moderately hypofractionated regimens are considered preferable in patients undergoing exclusive RT (NCCN 2022) but not in the adjuvant setting. According to the NCCN guidelines, the recommended standard fractionation

dose for adjuvant/salvage RT is 64-72 Gy (NCCN 2022). However, the data available on this topic are very heterogeneous. For instance, a systematic review on hypofractionated postoperative RT reported rates of Grade ≥ 2 late GU toxicity ranging between 0% and 66% (29).

The results of our analysis did not indicate a worse toxicity profile in patients undergoing hypofractionated RT. Furthermore, the multivariable analysis revealed a reduced rate of late GI toxicity after RT delivered with > 2 Gy per fraction. In contrast, Cozzarini et al. reported a significant increase in the rate of Grade ≥ 3 GU toxicity in patients receiving hypofractionated regimens compared to conventional fractionation (5-year risk: 18.1% versus 6.9%). This difference can be explained by comparing the equivalent doses delivered in our study and Cozzarini's et al. study. Assuming an a/b ratio of 3 Gy for late effects, patients undergoing hypofractionation in our study received a median dose of 68.7 Gy, while in Cozzarini's et al. study, the range was 68.4-80.8 Gy. Moreover, in Cozzarini's et al. study, the EQD2 was > 70 Gy in 79.8% of patients and > 79 Gy in 32.4% of subjects. Additionally, the EQD2 for PNI was 43.2 Gy in our series and 50.2 Gy in Cozzarini's et al. series. Even when using an a/b ratio of 5, as done by Cozzarini et al., our median EQD2 (67.0 Gy) was lower compared to their analysis (median: 70.4 Gy, IQR: 70.4-79.2 Gy).

Taken together, the results from the two studies suggest a possible association between dose and late urological toxicity in this setting, highlighting the need for further investigation. It is also worth noting that the safety of hypofractionation observed in our data is consistent with recent analyses (30–32). Probably, the lower incidence of late toxicity recorded in patients treated with hypofractionation in our study, despite a significantly higher EQD2a/b=3 value, may derive from the delivery of RT in more recent times, and therefore with more precise techniques.

The paradoxical result of our analysis, of reduced late gastrointestinal toxicity in patients undergoing PNI, remains to be explained. The only interpretation we can propose is that patients with better general conditions and fewer comorbidities (particularly at the intestinal level) were more frequently referred to PNI.

Our study has certain limitations. The scales used to score acute and late toxicity are outdated, and an assessment of the treatment impact on quality of life is lacking. Furthermore, despite efforts to include as many parameters as possible in the analysis, some were missing from our database. Among these, several factors have shown a significant impact on toxicity rates in previous studies, such as baseline symptoms (16) drug therapy during RT (16), planning dose/volume indices (14, 17), body mass index (17), and tobacco history (17).

On the other hand, the strengths of this study lie in the large number of cases analyzed and the comprehensive inclusion of numerous parameters related to both patients and treatments, as well as RT techniques in the analysis.

In conclusion, the results of our analysis demonstrate that although adjuvant RT significantly increases the overall rate of adverse events in PCa patients, the risk of severe toxicity is low. Additionally, acute toxicity rates were higher in younger patients, while a protective effect of hypofractionation was observed in terms of late GI toxicity.

To minimize the negative impact of adjuvant RT, further studies are warranted. These analyses should aim to: i) develop predictive models of toxicity combined with the risk of recurrence based on a comprehensive range of clinical, genetic-molecular, and treatment-related parameters, to guide the careful selection of patients for immediate adjuvant RT; ii) analyze toxicity rates in patients undergoing tailored/intensified

adjuvant RT. For example, studies have shown that biochemical relapse-free survival can be improved by modulating postoperative RT, such as adjusting the dose based on surgical margin status, delivering PNI in selected cases, and administering ADT based on the risk of treatment failure (33–36); iii) clarify the impact of hypofractionation on late GU toxicity, given the conflicting evidence in the literature (29).

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin (2018) 68(6):394–424. doi: 10.3322/ caac.21492

2. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA (2006) 296(19):2329–35. doi: 10.1001/jama.296.19.2329

3. Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostatespecific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol (2009) 27(18):2924–30. doi: 10.1200/JCO.2008.18.9563

4. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet (2012) 380(9858):2018–27. doi: 10.1016/S0140-6736(12)61253-7

5. Hackman G, Taari K, Tammela TL, Matikainen M, Kouri M, Joensuu T, et al. Randomised trial of adjuvant radiotherapy following radical prostatectomy versus radical prostatectomy alone in prostate cancer patients with positive margins or extracapsular extension. Eur Urol (2019) 76(5):586–95. doi: 10.1016/j.eururo.2019.07.001

6. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol (2009) 181(3):956–62. doi: 10.1016/j.juro.2008.11.032

7. Parker CC, Clarke NW, Cook AD, Kynaston HG, Petersen PM, Catton C, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. Lancet (2020) 396(10260):1413–21. doi: 10.1016/S0140-6736 (20)31553-1

8. Sargos P, Chabaud S, Latorzeff I, Magné N, Benyoucef A, Supiot S, et al. Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUGAFU 17): a randomised, phase 3 trial. Lancet Oncol (2020) 21(10):1341–52. doi: 10.1016 S1470-2045(20)30454-X

9. Kneebone A, Fraser-Browne C, Duchesne GM, Fisher R, Frydenberg M, Herschtal A, et al. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. Lancet Oncol (2020) 21(10):1331–40. doi: 10.1016/S1470-2045(20) 30456-3

10. Vale CL, Fisher D, Kneebone A, Parker C, Pearse M, Richaud P, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. Lancet (2020) 396(10260):1422–31. doi: 10.1016/S0140-6736(20) 31952-8

11. Swanson GP, Goldman B, Tangen CM, Chin J, Messing E, Canby-Hagino E, et al. The prognostic impact of seminal vesicle involvement found at prostatectomy and the effects of adjuvant radiation: data from Southwest Oncology Group 8794. J Urol (2008) 180(6):2453–7; discussion 2458. doi: 10.1016/j.juro.2008.08.037

12. Van der Kwast TH, Bolla M, Van Poppel H, Van Cangh P, Vekemans K, Da Pozzo L, et al. Identification of patients with prostate cancer who benefit from immediate postoperative radiotherapy: EORTC 22911. J Clin Oncol (2007) 25 (27):4178–86. doi: 10.1200/JCO.2006.10.4067

13. Choo R, Pearse M, Danjoux C, Gardner S, Morton G, Szumacher E, et al. Analysis of gastrointestinal and genitourinary morbidity of postoperative radiotherapy for pathologic T3 disease or positive surgical margins after radical prostatectomy using national cancer institute expanded common toxicity criteria. Int J Radiat Oncol Biol Phys (2008) 72(4):989–95. doi: 10.1016/j.ijrobp.2008.02.044

14. Perna L, Alongi F, Fiorino C, Broggi S, Cattaneo Giovanni M, Cozzarini C, et al. Predictors of acute bowel toxicity in patients treated with IMRT whole pelvis irradiation after prostatectomy. Radiother Oncol (2010) 97(1):71–5. doi: 10.1016/ j.radonc.2010.02.025

15. Cozzarini C, Fiorino C, Deantoni C, Briganti A, Fodor A, La Macchia M, et al. Higher-than-expected severe (Grade 3-4) late urinary toxicity after postprostatectomy hypofractionated radiotherapy: a single-institution analysis of 1176 patients. Eur Urol (2014) 66(6):1024–30. doi: 10.1016/j.eururo.2014.06.012

16. Martınez-Arribas CM, Gonza dez-San Segundo C, Cuesta-Á lvaro P, CalvoManuel FA. Predictors of urinary and rectal toxicity after external conformed radiation therapy in prostate cancer: Correlation between clinical, tumour and dosimetric parameters and radical and postoperative radiation therapy. Actas Urol Esp. (2017) 41(10):615–23. doi: 10.1016/j.acuro.2017.03.010

17. Akthar AS, Liao C, Eggener SE, Liauw SL. Patient-reported outcomes and late toxicity after postprostatectomy intensity-modulated radiation therapy. Eur Urol (2019) 76(5):686–92. doi: 10.1016/j.eururo.2019.05.011

18. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the european organization for research and treatment of cancer (EORTC). Int J Radiat Oncol Biol Phys (1995) 31(5):1341–6. doi: 10.1016/0360-3016 (95)00060-C

19. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. In: Kotz S, Johnson NL, editors. Breakthroughs in Statistics: Methodology and Distribution. New York, NY: Springer (1992). p. 319–37. doi: 10.1007/978-1-4612- 4380-9_25

20. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. J R Stat Soc Ser A (General) (1972) 135(2):185–207. doi: 10.2307/2344317

21. Cox DR. Regression models and life-tables. J R Stat Soc Ser B (Methodological) (1972) 34(2):187–220. doi: 10.1111/j.2517-6161.1972.tb00899.x

22. Deodato F, Cilla S, Massaccesi M, Macchia G, Ippolito E, Caravatta L, et al. Daily on-line set-up correction in 3D-conformal radiotherapy: is it feasible? Tumori (2012) 98(4):441–4. doi: 10.1177/030089161209800407

23. Ilie G, Bradfield J, Moodie L, Lawen T, Ilie A, Lawen Z, et al. The role of response-shift in studies assessing quality of life outcomes among cancer patients: A systematic review. Front Oncol (2019) 9:783. doi: 10.3389/fonc.2019.00783

24. Fiorino C, Alongi F, Perna L, Broggi S, Cattaneo GM, Cozzarini C, et al. Dose– volume relationships for acute bowel toxicity in patients treated with pelvic nodal irradiation for prostate cancer. Int J Radiat OncologyBiologyPhysics (2009) 75(1):29–35. doi: 10.1016/j.ijrobp.2008.10.086

25. Waldstein C, Dörr W, Pötter R, Widder J, Goldner G. Postoperative radiotherapy for prostate cancer: Morbidity of local-only or local-plus-pelvic radiotherapy. Strahlenther Onkol (2018) 194(1):23–30. doi: 10.1007/s00066-017- 1215-9

26. Deville C, Vapiwala N, Hwang WT, Lin H, Ad VB, Tochner Z, et al. Comparative toxicity and dosimetric profile of whole-pelvis versus prostate bed-only intensitymodulated radiation therapy after prostatectomy. Int J Radiat Oncol Biol Phys (2012) 82(4):1389–96. doi: 10.1016/j.ijrobp.2011.04.041

27. Flores-Balcázar CH, Urıas-Arce DM, Bourlon MT, Gabilondo-Navarro F, Pe dtezÁ lvarez SI, Ramos-Prudencio R, et al. Transitioning from conformal radiotherapy to intensity-modulated radiotherapy after radical prostatectomy: Clinical benefit, oncologic outcomes and incidence of gastrointestinal and urinary toxicities. Rep Pract Oncol Radiother (2020) 25(4):568–73. doi: 10.1016/j.rpor.2020.04.018

28. Goenka A, Magsanoc JM, Pei X, Schechter M, Kollmeier M, Cox B, et al. Improved toxicity profile following high-dose postprostatectomy salvage radiation therapy with intensity-modulated radiation therapy. Eur Urol (2011) 60(6):1142–8. doi: 10.1016/j.eururo.2011.08.006

29. Siepe G, Buwenge M, Nguyen NP, Macchia G, Deodato F, Cilla S, et al. Postoperative hypofractionated radiation therapy in prostate carcinoma: A systematic review. Anticancer Res (2018) 38(3):1221–30. doi: 10.21873/anticanres.12343

30. Tramacere F, Arcangeli S, Pignatelli A, Bracci S, Vinella M, Portaluri M. Postoperative hypofractionated radiotherapy for prostate cancer. Anticancer Res (2018) 38(5):2951–6. doi: 10.21873/anticanres.12544

31. Mahase S, Nagar H. Hypofractionated postoperative radiotherapy for prostate cancer: is the field ready yet? Eur Urol Open Sci (2020) 22:9–16. doi: 10.1016/ j.euros.2020.10.001

32. Moll M, D'Andrea D, Zaharie A, Grubmüller B, Paschen C, Zehetmayer S, et al. Comparative effectiveness of moderate hypofractionation with volumetric modulated arc therapy versus conventional 3D-radiotherapy after radical prostatectomy. Strahlenther Onkol (2022) 198(8):719–26. doi: 10.1007/s00066-022-01909-2

33. Mantini G, Siepe G, Alitto AR, Buwenge M, Nguyen NP, Farioli A, et al. Tailored postoperative treatment of prostate cancer: final results of a phase I/II trial. Prostate Cancer Prostatic Dis (2018) 21(4):564–72. doi: 10.1038/s41391-018-0064-7

34. Cozzarini C, Montorsi F, Fiorino C, Alongi F, Bolognesi A, Da Pozzo LF, et al. Need for high radiation dose (>or=70 gy) in early postoperative irradiation after radical prostatectomy: a single-institution analysis of 334 high-risk, node-negative patients. Int J Radiat Oncol Biol Phys (2009) 75(4):966–74. doi: 10.1016/j.ijrobp.2008.12.059

35. Ost P, Cozzarini C, De Meerleer G, Fiorino C, De Potter B, Briganti A, et al. High-dose adjuvant radiotherapy after radical prostatectomy with or without androgen deprivation therapy. Int J Radiat Oncol Biol Phys (2012) 83(3):960–5. doi: 10.1016/ j.ijrobp.2011.09.007

36. Katayama S, Habl G, Kessel K, Edler L, Debus J, Herfarth K, et al. Helical intensity-modulated radiotherapy of the pelvic lymph nodes with integrated boost to the prostate bed - initial results of the PLATIN 3 Trial. BMC Cancer (2014) 14:20. doi: 10.1186/1471-2407-14-20

Salvage radiotherapy in prostate cancer: the role of prophylactic nodal irradiation.

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 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 showed improved bRFS, RC and DFS in Patients receiving PNI.

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 (Stephenson 2005, Pollack 2004). However, a subsequent analysis showed their limits in terms of predictive power (Simon 2006). 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 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.

Inclusion criteria

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 (11) and compared with the log-rank test (12). Variables with *P* value less than 0.05 or a trend in the univariate analysis were entered into a multivariate Cox regression model (13). $P < 0.05$ value was considered statistically significant. Acute toxicity was assessed by RTOG scale while late toxicity was evaluated with the RTOG/EORTC scale (14).

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, data on fractionation, RT dose and EQD2.

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 – Appendix 1), 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 – Appendix 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).

Table 1. Patient characteristics of the analyzed cohort with the number of patients and percentage of the total number of patients [%] and survival differences

Variable	Value	No of patients [%]	bRFS [%]	P	LC [%]	P	RC [%]	P	MFS [%]	P	DFS [%]	p	OS [%]	p
Age	Median (range)	68 (45-82)												
Age category	< 63 years	92 (20.3)	50.2	.898	88.9	.522	95.2	.247	80.1	.684	67.3	.265	91.5	.892
	≥ 63 years	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 cat	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	

Table 2. Treatment characteristics with number of patients [%] and survival differences

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	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	

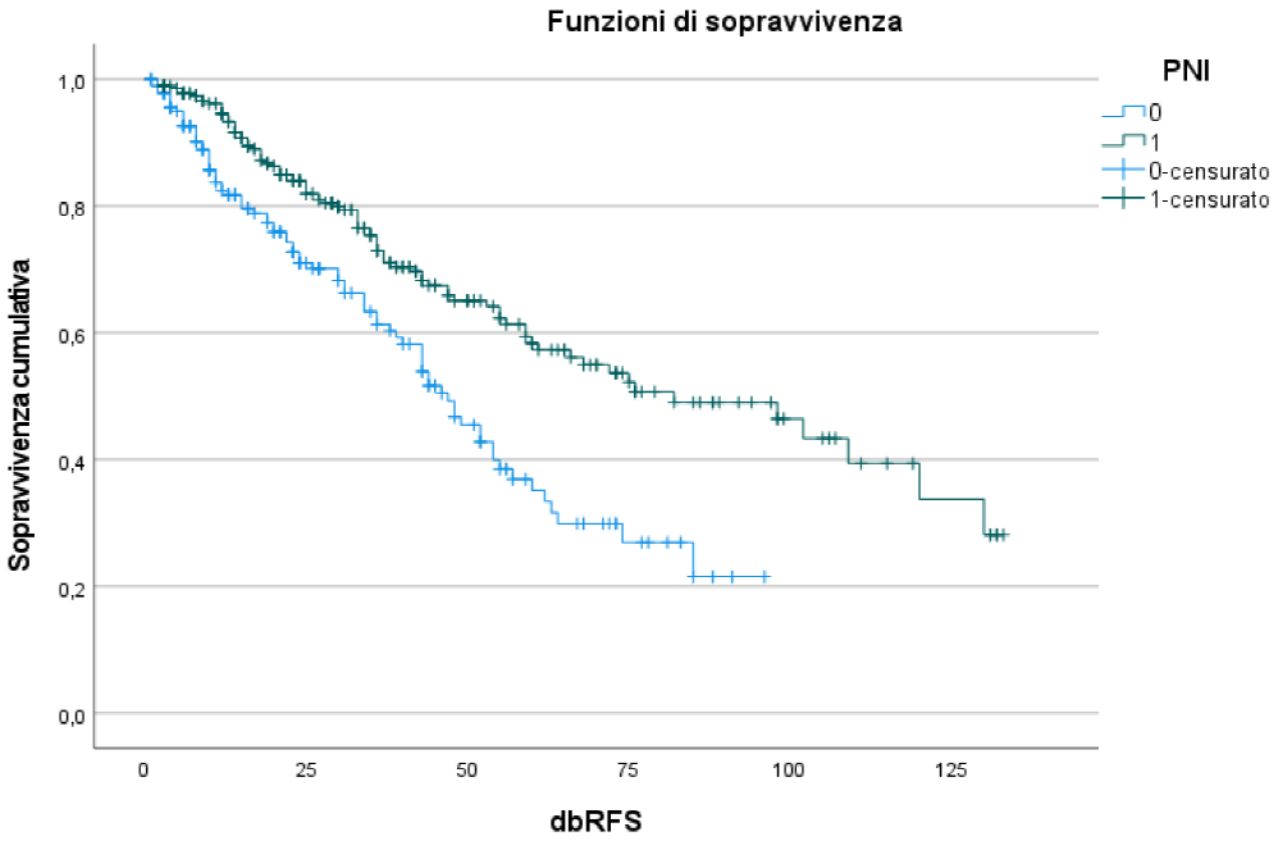
Appendix 1: **Biochemical relapse-free survival (bRFS) and Prophylactic Nodal Irradiation**

PNI	Total number of cases	bRFS (%)
No	184	35.1
Yes	270	58.3

Global comparisons

	Chi-quadrato	gl	Sign.
Log Rank (Mantel-Cox)	17,474	1	**<,001**
Breslow (Generalized Wilcoxon)	14,733	1	<,001

Test of equality of survival distributions for different levels of PNI.



Biochemical relapse-free survival and Prophylactic Nodal Irradiation.

0: No PNI, 1: Yes PNI

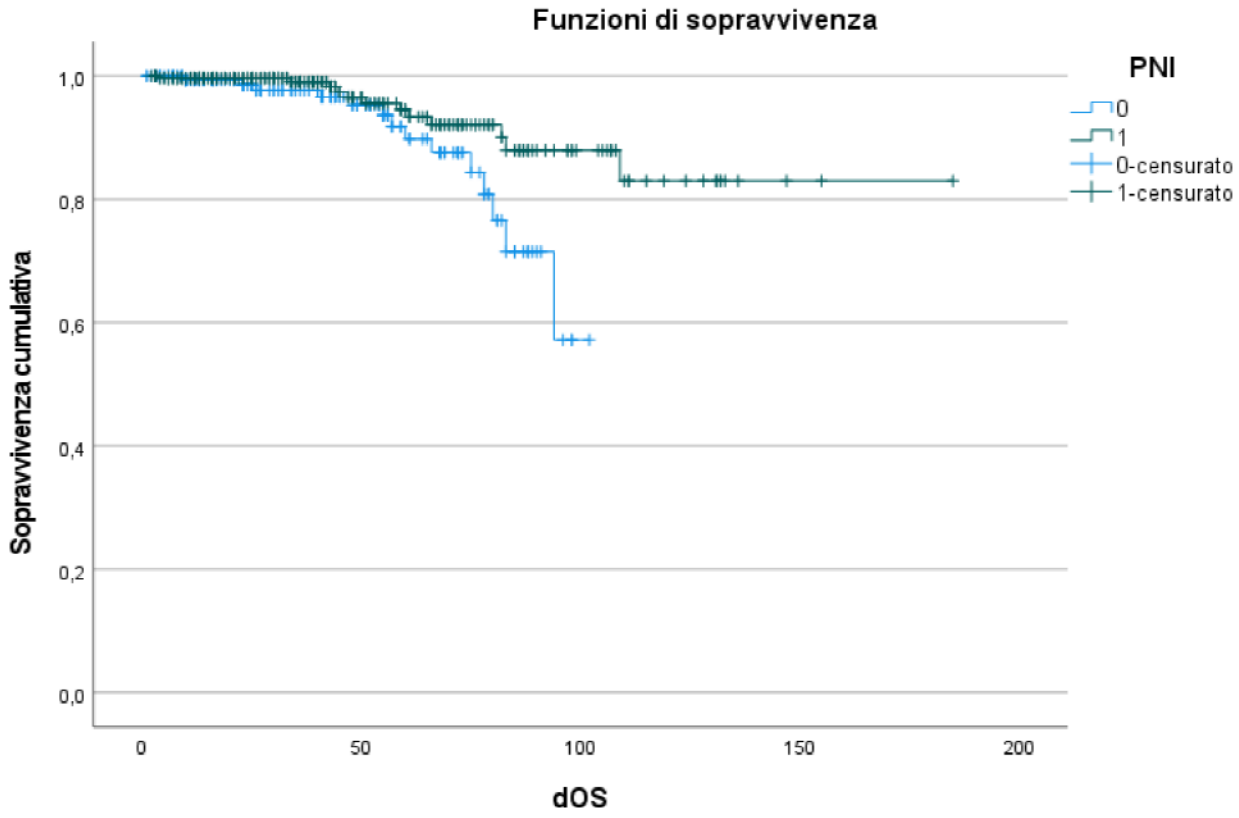
Appendix 2: **Overall survival and Prophylactic Nodal Irradiation**

PNI	Total number of cases	OS (%)
No	184	89.8
Yes	270	94.5

Global comparisons

	Chi-quadrato	gl	Sign.
Log Rank (Mantel-Cox)	5,053	1	**,025**
Breslow (Generalized Wilcoxon)	2,121	1	,145
Tarone-Ware	3,288	1	,070

Test of equality of survival distributions for different levels of PNI.



Overall survival and Prophylactic Nodal Irradiation.

0: No PNI, 1: Yes PNI

Table 3. Dose characteristics with number of patients [%] and 5-year survival

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	
RT 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	

Treatment fields

The fields of radiation treatment change a lot depending on whether exclusively the prostatic lodge or prostatic lodge and pelvic lymph nodes are treated (Fig. 1).

Consequently, toxicity to organs at risk can also vary depending on the size of the radiation treatment field, RT techniques and dose distribution (Fig.2).

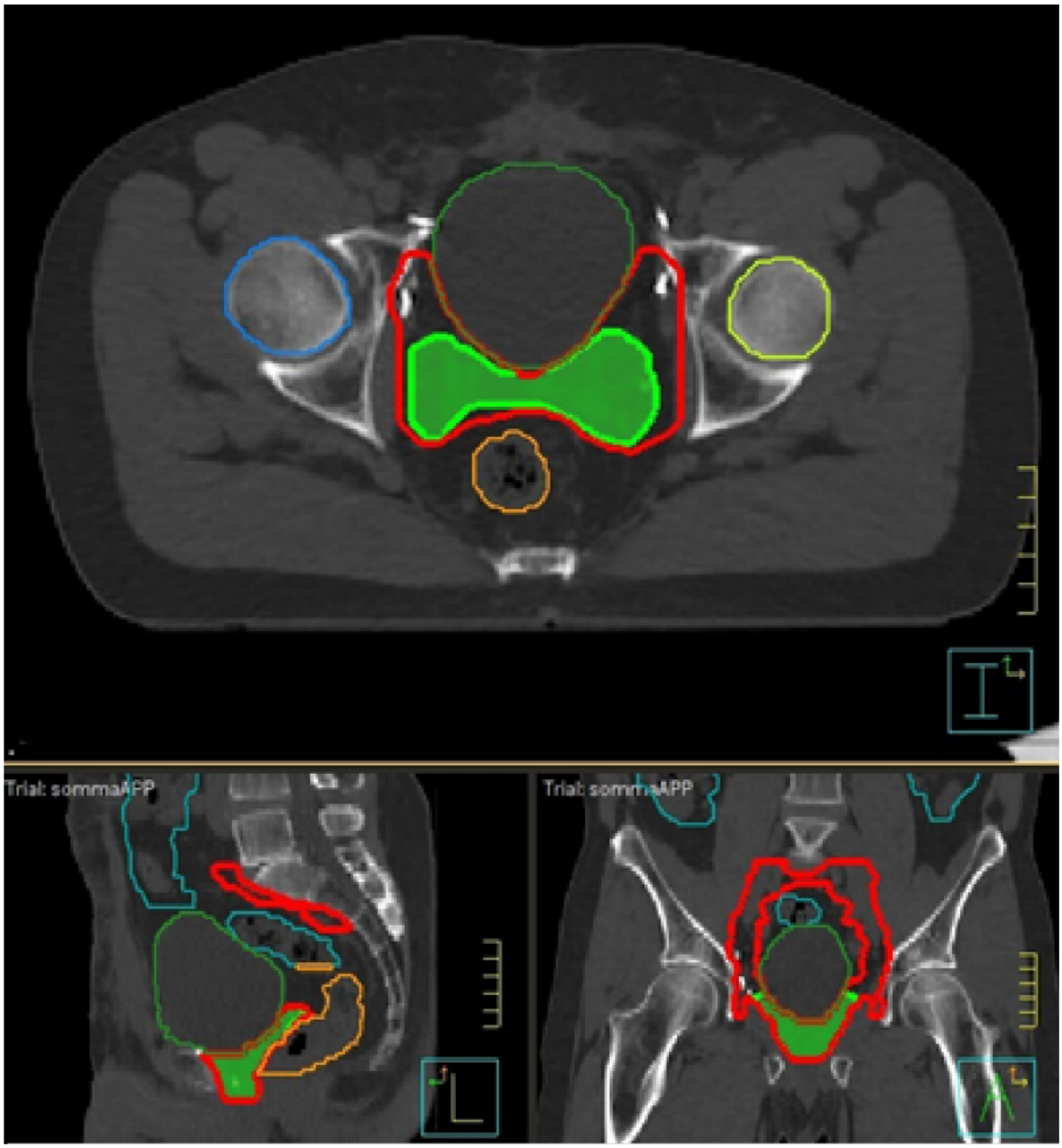


Fig. 1: RT treatment fields.

In green: prostatic lodge, in red: prostatic lodge + pelvic lymph nodes.

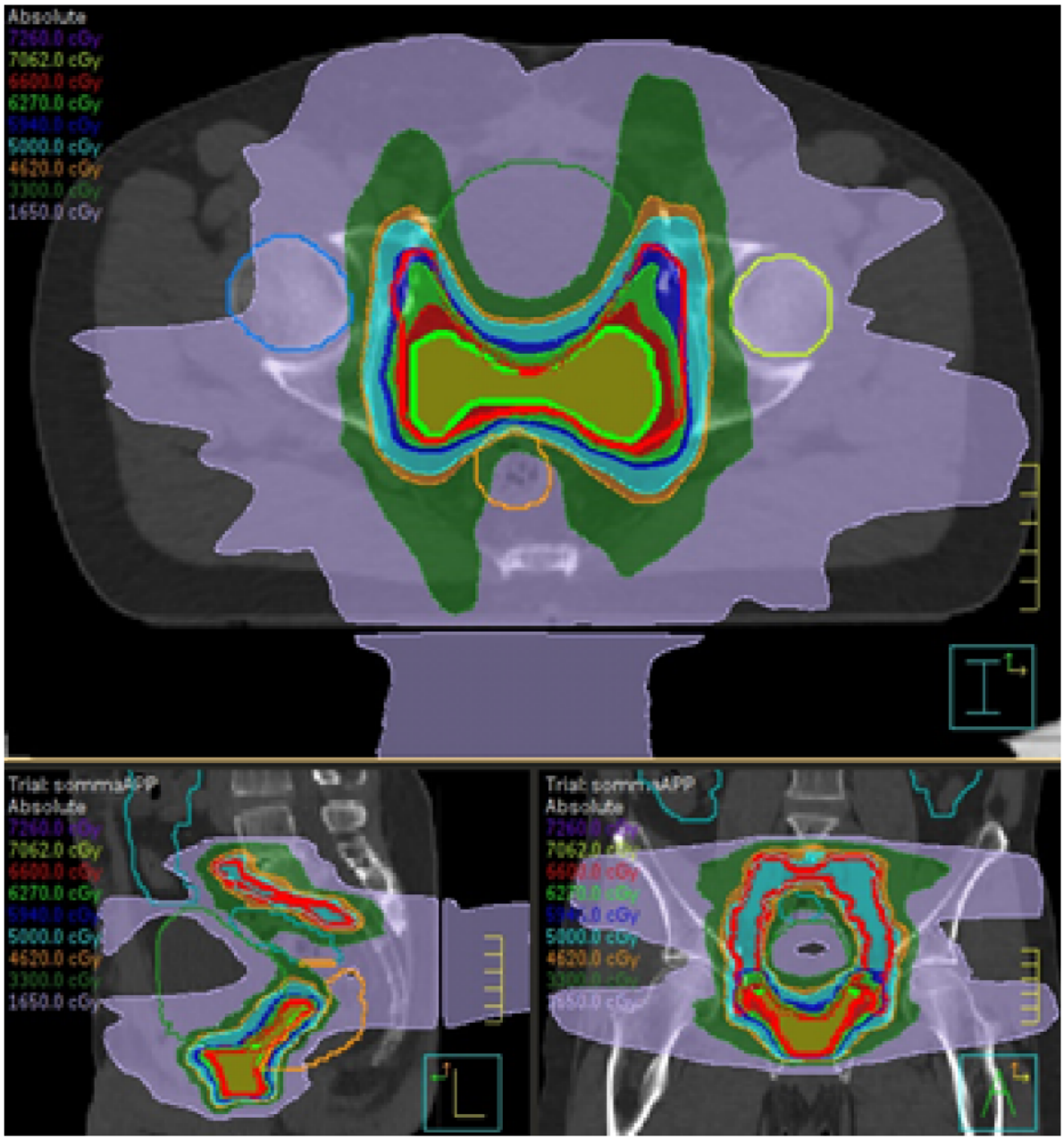


Figure 2: RT Dose distribution and organ at risks

Toxicity

In our analysis, the majority of patients did not present significant acute genitourinary, gastrointestinal or skin toxicity. Only four Patients (0.9%) reported G3 GI toxicity and three Patients (0.7%) genitourinary toxicity (Table 4).

Table 4: Acute toxicity

	0	1	2	3
Gastrointestinal	215 (47.4)	140 (30.8)	95 (20.9)0.	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)

No significant correlations were recorded between grade > 2 acute toxicity and the analyzed parameters (Table 5).

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 pro 10	< 68.3 Gy	36 (19.8)	.231	1 (0.5)	.473	32 (17.6)	.434	2 (1.1)	.527
	≥ 68.3 Gy	63 (23.2)		3 (1.1)		45 (16.5)		2 (0.7)	
EQD2 to the LN 10	≤ 44.3 Gy	45 (25.1)	.339	4 (2.2)	.191	42 (23.5)	.031	2 (1.1)	.439
	> 44.3 Gy	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)	

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).

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

		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$\alpha/\beta_{1.5}$ (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	

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.

Table 7: Multivariate analysis

Variable	*value*	***bRFS***		
pN stage	*No*	*1.00 (Ref)*		
	Yes	*1.91*	*1.29-2.83*	***.001***
Gleason score new (ISUP grade)	*6*	*1.00 (Ref)*		***.000***
	7 (3+4)	*1.05*	*0.54-2.04*	*.884*
	7 (4+3)	*2.37*	*1.34-4.19*	***.003***
	8	*2.09*	*1.16-3.79*	***.014***
	9-10	*3.99*	*2.28-7.01*	***.000***
Nodal irradiation	*No*	*1.00 (Ref)*		
	Yes	*0.44*	*0.32-0.61*	***.000***

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 Gleason score categories, the 2 nodal stage categories, and the two nodal irradiation categories to define 20 different groups of patients (Table 8). At this point we arranged these 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%) (Table 9).

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: PNI= prophylactic nodal irradiation

Table 9: risk categorization (5-year biochemical Relapse–Free Survival)

<table>
<tr><th colspan="2" rowspan="2"></th><th colspan="2">pN0</th><th>pN1</th></tr>
<tr><th>PNI</th><th>No PNI</th><th>PNI</th></tr>
<tr><td rowspan="5">Gleason (ISUP Grade)</td><td>6</td><td>Low (>80%)</td><td rowspan="2">High (40-60%)</td><td rowspan="2">Very high (<40%)</td></tr>
<tr><td>7 (3+4)</td><td rowspan="3">Intermediate (60-80%)</td></tr>
<tr><td>7 (4+3)</td><td colspan="2" rowspan="3">Very high (<40%)</td></tr>
<tr><td>8</td></tr>
<tr><td>9-10</td><td>High</td></tr>
</table>

PNI: prophylactic nodal irradiation

Table 10: Comparison between published analysis

AUTHORS/ YEAR	CENTRE/ TRIAL	INCLUSION CRITERIA	STUDY DESIGN	NUMBER OF PATIENTS	MAIN RESULTS	NOTES
POLLACK A. ET AL (2022)	RTOG 0534 (SPPORT) trial.	Post-RP that had a persistently detectable or an initially undetectable and rising PSA of between 0.1 and 2.0 ng/mL.	randomized, phase 3 trial	1792: Arm 1:592 PBRT alone, Arm 2:602 PBRT plus short-term ADT, Arm 3:598 PLNRT plus PBRT plus short-term ADT. 76 patients were excluded, thus, the final patient population was 1716 patients.	Compared with PBRT alone, PLNRT+ADT was associated with significantly better five-year freedom from progression (5y-FFP), a lower risk of distant metastases (DM), and fewer prostate cancer-specific deaths (PCaSD). However, when compared with PBRT+ADT, there was only a trend toward the benefit of PLNRT that was not statistically significant for 5y-FFP, risk of DM or PCaSD.	No significant difference between arm 2 vs. arm 3.
SONG C. ET AL (2019)	Seoul National University College of Medicine	Post-RP with newly rising PSA. Exclusion criteria: patients with LN met at the time of RP, adjuvant RT, ADT initiated either prior to RP or >6 months prior to SRT, a Roach score ≤15% for the risk of LN involvement, and clinical follow-up period less than 1 year, pts that did not receive	Retrospective	191 pts. 108 WPRT. 83 PBRT.	The 5-year bRFS of the WPRT group was significantly higher than that of the PBRT group.	The benefit of WPRT on bRFS was maintained in subgroup analyses, especially in patients with preoperative PSA level ≤20 ng/mL or pre-SRT PSA level ≥0.4 ng/mL.

		PLND, or if they received either WPRT or PBRT discordant with the institution's preference.				
RAMEY S J. ET AL (2018)	University of Miami Miller School of Medicine/Sylvester Comprehensive Cancer Center	Pts post-RP with PSA >0.01 ng/ml; pT1-4, Nx/0, cM0; and GS ≥7 treated between 1987 and 2013.	Retrospective	1861 pts. 1366 PBRT, 176 WPRT, 250 PBRT+ADT, 69 WPRT+ADT.	Overall, WPRT was associated with a significantly higher 5-yr FFBF versus PBRT. No significant differences in DM cumulative incidence were found.	
BYUN S J. ET AL (2018)	Dongsan Medical Center, Keimyung University School of Medicine.	Patients with high-risk PCa who received SRT for biochemical recurrence following prostatectomy	Retrospective	170 pts receiving WPRT.	The 5-year BCPFS was 38.6%, which seems to be inferior to that reported in previous studies. However, the other studies had different factors such as more favorable GS, initial PSA, and T stage, or conversely, additive use of ADT therapy.	PreSRT PSA was the only controllable prognostic factor, suggesting the benefit of early SRT.
EMMETT L. ET AL (2017)	St. Vincent's Public Hospital, The Garvan Institute of Medical Research/The Kinghorn Cancer Centre, University of New South Wales.	Men post-RP that were diagnosed with PSA ≥0.05 and <1.0 ng/mL, suitable for SRT.	RCT	140: 60/140 had a negative and 80/140 a positive PSMA PET/CT scan. 44% (n=27/60) of patients with a negative PSMA underwent SRT. 85% (n=23/27) demonstrated a treatment response.	This study shows that PSMA-PET effectively stratifies men in the cohort of salvage fossa RT into those with a high versus low response to salvage radiation treatment.	High treatment responders: with negative PSMA PET or with disease confined to the fossa. Low responders: PSMA avidity in nodes or distantly.

SONG C. ET AL (2015)	Seoul National University College of Medicine.	Men undergoing SRT post-RP with persistently elevated PSA≥0.1 ng/mL or an elevation of serum PSA levels ≥0.1 ng/mL after achieving <0.1. Exclusion criteria: no LN met at time of RP, no SRT for palliation.	Retrospective	163 after exclusion. 29 received WPRT. 134 PBRT.	The 4-year bRFS of the WPRT group was significantly higher compared to the PBRT group.	Subgroup analysis showed that the bRFS of patients who had two or more risk factors (seminal vesicle invasion, Roach score for lymph node invasion ≥ 45%, and number of harvested lymph nodes ≤ 5) and were treated with WPRT was significantly improved compared to those who received PBRT.
MOGHANAKI D. ET AL (2012)	Virginia Commonwealth University	Patients were excluded if they had either clinical or pathologic LN involvement, if they received ADT at any time before post-SRT biochemical progression or if they received either WPRT or PBRT discordant with the institution's preference.	International retrospective cohort study	247. 112 who received WPRT, and 135 who received PBRT.	This report fails to demonstrate a clear benefit from WPRT in all men who received postprostatectomy SRT for biochemical failure.	A benefit for WPRT may exist for patients who have pre-SRT PSA levels ≥0.4 ng/mL. However, no OS benefit was demonstrated.
SPIOTTO M T. ET AL (2007)	Stanford University School of Medicine	Pts post-RP undergoing SRT or adjuvant RT (RT was defined as adjuvant if	Retrospective	160 pts. 97 WPRT 63 PBRT Risk stratification: 114 pts. 72 WPRT	WPRT resulted in improved bRFS compared with PBRT for patients at high risk of nodal involvement who	High risk of nodal involvement: GS ≥8, a preoperative PSA level >20 ng/mL,

		given within 6 months of RP and a postoperative PSA level was detectable)		42 PBRT	were treated with adjuvant or salvage RT after RP.	pT3, or pathologic lymph node involvement
KIM B S. ET AL (2004)	University of California Los Angeles Medical Center	Post-RP pts with biochemical relapse who received EBRT to the pelvis for salvage intent from 1987 to 1999. Exclusion: Hormone therapy prior to\during RT. Gross tumor recurrence. Lost to follow-up.	Retrospective	Out of 68 patients, 46 patients were retrospectively reviewed due to exclusion criteria. They were divided into 2 groups: 21 received extended fields (EF) RT, which include prostatic fossa and pelvic lymph nodes. 25 received limited fields (LF) RT, which include prostatic fossa only.	Overall, no significant influence on biochemical DFS, DMFS, and OS by increasing the radiation treatment volume was documented. However, results suggest that EF radiation with coverage of pelvic lymphatics shows better PSA control in those patients with adverse pathologic features, although statistical significance was not achieved.	

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, 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.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68:394-424.

2. Thompson IM Jr, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, Messing E, Forman J, Chin J, Swanson G, Canby-Hagino E and Crawford ED: Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA 296:2329-2335, 2006.3.

3. Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, Willich N, Semjonow A, Souchon R, Stöckle M, Rübe C, Weissbach L, Althaus P, Rebmann U, Kälble T, Feldmann HJ, Wirth M, Hinke A, Hinkelbein W and Miller K: Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen. ARO 96-02/AUO AP 09/95 J Clin Oncol 27:2924-2930, 2009.

4. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, Verbaeys A, Bosset JF, van Velthoven R, Colombel M, van de Beek C, Verhagen P, van den Bergh A, Sternberg C, Gasser T, van Tienhoven G, Scalliet P, Haustermans K and Collette L: European Organisation for Research and Treatment of Cancer, Radiation Oncology and Genito-Urinary Groups. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 380:2018- 2027, 2012.

5. Gandaglia G, Briganti A, Clarke N, Karnes RJ, Graefen M, Ost P, Zietman AL, Roach M 3rd. Adjuvant and Salvage Radiotherapy after Radical Prostatectomy in Prostate Cancer Patients. Eur Urol. 2017 Nov;72(5):689-709.

6. Shipley WU, Seiferheld W, Lukka HR, Major PP, Heney NM, Grignon DJ, Sartor O, Patel MP, Bahary JP, Zietman AL, Pisansky TM, Zeitzer KL, Lawton CA, Feng FY, Lovett RD, Balogh AG, Souhami L, Rosenthal SA, Kerlin KJ, Dignam JJ, Pugh SL, Sandler HM; NRG Oncology RTOG. Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer. N Engl J Med. 2017; 376: 417-428.

7. Carrie C, Hasbini A, de Laroche G et al (2016) Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. Lancet Oncol 17(6):747–756.

8. Stephenson AJ, Scardino PT, Eastham JA, Bianco FJ Jr, Dotan ZA, DiBlasio CJ, Reuther A, Klein EA, Kattan MW. Postoperative nomogram predicting the 10-year probability of 62 prostate cancer recurrence after radical prostatectomy. J Clin Oncol. 2005 Oct 1;23(28):7005- 12. PubMed PMID: 16192588; PubMed Central PMCID: PMC2231088.

9. Pollack A, Hanlon AL, Horwitz EM, Feigenberg SJ, Uzzo RG, Hanks GE. Prostate cancer radiotherapy dose response: an update of the fox chase experience. J Urol. 2004 Mar;171(3):1132-6. doi: 10.1097/01.ju.0000111844.95024.74. PMID: 14767286.

10. Simon MA, Kim S, Soloway MS. Prostate specific antigen recurrence rates are low after radical retropubic prostatectomy and positive margins. J Urol. 2006 Jan;175(1):140-4; discussion 144-5. doi: 10.1016/S0022-5347(05)00050-9. PMID: 16406892.

11. Kaplan FL, Meier P. Nonparametric estimation from incomplete observations. Am J Stat Assoc 1958; 53:457- 481.

12. Peto R, Peto J. Asymptotically efficient rank invariant procedures. J R Stat Soc 1972; 135:185-207.

13. Cox DR. Regression model and life tables. J Royal Stat Soc Series 1972; B 34: 187-220.

14. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31: 1341-1346.

15. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, Fossati N, Gross T, Henry AM, Joniau S, Lam TB, Mason MD, Matveev VB, Moldovan PC, van den Bergh RC, Van den Broeck T, van der Poel HG, van der Kwast TH, Rouvière O, Schoots IG, Wiegel T, Cornford P. EAU – ESTRO - SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2017; 71:618-629.

16. National Comprehensive Cancer Network. Prostate Cancer (Version 4.2019). http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed October 5, 2019.